Histol Histopathol (2015) 30: 413-424
DOI: 10.14670/HH-30.413

http://www.hh.um.es

Histology and Histopathology
Cellular and Molecular Biology

Review

Small cell carcinoma of the prostate: Molecular basis and clinical implications

Lisha Wang[1,2], Darrell D. Davidson[3], Rodolfo Montironi[5], Antonio Lopez-Beltran[6], Shaobo Zhang[3], Sean R. Williamson[7], Gregory T. MacLennan[8], Chaofu Wang[1,2], Mingsheng Wang[3], Robert E. Emerson[3], Xiang Du[1,2] and Liang Cheng[3,4]

[1]Department of Pathology, Fudan University Shanghai Cancer Center, Shanghai, China, [2]Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China, [3]Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN, USA, [4]Department of Urology, Indiana University School of Medicine, Indianapolis, IN USA, [5]Institute of Pathological Anatomy and Histopathology, School of Medicine, Polytechnic University of the Marche Region (Ancona), United Hospitals, Ancona, Italy, [6]Department of Pathology, Cordoba University, Cordoba, Spain, [7]Department of Pathology, Henry Ford Health System, Detroit, MI and [8]Department of Pathology, Case Western Reserve University, Cleveland, OH, USA

Summary. Small cell carcinoma of the prostate (PSCC) is a rare and highly aggressive malignancy with a dismal prognosis. Most patients present with advanced disease, including metastases to bone, viscera, and the central nervous system. Histologically, PSCC is indistinguishable from its pulmonary counterpart. Although PSCC may occur in pure form, as in small cell lung carcinoma, it also occurs in conjunction with conventional glandular prostate carcinoma, and may evolve from conventional adenocarcinoma during the course of hormonal therapy. Immunohistochemical staining is extremely helpful in establishing the diagnosis, a prerequisite, as in small cell lung cancer, for optimal therapeutic strategy. Currently, combinations of surgical resection, chemotherapy, and radiation therapy represent the main treatment options. Improvement in survival may depend upon the identification of new molecular markers to facilitate earlier diagnosis and the development of novel targeted therapies. This review will discuss general aspects of PSCC, focusing on ways in which our understanding of PSCC has been advanced by studies of the histopathologic, immunohistochemical and molecular alterations in this disease.

Offprint requests to: Dr. Liang Cheng, Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, 350 West 11th Street, IU Health Pathology Laboratory Room 4010, Indianapolis, IN 46202, USA. e-mail: liang_cheng@yahoo.com; or Dr. Xiang Du, Department of Pathology, Fudan University Shanghai Cancer Center, Shanghai, China. e-mail: dx2008cn@163.com

Key words: Prostatic small cell carcinoma, Androgen receptor, TMPRSS2-ERG rearrangement, Clonal origin, Carcinogenesis, Differential diagnosis, Molecular cytogenetics

Introduction

The first description of small cell carcinoma of the prostate (PSCC) by Wenk et al. in 1977 highlighted paraneoplastic syndromes sometimes associated with the disease (Wenk et al., 1977). PSCC is a rare manifestation of prostate cancer, comprising 0.5-2% of all prostatic carcinomas. About one-half of all patients with PSCC have pure small cell carcinoma at initial presentation. Approximately 25-50% of cases are mixed with a conventional prostatic adenocarcinoma (PCA). Another 25-40% of cases are initially diagnosed as prostatic adenocarcinoma and recur as small cell carcinoma after hormonal therapy (Bostwick and Cheng, 2014). The demographic distribution of nontreatment-related PSCC is similar to that of conventional prostatic adenocarcinoma. Most patients have multifocal disease but also have a dominant nodule located in the peripheral zone. PSCC is a highly aggressive malignancy with metastases to hematogenous sites uncommon for prostate cancer, such as visceral organs, liver, lung, and brain (Anker et al., 2008; Wang and Epstein, 2008; Deorah et al., 2012; Nadal et al., 2014). PSCC often coexists with conventional acinar adenocarcinoma, and shared molecular alterations support the hypothesis that

both forms of prostate cancer have the same clonal origin (Williamson et al., 2011).

The aim of this review is to provide a comprehensive discussion of PSCC, including epidemiology, clinical presentation, pathologic features, putative histogenesis, and updated information regarding immunohistochemistry, molecular genetics, treatment, and prognosis.

Epidemiology

Geographic and ethnic differences in prostate cancer incidence are attributed to diet or environmental influence (Tetu et al., 1987). For example, Asians have the lowest incidence of prostate cancer, while Asian immigrants who have adopted Western-style high fat diets have an increased incidence of the disease approaching that of the white population. The overall risk of developing prostatic small cell carcinoma increases with age, typically occurring in men older than 60 years. The mean age of diagnosis is 65-69 years, similar to conventional prostatic adenocarcinoma. This finding is not surprising, since many patients actually have prostatic adenocarcinoma with a component of small cell carcinoma. A prior history of usual prostatic carcinoma followed by hormonal therapy occurs in a third of PSCC patients (Wang and Epstein, 2008; Humphrey, 2012). The interval between the diagnosis of PSCC and prior prostatic cancer diagnosis ranges from 1 month to 25 years with a median of 25 months (Wang and Epstein, 2008). A morphologic and immunohistochemical study of 95 cases diagnosed at the Johns Hopkins Medical Institutions showed that the mean age at diagnosis is 69 years, ranging from 44 to 92 years (Wang and Epstein, 2008). Wang et al. reported a series of 61 patients with a mean age at PSCC diagnosis of 73.5 years, ranging from 43 to 90 years (Epstein et al., 2014; Wang et al., 2014).

Clinical features

The clinical features of PSCC and those of prostatic acinar adenocarcinoma differ significantly. Distinctive clinical features of PSCC include a lower frequency of elevated serum PSA at diagnosis, despite large primary tumors and metastatic disease in many cases (Bostwick and Cheng, 2014). There is a propensity for rapid and widespread hematogenous metastasis, poor response to androgen deprivation therapy and short survival (Papandreou et al., 2002). An intriguing and important feature of PSCC is that it is often encountered in patients with metastatic conventional prostatic acinar adenocarcinoma treated with hormonal therapy.

Most patients diagnosed with PSCC are symptomatic. Obstructive voiding symptoms are the most common presenting symptom. Additional local symptoms include abdominal or pelvic pain, gross hematuria, rectal bleeding or bowel obstruction due to an enlarging pelvic mass (Palmgren et al., 2007). Symptoms from metastatic disease are common at the time of diagnosis. Unlike conventional PCA, bone metastases are usually lytic rather than sclerotic. Spinal cord compression and other neurologic complications are relatively frequent findings (Terada, 2012). Systemic symptoms include anorexia, weight loss, fever, and fatigue. Occasionally, patients have paraneoplastic syndromes. Cushing syndrome appears to be the most common due to ectopic adrenocorticotropic hormone production. Others paraneoplastic syndromes include hypocalcaemia, peripheral neuropathy, and hyperglucagonemia (Wenk et al., 1977).

Pathologic findings

Grossly, the prostate is extensively involved, sometimes with complete replacement by tumor. At autopsy, cut surfaces are grey-whitish and nodular with extraprostatic extension into seminal vesicles, periprostatic soft tissue and the bladder. Histologically, PSCC is identical to its lung counterpart (Brambilla et al., 2001). The tumor consists of sheets or nests of small or intermediate cells with nuclear molding, scant cytoplasm, inconspicuous nucleoli, and evenly dispersed "salt-and-pepper chromatin." Mitotic activity is brisk. Crush artifact is frequently seen, which can make diagnosis difficult in biopsy specimens. Punctate or geographic necrosis is common. Occasionally, tumor rosettes are present. Gleason grading does not apply to PSCC (Bostwick and Cheng, 2014).

The acinar adenocarcinoma component in mixed PSCC and adenocarcinoma is variable in both extent and grade. In the study by Wang, pure small cell carcinoma was seen in 57% (54/95) of cases with PSCC admixed with usual PCA in remaining cases (Wang and Epstein, 2008). In mixed cases with adenocarcinoma, 20.5% had a sharp demarcation between PSCC and usual PCA. In the other cases, there was a gradual merging together of the 2 components, reflecting the aggressively invasive behavior of PSCC. The Gleason score of the admixed adenocarcinoma ranged from 4 to 10 in these cases, but was typically 8 or higher (85%). Similarly, a multi-institutional study of 54 cases by Schelling et al. found 64.8% were pure PSCC and 19 cases (35.2%) consisted of PSCC admixed with conventional PCA (Schelling et al., 2013). In a series of 22 cases, Lotan et al. reported that mixed PSCC and adenocarcinoma was present in 6 patients (27%) on the tissue microarray (Lotan et al., 2011). In this series 66% (4/6) cases had a Gleason score of ≥9 in the acinar component, whereas 33% (2/6) cases had a Gleason score of 7-8. Rare examples of PSCC admixed with malignant cells other than adenocarcinoma include coexistence with Paneth cell-like change, squamous cells and a spindle cell sarcomatoid pattern (Humphrey, 2012).

