Histological subtypes of prostatic cancer: a comparative survival study

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Introduction: *Variant histological subtypes of prostatic cancer occur uncommonly and are associated with poor survival, as has been ascertained through limited series and case reports. Here a population-based analysis of prostatic cancer is provided, to better analyze the survival behavior of these subtypes.*

Materials and methods: *The American SEER registry was used to review prostatic cancer diagnosed from 1988 to 2003, classified according to the International Classification of Diseases for Oncology. Kaplan-Meier and proportional hazards analyses were performed on adenocarcinomas and five infrequent variant subtypes to determine their overall survival behavior, allowing corrections for follow up inequity, age, stage, histological grade, and year of diagnosis.*

Results: *A total of 455,296 cases of prostatic cancer were reviewed, of which over 99% were conventional adenocarcinomas. The remaining variants studied included ductal carcinomas (0.141%), mucinous adenocarcinomas (0.103%), small cell carcinomas (0.056%), carcinosaromas (0.07%) and embryonal carcinosarcomas (0.06%). With age, stage and grade effects were corrected for in the multivariate analysis, conventional adenocarcinomas, mucinous adenocarcinomas and ductal carcinomas exhibited similar survival behavior. Small cell carcinomas and carcinosarcomas exhibited poor survival, even with correction. The embryonal variant of carcinosarcoma affected pediatric patients and had an overall survival similar to conventional prostatic cancer. Ductal carcinomas, small cell carcinomas and both types of carcinosarcoma tended to present with metastases more frequently than conventional disease.*

Conclusions: *Prostatic cancer subtype can have a major bearing on overall survival and likely reflects intrinsic differences in biological behavior.*

Key Words: prostate cancer, histological subtypes, overall survival

Introduction

Most prostatic cancers are adenocarcinomas.[1] Other histological subtypes occur much less frequently, and can display different clinical behaviors.[2] For the most part, these less frequent subtypes have been thought to behave more aggressively with a greater propensity for metastases at diagnosis and shorter overall survival.

Since these other subtypes are comparatively rare, their clinical description has been derived from case reports and small series. The Surveillance, Epidemiology and End Results (SEER) registry provides detailed histological and clinical data on a large cohort of men with prostatic cancer, drawn from the general American population. These SEER data will be used here to review the clinical features of these subtypes. The aim was to provide a more comprehensive comparison of their overall survival patterns than can be derived from literature review.

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Materials and methods

The study population was derived from the April 2009 release of the SEER 17 cancer registry, of individuals diagnosed with prostatic cancer from 1988 to 2003. Only individuals with microscopically confirmed prostatic cancer and known age at diagnosis were analyzed. Information retrieved included age at diagnosis, year of diagnosis, year of birth, histological subtype, SEER modified American Joint Committee on Cancer (AJCC) stage, histological grade, race/ethnicity, survival time and vital status. For the purposes of analysis, the SEER histological subtypes were classified into six groups: conventional prostatic adenocarcinoma, mucinous adenocarcinoma, ductal carcinoma and cribriform carcinoma, small cell carcinoma and neuroendocrine carcinoma, carcinosarcoma, and an embryonal variant of carcinosarcoma, Table 1.

SEER used the following grading system: Grade 1, well differentiated or Gleason score 2-4; Grade 2, moderately well differentiated or Gleason score 5-6; Grade 3, poorly differentiated or Gleason score 7-10; and Grade 4, Undifferentiated or Anaplastic (http://training.seer.cancer.gov/prostate/abstract-code-stage/morphology.html). Small cell carcinoma was graded according to this system, and small cell carcinomas were not all automatically assigned as high grade tumors.

Descriptive statistics were determined using Statistica 9 (StatSoft Inc., Tulsa, OK, USA). Median overall survival was estimated by the method of Kaplan-Meier using STATA SE 10.0 (StataCorp LP, College Station, TX, USA). Proportional hazards analyses were conducted using STATA, based on overall survival, with attained age as the timescale and stratification by birth cohorts in 10-year increments.[3] Left-truncation of data was fully accounted for.

TABLE 1. **General characteristics of the histological subtypes of prostate cancer**

