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# Prostate Gland Large Cell Neuroendocrine Carcinoma

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***ABSTRACT***
*It is known that well-differentiated carcinoid tumours and small- or large-cell, poorly differentiated tumours fall under the category of neuroendocrine tumours in the 2016 World Health Organization classification of prostate cancer. Only 20 examples of large-cell neuroendocrine tumours of the prostate gland (LCNTPs) were known to exist as of May 2021; 9 of these cases included original tumours. LCNTPs are a rare histological entity with different characteristics from conventional prostate adenocarcinomas in terms of their evolutionary profile and treatment potential. Prostate primary neuroendocrine tumours may be adenocarcinoma-free or mixed with other tumour types. When detected early at a localised stage, mixed forms of large cell neuroendocrine tumours of the prostate gland (LCNECPs) typically have a better prognosis. However, the majority of (LCNTPs) cases at the time of the initial diagnosis may be progressed, locally advanced, or metastatic. Although most large LCNECPs have been found to be metastatic large cell neuroendocrine carcinomas that had metastasized from other sites of the body, such as the lung, despite the fact that most LCNECPs that are initially diagnosed tend to be primary prostate cancers that may be pure primary prostate cancers. Similar to primary prostate gland cancer, primary LCNECP frequently presents with symptoms of the lower urinary tract, haematuria, or indications of obstruction of the upper urinary tract or difficulty emptying the bladder. Primary LCNECP cases that present frequently also have symptoms connected to the metastases' locations. Although serum levels of prostate-specific antigen are typically not as high as they are in the majority of instances of advanced, locally progressed, or metastatic primary adenocarcinomas of the prostate gland, they do tend to be somewhat increased in cases of primary LCNECP. In order to diagnose LCNECPs, histopathology and immunohisto chemistry staining examinations of prostate specimens taken from prostate biopsies, trans-urethral reception of prostate specimens, or prostatectomy specimens are typically conducted..*

*The following is a summary of the characteristics of the prostate gland's microscope histopathological examination:*
***(a)*** *Massive island or sheets of tumor cells are frequently seen during LCNECP gland histopathology examinations.*
***(b)*** *Prostate tumour specimens typically show large tumour cells with noticeable neuroendocrine characteristics, such as salt-and-pepper chromatin and tiny nucleoli.*
***(c)*** *When LCNECP specimens are examined under a microscope, high grade traits like a lack of glandular development, numerous mitoses, apoptotic bodies, and tumour necrosis are frequently discovered.*

*Features of LCNECP's immunohistochemistry staining include:*
***(a)*** *Immunohistochemistry staining should show at least one of the following neuroendocrine tumour markers, including the presence of positive staining for chromogranin A, synaptophysin, neuron specific enolase, and CD56:*
*o Less than 50% of LCNECP instances with TTFI likely to be positive.*
*o Positive AMACR immunohistochemical staining, albeit this may be more localised or weaker than for prostate-specific cancer.*
*o Positive markers, such as PSA, PSMA, and NKX3.1 prostein (P501S), are typically negative in most cases of LCNECP, but they may be focally positive in a small percentage of tumours.*

*It has been noted that immunohistochemical staining investigations for the following markers frequently show negative staining in LCNECP cases:*
*• Urothelial markers such CK5/CK6, GATA3, and p63, as well as high-molecular-weight cytokeratins.*
*• CD99.*
*• A prostate gland carcinoid tumour.*
*• Prostate gland PNET/Ewing sarcoma.*
*• Prostate adenocarcinoma with localised neuroendocrine differentiation.*
*• Neuroendocrine differentiation in urothelial cancer.*

*In order to diagnose early cases of primary large cell neuroendocrine carcinomas, early prostate gland biopsies must be performed on all patients who have significant lower urinary tract symptoms and who have serum prostate specific antigen (PSA) levels that are slightly elevated or elevated, even if Tamsulosin has been started to help with voiding symptoms. Since there is no universal agreement regarding the optimal treatment for LCNECP, it is necessary to establish a global multi-centre trial comparing the numerous treatment options for the disease in order to determine the most effective ones.*

***KEYWORDS:*** *Large Cell Neuroendocrine Carcinoma of Prostate Gland; Prostate Biopsy; Trans-Urethral resection of Prostate; Prostatectomy; Radiotherapy; Chemotherapy; Histopathology; Immunohistochemistry; Aggressive Treatment; Early Diagnosis; Global multi-centre Trial.*

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## I. INTRODUCTION

Large-cell neuroendocrine carcinoma (LCNEC) of the prostate gland is a remarkably uncommon form of prostate cancer, according to previous reports. [1] and that, as of 2020 [1-5], just eighteen case reports had been reported in the literature. Less than 25 cases of LCNEC have, to the author's knowledge, been documented in the literature; the reported cases total about 20 cases. According to reports, LCNEC of the prostate is highly aggressive and linked to broad metastases [1] [5] [6]. Metastasis had typically been observed to occur in the lymph nodes, lungs, bones, and visceral organs, particularly the liver. [1, 5, 6] Only two cases of brain metastasis from LCNEC of the prostate had been reported by Evans et al. [5], but no studies that included neuroimaging, a physical examination, or microscopic analysis of the brain lesion had been published [1, 5]. According to Aljarba et al. [1], their reported case was the first case to be published in the literature that described brain metastasis of LCNEC of the prostate gland with neuroimaging, gross, and microscopic evaluation with immunohistochemistry up until the time of publication of their article and in accordance with the SCARE criteria. [1] [7].

The subsequent article, Large Cell Neuroendocrine Carcinoma of the Prostate Gland: is composed of two sections:

**(A)** Overview, which contains general statements on different aspects of Large Cell Neuroendocrine Carcinoma of the Prostate to give a bird's eye view of the cancer, and

**(B)** Various narrations and discussions related to some case reports, case series, and studies related to Large Cell Neuroendocrine Carcinoma of the Prostate to give a current status report on Large Cell Neuroendocrine Carcinoma of the Prostate.

## II. METHODS

The following online databases were looked up: Google, Google Scholar, Yahoo, and PubMed. Large Cell Neuroendocrine Carcinoma of the Prostate, Primary Large Cell Neuroendocrine Carcinoma of the Prostate, Metastatic Large Cell Neuroendocrine Carcinoma of the Prostate, and Prostatic Large Cell Neuroendocrine Carcinoma were some of the search terms that were utilised. The article about large cell neuroendocrine carcinoma of the prostate gland, which is divided into two parts, was written using 38 sources, which were found:

(A) Overview which contains general statements on various aspects of Large Cell neuroendocrine carcinoma of the prostate gland in order to provide a bird's eye view of the malignancy.

(B) Miscellaneous narrations and discussions related to some case reports, case series as well as studies related to Large Cell neuroendocrine carcinoma of the prostate gland in order to provide an update on Large Cell neuroendocrine carcinoma of the prostate gland.

## III. Overview

### Definition / General Statements

Large Cell neuroendocrine carcinoma of the prostate gland, is a terminology that is used for high grade prostatic carcinoma which is composed of large cells with diffuse neuroendocrine features. [8] . It has been iterated that neuro-endocrine differentiation of prostate carcinoma is classified as follows:[6] [9].Usual prostatic adenocarcinoma which is associated with neuroendocrine differentiation.

Prostatic adenocarcinoma which is associated with Paneth cell neuroendocrine differentiation.

o Carcinoid tumour

o Small cell carcinoma

o Large cell neuroendocrine carcinoma

o Mixed (small or large cell) neuroendocrine carcinoma which contain the usual prostatic adenocarcinoma

**Essential Features**

With regard to essential features, large Cell neuroendocrine carcinoma of the prostate gland is said to be composed of tumour cells that are larger than those in small cell (neuroendocrine) carcinoma, also which contain slightly more cytoplasm [8] [10] [11]; nevertheless, the size cut-off point has not been well established

• It has also been iterated that Large Cell neuroendocrine carcinoma of the prostate gland is similar to small cell carcinoma [8] [12] with regards to the ensuing features:

o high grade tumour, with no prominent glandular differentiation

o diffuse tumour, but with no focal neuroendocrine features

o the tumour contains high rates of mitosis and apoptosis

o the tumour tends to be associated with poor prognosis

• The tumour could be pure or mixed with conventional high grade prostatic adenocarcinoma, either acinar or ductal type.

• Within the tumour, Paraneoplastic syndromes such as Cushing syndrome (ACTH producing tumour induced) could be present but tend to be rare.

**Epidemiology**

• It has been stated often that prostatic adenocarcinoma and large cell neuroendocrine carcinoma have a similar epidemiology [8].

**Aetiology**

The ensuing iterations have been made with regard to the aetiology of Large Cell neuroendocrine carcinoma of the prostate gland: [8]

• The aetiology is not known

• Large Cell neuroendocrine carcinoma of the prostate gland might occur after androgen deprivation therapy for prostate cancer. [8] [13] Nevertheless, many cases of Large Cell neuroendocrine carcinoma of the prostate gland do develop de novo or in association with untreated high grade prostatic adenocarcinoma [12].

**Clinical Features**

Following is a summary of the clinical characteristics of large cell neuroendocrine carcinoma of the prostate gland: [8].

• Large Cell neuroendocrine carcinoma of the prostate often shares clinical characteristics with adenocarcinoma of the prostate.

• Despite the possibility of raised serum PSA levels, many cases with large cell neuroendocrine prostate cancer do not exhibit appreciable increases in serum PSA, especially when taken into account the large tumour volume.

• There may be additional signs and symptoms of advanced prostate cancer.

• In cases of large cell neuroendocrine carcinoma of the prostate gland, serum neuroendocrine markers such chromogranin may be increased.

**Diagnosis**

• It has been stated that tissue diagnosis with histology, whether from needle core biopsy of the prostate lesion, transurethral resection of prostate specimen, or prostatectomy specimen, is important for the diagnosis of Large Cell Neuroendocrine Carcinoma of the Prostate Gland.

• It has also been mentioned that cytology diagnosis of a primary tumour is not typically recognized as an initial diagnosis, although this might be used for metastatic sites.

• Biopsies of the prostate gland can be performed using a trans-perineal template or with the aid of trans-rectal ultrasound-guided biopsies of the prostate gland, but trans-perineal biopsies of the prostate gland are currently performed more frequently than trans-rectal ultrasound-guided biopsies of the prostate gland due to the tendency of the latter to be associated with more infections.

**Laboratory Studies**

**Microbiology**

**Urinalysis, urine microscopy and culture**

Regular urinalysis, urine microscopy, and culture are typically performed on all patients as part of the general assessment of patients with Large Cell neuroendocrine carcinoma of the prostate gland. If any evidence of a urinary tract infection is present, it would be treated appropriately based on the sensitivity pattern of the cultured organism in order to improve the patients' overall health state as part of their general management in addition to their stent placement.

