Clinical features and outcomes of 25 patients with primary adenosquamous cell carcinoma of the prostate

Jue Wang,[1] Fen Wei Wang,[2] Chad A. LaGrange,[3] George P. Hemstreet[3]

[1]Department of Internal Medicine, Section of Oncology-Hematology, University of Nebraska Medical Center, Omaha, NE, USA; [2]Department of Internal Medicine Creighton University School of Medicine, Omaha, NE, USA; [3]Urologic Surgery Section, Department of Surgery University of Nebraska Medical Center Omaha, NE, USA

Abstract

The aim of the present study was to examine the epidemiology, natural history, treatment and long-term survival of patients with adenosquamous cell carcinoma of the prostate. The Surveillance, Epidemiology, and End Results (SEER) Program database was used to identify ASCC of prostate cases between January 1973 and December 2006. Survival probabilities were estimated using the Kaplan-Meier methods and compared using the log-rank test. A total of 25 patients with adenosquamous cell carcinoma of the prostate were identified during the study period. The median age was 74 years (range 53-98). Twenty percent of study subjects presented with metastatic disease. Among those patients with known grade (n=16), 75% had poorly or undifferentiated histology. A total of 40% of study subjects received radical prostatectomy, while 24% of the patients had primary radiation therapy. The 1-, 3-, and 5-year cancer specific survival rates for the entire cohort were 55.2%, 37.8%, and 30.3%, respectively. For patients who underwent prostatectomy, the 1-, 3-, and 5-year survival rates were 78%, 78%, and 63%, respectively. For the patients who did not receive prostatectomy, the 1-year survival rates were 38.7% and none survived to three years. Adenosquamous cell carcinoma is a rare aggressive subtype of prostate cancer with poor cancer specific survival. The development of new therapeutic approaches for this aggressive tumor is urgently needed.

Introduction

While adenocarcinoma is the most common type of carcinoma of the prostate, mixed types of carcinoma of the prostate are rare.[1,2] Adenosquamous cell carcinoma (ASCC) is defined by the presence of both glandular (acinar) and squamous components. Glandular and squamous components can be distinct or can show direct transition. Squamous components constitute an average 40% of the tumor, with a range of 5-95%.[3] Since the first description by Thompson,[4] approximately 20 cases of ASCC of the prostate have been reported.[3,5-12] Of all ASCC cases reported in literature, two-thirds involved patients previously treated for prostatic adenocarcinoma with hormones and/or radiation.[3,5-9] The remaining one-third of patients had no history of prostate cancer or hormonal therapy.[10-13]

Little is known of molecular genetic abnormalities in this neuplasma. P53 was reported amulation in both glandular and squamous components.[9] DNA analysis on adenosquamous cancer revealed that the squamous component was aneuploid and tetraploid, and the adenocarcinoma component of the ASCC was diploid. The non-diploid pattern predicts an aggressive course.[14]

There are several theories to explain the histogenesis of ASCC of the prostate: i) meteplastic transformation of adenocarcinoma cells;[15] ii) collision-type tumor;[14,16] iii) ASCC is derived from pluripotent stem-cells capable of multidirectional differentiation;[9] iv) for ASCC occuring after radiation or androgen deprivation therapy, a more plausible explanation would be clonal evolution/divergence of persistent carcinoma, secondary to the selective pressure of therapy.[9]

Current literature on ASCC of the prostate consists predominantly of retrospective reports or histopathological studies from single institutional experiences. Available information on outcomes of treatments is lacking. After an extensive literature search, only a few cases of ASCC with long-term follow-up information were found and the majority of cases died within a year after the diagnosis;[6,12,15,17] so far no single institution study has had enough cases to allow a meaningful analysis of important prognostic factors.

The purpose of this study is to examine natural history, treatment pattern and long-term cancer specific survival of patients with primary ASCC who were identified in the population based Surveillance, Epidemiology, and End Results (SEER) Program database.