Histology/ SEER subtypes	No. cases (%)	Age at diagnosis*	African American no. (%)	Distant metastases at diagnosis no. (%)	Grade 3 & 4, no. (%)	Median overall survival (mths)†	5 year overall survival‡
Adenocarcinoma							
Adenocarcinoma, NOS Acinar cell carcinoma Carcinoma, NOS Signet ring carcinoma	453,184 (99.536)	69.0 [69.0-69.0]	53,409 (11.8)	39,866 (8.8)	99,952 (22.1)	134 [134-135]	77 [77.3-77.5]
Ductal carcinoma and cribriform carcinoma							
Infiltrating ductal carcinoma Cribriform carcinoma Papillary adenocarcinoma, NOS Endometriod carcinoma	643 (0.141)	71.4 [70.7-72.2]	60 (9.3)	116 (18.0)	213 (33.1)	102 [92-115]	78 [74.1-81.8]
Mucinous adenocarcinoma							
Mucinous adenocarcinoma Mucin-producing adenocarcinoma	470 (0.103)	65.7 [64.8-66.5]	83 (17.7)	47 (10.0)	132 (28.1)	140 [125-163]	65 [61.4-69.1]
Small cell carcinoma and neuroendocrine carcinoma							
Small cell carcinoma, NOS Neuroendocrine carcinoma	257 (0.056)	70.6 [69.3-72.2]	21 (8.2)	182 (70.8)	167 (65.0)	10 [9-12]	11 [7.0-14.8]
Carcinosarcoma							
Carcinosarcoma, NOS	31 (0.007)	75.3 [72.0-78.5]	2 (6.5)	17 (54.8)	18 (58.1)	10 [5-23]	4 [0.3-16.7]
Carcinosarcoma, embryonal type							
Carcinosarcoma, embryonal type	27 (0.006)	11.8 [6.6-16.9]	1 (3.7)	18 (66.7)	8 (29.6)	NSD	66 [45.4-80.9]

NOS = not otherwise specified; NSD = not sufficient data

*mean and 95% confidence interval; †median and 95% confidence interval; ‡percent and 95% confidence interval

Two proportional hazards models were performed. The first was compared overall survival between the 20 most frequent histological subtypes; it employed year of diagnosis and histological subtype as the only covariates. The second model also compared overall survival, but it also included cancer stage and grade as covariates to correct for these effects.

Results

Data regarding 455,296 individuals with prostatic cancer were retrieved. Conventional prostatic adenocarcinoma cancer comprised more than 99% of the study population, Table 1. This subtype was designated as a control to which the other subtypes could be compared. Individuals with conventional histology were diagnosed, on average, in their late seventh decade; 12% were African American; 9% had metastases at diagnosis; 22% had high grade tumors; and their median overall survival time was 134 months.

Small cell carcinoma and carcinosarcoma, had markedly poorer median overall survivals, in the range of 10 months. These unfavorable subtypes also tended to present more with metastatic disease and high grade tumors. On the other hand, mucinous adenocarcinoma, ductal carcinoma and the embryonal variant of carcinosarcoma had relatively more favorable overall survivals, although amongst these three subtypes the median survival observed for the ductal carcinomas was significantly poorer. We note that ductal carcinoma tended to present with distant metastases. Notably, too, small cell carcinoma and carcinosarcoma presented with even greater frequencies of distant metastases and high grade tumors.

The United States Census Bureau has estimated the percentage of African Americans within the general American population at 12.3%.[4] The corresponding percentages for conventional adenocarcinoma was similar. Mucinous adenocarcinoma appeared more highly represented amongst African Americans whereas this representation seemed less with ductal carcinoma, small cell carcinoma and carcinosarcoma.

One major difference between histological subtypes was age. Ductal carcinoma, small cell carcinoma and carcinosarcoma were diagnosed in older individuals than seen with conventional adenocarcinoma; in contrast, the embryonal variant of carcinosarcoma was a pediatric tumor. The effects of such age disparities on

TABLE 2. **Proportional hazards analyses based on overall survival**

	Model 1		Model 2	
Covariate	**Hazard ratio***	**p value**	**Hazard ratio***	**p value**
Yr of diagnosis	0.979 [0.978-0.981]	< 0.001	0.975 [0.973-0.976]	< 0.001
Grade 1			0.700 [0.684-0.715]	< 0.001
Grade 2			0.703 [0.689-0.716]	< 0.001
Grade 3			1.067 [1.046-1.088]	< 0.001
Grade 4			1.271 [1.206-1.339]	< 0.001
Stage 0			0.996 [0.964-1.029]	0.822
Stage 1			0.961 [0.949-0.975]	< 0.001
Stage 2			0.900 [0.885-0.916]	< 0.001
Stage 3			0.836 [0.821-0.851]	< 0.001
Stage 4			2.484 [2.448-2.520]	< 0.001
Adenocarcinoma	0.389 [0.355-0.426]	< 0.001	0.517 [0.472-0.567]	< 0.001
Ductal carcinoma and cribriform carcinoma	0.483 [0.418-0.557]	< 0.001	0.556 [0.482-0.642]	< 0.001
Mucinous adenocarcinoma	0.453 [0.382-0.538]	< 0.001	0.573 [0.483-0.681]	< 0.001
Small cell carcinoma and neuroendocrine carcinoma	4.225 [3.603-4.954]	< 0.001	2.694 [2.297-3.161]	< 0.001
Carcinosarcoma	2.702 [1.867-3.909]	< 0.001	1.866 [1.290-2.700]	0.001
Carcinosarcoma, embryonal subtype	0.219 [0.040-0.996]	0.049	0.207 [0.487-0.881]	0.033

*with 95% confidence interval

survival were corrected for in the proportional hazard analysis, and similarly disparities in follow up times were accounted for.