**Haematology**

All patients with Large Cell Neuroendocrine Carcinoma of the Prostate undergo routine haematology blood tests, such as a full blood count and an INR, and those who are found to have anaemia receive treatment to treat their anaemia as part of their general management as well as the appropriate management of their malignant carcinoma.

**Biochemistry**

All patients with Large Cell Neuroendocrine Carcinoma of the Prostate Glands typically undergo routine biochemistry blood tests, such as serum urea, EGFR, CRP, blood glucose, liver function tests, and bone profile, as part of their general assessment. If there is any abnormality, it would be investigated further and treated to improve each patient's overall state of health. On the basis of radiology imaging, such as an ultrasound scan of the renal tract, if there is evidence of impaired renal function and there is evidence of obstruction of the ureter by prostate cancer, nephrostomy insertion plus/minus insertion of antegrade ureteric stent or cystoscopy and insertion of retrograde ureteric stent into the obstructed ureter would be undertaken to improve renal function of the patient as part of the general procedure. Large cell neuroendocrine carcinomas of the prostate would result in elevated serum levels of the prostate-specific antigen (PSA), however they might not be as high as in cases of pure adenocarcinomas of the prostate.

**Radiology Imaging**

**Chest X-Ray**

The majority of hospitals in developing countries, especially those where facilities for computed tomography scan and magnetic resonance imaging scan are not typically available, tend to perform chest X-rays as part of the general assessment of patients to determine if there is any obvious metastatic lesion within the lungs. among the developed nations Routine chest X-rays have been replaced by computed tomography and magnetic resonance imaging scans, which are used in radiology staging and follow-up evaluation imaging.

**Ultrasound Scan**

In many centres, ultrasounds of the prostate, the renal tract, and trans-rectal ultrasound scan-guided prostate biopsy procedures are often performed. Nephrostomy insertion into the obstructed upper renal tract plus/minus antegrade ureteric stent insertion into the obstructed upper urinary tract or cystoscopy and insertion of retrograde ureteric stent into the obstructed upper renal tract are performed as part of the general management of each patient if there is evidence of ureteral obstruction caused by prostate cancer.

**Computed Tomography (CT) Scan**

Patients with large cell neuroendocrine prostate cancer frequently undergo CT scans of the chest, abdomen, pelvis, and prostate as part of general staging and follow-up procedures. Additionally, the initial prostate gland CT scan would reveal problematic regions that might be targeted for biopsy of the prostate as part of their template biopsies of the prostate gland based on the radiological imaging findings.

**Magnetic Resonance Imaging (MRI) Imaging**

Large Cell Neuroendocrine Prostate Carcinoma patients typically undergo MRI scans of the chest, abdomen, pelvis, and prostate as part of standard staging and follow-up procedures. Additionally, based on the results of the radiology imaging, the initial MRI scan of the prostate gland would show problematic spots within the prostate gland that may be targeted for biopsy of the prostate as part of their template biopsies of the prostate gland.

**Isotope Bone Scan**

Isotope bone scan tends to be undertaken to ascertain if patients who have large cell neuroendocrine carcinoma of the prostate gland have or do not have bone metastasis in order to plan their further management.

**Positron Emission Tomography / Computed Tomography Scan**

To detect early metastatic lesions and locally recurring lesions in patients with large cell neuroendocrine carcinoma of the prostate gland, radiological imaging techniques such as positron emission tomography (PET) and computed tomography (CT) scan are frequently used in follow-up evaluations**.**

**Prognostic Factors**

The prognostic variables for large cell neuroendocrine carcinoma of the prostate gland have been summarized as follows: [8] When large cell neuroendocrine prostate cancers are initially diagnosed, they frequently already

have advanced disease. Prostate cancers known as large cell neuroendocrine carcinomas are more common, have a worse prognosis, and tend to be high volume diseases.

**Treatment**

The following summaries have been provided regarding the therapy for large cell neuroendocrine prostate cancer: [8] Because large cell neuroendocrine prostate cancer is uncommon and likely under reported, there is very little treatment experience reported in the literature. Although large cell neuroendocrine carcinoma of the prostate gland typically requires systemic therapy comparable to that used for small cell carcinoma, it may not react favourably to either of these approaches.

**Macroscopic Description**

According to a report, massive tumour nodules with a significant volume of disease within the prostate gland are frequently seen upon gross examination of specimens of large cell neuroendocrine carcinoma of the prostate gland. [8]

**Microscopic (histology examination) Description**

The following is a summary of the features identified by microscopy and histopathology in large cell neuroendocrine prostate cancer: [8] . Big islands or sheets of tumour cells are frequently seen in the prostate gland's large cell neuroendocrine carcinoma under the microscope. Prostate tumour specimens typically show large tumour cells with significant neuroendocrine characteristics including salt and pepper chromatin and tiny nucleoli. When prostatic large cell neuroendocrine carcinoma samples are examined under a microscope, high grade traits such lack of glandular development, numerous mitoses, apoptotic bodies, and tumour necrosis are frequently discovered.

**Immunohistochemistry staining features of Large Cell neuroendocrine carcinoma of the prostate gland**

**Positive Immunohistochemistry Staining:**

The positive immunohistochemistry staining which has tended to be found in cases of Large Cell neuroendocrine carcinoma of the prostate gland before a diagnosis is made have been summarized as follows: [8]

• At least one of the ensuing neuroendocrine tumour markers should be demonstrated upon immunohistochemistry staining including exhibition of positive immunohistochemistry staining for: chromogranin A, synaptophysin, neuron specific enolase, CD56.

• May be positive:

It has been stated that immunohistochemistry staining studies may exhibit positive staining in cases of Large Cell neuroendocrine carcinoma of the prostate gland with utilization of the following:

• TTFI tends to be positive in less than 50% of cases of Large Cell neuroendocrine carcinoma of the prostate gland.

• Positive AMACR immunohistochemistry staining, but may be focal or weaker than for adenocarcinoma of the prostate gland.

• Positive markers including: PSA, PSMA, NKX3.1 prostein (P501S) tend to be negative in majority of cases of Large Cell neuroendocrine carcinoma of the prostate gland, but they could be focally positive in a small subset of the tumours.

**Negative stains**

• It has been documented that in cases of Large Cell neuroendocrine carcinoma of the prostate gland, immunohistochemistry staining studies tend to demonstrate negative staining for the ensuing markers: [8]

• Urothelial markers such as GATA3, p63, and high molecular weight cytokeratins such as CK5 / 6.

• CD99.

**Differential Diagnoses**

**Miscellaneous Narrations and Discussion from some case reports, case series, and studies related to Large Cell Neuroendocrine Carcinoma of the Prostate Gland.**

Following have been added to the list of differential diagnosis for large cell neuroendocrine carcinoma of the prostate gland: [8]

•Carcinoid tumour of the prostate gland.

•Ewing sarcoma/PNET of the prostate.

• Prostate adenocarcinoma with neuroendocrine development in the focal region.

• Cancer of the urothelium with neuroendocrine differentiation.

Yang [14] described a 69-year-old man who received a prostate needle core biopsy but had no history of prostate cancer. In every tissue core from each of the six places analyzed, a large neuroendocrine carcinoma was found. A single little adenocarcinoma focus was found. The tumor's immunohistochemistry labelling revealed that the tumour cells had shown positive NSE, synaptophysin, and chromogranin staining as well as AMACR negativity for PSA and significant Ki67 proliferative activity. After the patient rejected chemotherapy and other therapies, his illness quickly got worse. He was discovered to have several metastatic lesions in his bone, lymph nodes, and internal organs a few months later. His diagnosis of metastatic big neuroendocrine carcinoma of the prostate gland was confirmed by a biopsy of a lymph node and a pathology investigation of the specimen. The patient underwent radiotherapy for bone lesions, but the treatment had a bad outcome and was unable to stop the disease's progression. After receiving his original cancer diagnosis 11 months prior, he was transferred to a hospice for palliative treatment. His tumour specimen underwent a pathology analysis, and the results revealed that he had a big neuroendocrine carcinoma of the prostate gland, which was made up of huge tumour cells with fine "salt-pepper" chromatin and a little extra cytoplasm. The tumour cells showed significantly and widely positive staining when stained with chromogranin. Yang [4] provided the following summary of the case's pathology examination results: A 69-year-old man had a big neuroendocrine carcinoma of the prostate gland that was made up of sheets of massive tumour cells with "salt and pepper" chromatin (A). Coexisting prostate adenocarcinoma was also considered to be a minor contributing factor. The Neuroendocrine (NEC) tumour cells stained negatively for HMWCK, p63, and PSA, but they stained diffusely positively for chromogranin and AMACR, a triple stain. The tumor's Ki67 proliferative index ranged from up to 50% of tumour cells.

The following iterations were made by Sleiman et al. [15]:
Well-differentiated carcinoid tumours and small- or large-cell, poorly differentiated tumours are under the category of neuroendocrine tumours in the 2016 World Health Organization classification of prostate cancer [16]. There had only been 20 examples of large-cell neuroendocrine prostate tumours reported in the literature, nine of which were primary tumour cases. [17] . Large-cell neuroendocrine prostate tumours are an uncommon histological entity with different characteristics from ordinary adenocarcinoma in terms of their evolution and therapeutic potential. Primary neuroendocrine tumours of the prostate may be adenocarcinoma-free or mixed with other tumour types. When mixed forms of the tumour were discovered early and at a limited stage, their prognosis was better.

A 68-year-old Caucasian patient who presented with an increased serum level of prostate-specific antigen (PSA) in September 2015 was described by Sleiman et al. in their study. Diabetes mellitus, hypertension, dyslipidemia, hyperuricemia, and moderate renal failure were all present in the patient's prior medical history. In February 2015 and September 2015, the patient's serum PSA levels were 6.67 ng/ml and 9.65 ng/ml, respectively. A medium-sized prostate with palpable induration of the left lobe of the prostate gland was discovered during a clinical examination; this prostate was clinically categorized as stage T2b cancer. In October 2015, twelve prostate core biopsies were performed under the guidance of an ultrasound scan. All of the biopsied tissues from the two lobes included tumours that were infiltrated by large-cell neuroendocrine carcinomas that were connected to acinar adenocarcinomas with Gleason scores of 7(3 + 4), with perineural invasion, but without any infiltration of the prostate capsule. In December 2015, a multiparametric magnetic resonance imaging scan of the prostate revealed a 43-gram prostate gland with a suspicious Pi-Rads 5/5 lesion in the posterior peripheral zone, between the apex and the mid-gland of the left lobe of the prostate, free of seminal vesicles infiltration, capsular invasion, or pelvic adenopathy. In November 2015, a bone scan was performed; it revealed no bone secondaries. An 18F-fluorodeoxyglucose positron emission tomography/computed tomography ([18F]FDG PET/CT) was performed in November 2015 because the majority component revealed on pathology examination of the biopsies was the neuroendocrine component. This test revealed a prostate metabolic hyper-fixation without suspicious distant fixation (see Figure 1).