Materials and Methods

Data source and study population

SEER currently consists of 18 statewide and regional tumor registers spread across the US, covering approximately 26% of the population. SEER routinely collects data on patient demographics (age at diagnosis, gender, race/ethnicity and geographical residence at the time of diagnosis), tumor characteristics (size, grade, stage), first course of treatment, as well as follow-up documentation of vital status (date and cause of death).[18]

The cases of ASCC of the prostate were extracted from the SEER on the basis of anatomic site and histology type. All patients over the age of 18 years, first diagnosed with ASCC between January 1973 and December 2006 (n=25), were enrolled in this study.

SEER summary stage is produced using the extent of disease information from medical records and pathology reports reviewed at the time of diagnosis. SEER general summary stage[18] classifies patients as having local, regional (extension into adjacent tissues or nodal involvement) or distant disease. Since the Gleason grading scheme can be used for the glandular component but not for the squamous component of ASCC, the World Health Organization's standard grading system was used in this study. "Well, moderately well differentiated histology", and "poorly differentiated, undifferentiated histology" were categorized to low- and high-grade, respectively.

Statistical analysis

Discrete data are reported as frequencies and compared by χ^2 and Fisher's exact tests as

Correspondence: Jue Wang, Section of Oncology-Hematology, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska 68198-7680, USA.
E-mail: juewang@unmc.edu

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appropriate. Continuous data are reported as mean ± SD and compared by Student's t-test. Survival duration was measured by the Kaplan-Meier method and compared by the log rank test. Multivariable Cox's proportional hazards model was used to identify independent predictors of long-term cancer specific death. Cases identified at the time of autopsy or by death certificate only were excluded from the survival analyses. All statistical calculations were performed by SPSS 12.0 (Apache Software Foundation 2000).

Results

Patients' and tumor characteristics

Of the 25 patients with ASCC of the prostate identified in the SEER database during the study period, the median age at diagnosis was 74 years, with a range of 53 to 98 years. The majority of patients (84%) were Caucassian while 4 patients belonged to the other ethnic groups (16%). Twenty percent of patients presented with metastatic disease. Of 16 patients whose histology grade information was available in the SEER database, 12 (75%) had poorly or undifferentiated histology. Overall, 10 patients (40%) underwent radical prostatectomy and 6 patients (24%) received primary radiation therapy. Details of patients' and tumor characteristics are shown in Table 1.

Long-term survival

The median duration of follow up of the entire cohort was 11 months (range 0-95 months); 23 of 25 (92%) patients died during the follow-up period.

One patient who was diagnosed at the time of autopsy was excluded from the cancer specific survival analyses. A total of 24 patents were included in the final survival analysis. The median cancer specific survival was 16 months (95% CI 0-32) (Figure 1A). There is a significant difference in cancer specific survival rates between patients with localized/regional disease and patients with distant disease (P=0.001) (Figure 1B). In patients with local/regional disease, there is also a significant cancer specific survival advantage in patients who were treated with prostatectomy compared to those who were not (P=0.02) (Figure 1C).

Table 2 presents the 1-, 3- and 5-year cancer specific survival rates according to patients' and tumor characteristics. The 1-, 3- and 5-year cancer specific survival rates were 55.2%, 37.8% and 30.3%, respectively (Table 2). Patients with local disease have a better survival rate than patients who presented with advanced disease. The 1-, 3- and 5-year cancer specific survival rates for patients with local-

