Published in final edited form as:

Nat Rev Urol. 2014 April ; 11(4): 213–219. doi:10.1038/nrurol.2014.21.

Small cell carcinoma of the prostate

Rosa Nadal,

Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, 1650 Orleans Street, Baltimore, MD 21231-1000, USA

Michael Schweizer,

Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, 1650 Orleans Street, Baltimore, MD 21231-1000, USA

Oleksandr N. Kryvenko,

Department of Pathology, University of Miami Miller School of Medicine, 1400 NW 12th Avenue, Room 4100, Miami, FL 33136, USA

Jonathan I. Epstein, and

Department of Pathology, Johns Hopkins Hospital, The Weinberg Building, Room 2242, 401 North Broadway Street, Baltimore, MA 21231, USA

Mario A. Eisenberger

Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, 1650 Orleans Street, Baltimore, MD 21231-1000, USA

Abstract

Pure small-cell carcinoma (SCC) of the prostate is a rare entity and one of the most aggressive malignancies of the prostate. Histologically, prostatic SCCs of the prostate are part of a spectrum of anaplastic tumours of the prostate and are similar to SCCs of the lungs. In most cases, SCC of the prostate is associated with conventional prostatic adenocarcinoma. Both components of these mixed tumours frequently share molecular alterations such as *ERG* gene rearrangements or *AURKA* and *MYCN* amplifications, suggesting a common clonal origin. The clinical behaviour of small-cell prostate carcinomas is characterized by extensive local disease, visceral disease, and low PSA levels despite large metastatic burden. Commonly, the emergence of the SCC occurs in patients with high-grade adenocarcinoma who are often treated with androgen deprivation treatment (ADT). However, SCCs do not usually benefit from ADT. A biopsy of accessible lesions is strongly recommended to identify those with SCC pathological features, as management is undoubtedly affected by this finding. Chemotherapy is the standard approach for treating patients with either localized or advanced prostatic SCC. Despite the emergence of more-aggressive treatment modalities, the prognosis of men with prostatic SCC remains dismal.

© 2014 Macmillan Publishers Limited. All rights reserved

Correspondence to: M.A.E. eisenma@jhmi.edu.

Competing interests: The authors declare no competing interests.

Author contributions: R.N., M.S., and O.N.K. researched data and were involved in writing the article. J.I.E. and M.A.E. contributed to discussions of content and reviewed and edited the manuscript before submission.

Introduction

Neuroendocrine tumours of the prostate represent a heterogeneous group that includes conventional adenocarcinomas of the prostate with focal differentiation, tumours with Paneth-cell-like neuroendocrine differentiation, carcinoid tumours, large-cell neuroendocrine carcinomas (LCNECs) and small-cell carcinomas (SCCs).¹ Neuroendocrine markers such as chromogranin A (CgA) and synaptophysin are expressed in nearly all cases of conventional prostatic adenocarcinoma, with the proportion of cells that stain positive for these markers increasing during castration.² Most studies have shown no effect of neuroendocrine differentiation in conventional prostatic adenocarcinoma on patient outcomes.^{3–14} In contrast, SCC of the prostate is a clinically distinct disease, generally associated with a very poor prognosis, which is primarily defined based on its morphology on routine haematoxylin-stained and eosin-stained sections.

Prostatic SCC was first described by Wenk *et al.*¹⁵ more than 30 years ago. Since then, it has been reported to occur in 0.5–2% of men with prostate cancer, although autopsy studies of men who have died of castration-resistant prostate cancer (CRPC) have reported the presence of SCC in up to 10–20% of cases.^{16–19} In this article, we review the pathological features, biology, clinical characteristics, and diagnostic challenges of SCC of the prostate, summarize the available treatment options, and highlight promising therapeutic strategies.

Pathological features

The diagnosis of SCC of the prostate is reached based on the presence of morphological features similar to those found in SCC of the lung, as defined in the 1999 WH classification criteria of pulmonary neoplasms (Figure 1).^{20–22} These criteria include a proliferation of small cells (>4 lymphocytes in diameter) with unique and strict morphological features, scant cytoplasm, ill-defined borders, finely granular ‘salt and pepper’ chromatin, absent or inconspicuous nucleoli, frequent nuclear molding, and a high mitotic count. Morphological variations of prostatic SCC include intermediate-cell-type tumours with slightly-more-open chromatin and visible small nucleoli seen in about 30–40% of cases—tumours that would probably not be included in the strict diagnosis of SCC of the lung.²³ Using immunohistochemical techniques, the small-cell component is positive for one or more neuroendocrine marker (for example, neuron-specific enolase, synaptophysin, chromogranin, and CD56) in almost 90% of cases.^{21,23} PSA and other prostatic markers, such as P501S, are positive in about 17–25% of cases, although often very focally (Table 1).^{21,23} In 24% and 35% of cases, marker positivity is noted for p63 and high-molecular-weight cytokeratin, markers that are typically negative in prostatic carcinoma.²¹ Studies have demonstrated thyroid transcription factor 1 (TTF-1) expression in over 50% of SCCs of the prostate, limiting its utility in distinguishing primary SCC of the prostate from a metastasis from the lung.^{21,23–25} The finding of *TMPRSS2:ERG* gene fusion by fluorescence *in situ* hybridization can also be used to confirm a prostatic origin for SCCs, although this is not generally necessary.^{26–31} In the absence of a primary SCC at another site (for example, the lung), the finding of SCC on prostate biopsy is almost undoubtedly an indication of prostatic origin.