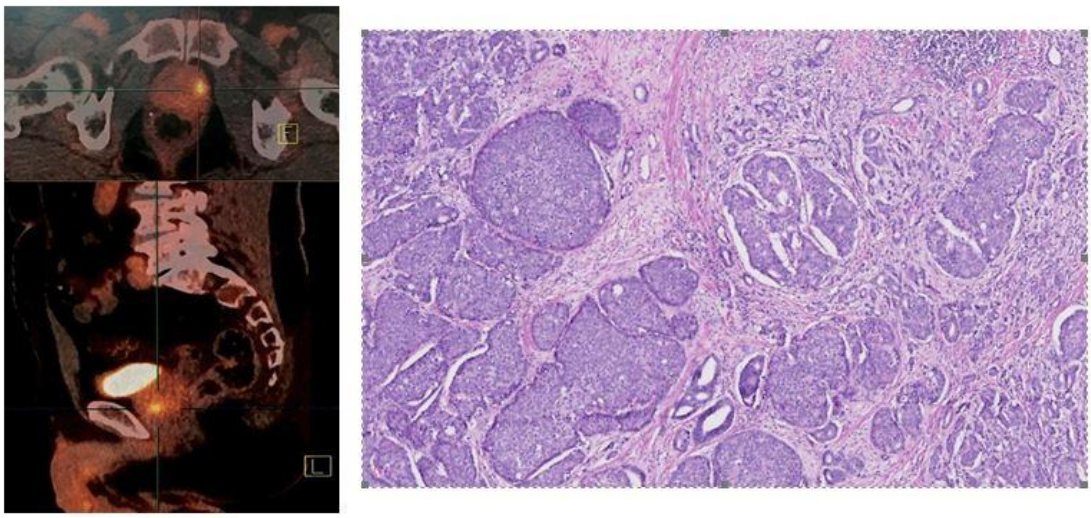

**FIGURE 1 :** 18F-Fluorodeoxyglucose positron emission tomography/computed tomography: isolated metabolic uptake of the left lobe of the prostate. Reproduced from: Sleiman et al [15].

**FIGURE 2 :** Operative specimen from total prostatectomy: haematoxylin and eosin staining. Some small adenocarcinoma glands can be seen between clusters of the large-cell neuroendocrine component. Reproduced from: Sleiman et al [15] under the Creative Commons Attribution 4.0 International License.

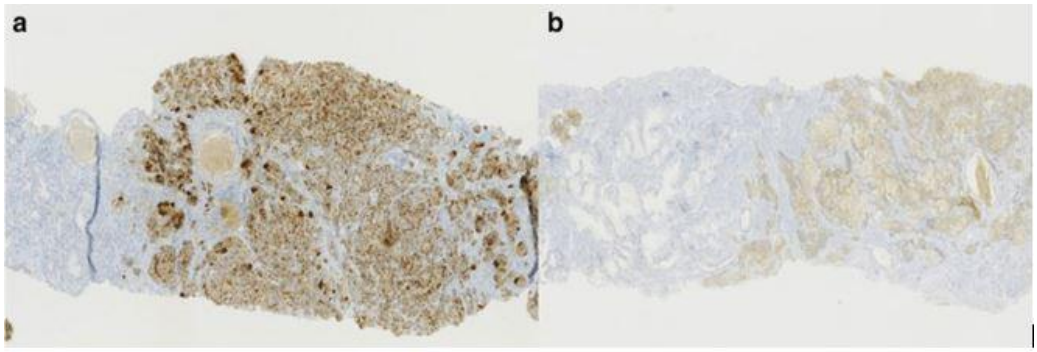


**FIGURE 3 :** Operative specimen from total prostatectomy: immunohistochemistry. Positive labelling for chromogranin A. **(a)** and synaptophysin **(b).** These two markers are positive for the neuroendocrine component and negative for the adenocarcinomatous component. Reproduced from: Sleiman et al. [15] under the Creative Commons Attribution 4.0 International License.

Sleiman et al. [15] chose to do a radical prostatectomy with bilateral extended pelvic lymph node dissection as a curative surgical procedure due to the rarity of the tumor's histological type and the tumor's confined nature. The surgical procedure was carried out in January 2016. During surgery, it was discovered that the prostate tumour had spread to the trigone and neck of the bladder. Bilateral ureterovesical re-implantation, radical prostatectomy, bilateral pelvic lymph node dissection, partial cystectomy involving the bladder neck and trigone in macroscopically tumor-free limits, and all of these procedures were performed.Sleiman et al[15] .'s analysis of the tumor's histology revealed that it was a bilateral mixed prostate cancer that had penetrated 80% of the prostate gland. The acinar adenocarcinoma component made up the remaining 30% of the tumour, while the large-cell neuroendocrine component made up 70% of it. The tumor's adenocarcinoma component has a Gleason score of 7(3 + 4). The right lobe of the prostate gland's base showed signs of the tumor's capsular invasion. Along with the neurovascular bands, the urinary bladder neck and seminal vesicles were discovered to be invaded. Additionally, there was evidence of vascular embolism and perineural invasion (see figure 2). Immunohistochemistry labelling experiments using synaptophysin and chromogranin A, together with a significant proliferative activity (Ki67 expression was at 80%), were used to demonstrate the large-cell neuroendocrine component (see figure 3). One of the seven lymph nodes removed from the left side was metastatic and showed evidence of invasion by the large-cell neuroendocrine component, while all of the lymph nodes dissected on the right side were confirmed to be negative. As a result, the tumour was identified as pT4 N1 (1/13) R1. Post-operative serum PSA level for the patient was 0.01 ng/ml. Following a multidisciplinary

medical review, it was determined that the patient would receive radiotherapy to the prostatic bed and pelvis before chemotherapy (etoposide carboplatin [VP16]) as an adjuvant therapy.

In September 2016, a [18F] FDG PET/CT scan was performed, and it revealed that there were no hypermetabolic sites. Etoposide carboplatin (VP16) chemotherapy was started in February 2016 and stopped in May 2016 after the second round because the patient experienced renal toxicity.

Despite a blood PSA of 0.01 ng/ml, a [18F] FDG PET/CT scan performed in June 2016, six months after the surgical procedure, had revealed two left latero-aortic hypermetabolic lymph nodes. His serum PSA was 0.01 ng/ml, and the [18F] FDG PET/CT scan performed in August 2016, 4 months after the end of chemotherapy, revealed a significantly reduced metabolic character of the left latero-aortic infra-centimetric lymph node as well as the absence of a second suspicious hypermetabolic lesion. Between November and December 2016, the prostatic bed underwent intensity-modulated radiation treatment (IMRT; 6 MV photons) with 70 Gy, which was given in 35 sessions. Then, based on the serum PSA level for the adenocarcinoma component and the results of the [18F] FDG PET/CT for the large-cell neuroendocrine component, the patient's follow-up evaluation was arranged. The patient initially displayed an elevated serum PSA level of 2.75 ng/ml in July 2017; by November 2017, the level had increased to 4.77 ng/ml. The November 2017 [18F]FDG PET/CT scan revealed bilateral supra-centimetric iliac lymph nodes that were only mildly hypermetabolic and more suggestive of the cancer component. In December 2017, the luteinizing hormone-releasing hormone (LHRH) agonist triptorelin was started as part of an androgen deprivation therapy. Between November and December 2016, the prostatic bed underwent intensity-modulated radiation treatment (IMRT; 6 MV photons) with 70 Gy, which was given in 35 sessions. Then, based on the serum PSA level for the adenocarcinoma component and the results of the [18F] FDG PET/CT for the large-cell neuroendocrine component, the patient's follow-up evaluation was arranged. The patient initially displayed an elevated serum PSA level of 2.75 ng/ml in July 2017; by November 2017, the level had increased to 4.77 ng/ml. The November 2017 [18F]FDG PET/CT scan revealed bilateral supra-centimetric iliac lymph nodes that were only mildly hypermetabolic and more suggestive of the cancer component. In December 2017, the luteinizing hormone-releasing hormone (LHRH) agonist triptorelin was started as part of an androgen deprivation therapy. His serum testosterone level was 0.2 ng/ml and his serum PSA level was 0.01 ng/ml three months after the initial triptorelin injection, indicating a favourable biological response. He underwent a [18F] FDG PET/CT scan in June 2018, six months after beginning his androgen deprivation therapy, and the results showed a full metabolic response.

The patient underwent biological follow-up, including metabolic imaging with [18F] FDG PET/CT scans every 6 months for the large-cell neuroendocrine component and serum PSA testing every 3 months for the adenocarcinoma component. After having androgen deprivation therapy with triptorelin for 54 months, the patient was still getting treatment at the time of his case report, with a full biological and metabolic response. His serum PSA level was 0.01 ng/ml at the most recent follow-up evaluation in March 2020, and his [18F] FDG PET/CT scan showed a full metabolic response.

Sleiman et al. [15] summarised the subsequent talks as follows:

It was highlighted that the earliest descriptions of neuroendocrine system cells were quite recent, dating from the middle of the 20th century. After puberty, the prostate tissue often has an increase in the number of neuroendocrine cells. Acini, which could give rise to typical prostate cancer, tend to have less neuroendocrine cells. Prostatic epithelium growth and secretory activities are influenced by neuroendocrine cells [18]; these cells can be identified by their lack of androgen receptors as well as by the presence of specific immunohistochemical tumour markers such chromogranin and synaptophysin. An essential need for identifying neuroendocrine cells in immunohistochemical studies of the tumour is PSA negativity [19]. It is crucial to understand that neuroendocrine tumours may express PSA focally and that high-grade acinar adenocarcinomas may also express neuroendocrine markers, allowing for a differential diagnosis with large-cell neuroendocrine tumours. [17]. In the several investigations that histologically evaluated primitive tumours and metastases, the prevalence of neuroendocrine cells in conventional prostatic cancer did vary [20].