Histogenesis

The origin of PSCC has not been fully established.

Several hypotheses have been proposed to explain the histogenesis (Williamson et al., 2011; Schelling et al., 2013). One theory is that PSCC is the product of a final dedifferentiation of an adenocarcinoma cell population according to the model of divergent differentiation. This is supported by the observation that small cell carcinoma frequently coexists with adenocarcinoma. PSCC often develops within castration resistant prostate cancer. This suggests a selective pressure induced by reduced androgen level blocking the usual signal transduction pathway causing the tumor to upregulate alternate pathways (Hirano et al., 2004). Beltran et al. speculated that with potent novel AR targeting drugs, the incidence of PSCC may increase (Beltran et al., 2011).

Seeking answers to the question of coexisting PSCC and PCA origin, Williamson et al. found that *TMPRSS2-ERG* rearrangement is shared by both the PCA and PSCC components, indicating a monoclonal origin (Williamson et al., 2011). This could indicate that PSCC and adenocarcinoma differentiation patterns may arise from a tumor clone with stem-like properties that gives rise to distinct histologic components. Furthermore, Hansel et al. demonstrated that both the PCA and PSCC components share the same *TP53* mutation, again providing evidence that both derive from a single parent clone (Hansel et al., 2009). Another theory is that small cell carcinoma originates from the neural crest amine precursor uptake and decarboxylase cell system, now called the neuroendocrine system. The cell of origin for PSCC may be neuroendocrine cells of either benign prostate or PCA, likely the latter (Li et al., 2013). This variant of the stem cell selection theory could be considered the progenitor cell selection theory. A wide variety of secretory products are detected within the PSCC, including chromogranin, synaptophysin, neuron-specific enolase (NSE) and other neuroendocrine cell products. PSCC also expresses many genes (*ASCL1, INA,* and *SV2B*) that reflect characteristics of a neuroendocrine cell origin (Clegg et al., 2003).

A third theory postulates a pure pluripotent stem cell phenotype PSCC, based on the absence of the usual prostatic epithelial cell antigens (PSA expression), coupled with the exceedingly high proliferation rate (Ro et al., 1987). Ki67 indices for PSCC are typically greater than those of dedifferentiated adenocarcinoma (Helpap et al., 1999; Mehra et al., 2007). The strong and diffuse expression of CD44 in PSCC (a putative marker of prostate cancer stem/progenitor cells) also suggested that the tumor cells may retain cancer stem cell features (Simon et al., 2009).

Pathogenesis

There is still much to learn about the molecular pathogenesis of PSCC. A number of studies have suggested that loss of both *RB1* and *TP53* tumor suppressors is critical for neuroendocrine carcinoma development in various organ systems (Nikitin et al., 1999; Peifer et al., 2012). Tan et al. reported that loss of *RB1* by deletion is a common event in PSCC, similar to small cell carcinoma of the lung (Tan et al., 2014). Chen et al. found that *TP53* mutation inactivates the IL8-CXCR2 pathway, leading to increased proliferation and invasive biological behavior of neuroendocrine tumor cells of PSCC in response to chemokine release from stromal macrophages and endothelial cells (Chen et al., 2012).

The genetic changes specific to prostatic small cell carcinoma are not well characterized. The molecular features of PSCC are similar to those of PCA but with additional genetic alterations making these tumors androgen independent and more aggressive than PCA. This evolution of malevolent traits is particularly true in tumors that are recurrent after hormonal treatment for conventional PCA (Tanaka et al., 2001).

PSCC has higher expression of AURKA and MYCN than PCA. Overexpression of either AURKA or MYCN in prostate cancer cell lines accompanies induction of neuroendocrine marker expression (Beltran et al., 2011). Mosquera et al. studied primary prostate tissue from 15 hormone naive PCAs, 51 castration-resistant prostate cancers, and 15 metastatic tumors from 72 patients at different stages of disease progression to neuroendocrine/small cell phenotype. *AURKA* amplification was identified in 65% of all PCAs (hormone naive and treated) from patients that developed neuroendocrine phenotype and in 86% of metastatic PCA. Concurrent amplification of *MYCN* was present in 70% of primary PCAs, 69% of treated PCAs, and 83% of metastases. In contrast, for an unselected PCA cohort, *AURKA* and *MYCN* amplifications were identified in only 5% of 169 cases (Mosquera et al., 2013). When metastatic small cell carcinoma was compared to primary PCA from the same patients, there was 100% concordance of *ERG* rearrangement, 100% concordance of *AURKA* amplification, and 60% concordance of *MYCN* amplification. In tumors with mixed features, there was also 100% concordance of *ERG* rearrangement and 94% concordance of *AURKA* and *MYCN* coamplification between areas of small cell carcinoma and adenocarcinoma (Mosquera et al., 2013).

AURKA is a serine/threonine kinase with oncogenic properties involved in mitotic spindle formation, centrosome separation, and the cell cycle G2-M transition (Zhou et al., 1998). In human neuroblastoma models, AURKA interacts with and stabilizes the oncogene MYCN (Otto et al., 2009). Beltran and colleagues identified AURKA and *MYCN* over-expression and coamplification in PSCC, although the genes are located on separate chromosomes (2p24 and 20q13, respectively) (Aparicio et al., 2011; Beltran et al., 2011). This is evidence that they functionally cooperate to induce a neuroendocrine phenotype in PSCC. Tzelepi et al. in xenograft models found high expression of the M phase gene *UBE2C* and *RB* gene with loss of cyclin D1 and absence of AR expression in PSCC (Tzelepi et al., 2012). Amplification of the *UBE2C* locus and microdeletions of *RB1* were present in a subset of

patients. These observations suggest that loss of RB and cyclin D1 precede AR loss and deregulation of mitotic controls (Tzelepi et al., 2012).

Small cell carcinoma could arise from adenocarcinoma after additional genetic alterations (Cheng and Eble, 2013; Cheng et al., 2013). Recently, loss of RB protein expression was demonstrated in PSCC (85%, 11/13) (Tan et al., 2014). High-grade conventional PCA does not typically harbor this genetic abnormality (7%; 10/150), which may indicate a genetic breakpoint for the divergence of PCA and PSCC (Tan et al., 2014).

Between 45% and 47% of PSCC cases harbor ERG gene rearrangement, a rate similar to that of PCA (Williamson et al., 2011). Among patients with coexisting small cell and conventional carcinoma, the majority of cases show concordant ERG gene rearrangement in both components (Lotan et al., 2011). These findings strongly suggest a common pathway for genesis of conventional acinar carcinoma mixed with PSCC. Thus in many cases PSCC and PCA share not only a common cell of origin but also a common oncogenic pathway.

Another significant finding came from the discovery by Lapuk et al. that RE1-silencing transcription factor (REST) downregulation is associated with the neuroendocrine phenotype in prostate cancers (Lapuk et al., 2012). Downregulation of *REST*, which encodes a transcription factor crucial to the repression of neuronal differentiation, and the consequent upregulation of the neuronal phenotype is characteristic of PSCC and mixed PSCC-PCA (Lapuk et al., 2012). In LNCaP cells, REST depletion resulted in upregulation of several neuroendocrine markers (Lapuk et al., 2012). Another study confirmed these findings and revealed novel molecular pathways linking the androgen/AR axis, REST and neuroendocrine differentiation (Svensson et al., 2014). In 2005, Tomlins et al. uncovered a recurrent gene fusion in 40-60% of prostate cancers, making it one of the most common rearrangements in any type of human cancer (Tomlins et al., 2005). This rearrangement occurs between the 5' untranslated region of the androgen-regulated gene TMPRSS2 (21q22.3) and the highly conserved 3' DNA binding domain of an ETS transcription factor family member, most commonly ERG (21q22.2) (Tomlins et al., 2005; Mehra et al., 2007). PSCC also harbors this gene fusion at a rate similar to PCA, ranging from 45% to 86% (Han et al., 2009; Guo et al., 2011; Lotan et al., 2011; Williamson et al., 2011). Our previous studies have demonstrated that TMPRSS2-ERG rearrangement is often shared by both components of mixed PCA and PSCC, supporting the idea that both of these populations derive from the same original clone. The absence of ERG rearrangement in bladder or lung small cell carcinomas highlights the value of screening for ERG rearrangement in small cell carcinomas of unknown primary (Lotan et al., 2011). The clinicopathological significance of this genetic rearrangement warrants further study.