A related disease to prostate SCC is LCNEC of the prostate, which is the least common and the least studied of all the prostatic neuroendocrine tumours.³² Diagnostic criteria for this uncommon disease subtype are not well established, and diagnosis is restricted to cases with a large nesting pattern, peripheral palisading, abundant cytoplasm, and prominent nucleoli that demonstrate extensive immunohistochemical evidence of neuroendocrine differentiation and usually show signs of necrosis and lack expression of PSA and other prostate-specific markers. As with SCC, its associated prognosis is generally poor.³²

Biology

An early hypothesis suggested that SCC of the prostate originated from the migration of cells from the neural crest.³³ However, more-recent data suggest that SCC of the prostate shares a common origin with conventional prostatic adenocarcinoma, according to the model of divergent differentiation.³⁴ The fact that a tumour shares phenotypic similarities with a tissue type (for example, neuroendocrine tissue) does not necessarily indicate that the tumour in question was derived from a common stem cell progenitor. This model is not only applicable to prostatic carcinomas, but to a wide array of malignancies. In the case of SCC of the prostate, a lower but detectable level of PSA expression in neuroendocrine cells and common molecular alterations between adenocarcinoma and SCC components of mixed prostate tumours under conditions of androgen deprivation support this hypothesis.^{26,35–38} SCC of the prostate is significantly more common in men with CRPC after exposure to ADT.^{23,39} Indeed, based on experiences at single institutions, most of the patients who develop SCC have received ADT as treatment for prostatic adenocarcinoma. Rather than fully differentiated adenocarcinoma cells dedifferentiating into SCC, it has been suggested that certain stem cells can differentiate into both adenocarcinoma and SCC.^{40,41} In some men treated with ADT, development of SCC might represent the ‘escape’ of a subpopulation of hormone-independent cells resulting from the selective pressure of hormonal therapy.^{16,42,43}

Alternatively, other experimental data suggest that SCC of the prostate might transdifferentiate from conventional prostatic adenocarcinoma. Recurrent ERG rearrangements in the androgen-regulated 5'-end partners (for example, *TMPRSS2*, *SLC45A3*, and *NDRG1*) and *ETS* genes (including *ETV1*, *ETV4*, and *ETV5*), which are considered to be prostate-cancer-specific mutations,⁴⁴ have been reported in approximately 50% of men with SCC of prostatic origin.^{26–28,30} This incidence is similar to that in men with conventional prostatic adenocarcinoma,⁴⁵ further supporting a common origin for these cancers.²⁶ Downregulation of *REST*, which encodes a transcription factor that is considered crucial to the repression of neuronal differentiation, and the consequent upregulation of the neuronal signature has been observed in SCC of the prostate and mixed SCC with conventional prostatic adenocarcinoma.⁴⁶ Hansel *et al.*⁴⁷ reported identical mutations in the DNA-binding domain of *TP53* in both SCC and conventional adenocarcinoma components, although the adenocarcinoma component retained a wild-type *TP53* allele, whereas the SCC component lost the wild-type allele.

Additional evidence to support the hypothesis of trans-differentiation comes from a recent study showing that *AURKA* and *MYCN* amplifications are present in approximately 65% of

primary prostate adenocarcinoma specimens that subsequently develop neuroendocrine prostate cancers (including prostatic SCC) following ADT and in about 90% of the corresponding metastatic tumours.³⁸ In contrast, these mutations were only identified in 5% of 169 unselected prostate adenocarcinoma samples.⁴⁸ Identification of *AURKA* amplification in primary prostate cancers might represent a new marker for predicting the risk of progression to transformed SCC of the prostate and a potential therapeutic target.

Molecular and gene expression studies of men with SCC of the prostate have provided interesting observations on the biology of this disease that potentially explain its more aggressive behaviour compared with conventional prostate adenocarcinoma. For example, prostatic SCCs demonstrate increased expression of genes involved in cellular proliferation, the cell cycle, neuroendocrine differentiation, and mitosis.^{46,49} In one study, greater upregulation of genes encoding proliferative markers (such as *PBK/TOPK*), neuroendocrine markers (such as *CTNNA2*, *FGFR3*, *FGF12*, and *NR0B1*) and tyrosine kinase receptors (*FGFR3*), as well as greater downregulation of genes encoding cell adhesion molecules (including *CLDN10*, *COL4A5*, and *MMP7*), was observed in the small-cell component of a single mixed tumour compared with the other components.⁴⁹ A recent study described the upregulation of mitotic genes, including *UBE2C*, in the absence of androgen receptor (*AR*), retinoblastoma (*RB*), and cyclin D1 (*CCND1*) expression in SCC and LCNEC xenografts, as well as human samples. In contrast, mixed adenocarcinomas (the adenocarcinoma component of the mixed tumours) frequently lack *RB* and *CCND1* expression but remain *AR*-positive with lower *UBE2C* expression levels,⁵⁰ suggesting that the SCC phenotype results from progression of androgen-responsive prostate carcinomas.