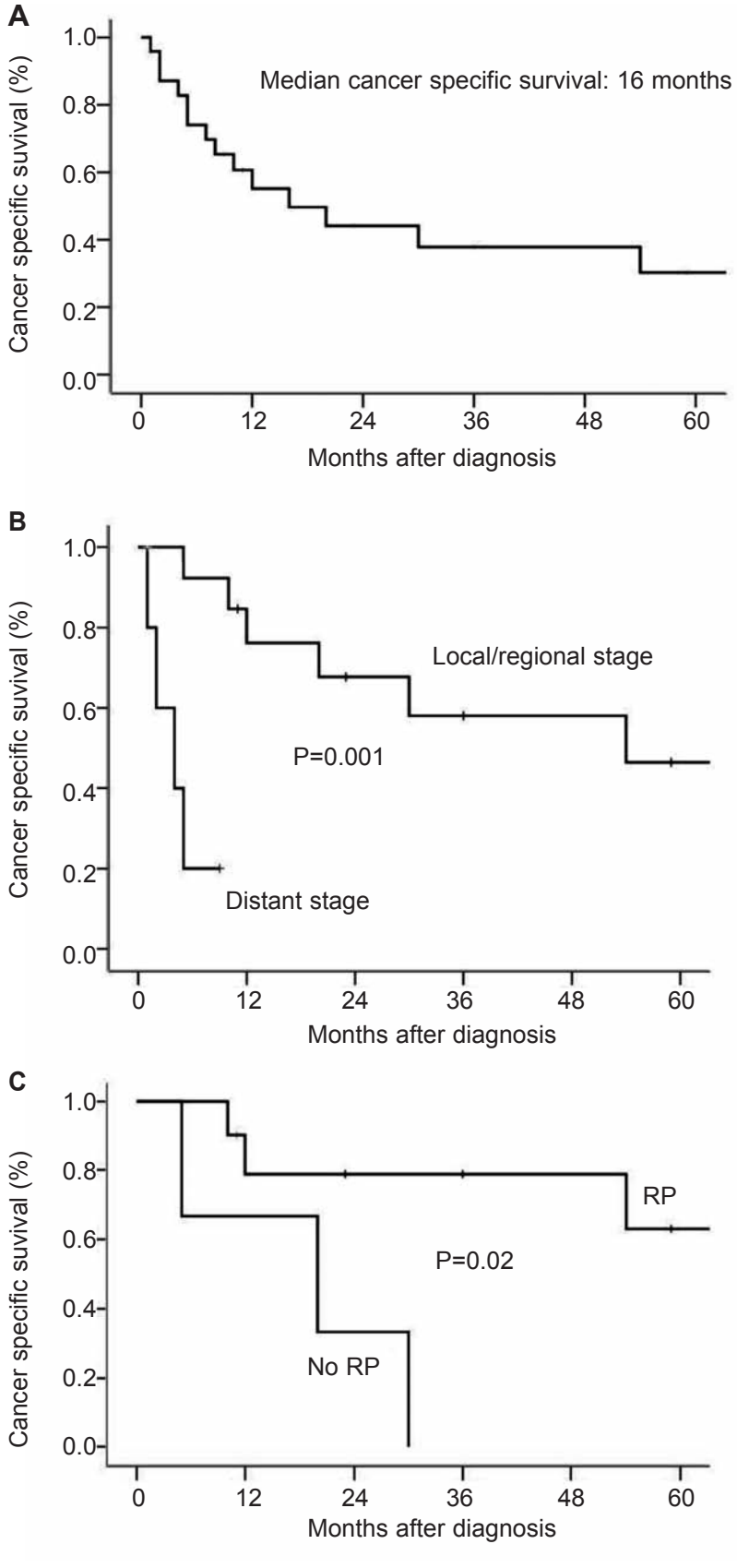

Figure 1. (A) Cancer specific survival rate of patients with ASCC of the prostate. (B) Comparison of cancerspecific survival rates of patients with ASCC of prostate according to SEER stage. (C) Comparison of cancer specific survival rates according to treatment in ASCC patients with localized/regional stage only. (RP: radical prostatectomy).

ized stage were 76.2%, 58.0% and 46.4%, respectively. However, the patients who presented with distant disease all died within a year after diagnosis; the 6-month survival rate for those patients was only 20%. The median cancer specific survival for patients who underwent prostatectomy was 65 months (95% CI 44-86). The 1-, 3- and 5-year cancer specific survival rates were 78.8%, 78.8% and 63%, respectively. For the patients who did not undergo prostatectomy, the 1- and 3-year cancer specific survival rates were 38.7% and 0%, respectively (Table 2).

Table 3 presents the results of multivariate survival analyses using Cox's proportional hazard model in patients with ASCC. After adjusting for the demographic, clinical and treatment related factors, prostatectomy was a significant predictor of cancer specific survival (HR 0.1, 95%CI 0.01-1.0).