Androgen receptor (AR) is a cytosolic steroid hormone receptor that binds androgens, dimerizes and activates nuclear hormone receptor elements in target tissues (Ryan and Tindall, 2011). During recent years, evidence has accumulated that AR plays a central role in the development and progression of prostate cancer. Expression of AR is detected both in androgen sensitive and in androgen deprivation therapy refractory prostate cancers (Feldman and Feldman, 2001; Heinlein and Chang, 2004). Scheble et al. found AR detectable by immunohistochemistry in 7 of 15 PSCCs (47%) (Scheble et al., 2010). We also identified AR protein expression in 23/61 (38%) PSCCs (Wang et al., 2014). In a study of neuroendocrine prostate cancers by Beltran et al. (2011), however, the neuroendocrine component uniformly lacked expression of AR. *AR* gene amplification is found in about one-third of prostate carcinomas that recur during androgen deprivation therapy, but not found in any untreated prostate tumors. This dichotomy suggests that AR gene amplification is involved in the failure of androgen deprivation therapy (Linja et al., 2001). Our previous study demonstrated that high *AR* gene copy number emerges during the development of PSCC, often in association with *TMPRSS2-ERG* rearrangement (Wang et al., 2014). The mechanism underlying these interactions warrants further study.

Immunohistochemical features

Although PSCC rarely presents a diagnostic difficulty, other malignancies such as Gleason pattern 5 high-grade prostate adenocarcinoma, malignant lymphoma and poorly differentiated squamous cell carcinoma occasionally must be considered in the differential diagnosis. Immunohistochemical studies are extremely helpful for confirming the diagnosis in some cases. However, there is no single marker consistently expressed in PSCC. For diagnostic purposes, a panel of several markers is necessary in borderline cases (Table 1). Tan et al. found retinoblastoma protein loss in 90% of PSCC cases (26/29) in contrast to 7% of primary high-grade prostate adenocarcinoma (10/150) (Tan et al., 2014).

Ten cases of high-grade prostate adenocarcinoma served as controls in a study by Yao et al. to evaluate the usefulness of immunohistochemical stains to differentiate PSCC from high-grade prostate adenocarcinoma (Yao et al., 2006). PSA was positive in only 17% of PSCC and some neuroendocrine markers were expressed in up to 40% of high-grade prostate adenocarcinoma. Yet some helpful markers for differentiating between PSCC and high-grade prostate adenocarcinoma were PSA, TTF1 and CD56 ($P<0.01$). Expression of other markers, including bombesin/GRP, KIT, BCL2, and EGFR, was more frequent in PSCC than in high-grade prostate adenocarcinoma, but not significantly. Nevertheless, these markers, including bombesin/GRP, KIT, BCL2, and EGFR, may indicate

potential therapeutic targets identifiable immunohistochemically in PSCC. PSCC is best diagnosed by following the World Health Organization diagnostic criteria for small cell lung carcinoma. However, immunohistochemical markers may help separate PSCC from high-grade prostate adenocarcinoma in histologically borderline cases.

PSCC typically exhibits both neuroendocrine and epithelial markers that have been helpful for confirming neuroendocrine differentiation in small cell lung carcinoma. These include chromogranin, synaptophysin, NSE, somatostatin, calcitonin and keratin cocktails (Ro et al., 1987; Yao et al., 2006). Wang et al. showed expression in PSCC of chromogranin, synaptophysin and NSE in 75% (33/44), 84% (27/32), and 85% (17/20), respectively (Wang and Epstein, 2008). Yao et al. demonstrated that PSCC was positive for chromogranin in 61% (11/18) and for synaptophysin in 89% (16/18) of cases (Yao et al., 2006). Negative stains for neuroendocrine markers should not exclude the diagnosis of small cell carcinoma as long as the morphology on routinely stained sections is diagnostic. Conversely, focal immunohistochemical evidence of neuroendocrine differentiation can be seen in an up to 100% of usual PCA and does not indicate PSCC (di Sant'Agnese, 1992). The expression of markers characteristic of the prostate is seen in a minority of PSCC, albeit mostly in a focal manner.

Four studies by independent groups have analyzed *ERG* rearrangement as a marker for PSCC, which may be histologically indistinguishable from small cell carcinomas of other sites (Scheble et al., 2010; Guo et al., 2011; Lotan et al., 2011; Williamson et al., 2011). All four studies found *ERG* rearrangements detected by FISH exclusively in PSCC (range 45-86%) but not in small cell carcinoma of other sites including bladder and lung. In comparison to markers previously proposed to differentiate between PSCC and small cell carcinoma of other organs, ERG clearly outperforms these. Other recommended markers include prostate specific antigen (PSA) and prostein, which were found in only 28% or fewer PSCC cases (Wang and Epstein, 2008). Using ERG to determine a prostatic origin of small cell carcinoma appears to be the best validated contribution of ERG rearrangement detection to prostate diagnostics.

Wang et al. showed expression of PSA, prostein (SLC45A3 gene product or P501S), and prostate-specific membrane antigen (PSMA) in 19% (14/73), 28% (17/61), and 25% (15/59) of PSCC cases, respectively (Wang and Epstein, 2008). P501S and PSMA were better in identifying the prostatic origin of small cell carcinoma than PSA (Wang and Epstein, 2008). Cytokeratin profiles using cytokeratin 7, cytokeratin 20, and cytokeratin AE1/AE3 were similar in PSCC and prostate carcinoma. There was, however, a perinuclear cytoplasmic dot-like pattern of keratin staining in PSCC, which was most marked with CAM5.2 (Yao et al., 2006).

PSCC also expresses markers common to small cell carcinoma of other sites, such as TTF1. Thyroid transcription factor 1 (TTF1) is a nuclear homeodomain transcription factor, upregulated in small cell carcinoma of the lung but also immunohistochemically positive for extrapulmonary sites (Agoff et al., 2000; Wang et al., 2007). TTF1 has been variably reported to be expressed in PSCC (Agoff et al., 2000; Yao et al., 2006). Yao et al. showed that 15 out of 18 (83%) PSCC cases had positive TTF1 staining (Yao et al., 2006). Wang et al. reported 23 out of 44 cases (52.3%) with positive TTF1 staining (Wang and Epstein, 2008). These findings indicate that TTF1 immunostaining is not reliable for distinguishing primary PSCC from metastatic small cell carcinoma originating elsewhere. When TTF1 is positive in metastatic small cell carcinoma of unknown primary origin, the prostate should be considered as a possible origin.

Traditionally, all small cell carcinomas, regardless of organ of origin, have been considered identical in morphology and immunohistochemical profile, thus possibly possessing similar genetic alterations. However, CD44, a putative cell surface marker for normal and cancerous stem cells in multiple organs, including the prostate, is expressed in PSCC but infrequently expressed in small cell carcinoma of other organs.

Table 1. Summarized immunohistochemical markers in prostate small cell carcinoma and high grade prostate adenocarcinoma.

IHC	PSCC (% Positive)	HGPCA (% Positive)
AR	17	90
CD44	90	0
CD56	83	0
Chromogranin	61	0
Cytokeratin AE1/3	94	70
ERG	65	60
GRP	88	10
HMW cytokeratin	35	0
KIT	94	30
P53	24	<5
P63	40	15
PSA	17	100
PSAP	24	100
PSMA	-/+	90
RB loss	90	7
Synaptophysin	89	40
TTF1	83	0

-: negative; +: positive; IHC: immunohistochemistry; PSCC: prostate small cell carcinoma; HGPCA: high grade prostate adenocarcinoma.