Clinical features

SCC of the prostate has a presentation that is distinct from its adenocarcinoma counterparts; unique features include an unresponsiveness to hormonal therapy, rapid progression, increased risk of lytic bone lesions, presence of visceral metastases, a markedly enlarged prostate, and low PSA relative to disease burden (Box 1).⁵¹ Patients with SCC of the prostate most frequently present with voiding symptoms, neurological symptoms (such as con-fusion and sensory or motor deficits), or constitutional symptoms.⁵¹ Importantly, the median time to development of SCC in patients with a history of prostatic adenocarcinoma is approximately 18–25 months from prostatic adenocarcinoma diagnosis, but ranges widely from a few months to several years.^{20,23}

As for neuroendocrine tumours, including SCCs, in other locations, prostatic SCC is associated with the release of a wide array of ectopic neuropeptides, including CgA, adrenocorticotrophic hormone, and gastrin-releasing peptide.⁵² Given its proclivity to release ectopic peptides, SCC of the prostate has also been associated with paraneoplastic syndromes such as Cushing syndrome, hypercalcaemia, Eaton-Lambert syndrome, and syndrome of inappropriate antidiuretic hormone.^{20,34,51,53}

Several prospective studies in patients with clinically suspected or histologically confirmed (in the minority of cases) prostatic SCC have enrolled patients on the basis of one or more classical features associated with prostatic SCC.^{54–57} For example, a recent report evaluated

platinum-based therapy in men with CRPC and at least one of the following features: histological evidence of small-cell prostate carcinoma (pure or mixed), exclusively visceral metastases, predominant lytic bone metastases by plain radiography or CT, bulky (> 5 cm) lymphadenopathy or bulky (> 5 cm) Gleason grade ≥ 8 tumour mass in the prostate or pelvis, PSA of > 10 ng/ml at initial presentation (before androgen deprivation or at symptomatic progression in the castrate setting) plus high-volume (> 20) bone metastases, presence of neuroendocrine markers on histology or in serum at initial diagnosis or at progression plus elevated serum lactate dehydrogenase (LDH), malignant hypercalcaemia or elevated serum carcinoembryonic antigen (CEA), or poor response (< 6 months) to ADT that results in androgen-independent progression.⁵⁴ Another feature of SCC of the prostate that distinguishes it from prostatic adenocarcinoma is a greater tendency to metastasize to the brain, often presenting with symptoms related to central nervous system involvement.⁵⁸ In general, prostatic SCC is usually suspected on the basis of one or more of the aforementioned presenting features, which should trigger a prompt diagnostic work up.

Diagnostic work-up

Staging of suspected prostatic SCC is similar to that of prostatic adenocarcinoma, and evaluation of metastatic disease should generally involve a bone scan, as well as a thoracic, abdomen, and pelvic CT or MRI.⁵¹ Brain imaging (preferably MRI, although CT is also an option) might be performed in patients with localized disease and is recommended for men with neurological symptoms. Given the aggressiveness of the tumour, stage T1 disease is rare. When the level of suspicion for an SCC is high (for example, when a patient has a low serum PSA level and bulky visceral metastases), a biopsy of one of the suspected lesions is strongly recommended. For patients with known CRPC and clinical suspicion of SCC, treatment can be selected on the basis of clinical features if tissue is not readily accessible or if it is unsafe to wait for a pathological diagnosis. Increased expression of plasma CgA—along with other plasma markers, such as CEA, Ca19.9, neuron-specific enolase, bombesin, 5-hydroxytryptamine, and gastrin—might provide supporting evidence for the diagnosis of prostatic SCC,^{40,54,59,60} and could have a role in monitoring response to therapy. Many questions relating to the optimal use of serum neuroendocrine and epithelial markers remain unanswered and there is no consensus regarding their use in routine clinical practice.

Management

It is important to make the distinction between SCC of the prostate and non-small-cell neuroendocrine-differentiated prostatic adenocarcinoma, given that the latter should be treated per a prostatic adenocarcinoma paradigm and the former should be managed similarly to other nonprostatic SCCs. Indeed, much of the management of SCC of the prostate is based on our experience with small-cell lung cancer. Like its pulmonary counterpart, prostatic SCC tends to be sensitive to chemotherapy and radiotherapy; however, these responses are typically fleeting. Given the relative rarity of this entity, prospective trials are lacking, and standard treatment approaches are generally extrapolated from small case series or a handful of single-arm clinical trials.^{20,34,55–57,61–65}

The optimal management of nonmetastatic disease is not well delineated given that it is common to present with metastases.^{51,66} Rarely, prostatectomy alone has been shown to be curative; however, these cases are likely to be exceptional.⁶⁷ As with small-cell lung cancer, adjuvant chemotherapy with a platinum-containing doublet (such as cisplatin or etoposide) should be considered after prostatectomy.^{68,69} Adjuvant radiation might also be of benefit in men with positive surgical margins or identifiable T3a disease from the surgical pathology specimen. When radiation is planned, concurrent platinum therapy should also be considered.⁷⁰ The role of prophylactic cranial irradiation in men with prostatic SCC in complete remission is not established, although it has been suggested as an option given known similarities in its natural history with SCC of the lung.⁷¹

With respect to metastatic disease, a few nonrandomized trials have been reported (Table 2). Enrolment criteria have differed substantially for these trials, with histological diagnosis not necessarily required, presumably in an effort to avoid the morbidity associated with performing biopsies in patients with advanced cancer. In fact, only one study included patients with histologically proven SCC;⁶⁵ other studies presumed SCC based on clinical features, previously reported as characteristic of SCC of the prostate,^{20,34,39,54} or verified prostatic adenocarcinoma on the basis of neuroendocrine differentiation.^{54–57,64} Interestingly, Aparicio *et al.*⁵⁴ found that histological confirmation of SCC was not significantly associated with decreased overall or progression-free survival, compared with cases when the diagnosis was based on clinical grounds (for example, low PSA, exclusive visceral metastases, and lytic bone metastases). This observation perhaps indicates that, despite the fact that only 25% of individuals in that particular study had pathologically documented SCC, the patient cohort was reasonably homogenous after applying clinical criteria to select cases suggestive of SCC.⁵⁴ Despite its complexity, future clinical trials should make a broader effort to distinguish between proven SCC and other cancers that are suggestive of SCC, and establish whether differences exist between these cancers in terms of response to treatment and prognosis. Regimens prospectively evaluated have typically consisted of a platinum agent combined with one or more of the following: docetaxel, etoposide, doxorubicin, and estramustine.⁷⁰