There is a correlation between focal neuroendocrine characteristics and high-grade and undifferentiated tumours in prostate adenocarcinomas. It has been emphasized that it is crucial to evaluate the traditional morphological features of neuroendocrine tumour cells because adenocarcinomas and neuroendocrine cells may occasionally share hybrid immunohistochemistry findings. Large neuroendocrine carcinoma cells typically occur in dense clusters with surrounding palisading. [9]. The rise in life expectancy and awareness of the discovery of focal neuroendocrine foci within prostate adenocarcinomas may possibly be attributed to heterogeneity in characterizing the neuroendocrine status in prostate tumours. The detection of neuroendocrine characteristics may also be hampered by treatments based on inhibiting androgen receptor signalling, as in the case of metastatic biopsy. [21] [22]. In relation to the pathophysiology of prostate neuroendocrine tumours, two processes have been identified. The most common and first-postulated process is the trans-differentiation of an

acinar adenocarcinoma while receiving long-term hormone therapy, along with androgen receptor loss. Because of improved survival rates and the use of novel hormone therapies, neuroendocrine symptoms of prostate cancer are growing. The second proposed process involves neuroendocrine cells, which are typically found within prostatic glands, undergoing a malignant change. [5]. Prostate neuroendocrine cell carcinogenesis animal studies have supported this de novo tumorigenesis mechanism [23].

The risk factors for the emergence of de novo neuroendocrine tumours have not yet been identified, taking into account the small number of published cases and series [17]. Three entities of prostate neuroendocrine carcinoma were described in the 2016 Histological Classification of Tumors of the Urinary and Genital System: Neuroendocrine Differentiation of Adenocarcinoma, Well Differentiated Neuroendocrine Tumors or Carcinoid Tumors, and Poorly Differentiated Neuroendocrine Small- or Large-Cell Tumors. Neuroendocrine tumour identification is predicated on morphological, functional, and immunohistochemistry staining standards. [16]. Due to the absence of PSA secretion, resistance to hormone therapy, early metastasis, and rapid development, neuroendocrine tumours do vary from adenocarcinomas. [19] When compared to large-cell tumours, which had previously been rare, small-cell tumours are by far more common. Within the same tumour, the coexistence of the two types may be shown. [19] De novo large-cell tumours are uncommon or rare. Only roughly 20 examples were included in the most recent evaluation of the literature, which was published in 2019. Of those, 17 were associated with primitive prostate tumours, which comprised seven de novo and eight after hormone therapy. Only three observations had documented mixed tumours with two components, neuroendocrine and adenocarcinoma components, among the published cases of large-cell de novo tumours. The hormone therapy used in these three recorded cases produced positive results. [17] Due to some degree of hormone sensitivity, de novo neuroendocrine tumours with either small or big cells and an adenocarcinoma component did seem to have a better prognosis than pure forms. The difference in prognosis between the two kinds is determined by this idea or concept of androgen reliance or resistance. [6] Mixed types of the tumour often lend themselves to early identification at the localised stage due to PSA secretion, offering the potential for curative therapy.Often, pure versions of the tumour that did not secrete PSA were discovered at an advanced stage. Three examples of de novo large-cell pure neuroendocrine tumours with an unfavourable outcome under treatment were described by Xiang Tu et al. after trans-urethral excision of the prostate gland. [17] Evans et al. had described a case with a stage pT3a tumour that had undergone radical prostatectomy and that manifested as local and metastatic brain recurrence while receiving adjuvant treatment. [5] [20]. Given the resistance to hormone therapy, the therapeutic options for treating these types of tumours are comparable to those for treating lung large-cell neuroendocrine tumours, and these primarily entail chemotherapy. In the locally advanced and metastatic stages, the prognosis has typically proven to be poor, with a very low chance of survival. [3], [24] Their described case was identified after ultrasound-guided biopsies were completed at a locally advanced stage. They chose radical prostatectomy over radiotherapy due to the rarity of the histological type and the mild renal failure, which had reduced the options for following chemotherapy. In comparison to choline, [18]F-FDG PET/CT follow-up was justified for a superior detection of neuroendocrine cell metabolism. After ganglionic recurrence, the positive and full response to hormone therapy could be attributed to the coexistence of an adenocarcinoma component and a neuroendocrine component inside the same tumour. Complete remission and relatively long survival in comparison to previously published cases had heavily depended on the early diagnosis, curative initial surgical treatment, as well as routine radiology imaging during the follow-up that allowed an early detection and tailored treatment of lymph node recurrences.

Sleiman et alfindings .'s [15] were as follows:

Prostate large-cell primary neuroendocrine carcinoma is a rare and aggressive histopathological condition. Curative surgery should be considered for both localised and locally progressed large-cell neuroendocrine carcinomas of the prostate gland. The therapeutic options for metastatic forms are constrained by hormone resistance in the pure forms. The prognosis is improved by the presence of a hormone-sensitive adenocarcinoma component. With significantly improved care, the advancement of nuclear radiology imaging techniques does allow for better follow-up and early recurrence diagnosis.

What follows was said by Evans et al. [5]: Immunohistochemistry staining investigations often identify neuroendocrine (NE) differentiation in prostate cancer as single cells in conventional adenocarcinoma. Large cell NE cancer (LCNEC) has only been recorded in case reports, and prostatic NE tumours such carcinoid or small cell carcinoma are uncommon or rare. Seven cases of LCNEC had been found, and their clinicopathologic characteristics had been collated by Evans et al. [5]. According to Evans et al[5] .'s research, hormone therapy was used to treat 6 instances of adenocarcinoma for a mean duration of 2.4 years and a range of 2 to 3 years. De novo LCNEC was present in the last case of Evans et al. [5]. In 5 cases, LCNEC was unintentionally discovered in specimens from palliative transurethral resections. The patients' ages ranged from 43 to 81 years old, with a mean age of 67 at the time of diagnosis with LCNEC. According to reports, the LCNEC is made up of solid

sheets and ribbons of cells with abundant pale to amphophilic cytoplasm, big nuclei with coarse chromatin and conspicuous nucleoli, fast mitotic activity, and necrotic foci. There were foci of admixed adenocarcinoma in 6 instances, 4 of which had shown effects of hormone therapy. LCNEC had significantly positive staining for CD56, CD57, chromogranin A, synaptophysin, and P504S/alpha methylacyl CoA racemase after immunohistochemical staining investigations. Strong bcl-2 overexpression, MIB1 expression, p53 expression in more than 50% of nuclei, focally positive prostate-specific antigen and prostatic acid phosphatase staining, and negative androgen receptor staining were all present. Follow-up information was provided for 6 patients, all of whom passed away from metastatic disease at an average age of 7 months, ranging from 3 to 12 months after receiving platinum-based chemotherapy. According to Evans et al. [5], prostatic LCNEC is a unique clinicopathologic entity that generally presents after long-term hormone therapy for prostatic adenocarcinoma and most likely arises through clonal development under the selection pressure of medication.

According to Alijarba et al. [1], a 79-year-old man visited the neurosurgery clinic complaining of a headache, dizziness, upper and lower limb weakness over the previous 8 months, and urinary incontinence over the previous 2 months. He also reported that he had been experiencing urinary incontinence. The patient was known to have diabetes, hypertension, and a history of prostate cancer with lung metastases. He received a prostate biopsy, and a pathology analysis of the specimen revealed high-grade prostate cancer with a Gleason score of (4 + 5 = 9). Nine years ago, he had had androgen deprivation therapy (ADT). His lung lesion had vanished and no further metastases were discovered during follow-up bone scans and computed tomography (CT) scans of the chest, abdomen, and pelvis two years prior to his manifestation. Upon clinical examination, the patient was found to be alert and oriented to time, place, and person with GCS of 15/15, the pupils were equal and bilaterally reactive, and the power was 4/5 in both his upper and lower limbs. At the time of his admission, his total prostate-specific antigen (PSA) and free-PSA levels were 12.3 ng/mL and 1.8 ng/mL, respectively. He underwent an unenhanced computed tomography (CT) scan of the brain, which revealed a significant right frontal lobulated peripherally hyper-attenuating mass with punctuating foci of calcification and a central hypo-density that was surrounded by vasogenic oedema. It was also reported to be having a mass effect on the right frontal horn and causing a mild leftward midline shift (see new figure 4). His chest, abdominal, and pelvic contrast-enhanced CT scans did not show any metastatic lesions. A modified pterional and orbital osteotomy technique was used to eliminate the lesion. Macroscopic analysis of the tumour revealed a 5.5 cm 4.5 cm 2 cm grey-tan mass with a lobulated outer surface and an associated strap of dura mater. The bulk was serially sectioned to show zones of necrosis. Haematoxylin and eosin staining performed during the specimen's histopathology examination revealed a monomorphic infiltrate of large cells with prominent nuclei and poorly defined cytoplasmic membrane that were arranged in nests of varying sizes with obvious necrosis and a mitotic rate greater than 4/10 high-power fields (see figure 5). The tumor's immunohistochemistry staining research (IHC) revealed that the tumour had positive reactions to the antibodies EMA, Cam 5.2, synaptophysin, PSA, and AMACAR, whereas the tumour cells had negative reactions to the antibodies S100, TTF-1, CK7, CK20, and CDX2 (see figure 6). The tumor's histopathological characteristics and focal positive for PSA, AMACR, and synaptophysin (a NE marker) had supported the prostatic origin diagnosis for LCNEC.

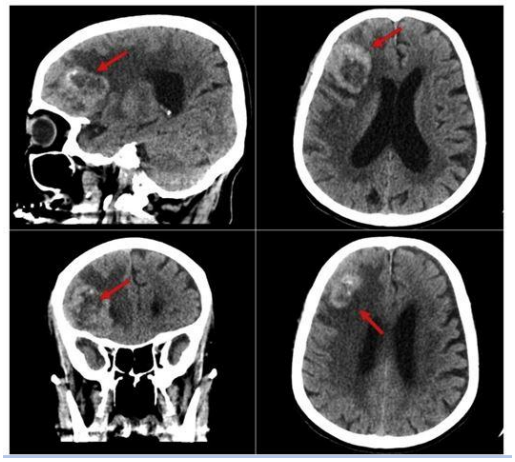

**FIGURE 4 :** A large right frontal lobulated peripherally hyper-attenuating mass with punctuate foci of calcification and central hypodensity, probably representing necrotic component. The mass measures 4.5 × 4 × 3.5 cm in AP, CC and transverse dimensions, respectively. It was surrounded by vasogenic oedema and causing a mass effect on the right frontal horn with mild leftward midline shift by 5 mm. Reproduced from: [1] under the terms of the Creative Commons CC-By license.