Discussion

Although a single center study reported an incidence rate of 0.79%,[4] the true incidence of adenosquamous cell carcinoma (ASCC) of the prostate is unknown. In this study, we identified only 25 patients with ASCC of the prostate in the SEER database during the study period. The incidence in this population study is much lower than that reported in the single institution study.[13] There are several possible explanations for this interesting finding. First of all, "referral bias" likely exists in single institution studies which are usually from large, tertiary-care referral centers. The patients with rare tumors are most likely to visit referral centers for a second opinion. In comparison with their community counterparts, pathologists from centers of excellence are more likely to have the expertise to indentify this rare subtype of histology. Second, there may be "anatomical bias". Most cases of ASCC of the prostate were found at the prostatic urethra and/or adjacent tissues,[13] making them more readily accessible by transurethral resection for bladder tumor (TURP) than by core needle biopsies. However, TURP was only performed in patients with symptoms of obstruction. With the wide use of PSA screening, which usually leads to detection of asymptomatic prostate cancer by needle biopsy, a squamous component in the prostate but not in the needle biopsy sample may be missed. Third, practice pattern bias may also have contributed to current findings. Two-thirds of ASCC cases were reported to have been found in cases of prostate adenocarcinoma previously treated with hormone or radiation therapy.[3,5-9] In current clinical practice, a second biopsy is seldom performed in patients with prostate cancer; this is because of the perception that the

Table 1. Demographic and clinical characteristics of 25 patients with primary adenosquamous cell carcinoma of prostate.

Characteristics	Group	N	%
Total		25	100
Age (years)	50-59	2	8
	60-69	7	28
	70-79	8	32
	≥80	8	32
Ethnicity	White	21	84
	Others	4	16
Marital status	No	5	20
Yes	5	20	80
Grade	Low	4	16
	High	12	48
	Unknown	9	36
SEER Stage	Localized/regional	13	52
	Distant	5	20
	Unknown	7	28
Prostatectomy	Yes	10	40
	No	15	60
Radiation	Yes	6	24
	No	19	76
Year of diagnosis	1973-1994	15	60
	1995-2006	10	40

Table 2. Median, 1-, 3-, 5- year cancer specific survival of patients with adenosquamous cell carcinoma of the prostate according to demographic and clinical characteristics.

Characteristics	Median cancer specific survival months (95%CI)	Survival (%) 1-year	3-year	5-year	P
All	16 (0-32)	55.2	37.8	30.3	
SEER Stage					
Localized	54 (14-93)	76.2	58.0	46.4	0.001
Distant*	4 (0-8)	00.0	00.0	00.0	
Unknown	8 (0-11)	40	0	0	
Prostatectomy					
No	7 (3-11)	38.7	00.0	00.0	<0.001
Yes	65 (44-86)	78.8	78.8	63.0	
Year					
1973-1994	16 (0-64)	55.1	45.9	30.6	0.56
1995-2006	20 (0-56)	56.3	28.1	28.1	

*Six months survival rate 20%. CI=confidence interval.

Table 3. Multivariate analyses of factors associated with cancer specific mortality in patients with adenosquamous cell carcinoma.

Characteristics	Group	Hazard ratio	95% confidence interval	P
Age	Continuous	0.99	0.93-1.05	0.76
Year of diagnosis	1980-1994	1.00		
	1995-2004	0.73	0.17-3.20	0.68
SEER stage	Local/regional	1.00		
	Distant	4.36	0.54-35.1	0.17
	Unstaged	1.47	0.16-13.4	0.73
Radiation	No	1.00		
	Yes	0.80	0.20-3.24	0.76
Prostatectomy	No	1.00		
	Yes	0.10	0.01-1.0	0.05