SCC of the prostate is often characterized by an aggressive course with a poor response to conventional ADT, consistent with lack of the androgen receptor in prostatic SCC.⁵¹ PSA levels tend to be low relative to the tumour burden and an unreliable indicator of response to therapy in men with this variant of prostate cancer.^{39,72} The use of hormonal therapy in men with metastatic small-cell prostate carcinoma is somewhat controversial given the unresponsiveness of prostatic SCC to ADT alone. Although chemotherapy is generally viewed as the backbone of treatment for metastatic SCC of the prostate, ADT should be considered in combination with chemotherapy given the theoretical concern that a subpopulation of adenocarcinomas might survive chemotherapy.⁷³ Moreover, a trial of antiandrogen withdrawal is not recommended in patients with transformed or treatment-related prostatic SCC before the initiation of chemotherapy, as these tumours are unlikely to be dependent on androgen receptor signalling.¹ As for metastatic adenocarcinoma of the prostate, radiation therapy might be a useful palliative adjunctive therapy for SCC of the prostate.⁷⁴ Patients with *AURKA*-amplified prostate cancer might benefit from treatment

with Aurora kinase A inhibitors. Although these inhibitors are still in the early stages of drug development, they hold promise and clinical evaluation is ongoing.⁷⁵ Complete suppression of neuroendocrine marker expression has been observed following Aurora kinase inhibitor therapy.⁴⁸

Prognosis

Several studies of patients with clinically suspicious or histologically proven prostatic SCC have found that serum neuroendocrine markers are not predictive of survival in multivariate models.^{54,56,65} By contrast, Aparicio *et al.*⁵⁴ demonstrated that increased CEA or LDH levels strongly predicted overall survival. However, the definition of neuroendocrine differentiation has been somewhat inconsistent between studies, with many defining its presence solely on the basis of positive CgA staining. Furthermore, given that only 84% of all prostatic SCCs stain positive for CgA, one has to question the legitimacy of including patients in pathological small-cell series solely on the basis of neuroendocrine marker staining.²³

Owing to the rarity of prostatic SCC, only a few reports in the literature have described the prognosis of this neoplasm.^{34,39,66,72,76} Surveillance, Epidemiology, and End Results (SEER) data relating to 191 men diagnosed with SCC of the prostate between 1973 and 2003 reveal that approximately 60% of men present with metastasis, and death occurs at a median of 18 months following diagnosis.⁶⁶ Age, concomitant low-grade prostatic adenocarcinoma, and disease stage seem to be the strongest predictors of survival for patients with prostatic SCC.⁶⁶

Median overall survival in prospective trials of men with metastatic prostate cancer and histologically verified or clinically suspected prostatic SCCs treated with platinum-based combination therapies range from 10–19 months, despite high response rates.^{54–57,65} One of the few single-institution trials involving pure or mixed prostatic SCCs showed that men with metastatic mixed prostatic SCC live only 3 months longer than those with pure SCC of the prostate (12.3 months versus 9.16 months).⁶⁵ Taken together, these studies highlight the aggressive nature of pure or mixed SCC of the prostate, even in its localized form.⁷⁶

Conclusion

Prostatic SCC is a rare aggressive prostate cancer variant that is biologically, morphologically, and clinically distinct from the differentiated adenocarcinoma type. Clinically, this entity is characterized by low PSA levels, visceral metastases, predominantly lytic bone lesions, and large prostatic or nodal masses. SCC of the prostate is often found on repeat biopsies in men with progressive CRPC and its underlying biology is implicated in the lethal progression of many prostate cancers. Thus, with increased life expectancy resulting from more-effective targeting of the androgen receptor signalling axis, the incidence of prostatic SCC might increase owing to clonal pressure exerted on malignant prostate cells. Early recognition of histological or clinical features of prostatic SCC might influence the treatment decision-making process. Although the optimal treatment of prostatic SCC has not been clearly established, it is distinct from that of conventional

adenocarcinoma. As SCC is frequently identified in a mixed phenotype tumour consisting of both AR-negative SCC and AR-positive adenocarcinoma of prostate, cisplatin-based chemotherapy is considered the backbone combination therapy for advanced SCC of the prostate, and ADT should be contemplated in combination with chemotherapy. Importantly, mitotic and neural development pathways have been implicated in the progression to androgen-independent SCC and offer targets, such as small-molecule inhibitor of AURKA, that might change the aggressive natural history of this disease. Improvements to therapy will come from understanding disease biology, which could enable physicians to identify new targeted therapies and achieve better clinical outcomes for patients with this subtype of prostate cancer.