Predictive markers and therapeutic targets

PSCC is a highly aggressive neoplasm. A number of investigators have evaluated the usefulness of various immunomarkers for predicting its prognosis (Cheng and Eble, 2013; Cheng et al., 2013). p53 protein, encoded by *TP53* tumor suppressor gene, is a key regulator of the cell cycle, cell growth and proliferation. Positive nuclear staining for p53 is a surrogate marker for p53 mutation

because the abnormal protein coded by mutant *TP53* is more stable, has a longer half-life and subsequently accumulates in affected cells more than wild-type *TP53*. Hansel et al. showed strong p53 staining in both the adenocarcinoma and small cell carcinoma components of mixed tumors, suggesting a p53 mutation in both (Hansel et al., 2009). Similarly, Li and colleagues found strong and diffuse p53 expression in the majority of 31 PSCC cases (Li et al., 2013). These investigators suggest that p53 mutation is an essential step in the development of such tumors. Numerous studies have shown that p53 expression is associated with high grade, high stage and poor prognosis in a variety of malignancies (Linderholm et al., 2001; Li et al., 2012). However, no correlation between p53 expression and prognosis has been demonstrated in studies of PSCC, possibly because of the poor overall survival and high prevalence of p53 mutation for this neoplasm.

CD44, a transmembrane glycoprotein, mediates cell-cell and cell-matrix adhesion, the latter by serving as a receptor for hyaluronate binding (Wang et al., 2007). A study by Simon et al. comparing the immunoreactivity of PSCC, PCA, and small cell neuroendocrine carcinoma of other organs found CD44 to be strongly and diffusely expressed in 100% of the PSCC cases (Simon et al., 2009). In conventional PCA, positive staining was seen only in rare scattered tumor cells. CD44 staining was negative in most small cell neuroendocrine carcinomas of nonprostate origin. Basal cell markers p63 and high molecular weight cytokeratin

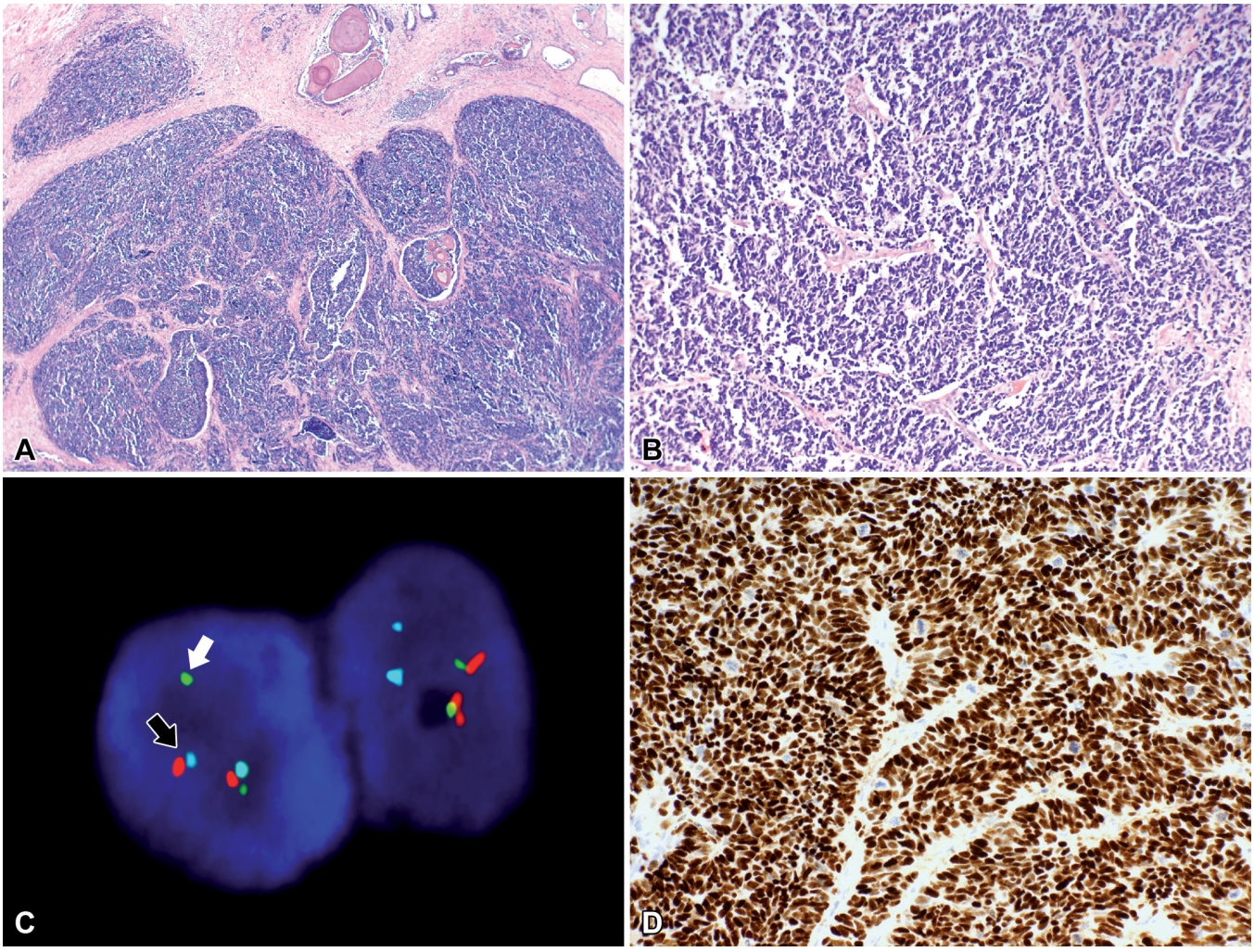

Fig.1. Prostatic small cell carcinoma. **A, B.** Typical prostatic small cell carcinoma was composed of closely packed tumor cells, arranged in cords, nests, or sheets, with nuclei demonstrating hyperchromasia, molding, speckled chromatin, small punctate nucleoli, brisk mitotic activity, and numerous apoptotic cells. **C.** TMPRSS2-ERG rearrangement was evident in approximately half of prostatic small cell carcinomas, as demonstrated by the green signal (ERG 5', white arrow) separated or split from the red-aqua signal pair (TMPRSS2-ERG fusion, black arrow). **D.** Strong immunohistochemical expression of androgen receptor was seen.

were expressed in one-third of PSCC cases studied by Yao et al. but these markers were almost invariably negative in PCA (Yao et al., 2006). These data suggest that tumor cells in PSCC possess features of cancer stem cells, which may explain why such tumors are extremely aggressive and unresponsive to hormonal therapy (Wood et al., 2013).

Many innovative therapeutic approaches are being developed for small cell lung carcinoma. These include inhibitors of membrane receptor tyrosine kinases such as KIT (Gleevec), immunoconjugate targeting of the membrane glycoprotein CD56 neural cell adhesion molecule, recombinant humanized monoclonal antibody to VEGF (Bevacizumab) and gastrin releasing peptide (GRP) receptor antagonists (Chua et al., 2004; Murray et al., 2004; Wakelee and Kelly, 2004; Joshi et al., 2013). Success with these agents against small cell lung carcinoma and pediatric neuroblastoma has encouraged investigators to evaluate their potential therapeutic benefit of targeted therapy for PSCC as well.

Protooncogene *KIT* (CD117) and platelet-derived growth factor receptor, alpha peptide (PDGFRA), both map to 4q12. Both molecules are also transmembranous oncoproteins particularly instrumental in gastrointestinal stromal tumor tumorigenesis (Joensuu et al., 2013; Corless, 2014). Terada et al. investigated KIT and PDGFRA expression in PSCC, and found that 3 of 4 cases were immunoreactive to both KIT and PDGFRA, and one case did not express either (Terada, 2012). Positive KIT immunostaining was observed in 94% of