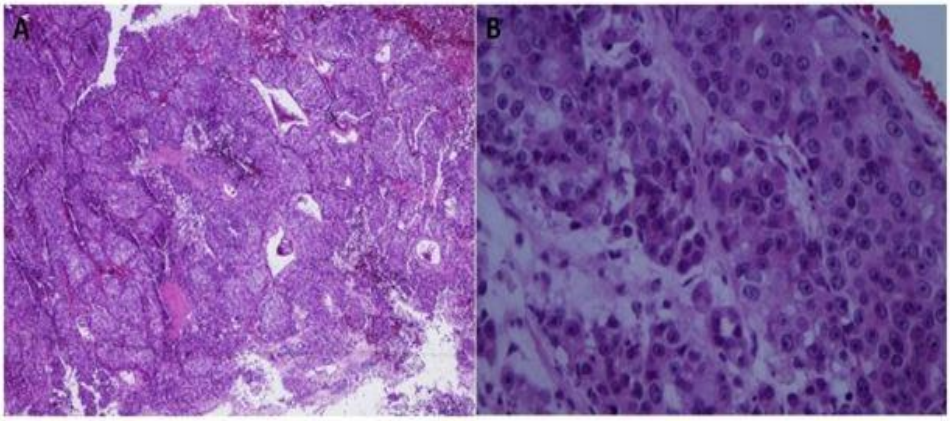


**FIGURE 5 :** Haematoxylin and eosin stain of the tumour with a low-power view (4×) shows irregular nests of epithelium with foci of necrosis

(A) and a high-power view (40×) showing large cells with large nuclei and inclusion-like nucleoli.
(B) . Reported from [1] under the terms of the Creative Commons CC-By license.

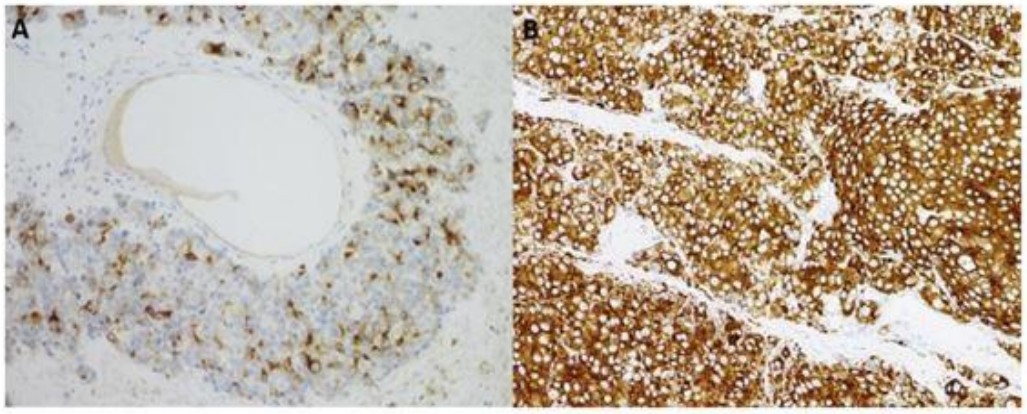


**FIGURE 6 :** Immunohistochemical staining shows a focal cytoplasmic positivity for prostatic specific antigen.
**(A). S**ynaptophysin granular cytoplasmic positivity
**(B).** Reported from: [1] under the terms of the Creative Commons CC-By license.

He underwent a postoperative MRI scan, however it did not clearly demonstrate any enhancement of a residual tumour with postoperative oedema and haemorrhage. The patient did experience meningitis and a mild surgical site infection following surgery, and an examination of his cerebrospinal fluid (CSF) revealed low glucose and high protein levels along with a negative CSF culture. The patient did experience tachycardia on the fourth post-operative day. An echocardiography was ordered, and the results showed significant aortic stenosis. Given the patient's age and co-morbidities, no intervention was undertaken and aspirin 81 mg was given to the patient every day instead. The patient experienced a decline in awareness on the fifth day after his surgery, with a GCS of 9/15. He also underwent a computed tomography (CT) scan, which revealed dilated ventricles. His elevated intracranial pressure (ICP) necessitated the insertion of an external ventricular drain (EVD). He underwent a follow-up CT scan, which revealed normal ventricular size and revealed a normal intracranial pressure (ICP) reading. The patient's neurological condition did not, however, get any better. Due to his numerous co-morbidities and poor clinical status, the patient was sent to the palliative care team for palliative care. 43 days after his surgery, the patient suffered a heart collapse and passed away.

Aljarba et al. [1] summarised the subsequent talks as follows:

Depending on the pathophysiology and molecular characteristics of the disease, the range of neuroendocrine (NE) differentiation in prostate cancers could be categorized using the 2016 WHO classification. [6] According to research using immunohistochemical staining, NE differentiation might appear as a localised differentiation within the typical acinar or ductal adenocarcinoma of the prostate gland [6]. Carcinoid tumour of the prostate gland does exhibit well-differentiated NE tumour occurring within the prostate gland [6] Small cell NE differentiation is a high-grade tumour of the prostate which had been defined by distinctive nuclear features

such as the lack of prominent nucleoli, nuclear moulding, and crush artifacts [6] It has been iterated that LCNEC is a high-grade NE tumour that is associated with distinctive morphological criteria of non–small cell carcinomas which does consist of large nests with peripheral palisading, large cell size, abundant cytoplasm, prominent nucleoli, vesicular clumpy chromatin, and frequent necrosis accompanied by a high mitotic rate and positive immunohistochemistry staining with at least one NE marker (synaptophysin, chromogranin, CD56) [6]

It has been documented that NE differentiation in carcinomas of the prostate gland tend to be very rare, and this does account for 1% to 5% of all cases of prostate cancer [5] Additionally, LCNEC has only been documented in occasional case reports and case studies, making it particularly unusual compared to other NE tumours of the prostate gland [5] [6]. Evans et al. described the largest case series, in which they discussed the pathology symptoms and the pattern of metastasis. [5]. Additionally, it has been established that there are two potential pathogenic paths by which LCNEC may develop. First, with respect to patients who had had treatment for conventional adenocarcinomas with long-term ADT, also known as trans-differentiation. [25] A decrease in androgen receptor expression was seen in cultures cultured without androgens, according to in vitro studies of the prostate cancer cell line LNCaP [25]. The reported case had a history of long-term ADT, which had put a selection pressure on non-NE tumour cells from the conventional adenocarcinoma, leading to evolution, clonal proliferation, and the emergence of NE carcinomas with hormone-refractory status. This mechanism is said to be consistent with what is observable in some clinical cases, including theirs. Their reported patient exhibited castrate resistance since, in spite of treatment, his serum PSA level had increased and a brain metastasis had developed. Interestingly, it had been hypothesized that non-malignant NE cells of the prostate gland could, under an adrenogenic, depurative environment, stimulate the paracrine proliferation of non-NE tumour cells by secreting growth-promoting neuropeptides. [25]. It has been said repeatedly that mixed NE carcinoma-acinar adenocarcinoma is one of the strongest pieces of trans-differentiation evidence, despite the fact that the evidence for LCNEC trans-differentiation had remained elusive. [5] [6]. The presence of mixed characteristics between LCNEC and conventional adenocarcinoma, such as the co-expression of NE markers and PSA, which does indicate the presence of intermediate forms of tumour cells and would further support the process of trans-differentiation, has been described as another piece of evidence. [5] It's interesting to note that the IHC results for their patient's tumour showed localised positive for PSA, AMACR, and synaptophysin, showing mixed traits between the LCNEC and traditional adenocarcinoma. The probasin-large T antigen (Tag) transgenic mouse line, which developed prostatic adenocarcinoma with progressive NE differentiation with advancing age, and metastasis that showed histological features and IHC of NE differentiation, is one of the most intriguing findings in animal models that also supported the process of trans-differentiation. [26] Second, LCNEC could develop from scratch when NE cells from the prostate gland undergo direct malignant transformation without any prior ADT. A few case reports mentioned this method. [2] [3] [4] [5].

There is still a need for more research on the connection between ADT and the development of adenocarcinoma into NE carcinoma. It is known that NE differentiation, whether small cell or LCNEC type, does emerge in a tiny percentage of individuals, and it is yet unknown exactly what range of circumstances contribute to the growth of such a dangerous tumour. Elevated serum PSA levels in their patient were a symptom. PSA is not expressed or secreted by well-differentiated NE tumours (carcinoid tumours) of the prostate gland [6]. However, it has been shown that LCNEC does express PSA variably, varying from total negative staining to localised positive with different levels of blood PSA. [2] [5] [6] The presence of cells with characteristics that are intermediate between those of LCNEC and conventional adenocarcinoma, the impact of treatment, and most critically, the ambiguous description and lack of comprehension of LCNEC, could all be contributing factors to this heterogeneity. It is obvious that brain metastasis is an uncommon occurrence, much as LCNEC of the prostate is. The patient's symptoms were a headache, dizziness, weakness in the upper and lower limbs, and incontinence. Neuro-radiology imaging revealed a significant right frontal mass in the patient. The brain mass had raised additional potential diagnoses, including high-grade meningioma or glioma, and was extremely suspicious for metastasis. The method of choice for big and symptomatic solitary brain metastases is surgical removal of the tumour, which does quickly relieve symptoms [28]. The patient experienced tachycardia following surgery as a result of an unexpectedly severe aortic stenosis, which was discovered after the procedure. The patient did not tolerate the procedure very well, mainly due to his age and co-morbidities. The patient developed a decreased level of consciousness and dilated ventricles, and despite adequate treatment, the neurological status of the patient did not improve. It was decided not to resuscitate the patient in case he developed a cardiac arrest by signing the do not resuscitate (DNR) form and he was referred for palliative care. The patient survived for 43 days pursuant to his surgery.

Aljarba et al. [1] made the ensuing conclusions:

Patients' complaints such as weakness, headache, altered consciousness, or focal deficits should be promptly investigated with detailed neurological history taking, physical examination, and neuroimaging. The prognosis for LCNEC of the prostate has been worse because to the late diagnosis, the patient's age, and the co-

morbidities. As the metastasis and advancement of NE trans-differentiation tend to be connected with the environment and age of the tumour, it is obvious that early detection and treatment of metastatic LCNEC of the prostate gland would significantly improve upon the results. Large cell neuroendocrine carcinoma (LCNEC) of the prostate gland is extremely uncommon, according to Tzou et al. [3], and it virtually exclusively manifests in males who have undergone androgen restriction therapy for prostate adenocarcinoma. A 66-year-old man who had transurethral prostate resection was unintentionally diagnosed with LCNEC, according to Tzou et al[3] .'s report of a case of de novo LCNEC. The tumour was at the T4N1M1 stage. As a result, the patient had treatment using 6 cycles of cisplatin and etoposide over the course of the following 6 months, which led to a partial remission. The chance of getting rid of the remaining mass has been lost.