second biopsy of these patients in the face of known prostate cancer is not warranted, especially in the case of advanced stage disease and elderly patients. Finally, "data source bias" likely also contributed to the difference in incidence. SEER routinely collects histological data at the time of initial diagnosis. Additional tissue diagnoses from subsequent biopsies were not collected; while this information is readily available in single center retrospective studies. Some investigators postulate that the incidence of ASCC and the clinical impact of this subtype is likely underestimated and underreported.[12] A more accurate estimate of the true incidence of this subtype of prostate cancer can only be achieved by tumor banking and pathological evaluation of additional tissue biopsy specimens from subjects with adenocarcinoma of prostate, including patients with hormone refractory disease or those who received radiation therapy. For example, The National Cancer Institute Cooperative Prostate Cancer Tissue Resource (CPCTR) represents one of the largest sources of pathology-characterized archival prostate cancer tissue with associated follow-up data in the world.[19] Similarly human frozen tumor tissue banks with corresponding diagnosis were also established in European cancer centers and universities.[20] Such infrastructures would improve tissue availability and accessibility to allow the study of true incidence and the clinical impact of this rare tumor subtype.

Since there is no clinical trial specifically designed for ASCC of the prostate, the optimal treatment strategy has not been established. Radical prostatectomy, radiation therapy, hormone or chemotherapy has been used alone or in combination. In this study, the patients with local/regional ASCC who received prostatectomy had a significant survival benefit compared to those who did not. Therefore, prostatectomy should be offered to those with localized prostate cancer, including healthier elderly patients with good performance status. Due to limited sample size, it is difficult to evaluate the true impact of radiation on patients' survival. Some authors suggested that ASCC of the prostate responds, at least initially, to hormone therapy,[10,11] while others reported that these tumors generally were refractory to hormone therapy.[13] However, information on response and efficacy of chemotherapy is lacking. Consistent with single institution studies[4,13] patients with ASCC of the prostate usually present with aggressive disease; 75% of the patients with known histology grade in our study had either poorly or undifferentiated histology. The prognosis for patients with ASCC is very poor and, notably, even in those patients with localized disease who subsequently underwent prostatectomy, suggesting this is a disease with propensity of early microscopic dissemination. The 5-year cancer specific survival rate of 30.3% was significantly lower compared to the 99.9% survival rate of prostate cancer as a whole.[21] Unfortunately, the outlook of this disease has not changed in the past three decades (Table 2). Collectively, the findings from this study and others[1,2] support the view that ASCC represents a distinct disease entity.

Prostate cancer is a clinically heterogeneous disease, ranging from indolent to rapid lethal disease, such as in the case of ASCC.[1,2,21] The observed clinical heterogeneity of prostate cancer likely reflects the underlying molecular heterogeneity among tumors. As our understanding of the genetic basis for prostate cancer grows, it is likely that prostate cancer will be subdivided into ever more specific categories. Indeed, microarray profiling studies in prostate cancer have identified clinically relevant gene-expression subtypes.[22-24] Further advancements in molecular biology and proteomics may accelerate this trend towards individual characterization of prostate cancer and, ultimately, personalized therapy will be tailored to their biological behaviors. Our finding of subtype-related differences in prostate cancer has significant therapeutic implications: better therapy of prostate cancer is more likely to be achieved by investigating each subtype of prostate cancer separately rather than grouping them all together.[20] Research on the rare subtype of prostate cancer may also have important ramifications for general oncological practice. For example, clear cell carcinoma is a subtype of kidney tumor. Characterization of the role of the *VHL* gene in oncogenesis of clear cell carcinoma[25] led to the development of antiangiogenesis therapy in the treatment of renal cell carcinoma.[26] The utility of tyrosine kinase inhibitors is now being defined in a wide variety of both rare and common neoplasms.[27]

There are several limitations to this study. First, the information regarding receipt of hormone or chemotherapy and patients' co-morbidities is not available in the SEER database, all of which may influence survival in cancer patients. However, the analysis reported here attempted to overcome this data limitation by measuring prostate cancer specific survival, rather than overall survival. The results from this study should be interpreted with caution since the sample size used may still not be big enough to fully describe the factors that affect the incidence, treatment choice, and survival of this rare prostate cancer subtype.

Conclusions

Adenosquamous cell carcinoma is a rare aggressive subtype of prostate cancer with a poor outcome. Further study to understand the molecular mechanism underlining the biological behavior of ASCC is planned. The development of new therapeutic approaches for this aggressive tumor is urgently needed.

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