References

1. di Sant'Agnese PA, Cockett AT. Neuroendocrine differentiation in prostatic malignancy. *Cancer*. 1996; 78:357–361. [PubMed: 8674017]
2. di Sant'Agnese PA. Neuroendocrine differentiation in prostatic carcinoma: an update on recent developments. *Ann Oncol*. 2001; 12(Suppl. 2):S135–S140. [PubMed: 11762341]
3. Casella R, et al. Focal neuroendocrine differentiation lacks prognostic significance in prostate core needle biopsies. *J Urol*. 1998; 160:406–410. [PubMed: 9679888]
4. Aprikian AG, Cordon-Cardo C, Fair WR, Reuter VE. Characterization of neuroendocrine differentiation in human benign prostate and prostatic adenocarcinoma. *Cancer*. 1993; 71:3952–3965. [PubMed: 7685237]
5. Cohen RJ, Gleason G, Haffejee Z. Neuro-endocrine cells—a new prognostic parameter in prostate cancer. *Br J Urol*. 1991; 68:258–262. [PubMed: 1913066]
6. Shariff AH, Ather MH. Neuroendocrine differentiation in prostate cancer. *Urology*. 2006; 68:2–8. [PubMed: 16844446]
7. Abrahamsson PA, Cockett AT, di Sant'Agnese PA. Prognostic significance of neuroendocrine differentiation in clinically localized prostatic carcinoma. *Prostate Suppl*. 1998; 8:37–42. [PubMed: 9690662]
8. Allen FJ, Van Velden DJ, Heyns CF. Are neuroendocrine cells of practical value as an independent prognostic parameter in prostate cancer? *Br J Urol*. 1995; 75:751–754. [PubMed: 7613832]
9. Ahlgren G, et al. Regressive changes and neuroendocrine differentiation in prostate cancer after neoadjuvant hormonal treatment. *Prostate*. 2000; 42:274–279. [PubMed: 10679756]
10. Tan MO, et al. Prostate cancer and neuroendocrine differentiation. *Int Urol Nephrol*. 1999; 31:75–82. [PubMed: 10408306]
11. Cohen MK, et al. Neuroendocrine differentiation in prostatic adenocarcinoma and its relationship to tumour progression. *Cancer*. 1994; 74:1899–1903. [PubMed: 8082095]
12. Ishida E, Nakamura M, Shimada K, Tasaki M, Konishi N. Immunohistochemical analysis of neuroendocrine differentiation in prostate cancer. *Pathobiology*. 2009; 76:30–38. [PubMed: 19188748]
13. Jeetle SS, et al. Neuroendocrine differentiation does not have independent prognostic value in conservatively treated prostate cancer. *Virchows Arch*. 2012; 461:103–107. [PubMed: 22767265]
14. Aprikian AG, et al. Neuroendocrine differentiation in metastatic prostatic adenocarcinoma. *J Urol*. 1994; 151:914–919. [PubMed: 8126824]
15. Wenk RE, Bhagavan BS, Levy R, Miller D, Weisburger W. Ectopic ACTH, prostatic oat cell carcinoma, and marked hypernatraemia. *Cancer*. 1977; 40:773–778. [PubMed: 196743]
16. Miyoshi Y, et al. Neuroendocrine differentiated small cell carcinoma presenting as recurrent prostate cancer after androgen deprivation therapy. *BJU Int*. 2001; 88:982–983. [PubMed: 11851626]
17. Tanaka M, et al. Progression of prostate cancer to neuroendocrine cell tumour. *Int J Urol*. 2001; 8:431–437. [PubMed: 11555007]

18. Turbat-Herrera EA, et al. Neuroendocrine differentiation in prostatic carcinomas. A retrospective autopsy study. *Arch Pathol Lab Med.* 1988; 112:1100–1105. [PubMed: 2460064]
19. Shah RB, et al. Androgen-independent prostate cancer is a heterogeneous group of diseases: lessons from a rapid autopsy programme. *Cancer Res.* 2004; 64:9209–9216. [PubMed: 15604294]
20. Tetu B, et al. Small cell carcinoma of the prostate. Part I. A clinicopathologic study of 20 cases. *Cancer.* 1987; 59:1803–1809. [PubMed: 3030528]
21. Yao JL, et al. Small cell carcinoma of the prostate: an immunohistochemical study. *Am J Surg Pathol.* 2006; 30:705–712. [PubMed: 16723847]
22. Ro JY, Tetu B, Ayala AG, Ordonez NG. Small cell carcinoma of the prostate. II. Immunohistochemical and electron microscopic studies of 18 cases. *Cancer.* 1987; 59:977–982. [PubMed: 2434204]
23. Wang W, Epstein JI. Small cell carcinoma of the prostate. A morphologic and immunohistochemical study of 95 cases. *Am J Surg Pathol.* 2008; 32:65–71. [PubMed: 18162772]
24. Agoff SN, et al. Thyroid transcription factor-1 is expressed in extrapulmonary small cell carcinomas but not in other extrapulmonary neuroendocrine tumours. *Mod Pathol.* 2000; 13:238–242. [PubMed: 10757334]
25. Ordonez NG. Value of thyroid transcription factor-1, E-cadherin, BG8, WT1, and CD44S immunostaining in distinguishing epithelial pleural mesothelioma from pulmonary and nonpulmonary adenocarcinoma. *Am J Surg Pathol.* 2000; 24:598–606. [PubMed: 10757409]
26. Lotan TL, et al. ERG gene rearrangements are common in prostatic small cell carcinomas. *Mod Pathol.* 2011; 24:820–828. [PubMed: 21336263]
27. Han B, et al. Characterization of ETS gene aberrations in select histologic variants of prostate carcinoma. *Mod Pathol.* 2009; 22:1176–1185. [PubMed: 19465903]
28. Guo CC, et al. TMPRSS2-ERG gene fusion in small cell carcinoma of the prostate. *Hum Pathol.* 2011; 42:11–17. [PubMed: 21040948]
29. Williamson SR, et al. ERG-TMPRSS2 rearrangement is shared by concurrent prostatic adenocarcinoma and prostatic small cell carcinoma and absent in small cell carcinoma of the urinary bladder: evidence supporting monoclonal origin. *Mod Pathol.* 2011; 24:1120–1127. [PubMed: 21499238]
30. Scheble VJ, et al. ERG rearrangement in small cell prostatic and lung cancer. *Histopathology.* 2011; 56:937–943. [PubMed: 20636794]
31. Schelling LA, et al. Frequent TMPRSS2-ERG rearrangement in prostatic small cell carcinoma detected by fluorescence *in situ* hybridization: the superiority of fluorescence *in situ* hybridization over ERG immunohistochemistry. *Hum Pathol.* 2013; 44:2227–2233. [PubMed: 23850495]
32. Evans AJ, Humphrey PA, Belani J, van der Kwast TH, Srigley JR. Large cell neuroendocrine carcinoma of prostate: a clinicopathologic summary of 7 cases of a rare manifestation of advanced prostate cancer. *Am J Surg Pathol.* 2006; 30:684–693. [PubMed: 16723845]
33. Pearse AG. The diffuse endocrine system and the implications of the APUD concept. *Int Surg.* 1979; 64:5–7. [PubMed: 44272]
34. Oesterling JE, Hauzeur CG, Farrow GM. Small cell anaplastic carcinoma of the prostate: a clinical, pathological and immunohistological study of 27 patients. *J Urol.* 1992; 147:804–807. [PubMed: 1311395]
35. Ismail AH, Landry F, Aprikian AG, Chevalier S. Androgen ablation promotes neuroendocrine cell differentiation in dog and human prostate. *Prostate.* 2002; 51:117–125. [PubMed: 11948966]
36. Wright ME, Tsai MJ, Aebersold R. Androgen receptor represses the neuroendocrine transdifferentiation process in prostate cancer cells. *Mol Endocrinol.* 2003; 17:1726–1737. [PubMed: 12775765]
37. Yuan TC, et al. Androgen deprivation induces human prostate epithelial neuroendocrine differentiation of androgen-sensitive LNCaP cells. *Endocr Relat Cancer.* 2006; 13:151–167. [PubMed: 16601285]
38. Mosquera JM, et al. Concurrent AURKA and MYCN gene amplifications are harbingers of lethal treatment-related neuroendocrine prostate cancer. *Neoplasia.* 2013; 15:1–10. [PubMed: 23358695]
39. Spiess PE, et al. Treatment outcomes of small cell carcinoma of the prostate: a single-centre study. *Cancer.* 2007; 110:1729–1737. [PubMed: 17786954]