The tumour had advanced quickly three months later. Tzou et alfindings .'s [3] were :
The rare prostate cancer known as LCNEC. Their prior experience had demonstrated the efficacy of treatment with etoposide and cisplatin to produce a sizable remission. Despite this, because LCNEC has a very malignant character, post-chemotherapy surgery for the remaining mass should be taken into consideration as a possible course of action.

The following was said by Acosta-Gonzalez et al. [11]:

Large cell neuroendocrine carcinoma of the prostate (LCNEC), de novo in particular, is an extremely rare clinical entity which had only been described in the literature in case reports.

Historically, the majority of the cases of LCNEC that had been reported in the literature had represented typical adenocarcinomas of the prostate gland which had transformed after long standing androgen deprivation therapy (ADT). These cases were admixed with histological areas of usual adenocarcinoma and had shown hybrid features of both neuroendocrine and usual adenocarcinoma.

In a patient without a prior history of hormone therapy, Acosta-Gonzalez et al. [11] described a case of a de novo emerging LCNEC of the prostate gland without admixed regions. Additionally, the tumour had morphological signs of neuroendocrine development, including vast sheets and nests of cells with somewhat amphophilic cytoplasm and peripheral palisading, as well as vesicular clumpy chromatin and conspicuous nucleoli. Positive immunohistochemistry staining for PSA, PAP, PSMA, racemase, and Nkx3.1 supported the prostatic origin of the cancer. Electron microscopy analysis of the tumour that supported NE differentiation revealed diffusely positive staining for chromogranin and synaptophysin as well as the presence of secretory granules in the cytoplasm of the cancer cells. According to Acosta-Gonzalez et al. [11], while AR and ERG were positive in their reported case, NE prostate cancer typically does not express upon immunohistochemical staining of the tumour, AR, and it is resistant to ADT therapy.

The following was said by Okoye et al. [24]:

As a focal finding in conventional acinar adenocarcinoma, detectable by immunohistochemical staining, or as a primary NE tumour of the prostate gland, such as carcinoid tumour, small cell carcinoma, or large cell NE carcinoma of the prostate gland, neuroendocrine (NE) differentiation in carcinomas of the prostate gland can be observed. The big cell NE carcinoma, which had previously been documented in lone instances or small case series, is of great interest. A 48-year-old man who had trouble urinating and urine retention was diagnosed with a large cell NE carcinoma, according to Okoye et al. [24]. He had a cystoscopy, which showed that his prostate was enlarged and elongated and that a tumour was blocking the prostatic urethra inside the prostate. An external hospital then performed a transurethral resection of the prostate (TURP) with the clinical diagnosis of benign prostatic hyperplasia (BPH). The TURP material underwent microscopic pathology analysis, which revealed multiple foci of low-grade transitional-zone-type adenocarcinoma with a Gleason score of 5 (3 + 2) and a focus of high-grade large cell NE carcinoma. Neuroendocrine carcinomas (NECs), which make up less than 1% of prostate cancers, are extremely uncommon and account for more than 95% of cases of prostate cancer. Small cell neuroendocrine carcinomas (SmCC), carcinoids, and large cell neuroendocrine carcinomas (LCNEC) of the prostate gland are NECs. Only 15 cases of LCNEC had been documented at the time of their case, and the prognoses were not good.

Radical surgery and adjuvant androgen deprivation therapy were used to successfully treat a patient with a de novo LCNEC of the prostate gland, according to Miyakawa et al. [2]. (ADT). In August 2014, an 87-year-old man was visited in Miyakawa et aloutpatient .'s clinic with his primary concerns being difficulty voiding and obvious haematuria. He had previously undergone a transurethral resection of the bladder tumour (TURBT) for a urinary bladder tumour in June 2014 and a left nephroureterectomy for a renal pelvic tumour in July 2010. Low-grade pTa urothelial carcinoma (UC) of the left renal pelvis and high-grade pTa UC of the urinary bladder, respectively, were found during the pathology evaluation of the tumour specimens.After having a cystoscopy, it was discovered that he had a sessile tumour on the neck of his bladder, which was thought to be

muscle-invasive bladder cancer. He had magnetic resonance imaging (MRI) and computed tomography (CT) scans, none of which found any signs of metastases. Despite having a pre-treatment serum PSA level of 3.3 ng/mL, a digital rectal examination revealed that the patient's prostate was rock hard. He had TURBT in October 2014, and the tumor's pathological characteristics revealed high-grade pT2 UC of the urinary bladder. He received a right ureterocutaneostomy, a radical cystoprostatectomy, urethrectomy, and regional lymphadenectomy in November 2014. It was discovered that the tumour was mostly inside of the man's prostate gland and partially inside of his bladder. It was challenging to remove the prostate gland from his left side since it was firmly attached to the pelvic wall. The tumor's pathology investigation indicated LCNEC characteristics with a microscopic focus of acinar adenocarcinoma, with a Gleason score of 2 + 3. Large tumour cells that were part of the LCNEC featured fine granular cytoplasm, coarse nuclear chromatin, high mitotic rates, high nucleus-to-cytoplasm ratios, and rosette formations. The majority of the prostate organ had been replaced by the tumour, confirming that it originated from the prostate and had invaded the bladder. PSA and the androgen receptor had been detected in the LCNEC and adenocarcinoma by immunohistochemistry staining (IHS) tests (AR). Only the LCNEC showed positive results for synaptophysin, CD56, and chromogranin A. The patient was diagnosed by two pathologists (KT and SM) with pT4 LCNEC and adenocarcinoma of the prostate with bladder invasion. Retrospective analysis did identify LCNEC as the muscle-invasive component of the prior TURBT specimen. Miyakawa et al. [2] began adjuvant ADT even though there was no proof of lymph node metastases because the tumour had a positive surgical margin, perineural invasion, and extracapsular invasion. The patient had endured for 40 months after his diagnosis without showing any signs of a tumour recurrence.

Following this, Miyakawa et al. [2] created the following summarizing iterations: Prostate cancers with NECs are uncommon histological subtypes that typically have a poor prognosis; LCNEC is one of these subtypes. Up until the time of their case's report, fifteen cases of LCNEC had been documented.

Five of the ten cases that had developed as a result of de novo LCNEC had been long-term ADT-related. [4] [5] [11] [29] Table 1 shows the clinical characteristics of 6 patients with de novo LCNEC, including their reported case. ADT is probably useful for treating de novo LCNEC because these tumours do continue to be androgen-dependent, according to Azad et al. [29]. Out of five patients with de novo LCNEC whose prognoses were available in detail, three were alive without progression for more than 1 year. It has been stated that even though LCNEC generated after long-term ADT has a miserable prognosis, [5] it is considered that de novo LCNEC has a relatively good prognosis.

| Case | Age (years) | PSA (ng/mL) | Treatment after diagnosis | Outcome | Observation period | IHC of AR |
|---|---|---|---|---|---|---|
| Case 1 | 69 | 4.3 | RP→Carboplatin + Etoposide | DOD | Average 7 months after chemotherapy(a) | N/A |
| Case 2 | 70 | 9.6 | ADT | Alive | 15 months | N/A |
| Case 3. | 71 | 170 | ADT | Alive | 30 months | N/A |
| Case 4. | 66 | 97 | N/A | N/A(b) | N/A | + |
| Case 5. | 48 | N/A | Cisplatin +Etoposide + Paclitaxel +ADT → RP | DOD | 13 months | N/A |
| Their reported case | 87 | 3.3 | Cystoprostatectomy → ADT | Alive | 46 months | + |
| | | | | | | |

NECs are rare histological types of prostate cancer that tend to be associated with poor prognosis, and amongst them LCNEC is extremely rare. Fifteen cases of LCNEC had been reported up to the time of the report of their case Ten cases had occurred pursuant to long-term ADT, and five cases were de novo LCNEC. [4] [5] [11] [29]The clinical features of 6 cases of de novo LCNEC including their reported case were illustrated as in Table 1. Azad et al. [29] stated that ADT is likely effective for the treatment of de novo LCNEC because such tumours do remain androgen-dependency.Out of five patients with de novo LCNEC whose prognoses were available in detail, three were alive without progression for more than 1 year. It has been stated that even though LCNEC generated after long-term ADT has a miserable prognosis, [5] it is considered that de novo LCNEC has a relatively good prognosis.

**TABLE1:** Abbreviations: IHC, immunohistochemical staining; LCNEC, large cell neuroendocrine carcinoma; PSA, prostate specific antigen; AR, androgen receptor; RP, radical prostatectomy; DOD, died of disease; NA, not applicable; ADT, androgen deprivation therapy; (a) The observation period is described collectively with 6 cases, not respectively; (b) There is no description of outcome after diagnosis.

Two patients underwent immunohistochemistry staining investigations (HIS) of AR, and both of them showed evidence of positive AR staining. According to a report, neuroendocrine cells, which are frequently found in prostate tissue, including prostate cancer, tend to show negative AR staining and are thought to be androgen-independent. [30] The presence of ARs on IHS does suggest an androgen-dependent prostate malignancy. NEC's AR-positivity further suggests that ADT is androgen-dependent and effective. The hypothesis is supported by the long-term survival of their reported LCNEC of the prostate that was AR-positive and surgical margin-positive after adjuvant ADT.

The findings of Miyakawa et al. [2] were as follows:
Prostate LCNEC is incredibly uncommon. The majority of LCNEC cases develop as a result of long-term ADT, and chances of recovery are typically very slim. Their reported case had demonstrated that ADT was useful for treating prostate androgen-dependent LCNEC. It might be possible to forecast how well ADT will work on the prostate's LCNEC by using androgen receptor staining.

The claims presented by Aparichio et al. [31] are as follows:
A different clinical course and prognosis are predicted by the discovery of small-cell carcinoma (SCC), a castrate-resistant type of prostate cancer that is discovered at advancement in 10–20 percent of cases. In terms of the study's methodology, Aparichio et al. [31] reported that eight tumour fragments from a patient with castrate-resistant prostate carcinoma's salvage pelvic exenteration specimen were subcutaneously implanted into 6- to 8-week-old male CB17 SCID mice. Serial tissue slices and tissue micro-arrays of the resulting MDA PCa 144 xenograft lines were used to characterize the xenografts and their tissue of origin using histopathology and immunohistochemistry. For the purpose of gene-expression profiling, RNA from two representative xenograft sublines was employed. According to Aparichio et al[31] .'s summary of their findings: All eight fragments united to create tumours, with four of the MDA PCa 144 xenograft sublines exhibiting SCC morphology and four LCNEC morphology. All of them maintained a high level of faithfulness to the parent tumour tissue, which had endured numerous passes without changing. LCNEC does constitute a transitional stage between adenocarcinoma and SCC, according to morphological transformations within the specimen of origin. Between the SCC (MDA PCa 144-13) and LCNEC (MDA PCa 144-4) sublines, there were almost 2,500 genes with differential expression that were enriched in the "Nervous System Development" Gene Ontology subtree.