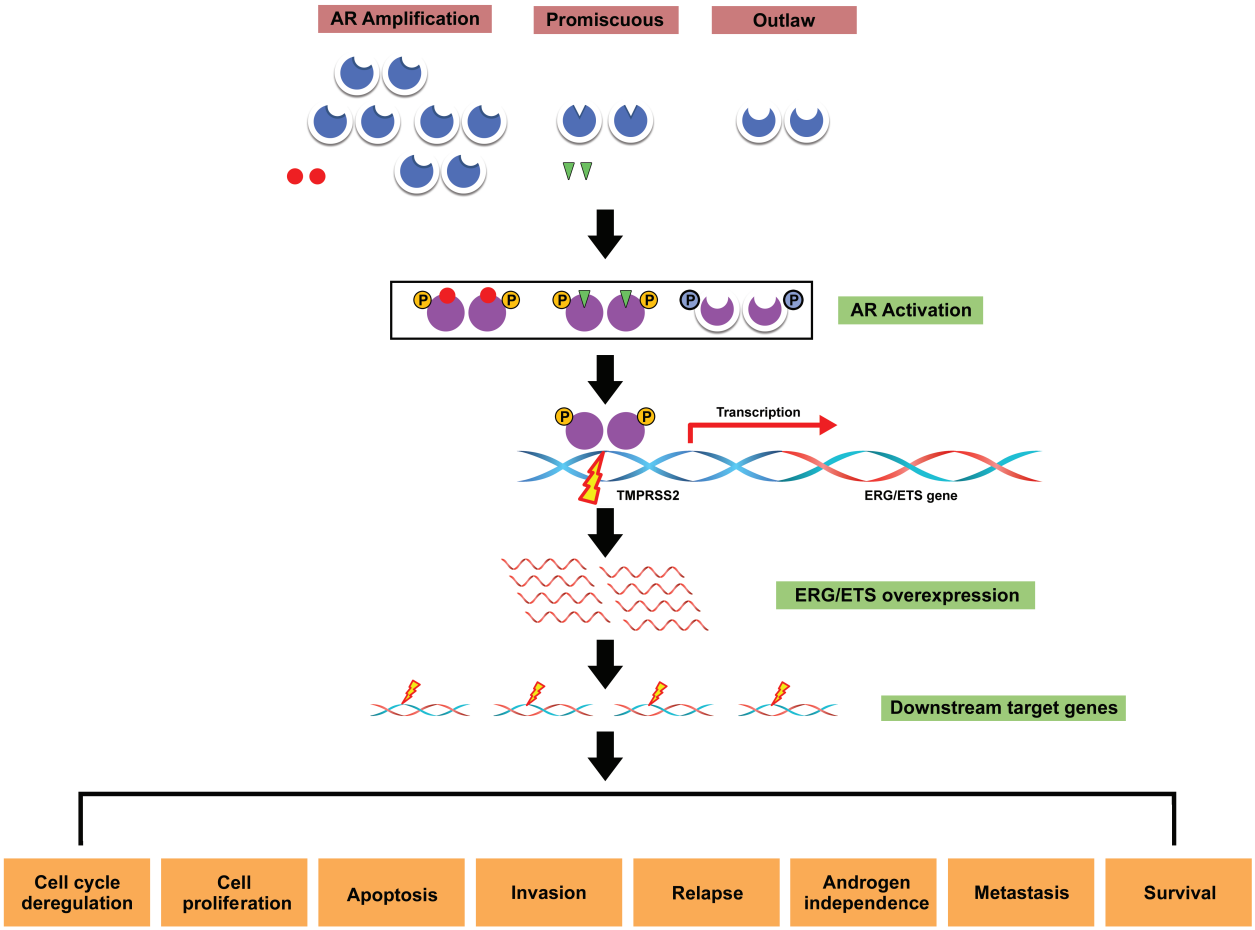

Fig. 2. AR hyper-activation is an important mechanism in the development of androgen deprivation refractory of prostate cancer. Activation of AR may be achieved through different molecular pathways: AR gene amplification, which generating a greater number of androgen receptor product; AR mutations that broaden the ligand specificity of AR (Promiscuous), rendering AR responsive to nonandrogen ligands; or AR phosphorylation through receptor tyrosine kinases (Outlaw), resulting in AR activation without ligand. Activated AR could further activate androgen responsive genes by binding to androgen responsive elements (ARE) in the promoter region to initiate transcription. In prostate cancer with TMPRSS2 fusion to ETS family partners, such as ERG, the binding of AR to TMPRSS2 ARE elements results in upregulation of ERG or other ETS genes. The overexpression of ERG can further exert its effects by binding to purine-rich sequences of target genes, resulting in activation or inhibition and thus generating a neoplastic phenotype and androgen refractory status.

cases (17/18) of PSCC by Yao et al., again suggesting that KIT may be a worthwhile therapeutic target in a subset of patients with PSCC (Yao et al., 2006).

Yao et al. found CD56 expression in 15 of 18 cases of PSCC, and Wang et al. found expression of CD56 in 92% (12/13) of cases (Yao et al., 2006; Wang and Epstein, 2008). Yao et al. also demonstrated EGFR overexpression in 73% (8/11) of cases (Yao et al., 2006). GRP is a member of the bombesin-like peptide family, the most commonly secreted neuropeptide in small cell lung carcinoma (Wakelee and Kelly, 2004). GRP expression was found in 88% (14/16), and BCL2 in 100% (18/18) of cases (Yao et al., 2006). These findings raise hopes that novel targeted therapy for small cell carcinoma of other organs may be also beneficial for treatment of PSCC.

Differential diagnosis

PSCC must be distinguished from other prostate malignancies, such as Gleason pattern 5 high grade adenocarcinoma, malignant lymphoma, large cell neuroendocrine carcinoma, poorly differentiated squamous cell carcinoma, and small cell carcinoma metastatic to the prostate from another organ. Ancillary techniques, particularly immunohistochemical staining, are helpful in distinguishing these neoplasms (Bostwick and Cheng, 2014).

Tumors classified as Gleason pattern 5 high-grade prostate adenocarcinoma can exhibit a solid or single cell pattern of growth with no evidence of gland formation, or large cribriform architecture with comedonecrosis (Bostwick and Cheng, 2014). These features may mimic PSCC but the distinction of high-grade prostate adenocarcinoma from PSCC is usually facilitated by adherence to strict histologic criteria for PSCC, especially nuclear features. The immunohistochemical profile of PSCC is quite different from that of high-grade prostate adenocarcinoma. Yao et al. recommended a panel of markers consisting of PSA, TTF1 and CD56 as the most helpful for differentiating borderline cases (Yao et al., 2006). Other markers, including bombesin/GRP, KIT, BCL2, and EGFR are more frequently expressed in PSCC than high-grade prostate adenocarcinoma (Yao et al., 2006). Simon et al. found that CD44 expression was tissue/organ specific for PSCC, and rarely seen in PCA (Simon et al., 2009). This stem cell marker was also negative in most small cell carcinomas of nonprostate origin.

Small cell carcinoma can occasionally mimic malignant lymphoma when the tumor cells of small cell carcinoma seem to grow in a discohesive pattern, a finding that may result from artifacts produced by fixation and specimen processing. Lymphoma shows positive immunostaining for leukocyte common antigen, and negative immunostaining for keratin and neuroendocrine markers, which typically are positive in small cell carcinoma.

A more recently recognized entity in the prostate that enters into the differential diagnosis of PSCC is large cell neuroendocrine carcinoma. The tumor cells of large cell neuroendocrine carcinoma are generally large and polygonal with moderate to abundant cytoplasm, coarsely granular nuclear chromatin and prominent nucleoli (Evans et al., 2006; Hiroshima et al., 2006). The tumor is often composed of solid sheets, ribbons, and nests of cells with areas of peripheral palisading (Bostwick and Cheng, 2014). Poorly differentiated squamous cell carcinoma may have scant cytoplasm, but does not express neuroendocrine markers such as synaptophysin or chromogranin.

Small cell carcinoma metastatic to the prostate is difficult to differentiate from primary prostate tumors without appropriate clinical information. As reviewed in the immunohistochemistry section, TTF1 is essentially of no value in distinguishing pulmonary from extrapulmonary small cell carcinoma (Jones et al., 2005), though TTF1 may be useful to distinguish PSCC from high grade (Gleason pattern 5) prostatic adenocarcinoma . Expression of organ-specific markers such as lung surfactant protein, PSA and PAP may be helpful, if present, but appropriate clinical information is the best arbiter between PSCC and metastatic small cell carcinoma in the prostate. Bezerra et al. demonstrated GATA3 expression in 30% (7/22) of bladder small cell carcinoma cases and absence in all 33 PSCCs, suggesting that GATA3 was of some value for differentiating PSCC from small cell carcinoma of urothelium (Bezerra et al., 2014). It is notable, however, that fluorescence in situ hybridization (FISH) analyses have demonstrated that TMPRSS2-ERG rearrangements are found in PSCC only, and not in small cell carcinoma from the urinary bladder or lung (Williamson et al., 2011; Cheng et al., 2012, Schelling et al., 2013).