40. Helpap B, Kollermann J, Oehler U. Neuroendocrine differentiation in prostatic carcinomas: histogenesis, biology, clinical relevance, and future therapeutical perspectives. *Urol Int.* 1999; 62:133–138. [PubMed: 10529661]
41. Bonkhoff H, Remberger K. Differentiation pathways and histogenetic aspects of normal and abnormal prostatic growth: a stem cell model. *Prostate.* 1996; 28:98–106. [PubMed: 8604398]
42. Stratton M, Evans DJ, Lampert IA. Prostatic adenocarcinoma evolving into carcinoid: selective effect of hormonal treatment? *J Clin Pathol.* 1986; 39:750–756. [PubMed: 3734111]
43. Burchardt T, et al. Transdifferentiation of prostate cancer cells to a neuroendocrine cell phenotype *in vitro* and *in vivo*. *J Urol.* 1999; 162:1800–1805. [PubMed: 10524938]
44. Scheble VJ, et al. ERG rearrangement is specific to prostate cancer and does not occur in any other common tumour. *Mod Pathol.* 2010; 23:1061–1067. [PubMed: 20473283]
45. Tomlins SA, et al. Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. *Science.* 2005; 310:644–648. [PubMed: 16254181]
46. Lapuk AV, et al. From sequence to molecular pathology, and a mechanism driving the neuroendocrine phenotype in prostate cancer. *J Pathol.* 2012; 227:286–297. [PubMed: 22553170]
47. Hansel DE, et al. Shared TP53 gene mutation in morphologically and phenotypically distinct concurrent primary small cell neuroendocrine carcinoma and adenocarcinoma of the prostate. *Prostate.* 2009; 69:603–609. [PubMed: 19125417]
48. Beltran H, et al. Molecular characterization of neuroendocrine prostate cancer and identification of new drug targets. *Cancer Discov.* 2011; 1:487–495. [PubMed: 22389870]
49. Clegg N, et al. Molecular characterization of prostatic small-cell neuroendocrine carcinoma. *Prostate.* 2003; 55:55–64. [PubMed: 12640661]
50. Tzelepi V, et al. Modeling a lethal prostate cancer variant with small-cell carcinoma features. *Clin Cancer Res.* 2012; 18:666–677. [PubMed: 22156612]
51. Palmgren JS, Karavadia SS, Wakefield MR. Unusual and underappreciated: small cell carcinoma of the prostate. *Semin Oncol.* 2007; 34:22–29. [PubMed: 17270662]
52. Abrahamsson PA. Neuroendocrine cells in tumour growth of the prostate. *Endocr Relat Cancer.* 1999; 6:503–519. [PubMed: 10730904]
53. Alshaikh OM, Al-Mahfouz AA, Al-Hindi H, Mahfouz AB, Alzahrani AS. Unusual cause of ectopic secretion of adrenocorticotrophic hormone: Cushing syndrome attributable to small cell prostate cancer. *Endocr Pract.* 2010; 16:249–254. [PubMed: 20061271]
54. Aparicio AM, et al. Platinum-based chemotherapy for variant castrate-resistant prostate cancer. *Clin Cancer Res.* 2013; 19:3621–3630. [PubMed: 23649003]
55. Flechon A, et al. Phase II study of carboplatin and etoposide in patients with anaplastic progressive metastatic castration-resistant prostate cancer (mCRPC) with or without neuroendocrine differentiation: results of the French Genito-Urinary Tumour Group (GETUG) P01 trial. *Ann Oncol.* 2011; 22:2476–2481. [PubMed: 21436186]
56. Lortot Y, et al. Combining carboplatin and etoposide in docetaxel-pretreated patients with castration-resistant prostate cancer: a prospective study evaluating also neuroendocrine features. *Ann Oncol.* 2009; 20:703–708. [PubMed: 19179557]
57. Culine S, et al. Docetaxel and cisplatin in patients with metastatic androgen independent prostate cancer and circulating neuroendocrine markers. *J Urol.* 2007; 178:844–848. [PubMed: 17631339]
58. McCutcheon IE, Eng DY, Logothetis CJ. Brain metastasis from prostate carcinoma: antemortem recognition and outcome after treatment. *Cancer.* 1999; 86:2301–2311. [PubMed: 10590371]
59. Cussenot O, Villette JM, Cochand-Priollet B, Berthon P. Evaluation and clinical value of neuroendocrine differentiation in human prostatic tumours. *Prostate Suppl.* 1998; 8:43–51. [PubMed: 9690663]
60. Heinrich E, et al. Neuroendocrine tumour cells in prostate cancer: evaluation of the neurosecretory products 5-hydroxytryptamine, bombesin, and gastrin—impact on angiogenesis and clinical follow-up. *Prostate.* 2011; 71:1752–1758. [PubMed: 21480309]
61. Ferrero-Pous M, Hersant AM, Pecking A, Bresard-Leroy M, Pichon MF. Serum chromogranin-A in advanced prostate cancer. *BJU Int.* 2001; 88:790–796. [PubMed: 11890255]