The following judgement was reached by Aparichio et al. [31]:
The eight presented xenograft models would be useful preclinical tools to investigate the pathophysiology and therapeutic strategies for this increasingly recognized subset of deadly prostate cancer. They do represent the range of neuroendocrine carcinomas in prostate cancer.

Yoo et al[32] .'s findings were as follows:
Lung large cell neuroendocrine carcinoma (LCNEC) is an uncommon, aggressive tumour that often has a bad prognosis. Additionally rare, lung cancer metastases to the prostate gland are typically discovered by accident during an autopsy. The majority of initial lung malignancies with prostate metastases that have been recorded are small cell carcinomas, while prostatic metastases from lung LCNEC have not previously been documented. A 70-year-old man with lung LCNEC with metastases in the prostate, brain, bone, liver, and lymph nodes was described by Yoo et al. in their study [32].

According to Zafarghandi et al. [4], a 71-year-old man who had increased, frequent, and urgent urination for three months was referred to their clinic. He did not exhibit any systemic symptoms, like fever, sweats at night, anorexia, or weight loss. The digital rectal examination revealed an enlarged prostate gland in him. It was determined that his serum PSA level (0.09 ng/mL) was within the normal range. His benign prostate hyperplasia and mild prostate gland enlargement as seen on an ultrasonography were also present (BPH). In light of his BPH diagnosis, tamsulosin was thus prescribed. After being treated with Tamsulosin for three months, he was referred once more without receiving any alleviation. His international prostate symptoms score (IPSS), which was 22 prior to starting medication, was still the same after three months. Because of the severity of his lower urinary tract problems and the patient's desire to have surgery, he had transurethral resection of the prostate (TURP). After his TURP, a histopathology study of the removed prostatic chips and a urine cytology were performed. A colonoscopy and a whole-body scan were conducted for the patient after the initial pathologist indicated a poorly differentiated cancer; both tests came out negative. His TURP specimen's haematoxylin and eosin slides showed sheets, and a sizable nest of high-grade neoplasia was seen to be diffusely infiltrating the prostate parenchyma and peripherally palisading. Large vesicular nucleases with conspicuous nucleoli and course chromatin as well as an abundance of amphophilic cytoplasm were characteristics of cancerous cells. Additionally, regional necrosis and intense mitotic activity were visible (see figure 8). These characteristics in

the reported specimen were said to mimic the histological description of LCNEC provided by Evans et al. [5] in the most comprehensive series on LCNEC that had been published. The entire specimen lacked conventional adenocarcinoma. To determine the tumor's origin and the degree of NE differentiation, immunohistochemistry (IHC) staining investigations of the tumour were conducted (see figure 8). PSA was not detected by IHC, while AMACR was positively stained in the tumour. IHC was performed for P63, CK20, CK7, and GATA-3 in order to rule out urinary bladder cancer. To determine NE differentiation, IHC labelling was done using neuroendocrine (NE) markers such as chromogranin, synaptophysin, and CD 56. The study's findings showed that every NE marker had diffusely and highly positive cytoplasmic staining (see figure 9).

Following this, Zafarghandi et al. [4] iteratedly summarised:

A well-known tumour, large cell carcinoma with neuroendocrine differentiation, has been sporadic documented to originate from the lung, cervix, and larynx, among other places (see Table 2). According to previous research, these tumours are a separate pathological entity and have a poor prognosis [33] [34]. The prostate gland cancer known as LCNEC is extremely rare. According to reports, NePCs typically manifests as symptoms that are frequently connected to prostate gland enlargement. [29] LCNEC frequently shows positive staining in immunohistochemistry investigations for neuroendocrine markers such synaptophysin, CD56, and chromogranin. In a case that was reported in 2014, a patient was evaluated for increased serum PSA level and he was finally diagnosed as having LCNEC [11]. Pelvic mass with rapid progression had previously been reported in some cases. [5] In their reported case, huge pelvic mass had caused obstructive uropathy and worsened the patient's clinical condition. The mean survival time of NePCs had been estimated to be less than 12 months and this had ranged between 3 months and 12 months. The patient who was being followed up on for six months was still alive. Metastasis and uropathy do frequently result in death, and the majority of LCNEC cases typically have metastatic illness due to delayed diagnosis. Additionally, their patient had metastases. Despite the fact that androgen-deprivation therapy (ADT) had been thought to be the main risk factor for NePCs, several documented cases had negative medical histories [35].

In a report by Okoye et al. [24], a 48-year-old male with LCNEC and no prior history of ADT was described. There were a total of 6 cases reported in Evans' study [5] where the patients had a history of ADT for prostate cancer, but their reported cases lacked any predisposing factors. Young guys may develop LCNEC, and it may have a hereditary basis. Studies using animal models had shown that prostate neuroendocrine cells could also undergo a malignant change. Other cases of de novo LCNEC are AR negative, despite the fact that some cases of de novo LCNEC do express androgen receptor (AR) and may be androgen dependent [11]. It is unknown what the primary, precise mechanism and underlying causes of LCNEC are. Evans et al. [5] had demonstrated that this immunohistochemical marker was positive in all LCNEC patients, and in their reported case, CD56 was as well. LCNEC cells do show positive immunohistochemical staining for CD56, chromogranin, and synaptophysin, according to earlier investigations. If one of the markers turns out to be positive, LCNEC may be identified.

Wynn et al. published the initial report of LCNEC Immunohistochemistry findings in 2000 [36].

And in cases when LCNEC is suspected, this marker needs to be examined. LCNEC were described by their distinct immunohistochemistry (IHC) and electron microscopy (EM) characteristics by Travis et al. [37]. They looked at 5 cases of LCNEC and did find that the prognosis for these patients ranged from atypical carcinoid to small cell carcinoma. According to estimates, patients who had NePCs would live an average of 9 to 12 months [5]. All of the patients that were mentioned in the study by Evans et al. [5] passed away shortly after their diagnoses. It had been noted that a worse prognosis and more aggressive disease types appeared to be associated with greater neuroendocrine differentiation [5]. Their stated patient had been released from the hospital and was still alive six months later. Their patient was reported to have experienced severe pelvic discomfort, which may have been brought on by neural invasion, the compression caused by big pelvic lymph nodes, or both. Large masses had caused urine retention in earlier case reports [24]. The tumour was not resectable in the majority of cases of LCNEC because it had been detected late or with delay. Patients who had LCNEC, like the patient who was the subject of their report, tended to frequently develop pelvic lymph node involvement and metastases.LCNEC had not reacted well to the usual NePCs treatment regimens. It has been suggested that more instances need to be assessed in order to define the precise treatment plan for LCNEC, while there are some recommendations for the use of unique and supplementary medication in these situations, such as somatostatin analogues. [6] [37] [38]

Zafarghandi et alfindings .'s [4] were as follows:
It is crucial to investigate LCNEC as a possible differential diagnosis in men with prostate cancer. It's crucial to be aware of the incidence of primary large cell neuroendocrine carcinoma of the prostate gland, even if it can occasionally appear as metastases from other organs, such as the lung.
However, in suspected cases, a thorough histological and immunohistochemistry (IHC) staining research assessment of an enlarged prostate with a normal PSA level is required since it affects the patients' prognosis and the selection of their therapeutic approach.

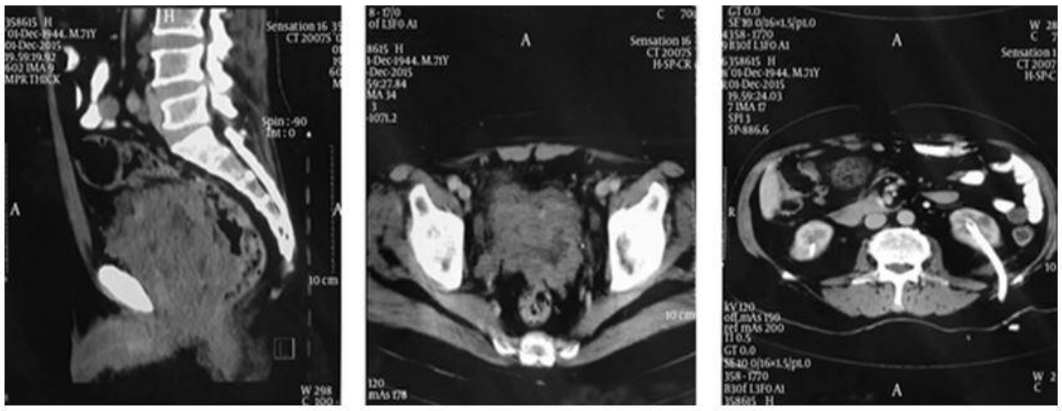

**FIGURE 7:** Massive Pelvis Mass with Neural Invasion and Nephrostomy. Reproduced from: [4] under the terms of the Creative Commons Attribution-Non-Commercial 4.0 International License

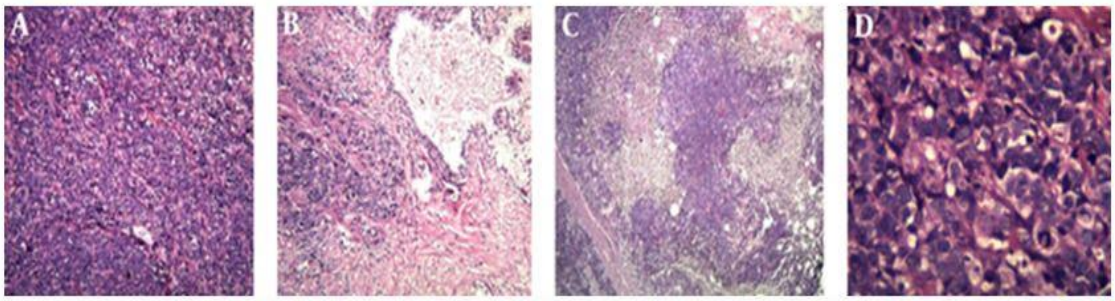


**FIGURE 8 :** A, Sheet of Neoplastic Cells; B, Infiltrating Prostate Parenchyma; C, with Geographic Necrosis; D, The Neoplastic Cells had Prominent Nucleoli. Reproduced from: [4] under the terms of the Creative Commons Attribution-Non-Commercial 4.0 International License

| Marker | Result |
|---|---|
| Synaptophysin | Diffusely Positive |
| Chromogranin | Diffusely Positive |
| CD56 | Positive |
| AMACR | Diffusely Positive |
| CK | Positive |
| CK7 | Negative |
| CK20 | Negative |
| CK5.6 | Negative |
| GATA3 | Negative |
| PSA | Negative |
| P63 | Negative |

**TABLE 2:** Reproduced from: [4] under the terms of the Creative Commons Attribution-Non-Commercial 4.0 International License

**Table 2: Abbreviations:** AMACR, alpha-methylacylcoA racemase; CD, cluster differentiation; CK, cytokeratin; GATA3, GATAbinding protein; PSA, prostatic specific antigen.