Staging, treatment and outcome

The outcome for patients with PSCC is discouraging, with a median average survival of 5-17.5 months (Oesterling et al., 1992; Deorah et al., 2012; Bostwick and Cheng, 2014). In a retrospective review of the literature, Mackey et al. reported 60 cases of PSCC in which patient age, histological features and stage did not influence prognosis (Mackey et al., 1998). Primary surgical therapy was the only parameter that predicted survival on univariate analysis but not on multivariate analysis. Deorah et al., on the other hand, studied 241 cases of PSCC and found that age at diagnosis and disease stage significantly affected the prognosis both on univariate analysis and on multivariate analysis (Deorah et al., 2012). Survival was progressively worse for older individuals and those with metastatic disease. Spiess et al., in their study of 83 patients, found that low albumin and high lactate dehydrogenase (LDH) at the time of diagnosis were associated with poor prognosis (Spiess et al., 2007). The median disease-specific survival of patients in this series with nonmetastatic PSCC was 17.1 months versus 12.5 months for those with metastatic

PSCC.

Primary PSCC may occur either in pure form or admixed with PCA. In the study by Deorah et al., survival of pure PSCC and of PSCC admixed with undifferentiated adenocarcinoma were not significantly different (Deorah et al., 2012). This finding, however, could be in part due to misclassification of some cases in this tumor registry based study. Nevertheless, Oesterling et al. also found no significant survival difference between pure PSCC and mixed histology containing PSCC (17.1 months vs 22.6 months) (Oesterling et al., 1992). However, the population study by Deorah et al. did show survival curves in which the prognosis was better when there was concomitant well- or moderately differentiated (Gleason 4-7) adenocarcinoma as opposed to concomitant poorly differentiated (Gleason ≥8) adenocarcinoma (Deorah et al., 2012). The most adverse survival curves were for pure PSCC and undifferentiated PCA.

The optimal treatment strategy for PSCC has not yet been defined, in part due to the rarity of this disease and in part due to its highly aggressive phenotype irrespective of the treatments previously used (Spiess et al., 2007). Local treatments can be directed to palliation of pelvic pain and urinary obstruction in the setting of advanced disease. There are reports of local therapy being curative in some cases of localized disease. Deorah et al. found that patients who underwent local control in the form of radical prostatectomy or radiation therapy survived longer than those who did not (Deorah et al., 2012). However, once adjusted for other covariates, local control no longer affected survival. Another approach has been to adapt the treatment paradigms for small cell lung carcinoma and to evaluate chemoradiation as a treatment option in clinical trials (Psyrri and Murren, 2001; Asmis et al., 2006; Deorah et al., 2012). For chemotherapy, a minimum of four cycles of carboplatin and docetaxel or etoposide and cisplatin are recommended (Aparicio et al., 2013). There may be an initial response to platinum-based chemotherapy and radiotherapy, but the outcome is not markedly improved with this therapy. Addition of doxorubicin to the etoposide and cisplatin regimen caused higher toxicity and failed to improve outcomes in a phase II study by Papandreou et al. (2002). The role of hormonal therapy in PSCC remains controversial (Yashi et al., 2006). Although some modern series have managed PSCC with a combination of androgen deprivation therapy and cisplatin-based neoadjuvant treatment followed by consolidative surgery or radiotherapy, most patients in these cohorts tend to progress rapidly (Fine, 2012). Improvement in therapy is likely to come from improved understanding of PSCC biology progression and integrating new targeted therapies into the treatment armamentarium.

As discussed in the section of immunohistochemistry, the recent observation of KIT, CD56, and BCL2 expression in more than 90% of patients, and expression of EGFR and GRP in more than 70% of patients with PSCC opens up new possibilities for the use of immunotherapy to manage this aggressive and deadly malignancy (Yao et al., 2006; Wang and Epstein, 2008). Further studies are needed to evaluate clearly potential clinical uses of these agents for treatment of PSCC.

Conclusions

PSCC is a rare type of prostate cancer with a poor prognosis. The histologic morphology of PSCC is indistinguishable from small cell carcinoma of the lung or other sites. The tumor cells express the usual neuroendocrine markers (chromogranin, synaptophysin, and NSE), as well as small cell carcinoma markers (TTF1, CD56) and prostate stem cell marker (CD44). Distinction of PSCC from other diseases is important because of prognostic and therapeutic implications. Local control for limited stage disease or combination chemotherapy using agents for small cell carcinoma of the lung in advanced disease can prolong life but not cure patients with PSCC. Improvement in survival may depend on the identification of new molecular markers for early diagnosis and for the development of novel targeted therapies.

References

Agoff S.N., Lamps L.W., Philip A.T., Amin M.B., Schmidt R.A., True L.D. and Folpe A.L. (2000). Thyroid transcription factor-1 is expressed in extrapulmonary small cell carcinomas but not in other extrapulmonary neuroendocrine tumors. Mod. Pathol. 13, 238-242.

Anker C.J., Dechet C., Isaac J.C., Akerley W. and Shrieve D.C. (2008). Small-cell carcinoma of the prostate. J. Clin. Oncol. 26, 1168-1171.

Aparicio A., Logothetis C.J. and Maity S.N. (2011). Understanding the lethal variant of prostate cancer: power of examining extremes. Cancer Discov. 1, 466-468.

Aparicio A.M., Harzstark A.L., Corn P.G., Wen S., Araujo J.C., Tu S.M., Pagliaro L.C., Kim J., Millikan R.E., Ryan C., Tannir N.M., Zurita A.J., Mathew P., Arap W., Troncoso P., Thall P.F. and Logothetis C.J. (2013). Platinum-based chemotherapy for variant castrate-resistant prostate cancer. Clin. Cancer Res. 19, 3621-3630.

Asmis T.R., Reaume M.N., Dahrouge S. and Malone S. (2006). Genitourinary small cell carcinoma: a retrospective review of treatment and survival patterns at The Ottawa Hospital Regional Cancer Center. BJU Int. 97, 711-715.

Beltran H., Rickman D.S., Park K., Chae S.S., Sboner A., MacDonald T.Y., Wang Y., Sheikh K.L., Terry S., Tagawa S.T., Dhir R., Nelson J.B., de la Taille A., Allory Y., Gerstein M.B., Perner S., Pienta K.J., Chinnaiyan A.M., Collins C.C., Gleave M.E., Demichelis F., Nanus D.M. and Rubin M.A. (2011). Molecular characterization of neuroendocrine prostate cancer and identification of new drug targets. Cancer Discov. 1, 487-495.

Bezerra S.M., Lotan T.L., Faraj S.F., Karram S., Sharma R., Schoenberg M., Bivalacqua T.J. and Netto G.J. (2014). GATA3 expression in small cell carcinoma of bladder and prostate and its potential role in determining primary tumor origin. Hum. Pathol. 45, 1682-1687.

Bostwick D.G. and Cheng L. (2014). Urologic surgical pathology. Third

edition. Elsevier/Saunders. Philadelphia, PA.

Brambilla E., Travis W.D., Colby T.V., Corrin B. and Shimosato Y. (2001). The new World Health Organization classification of lung tumours. Eur. Respir. J. 18, 1059-1068.

Chen H., Sun Y., Wu C., Magyar C.E., Li X., Cheng L., Yao J.L., Shen S., Osunkoya A.O., Liang C. and Huang J. (2012). Pathogenesis of prostatic small cell carcinoma involves the inactivation of the P53 pathway. Endocr. Relat. Cancer 19, 321-331.

Cheng L. and Eble J.N. (2013). Molecular surgical pathology. Springer. New York.

Cheng L., Lopez-Beltran A. and Bostwick D.G. (2012). Bladder pathology. Wiley-Blackwell. Hoboken, N.J.

Cheng L., Zhang D.Y. and Eble J.N. (2013). Molecular genetic pathology, Second edition. ed. Springer. New York.

Chua Y.J., Steer C. and Yip D. (2004). Recent advances in management of small-cell lung cancer. Cancer Treat. Rev. 30, 521-543.

Clegg N., Ferguson C., True L.D., Arnold H., Moorman A., Quinn J.E., Vessella R.L. and Nelson P.S. (2003). Molecular characterization of prostatic small-cell neuroendocrine carcinoma. Prostate 55, 55-64.

Corless C.L. (2014). Gastrointestinal stromal tumors: what do we know now? Mod. Pathol. 27 Suppl 1, S1-16.

Deorah S., Rao M.B., Raman R., Gaitonde K. and Donovan J.F. (2012). Survival of patients with small cell carcinoma of the prostate during 1973-2003: a population-based study. BJU Int. 109, 824-830.

di Sant'Agnese P.A. (1992). Neuroendocrine differentiation in human prostatic carcinoma. Hum. Pathol. 23, 287-296.