62. Amato RJ, et al. Chemotherapy for small cell carcinoma of prostatic origin. *J Urol*. 1992; 147:935–937. [PubMed: 1311396]
63. Hindson DA, Knight LL, Ocker JM. Small-cell carcinoma of prostate. Transient complete remission with chemotherapy. *Urology*. 1985; 26:182–184. [PubMed: 2992147]
64. Steineck G, et al. Cytotoxic treatment of aggressive prostate tumours with or without neuroendocrine elements. *Acta Oncol*. 2002; 41:668–674. [PubMed: 14651212]
65. Papandreou CN, et al. Results of a phase II study with doxorubicin, etoposide, and cisplatin in patients with fully characterized small-cell carcinoma of the prostate. *J Clin Oncol*. 2002; 20:3072–3080. [PubMed: 12118020]
66. Deorah S, Rao MB, Raman R, Gaitonde K, Donovan JF. Survival of patients with small cell carcinoma of the prostate during 1973–2003: a population-based study. *BJU Int*. 2012; 109:824–830. [PubMed: 21883857]
67. Bolton DM, Chiu ST, Clarke S, Angus D. Primary small cell carcinoma of the prostate: unusual modes of presentation. *Aust N Z J Surg*. 1994; 64:91–94. [PubMed: 7507315]
68. Kim KH, Kim YB, Lee JK, Kim YJ, Jung TY. Pathologic results of radical prostatectomies in patients with simultaneous atypical small acinar proliferation and prostate cancer. *Korean J Urol*. 2010; 51:398–402. [PubMed: 20577606]
69. Sule-Suso J, Brunt AM. Small cell carcinoma of the prostate. *Br J Radiol*. 1992; 65:726–728. [PubMed: 1382791]
70. NCC guidelines Index: Version 2.2013. Prostate Cancer. 2013. [online], http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
71. Auperin A, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med*. 1999; 341:476–484. [PubMed: 10441603]
72. Rubenstein JH, et al. Small cell anaplastic carcinoma of the prostate: seven new cases, review of the literature, and discussion of a therapeutic strategy. *Am J Clin Oncol*. 1997; 20:376–380. [PubMed: 9256893]
73. Moore SR, Reinberg Y, Zhang G. Small cell carcinoma of prostate: effectiveness of hormonal versus chemotherapy. *Urology*. 1992; 39:411–416. [PubMed: 1315995]
74. NCC guidelines Index: Version 2.2013. Adult cancer pain. 2013. [online], http://www.nccn.org/professionals/physician_gls/pdf/pain.pdf
75. Janssen A, Moedema RH. Mitosis as an anti-cancer target. *Oncogene*. 2011; 30:2799–2809. [PubMed: 21339734]
76. Stein ME, et al. Small cell (neuroendocrine) carcinoma of the prostate: aetiology, diagnosis, prognosis, and therapeutic implications—a retrospective study of 30 patients from the rare cancer network. *Am J Med Sci*. 2008; 336:478–488. [PubMed: 19092321]

Box 1**Clinical features of small-cell carcinoma of the prostate**

- Short or no response to ADT
- Marked clinical signs and symptoms associated with large prostatic or large soft-tissue pelvic mass, involvement of visceral sites, or bulky lymphadenopathy
- High prevalence of lytic bone metastases
- Intracranial metastasis (more common than in conventional adenocarcinoma of the prostate)
- Rapidly progressive disease
- Serum PSA level low or undetectable relative to tumour burden
- Paraneoplastic syndrome associated with ectopic production of hormones (parathyroid hormone and adrenocorticotrophic-hormone-like peptides)

Key points

- Small-cell carcinoma (SCC) of the prostate is a rare subtype of prostate cancer characterized by an aggressive clinical course
- Approximately 40–50% of men with prostatic SCCs have a history of conventional prostatic adenocarcinoma
- SCC of the prostate is usually not responsive to androgen deprivation and disease progression is not associated with rises in serum PSA levels
- A biopsy of accessible lesions should be considered when SCC is suspected
- Chemotherapy represents the backbone of management for men with advanced prostatic SCC
- SCC is radiosensitive and radiotherapy might offer local palliation of symptoms such as bladder outlet obstruction and pain

Review criteria

Full-text articles and abstracts were obtained by searching the PubMed and MEDLINE databases. When necessary and relevant, full-text articles were obtained by our institution's librarian. No limits were set based on dates of publications. Search terms included “small cell carcinoma of the prostate”, “neuroendocrine prostate cancer”, “small cell carcinoma of the prostate AND treatment”, “small cell carcinoma of the prostate AND molecular characterization”, “small cell carcinoma of the prostate AND new drugs” and “small cell carcinoma of the prostate AND pathology”. Reference lists of included articles were reviewed for relevant trials.