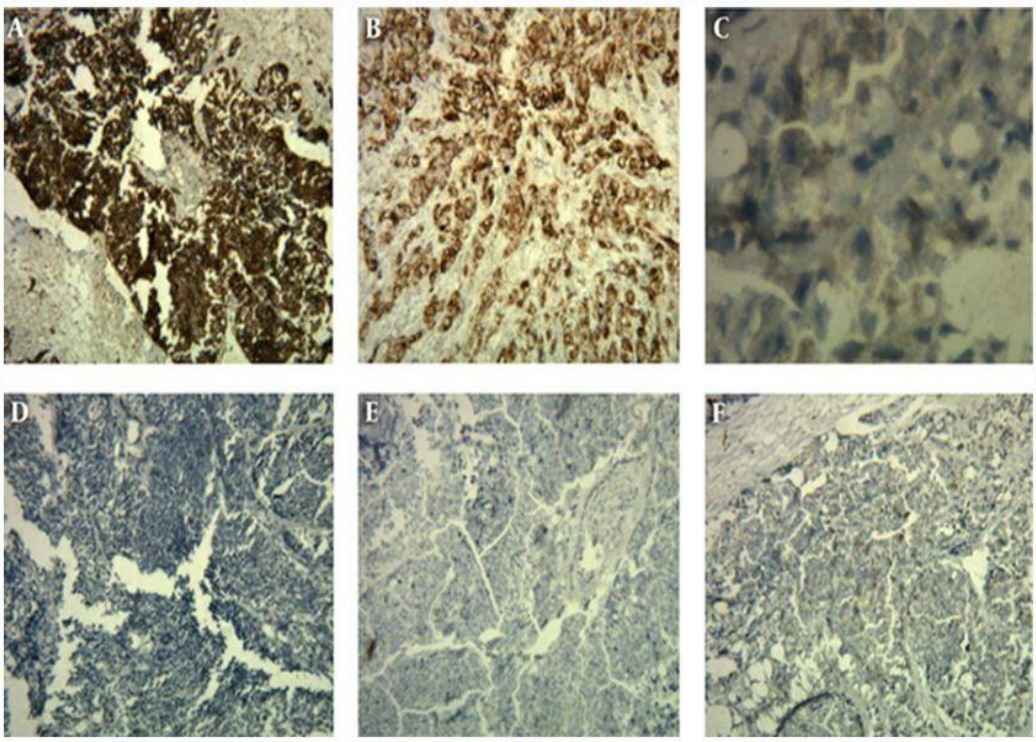


**FIGURE 9 :** A, Neoplastic Cells were positive for Synaptophysin; B, Chromogranin; C, AMACR; but negative for D, PSA; E, GATA; and F; CK20. Reproduced from: [4] under the terms of the Creative Commons Attribution-Non-Commercial 4.0 International License

The iterations made by Priemer et al. [6] are as follows:

In addition to existing in pure form and in conjunction with prostate adenocarcinoma, neuroendocrine neoplasms are a diverse collection of tumours that affect the prostate gland. From possessing high-grade neuroendocrine appearances akin to neuroendocrine malignancies of other organs to being morphologically indistinguishable from surrounding adenocarcinoma of prostate cells, neuroendocrine cells inside prostate neoplasms can range widely. On a molecular level, there has been a lot of recent research on neuroendocrine malignancies that do occur in the context of prostate adenocarcinoma. The majority of this research has supported the idea that neuroendocrine malignancy within the prostate does develop as a trans-differentiation from prostate adenocarcinoma. Although uncommon, pure neuroendocrine tumours had not received much attention, it was possible that they might have a distinct cell of origin and molecular origins. They examined the most recent molecular research on the topic of malignant neuroendocrine differentiation in prostatic adenocarcinoma and analyzed the morphological spectrum of malignant neuroendocrine prostate neoplasms. They had also talked about how to diagnose prostate neuroendocrine tumours according to the 2016 World Health Organization (WHO) classification after considering the most recent data. They had talked about how to describe these tumours, focusing on the distinction between pure and mixed neuroendocrine malignancies so that, at the very least, they could be quickly recognized for future clinical and laboratory-based research. Finally, they had proposed a name for a high-grade neuroendocrine prostate cancer that was difficult to classify or otherwise describe and whose characteristics prevented it from fitting neatly into one of the WHO diagnostic groupings.

Tu et al. [17] iterated that large cell neuroendocrine carcinoma (LCNEC) of the prostate gland is an extremely rare entity, and the clinicopathological course, potential effective treatment, as well as prognosis of the tumour are yet to be elucidated. Tu et al. [17] undertook a systematic search utilizing various internet data search bases from the inception of large cell neuroendocrine cancer of the prostate gland to January 2019. Tu et al. [17] studied each individual case of LCNEC of the prostate gland, and they summarized specific features and outcomes for this uncommon pathology entity.

Tu et al. [17] summarized the results as follows:

Thirteen studies with a total of 20 patients whose mean age was 70.3 years and whose ages had ranged between 43 years and 87 years were included in their review. Seventeen patients had primary LCNEC of the prostate gland, of which 9 patients were diagnosed as having de novo carcinoma, and 8 patients had a history of

adenocarcinoma of the prostate gland which had been treated by means of hormonal therapy over a mean duration time of 2.9 years and follow-up which had ranged between 2 years and 5 years. The other 3 patients were diagnosed as having metastatic LCNEC which had originated from the lung in 2 cases, and the urinary bladder in 1 case. All of the patients met the diagnostic criteria of the typical morphology characteristic features as well as immunohistochemistry staining features of large cell neuroendocrine carcinoma. Nearly all of the primary de novo LCNEC of the prostate gland were at a late stage at the time of their initial diagnosis. The pattern of distant metastasis simulated that of adenocarcinoma of the prostate gland with the commonest site as bone spread which was noted in 8 out of 16 cases that amounted to 50% of the cases. Majority of the patients had undergone systematic chemotherapy after initial diagnosis; nevertheless, the prognosis of the patients had remained poor and the patients' condition deteriorated rapidly but with exception. Three reported cases in the context of de novo LCNEC which were admixed with adenocarcinoma of the prostate gland, kept sustained response to androgen deprivation therapy (ADT) and they obviously achieved superior / better survival outcomes in comparison with other patients.

Tu et al. [17] made the ensuing conclusions:

LCNEC of the prostate gland is a rare entity which mostly does occur pursuant to long-standing hormonal therapy of adenocarcinoma of the prostate gland. The prognosis of LCNEC was universally poor irrespective of the systematic chemotherapy the patients received. Nevertheless, patients who have de novo tumour that is mixed with adenocarcinoma of the prostate gland may respond to ADT and they may have a better outcome in comparison with those patients who have pure de novo or post-ADT LCNEC of the prostate gland. Considering that globally the most common malignant tumour of the prostate gland that has been diagnosed is adenocarcinoma of the gland, there is the possibility that when some pathologists examine specimens of the prostate in which they find adenocarcinoma of the prostate gland, they may not extensively and critically examine every specimen and all areas of the prostate and they would establish a diagnosis of pure adenocarcinoma. However, perhaps if globally all pathologists thoroughly examine all areas of prostate specimens they receive, they may encounter mixed tumours including the possibility of LCNECP which they could report that would increase knowledge about the possibility of LCNECP being associated with adenocarcinoma of the prostate gland and if mixed tumours of the prostate gland including adenocarcinoma of the prostate and LCNECP is found the biological behaviour of mixed adenocarcinoma and LCNECP would be studied and reported. Additionally, if the immunohistochemistry staining antibodies that are utilized for the diagnosis of LCNECP are routinely used during the pathologist's examination of specimens of prostate cancer, perhaps more cases of LCNECP would be diagnosed globally Furthermore, if pathologists do not consider the possibility of LCNECP by undertaking a thorough examination of their prostate specimens, they would miss the diagnosis of LCNECP which does tend to portend a more aggressive biological behaviour and which does need an aggressive treatment in order to ensure good prognosis.

## IV. CONCLUSIONS

It's possible that pathologists around the world have trouble making the diagnosis of large-cell primary neuroendocrine carcinoma of the prostate gland since fewer cases of this aggressive and uncommon type of prostate cancer are reported, but it's impossible to know for sure. There have only been around 25 cases of big cell endocrine cancer documented in the literature. Given the documented aggressive biological behaviour of the tumour, curative surgery should be performed on localised and locally progressed types of primary big cell neuro-endocrine carcinoma of the prostate gland. However, the therapeutic options for metastatic forms are constrained by resistance in the pure forms of primary large cell neuroendocrine carcinomas (LCNECs) of the prostate gland. The prognosis does tend to improve when primary LCNEC of the prostate gland is present together with a hormone-sensitive prostate adenocarcinoma component. With significantly improved care, the introduction of nuclear imaging technologies does provide better follow-up and early recurrence diagnosis. In order to diagnose early cases of primary large cell neuroendocrine carcinomas, early prostate gland biopsies must be performed on all patients who have significant lower urinary tract symptoms and who have serum prostate specific antigen (PSA) levels that are slightly elevated or elevated, even if Tamsulosin has been started to help with voiding symptoms. Considering that there is no consensus opinion on the best management of large cell neuroendocrine carcinoma of the prostate gland, there is an urgent need for the establishment of a global multi-centre trial related to various management options for the disease in order to ascertain the best management of large cell neuroendocrine carcinoma of the prostate gland. Urologists, oncologists, and pharmacists globally should endeavour to undertake research that would identify safe and effective chemotherapy medicaments that would help improve upon the prognosis of large cell neuroendocrine carcinomas of the prostate gland as well as other primary large cell neuroendocrine carcinomas of various sites of the body.

**CONFLICTS OF INTERESTS**
The Author States there is NO ANY CONFLICTS OF INTERESTS .

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