The proportional hazards analyses were based on overall survival. In the first model analysis was essentially restricted to a comparison between subtypes; here conventional adenocarcinoma revealed a relatively low hazard ratio, Table 2. The embryonal variant of carcinosarcoma also had a low hazard ratio that was not significantly different from that of adenocarcinoma, mucinous adenocarcinoma and ductal carcinoma. Small cell carcinoma and carcinosarcoma had markedly higher hazard ratios, being several times that of the control.

Year of diagnosis was the only other covariate included in this first proportional hazards model. This was done to correct for potential secular trends that might have manifested over the study period. Since this covariate had a significantly decreased hazard ratio, a trend towards improved survival over time was thus demonstrable. Presumably this trend related to changes in staging and treatment that likely were implemented during the study period.

The second proportional hazards analysis included histological grade and AJCC stage as covariates, Table2. Increased grade was associated with an increased hazard ratio; whereas stage exhibited a major influence with the appearance of metastases. The inclusion of these two covariates allowed adjustments to be made for their effects on the different subtypes. With these corrections, the range of the hazard ratios amongst the subtypes decreased. The hazard ratios from the subtypes nonetheless correlated strongly between these two models ($r^2 = 0.993$, $p < 0.001$), indicating that the stage and grade corrections tended to not affect any particular subtype more than another.

Discussion

Retrospective SEER analyses of prostate cancer like this share inherent deficiencies. For example, the lack of information provided by SEER regarding either Gleason score or PSA values limited the analysis, and differences between the SEER histological grading system employed here and more modern systems.[5] Other deficiencies included the effects of unmeasured changes that likely occurred over the study period with staging and treatment practices, as well as inequities expected between surgically and clinically staged cases. Moreover, there were likely changes in histological definitions and nomenclature during the study period. Nevertheless, published case reports and series on this subject, when examined collectively, would likely share equivalent deficiencies. Given the quality controls on SEER data collection, the size of the database, and its population-based nature, the present analysis should be considered to provide some advantage relative to prior studies.

In contrast with the conventional notion that the clinical behavior of variant prostatic subtypes tended to be more aggressive, on multivariate analysis, ductal carcinoma, mucinous adenocarcinoma and the embryonal subtype of carcinosarcoma all seemed to exhibit similar overall survival hazards, Table 2. The reason for these differences can likely be attributed to the corrections for inequities in age, stage and grade provided for by multivariate analysis. We note that prior accounts of these subtypes tended not to employ multivariate methods. The two remaining subtypes had unfavorable hazard ratios consistent with previous studies that demonstrated poorer survival with small cell carinoma[1,2,6-8] and neuroendocrine carcinoma,[6] as well as carcinosarcoma.[1,2,9]

One promising area for research deals with the molecular changes associated with histological subtype and other morphologic features of prostate cancer. Mosquera has identified five morphological features of prostatic cancer that correlate with gene fusion of the TMPRSS12-ERG loci.[10] Such DNA rearrangements are characterized by androgen controlled genomic regulatory elements that become fused to ETS transcription factors causing their over-expression.[11] Other molecular changes of note include mutation and increased expression of the TP53 gene in small cell carcinoma of the prostate[12], increased expression of the MUC2 gene in mucinous adenocarcinoma of the prostate,[13] hypermethylation of the inhibin -subunit gene with cribriform carcinoma,[14] and an increased frequency of microsatellite instability with mucinous adenocarcinoma.[15] As well, there is the loss of heterozygosity at 11p15.5 associated with embryonal rhabdomyosarcoma.[16] No doubt, in time, the association of such molecular changes with morphological features will become more clearly understood, and lead to a better mechanistic understanding of behaviour of the different subtypes of prostatic cancer.

Conclusion

The sub-typing of prostatic cancer subtype is important, as it can have a bearing on clinical behavior and treatment. In this SEER-based analysis, uncommon prostatic subtypes comprised less than 1% of the total. This was less than the 5% to 10% that has been previously reported,[2] and it should be recognized that the population-based data used here would be less likely to be affected by reporting biases. Many of these uncommon subtypes have been ascribed relatively poorer outcomes in the past,[2] but this was not confirmed

with all of the variant subtypes examined here and once inequities in age, grade and staging were corrected for. Only small cell carcinoma and carcinosarcoma showed major detrimental survival hazards. The different behaviors between subtypes likely reflected intrinsic biological properties that remain to be better understood at the molecular level. □

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