Figure 1. Morphologic spectrum of prostatic neuroendocrine tumours. **a** | Adenocarcinoma of the prostate with focal neuroendocrine differentiation. **b** | Adenocarcinoma of the prostate with Paneth-cell-like changes. **c** | Primary prostatic carcinoid tumour. **d,e** | Prostatic SCC. **f** | Large-cell neuroendocrine carcinoma of the prostate.

Table 1
Immunohistochemical profile of prostatic neoplasms demonstrating neuroendocrine differentiation

Marker	Conventional prostate cancer with neuroendocrine differentiation	Paneth-cell-like prostate cancer	Carcinoid	SCC of the prostate	Large-cell neuroendocrine prostate cancer
PSA	Positive	Positive (generally weak staining) or negative	Negative	Typically negative; positive in about 20% of cases (typically rare cell types)	Negative
P501s	Positive	Positive (generally weak staining) or negative	Negative	Typically negative; positive in about 20% of cases (typically rare cell types)	Negative
NIKX3.1	Positive	Unknown	Negative	Typically negative; positive in about 20% of cases (typically rare cell types)	Negative
Androgen receptor	Positive	Unknown	Negative	Negative	Negative
Synaptophysin	Positive	Positive	Positive	Positive	Positive
Chromogranin A	Positive	Positive	Positive	Positive	Positive
Ki-67	Low percentage of ki-67-positive cells	Low	Low	80–100% of cells are ki-67-positive	80–100% of cells are ki-67-positive
Bcl2	Positive (rarely) or negative	Unknown	Positive	Positive	Positive
p53	Negative	Unknown	Negative	Positive	Unknown
ERG rearrangement	Positive (in 50% of cells) or negative	Unknown	Unknown	Positive (in 50% of cells) or negative	Unknown
MYC amplification	Positive (in <10% of cells) or negative	Unknown	Unknown	Positive (in 50% of cells) or negative	Unknown
Cytokeratin	Positive	Positive	Positive	Positive (often dot-like) or negative	Positive or negative
TTF1	Negative	Negative	Negative	Positive (in >50% of cells) or negative	Negative

Abbreviation: SCC, small cell carcinoma.

Table 2
Summary of clinical trials for SCC of the prostate

Trial	Study size (n)	Key inclusion criteria	Intervention	Outcome
Aparicio <i>et al.</i> ⁵⁴	113	At least one of the following: * histologically confirmed SCC; visceral metastases only; predominately lytic bone lesions; bulky lymphadenopathy; bulky high-grade prostatic or pelvic mass; low PSA level; neuroendocrine markers on histology or in serum; short interval to developing CRPC	Carboplatin plus docetaxel followed by cisplatin plus etoposide upon progression	PFS CD = 5.1 months (95% CI 4.2–6.0 months); PFS DE = 3.0 months (95% CI 1.6–3.5 months; <i>n</i> = 74); median overall survival = 16 months (95% CI 13.6–19.0 months)
GETUG P01 trial ⁵⁵	60	mCRPC with at least one of the following: visceral metastases (lung, liver, or lymph node involvement) except bone metastases; any elevated neuroendocrine serum marker (CgA or NSE) of 1.5-fold normal value	Carboplatin plus etoposide	Median overall survival = 9.6 months (95% CI 8.7–12.7); PFS = 2.9 months (95% CI 1.7–3.5)
Loriot <i>et al.</i> ⁵⁶	40 (45% with elevated CgA and 34% with elevated NSE)	Progressive CRPC following docetaxel	Carboplatin plus etoposide	Median PFS = 2.1 months (0.6–9.6 months); median overall survival = 19 months (2.1–27.7 months)
Culine <i>et al.</i> ⁵⁷	41	Progressive CRPC with elevated neuroendocrine markers CgA or NSE	Cisplatin plus docetaxel	Median PFS = 8 months (1–19 months); median overall survival = 12 months (1–38 months)
Papandreou <i>et al.</i> ⁶⁵	38	Patients with histologically proven SCC of the prostate; prior chemotherapy (except doxorubicin, etoposide, or cisplatin) allowed	Doxorubicin, etoposide, and cisplatin	Median PFS = 5.8 months; median overall survival = 10.5 months
Steineck <i>et al.</i> ⁶⁴	30	One of the following pathological profiles: prostatic adenocarcinoma without neuroendocrine elements; high-grade prostatic adenocarcinoma with neuroendocrine elements; pure SCC (high-grade neuroendocrine tumour); high-grade carcinoma for which the site of origin could not be assessed on the basis of morphology alone	Cisplatin (or carboplatin), etoposide, and estramustine	Overall survival = 8–941 days

* Men with histologically confirmed SCC were not required to have failed hormone therapy, but all others needed to have experienced progression during ADT or an unsatisfactory response to 1 month of ADT. Abbreviations: ADT, androgen deprivation therapy; CD, carboplatin plus docetaxel; CgA, chromogranin A; CRPC, castration-resistant prostate cancer; DE, cisplatin plus etoposide; mCRPC, metastatic CRPC; NSE, neuron-specific enolase; PFS, progression-free survival; SCC, small-cell carcinoma.