Evans A.J., Humphrey P.A., Belani J., van der Kwast T.H. and Srigley J.R. (2006). Large cell neuroendocrine carcinoma of prostate: a clinicopathologic summary of 7 cases of a rare manifestation of advanced prostate cancer. Am. J. Surg. Pathol. 30, 684-693.

Feldman B.J. and Feldman D. (2001). The development of androgen-independent prostate cancer. Nat. Rev. Cancer 1, 34-45.

Fine S.W. (2012). Variants and unusual patterns of prostate cancer: clinicopathologic and differential diagnostic considerations. Adv. Anat. Pathol. 19, 204-216.

Guo C.C., Dancer J.Y., Wang Y., Aparicio A., Navone N.M., Troncoso P. and Czerniak B.A. (2011). TMPRSS2-ERG gene fusion in small cell carcinoma of the prostate. Hum. Pathol. 42, 11-17.

Han B., Mehra R., Suleman K., Tomlins S.A., Wang L., Singhal N., Linetzky K.A., Palanisamy N., Zhou M., Chinnaiyan A.M. and Shah R.B. (2009). Characterization of ETS gene aberrations in select histologic variants of prostate carcinoma. Mod. Pathol. 22, 1176-1185.

Hansel D.E., Nakayama M., Luo J., Abukhdeir A.M., Park B.H., Bieberich C.J., Hicks J.L., Eisenberger M., Nelson W.G., Mostwin J.L. and De Marzo A.M. (2009). Shared TP53 gene mutation in morphologically and phenotypically distinct concurrent primary small cell neuroendocrine carcinoma and adenocarcinoma of the prostate. Prostate 69, 603-609.

Heinlein C.A. and Chang C. (2004). Androgen receptor in prostate cancer. Endocr. Rev. 25, 276-308.

Helpap B., Kollermann J. and Oehler U. (1999). Neuroendocrine differentiation in prostatic carcinomas: histogenesis, biology, clinical relevance, and future therapeutical perspectives. Urol. Int. 62, 133-138.

Hirano D., Okada Y., Minei S., Takimoto Y. and Nemoto N. (2004). Neuroendocrine differentiation in hormone refractory prostate cancer following androgen deprivation therapy. Eur. Urol. 45, 586-592; discussion 592.

Hiroshima K., Iyoda A., Shida T., Shibuya K., Iizasa T., Kishi H., Tanizawa T., Fujisawa T. and Nakatani Y. (2006). Distinction of pulmonary large cell neuroendocrine carcinoma from small cell lung carcinoma: a morphological, immunohistochemical, and molecular analysis. Mod. Pathol. 19, 1358-1368.

Humphrey P.A. (2012). Histological variants of prostatic carcinoma and their significance. Histopathology 60, 59-74.

Joensuu H., Hohenberger P. and Corless C.L. (2013). Gastrointestinal stromal tumour. Lancet 382, 973-983.

Jones T.D., Kernek K.M., Yang X.J., Lopez-Beltran A., MacLennan G.T., Eble J.N., Lin H., Pan C.X., Tretiakova M., Baldridge L.A. and Cheng L. (2005). Thyroid transcription factor 1 expression in small cell carcinoma of the urinary bladder: an immunohistochemical profile of 44 cases. Hum. Pathol. 36, 718-723.

Joshi M., Ayoola A. and Belani C.P. (2013). Small-cell lung cancer: an update on targeted therapies. Adv. Exp. Med. Biol. 779, 385-404.

Lapuk A.V., Wu C., Wyatt A.W., McPherson A., McConeghy B.J., Brahmbhatt S., Mo F., Zoubeidi A., Anderson S., Bell R.H., Haegert A., Shukin R., Wang Y., Fazli L., Hurtado-Coll A., Jones E.C., Hach F., Hormozdiari F., Hajirasouliha I., Boutros P.C., Bristow R.G., Zhao Y., Marra M.A., Fanjul A., Maher C.A., Chinnaiyan A.M., Rubin M.A., Beltran H., Sahinalp S.C., Gleave M.E., Volik S.V. and Collins C.C. (2012). From sequence to molecular pathology, and a mechanism driving the neuroendocrine phenotype in prostate cancer. J. Pathol. 227, 286-297.

Li X., Cheung K.F., Ma X., Tian L., Zhao J., Go M.Y., Shen B., Cheng A.S., Ying J., Tao Q., Sung J.J., Kung H.F. and Yu J. (2012). Epigenetic inactivation of paired box gene 5, a novel tumor suppressor gene, through direct upregulation of p53 is associated with prognosis in gastric cancer patients. Oncogene 31, 3419-3430.

Li Z., Chen C.J., Wang J.K., Hsia E., Li W., Squires J., Sun Y. and Huang J. (2013). Neuroendocrine differentiation of prostate cancer. Asian J. Androl. 15, 328-332.

Linderholm B.K., Lindahl T., Holmberg L., Klaar S., Lennerstrand J., Henriksson R. and Bergh J. (2001). The expression of vascular endothelial growth factor correlates with mutant p53 and poor prognosis in human breast cancer. Cancer Res. 61, 2256-2260.

Linja M.J., Savinainen K.J., Saramaki O.R., Tammela T.L., Vessella R.L. and Visakorpi T. (2001). Amplification and overexpression of androgen receptor gene in hormone-refractory prostate cancer. Cancer Res. 61, 3550-3555.

Lotan T.L., Gupta N.S., Wang W., Toubaji A., Haffner M.C., Chaux A., Hicks J.L., Meeker A.K., Bieberich C.J., De Marzo A.M., Epstein J.I. and Netto G.J. (2011). ERG gene rearrangements are common in prostatic small cell carcinomas. Mod. Pathol. 24, 820-828.

Mackey J.R., Au H.J., Hugh J. and Venner P. (1998). Genitourinary small cell carcinoma: determination of clinical and therapeutic factors associated with survival. J. Urol. 159, 1624-1629.

Mehra R., Tomlins S.A., Shen R., Nadeem O., Wang L., Wei J.T., Pienta K.J., Ghosh D., Rubin M.A., Chinnaiyan A.M. and Shah R.B. (2007). Comprehensive assessment of TMPRSS2 and ETS family gene aberrations in clinically localized prostate cancer. Mod. Pathol. 20, 538-544.

Mosquera J.M., Beltran H., Park K., MacDonald T.Y., Robinson B.D., Tagawa S.T., Perner S., Bismar T.A., Erbersdobler A., Dhir R., Nelson J.B., Nanus D.M. and Rubin M.A. (2013). Concurrent AURKA and MYCN gene amplifications are harbingers of lethal treatment-related neuroendocrine prostate cancer. Neoplasia 15, 1-

10.

Murray N., Salgia R. and Fossella F.V. (2004). Targeted molecules in small cell lung cancer. Semin. Oncol. 31, 106-111.

Nadal R., Schweizer M., Kryvenko O.N., Epstein J.I. and Eisenberger M.A. (2014). Small cell carcinoma of the prostate. Nat. Rev. Urol. 11, 213-219.

Nikitin A.Y., Juarez-Perez M.I., Li S., Huang L. and Lee W.H. (1999). RB-mediated suppression of spontaneous multiple neuroendocrine neoplasia and lung metastases in Rb+/- mice. Proc. Natl. Acad. Sci. USA 96, 3916-3921.

Oesterling J.E., Hauzeur C.G. and Farrow G.M. (1992). Small cell anaplastic carcinoma of the prostate: a clinical, pathological and immunohistological study of 27 patients. J. Urol. 147, 804-807.

Otto T., Horn S., Brockmann M., Eilers U., Schuttrumpf L., Popov N., Kenney A.M., Schulte J.H., Beijersbergen R., Christiansen H., Berwanger B. and Eilers M. (2009). Stabilization of N-Myc is a critical function of Aurora A in human neuroblastoma. Cancer Cell 15, 67-78.

Palmgren J.S., Karavadia S.S. and Wakefield M.R. (2007). Unusual and underappreciated: small cell carcinoma of the prostate. Semin. Oncol. 34, 22-29.

Papandreou C.N., Daliani D.D., Thall P.F., Tu S.M., Wang X., Reyes A., Troncoso P. and Logothetis C.J. (2002). 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. 20, 3072-3080.

Peifer M., Fernandez-Cuesta L., Sos M.L., George J., Seidel D., Kasper L.H., Plenker D., Leenders F., Sun R., Zander T., Menon R., Koker M., Dahmen I., Muller C., Di Cerbo V., Schildhaus H.U., Altmuller J., Baessmann I., Becker C., de Wilde B., Vandesompele J., Bohm D., Ansen S., Gabler F., Wilkening I., Heynck S., Heuckmann J.M., Lu X., Carter S.L., Cibulskis K., Banerji S., Getz G., Park K.S., Rauh D., Grutter C., Fischer M., Pasqualucci L., Wright G., Wainer Z., Russell P., Petersen I., Chen Y., Stoelben E., Ludwig C., Schnabel P., Hoffmann H., Muley T., Brockmann M., Engel-Riedel W., Muscarella L.A., Fazio V.M., Groen H., Timens W., Sietsma H., Thunnissen E., Smit E., Heideman D.A., Snijders P.J., Cappuzzo F., Ligorio C., Damiani S., Field J., Solberg S., Brustugun O.T., Lund-Iversen M., Sanger J., Clement J.H., Soltermann A., Moch H., Weder W., Solomon B., Soria J.C., Validire P., Besse B., Brambilla E., Brambilla C., Lantuejoul S., Lorimier P., Schneider P.M., Hallek M., Pao W., Meyerson M., Sage J., Shendure J., Schneider R., Buttner R., Wolf J., Nurnberg P., Perner S., Heukamp L.C., Brindle P.K., Haas S. and Thomas R.K. (2012). Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. Nat. Genet. 44, 1104-1110.

Psyrri A. and Murren J. (2001). Small cell lung cancer: strategies to optimize chemotherapy response. Cancer J. 7 Suppl 1, S28-34.

Ro J.Y., Tetu B., Ayala A.G. and Ordonez N.G. (1987). Small cell carcinoma of the prostate. II. Immunohistochemical and electron microscopic studies of 18 cases. Cancer 59, 977-982.

Ryan C.J. and Tindall D.J. (2011). Androgen receptor rediscovered: the new biology and targeting the androgen receptor therapeutically. J. Clin. Oncol. 29, 3651-3658.

Scheble V.J., Braun M., Wilbertz T., Stiedl A.C., Petersen K., Schilling D., Reischl M., Seitz G., Fend F., Kristiansen G. and Perner S. (2010). ERG rearrangement in small cell prostatic and lung cancer. Histopathology 56, 937-943.

Schelling L.A., Williamson S.R., Zhang S., Yao J.L., Wang M., Huang J., Montironi R., Lopez-Beltran A., Emerson R.E., Idrees M.T., Osunkoya A.O., Man Y.G., Maclennan G.T., Baldridge L.A., Comperat E. and Cheng L. (2013). 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. 44, 2227-2233.

Simon R.A., di Sant'Agnese P.A., Huang L.S., Xu H., Yao J.L., Yang Q., Liang S., Liu J., Yu R., Cheng L., Oh W.K., Palapattu G.S., Wei J. and Huang J. (2009). CD44 expression is a feature of prostatic small cell carcinoma and distinguishes it from its mimickers. Hum. Pathol. 40, 252-258.

Spiess P.E., Pettaway C.A., Vakar-Lopez F., Kassouf W., Wang X., Busby J.E., Do K.A., Davuluri R. and Tannir N.M. (2007). Treatment outcomes of small cell carcinoma of the prostate: a single-center study. Cancer 110, 1729-1737.

Svensson C., Ceder J., Iglesias-Gato D., Chuan Y.C., Pang S.T., Bjartell A., Martinez R.M., Bott L., Helczynski L., Ulmert D., Wang Y., Niu Y., Collins C. and Flores-Morales A. (2014). REST mediates androgen receptor actions on gene repression and predicts early recurrence of prostate cancer. Nucleic Acids Res. 42, 999-1015.

Tan H.L., Sood A., Rahimi H.A., Wang W., Gupta N., Hicks J., Mosier S., Gocke C.D., Epstein J.I., Netto G.J., Liu W., Isaacs W.B., De Marzo A.M. and Lotan T.L. (2014). Rb loss is characteristic of prostatic small cell neuroendocrine carcinoma. Clin. Cancer Res. 20, 890-903.

Tanaka M., Suzuki Y., Takaoka K., Suzuki N., Murakami S., Matsuzaki O. and Shimazaki J. (2001). Progression of prostate cancer to neuroendocrine cell tumor. Int. J. Urol. 8, 431-436; discussion 437.

Terada T. (2012). Small cell neuroendocrine carcinoma of the prostate: incidence and a report of four cases with an examination of KIT and PDGFRA. Prostate 72, 1150-1156.

Tetu B., Ro J.Y., Ayala A.G., Johnson D.E., Logothetis C.J. and Ordonez N.G. (1987). Small cell carcinoma of the prostate. Part I. A clinicopathologic study of 20 cases. Cancer 59, 1803-1809.

Tomlins S.A., Rhodes D.R., Perner S., Dhanasekaran S.M., Mehra R., Sun X.W., Varambally S., Cao X., Tchinda J., Kuefer R., Lee C., Montie J.E., Shah R.B., Pienta K.J., Rubin M.A. and Chinnaiyan A.M. (2005). Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. Science 310, 644-648.

Tzelepi V., Zhang J., Lu J.F., Kleb B., Wu G., Wan X., Hoang A., Efstathiou E., Sircar K., Navone N.M., Troncoso P., Liang S., Logothetis C.J., Maity S.N. and Aparicio A.M. (2012). Modeling a lethal prostate cancer variant with small-cell carcinoma features. Clin. Cancer Res. 18, 666-677.

Wakelee H. and Kelly K. (2004). Novel approaches for the treatment of small cell lung cancer. Hematol. Oncol. Clin North. Am. 18, 499-518.

Wang W. and Epstein J.I. (2008). Small cell carcinoma of the prostate. A morphologic and immunohistochemical study of 95 cases. Am. J. Surg. Pathol. 32, 65-71.

Wang X., MacLennan G.T., Lopez-Beltran A. and Cheng L. (2007). Small cell carcinoma of the urinary bladder--histogenesis, genetics, diagnosis, biomarkers, treatment, and prognosis. Appl. Immunohistochem. Mol. Morphol. 15, 8-18.

Wang L., Williamson S.R., Zhang S., Huang J., Montironi R., Davison D.D., Wang M., Yao J.L., Lopez-Beltran A., Osunkoya A.O., Maclennan G.T., Baldridge L.A., Du X. and Cheng L. (2014). Increased androgen receptor gene copy number is associated with TMPRSS2-ERG rearrangement in prostatic small cell carcinoma.

Mol. Carcinog. {Epub ahead of print].

Wenk R.E., Bhagavan B.S., Levy R., Miller D. and Weisburger W. (1977). Ectopic ACTH, prostatic oat cell carcinoma, and marked hypernatremia. Cancer 40, 773-778.

Williamson S.R., Zhang S., Yao J.L., Huang J., Lopez-Beltran A., Shen S., Osunkoya A.O., MacLennan G.T., Montironi R. and Cheng L. (2011). 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. 24, 1120-1127.

Wood A.C., Maris J.M., Gorlick R., Kolb E.A., Keir S.T., Reynolds C.P., Kang M.H., Wu J., Kurmasheva R.T., Whiteman K., Houghton P.J. and Smith M.A. (2013). Initial testing (Stage 1) of the antibody-maytansinoid conjugate, IMGN901 (Lorvotuzumab mertansine), by the pediatric preclinical testing program. Pediatr. Blood Cancer 60, 1860-1867.

Yao J.L., Madeb R., Bourne P., Lei J., Yang X., Tickoo S., Liu Z., Tan D., Cheng L., Hatem F., Huang J. and Anthony di Sant'Agnese P. (2006). Small cell carcinoma of the prostate: an immunohistochemical study. Am. J. Surg. Pathol. 30, 705-712.

Yashi M., Terauchi F., Nukui A., Ochi M., Yuzawa M., Hara Y. and Morita T. (2006). Small-cell neuroendocrine carcinoma as a variant form of prostate cancer recurrence: a case report and short literature review. Urol. Oncol. 24, 313-317.

Zhou H., Kuang J., Zhong L., Kuo W.L., Gray J.W., Sahin A., Brinkley B.R. and Sen S. (1998). Tumour amplified kinase STK15/BTAK induces centrosome amplification, aneuploidy and transformation. Nat. Genet. 20, 189-193.

Accepted November 10, 2014