A Limited-Versus-Extensive Staging Strategy for Small Cell Prostate Cancer

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Introduction: Small cell prostate cancer (SCPC) is a rare histologic subtype of prostate cancer, for which the optimal staging strategy remains unclear.

Method: The Surveillance, Epidemiology, and End Results database was used to analyze the incidence and outcomes of SCPC between the years 2004 through 2016. Limited-stage SCPC (LS-SCPC) was defined as SCPC without any metastasis regardless of local invasion. Extensive stage SCPC (ES-SCPC) was defined as any metastasis to lymph nodes and/or to distant organs.

Result: A total of 403 SCPC patients were included in the study cohort, accounting for 0.056% of all prostate cancer cases (n = 719,655). Of the 358 patients with known metastasis status, 275 (76.8%) patients had ES-SCPC, whereas 83 (23.2%) patients had LS-SCPC. LS-SCPC was associated with better overall survival (17 vs. 9 mo, $P < 0.001$) and disease-specific survival (25 vs. 10 mo, $P < 0.001$) compared with ES-SCPC. All LS-SCPC patients had a similar overall survival regardless of T stage. Similarly, all ES-SCPC patients had similar outcomes regardless of metastasis sites. High prostate-specific antigen (PSA) is paradoxically associated with superior outcome in both localized stage patients (PSA ≥ 4 vs. PSA < 4, 19 vs. 10 mo, $P = 0.002$) and extensive stage patients (PSA ≥ 20 vs. PSA < 20, 13 vs. 9 mo, $P = 0.02$). Multivariate analysis of treatment showed that chemotherapy was associated with improved survival in ES-SCPC with hazard ratio of 0.52.

Conclusion: Similar to small cell lung cancer, SCPC can be staged into LS-SCPC or ES-SCPC. The binary staging system correlates well with prognosis.

Key Words: prostate cancer, neuroendocrine tumor, small cell cancer, epidemiology, prostate-specific antigen

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Prostate cancer is the most common noncutaneous malignancy in adult males in the United States and accounts for about 20% of new cancer cases annually.[1] Adenocarcinoma is the most common histologic type and constitutes 95% of all prostate cancer cases.[2] Other histologic types, including small cell carcinoma, transitional cell carcinoma, and sarcomas are extremely rare.[3] Small cell prostate cancer (SCPC) is characterized by distinct morphologic features, high growth fraction, resistance to androgen ablation, short response to chemotherapy, and aggressive disease course. SCPC is one of the most common extrapulmonary small cell cancers as well as the most common histologic subtype in nonadenocarcinoma prostate cancer.[4] However, limited by its low incidence, the biology and clinical behavior of SCPC is poorly understood.

The lungs are the most commonly involved site of origin in small cell cancer. Given the distinct clinical course, small cell lung cancer (SCLC) is stratified into limited stage and extensive stage based on extent of disease, which is different from the staging system used for non-SCLC. The staging system for de novo SCPC and prostatic adenocarcinoma, however, remains the same. This system classifies the disease burden based on TNM stages (I to IV), Gleason

TABLE 1. Baseline Characteristics of Patients With SCPC and Adenocarcinoma

	n (%)		
	SCPC (N = 403)	**Adenocarcinoma (N = 690,660)**	***P***
Age			< 0.001
Median	71	66	
Range	30-96	13-120	
Median survival (mo)	9	Unreached	< 0.001
Survival rate			
1 y	96.8	36.6	< 0.001
3 y	90.6	11.7	< 0.001
5 y	84.5	8.2	< 0.001
Multiple primary			< 0.001
First malignancy	310 (76.9)	63,3150 (91.7)	
Not first malignancy	93 (23.1)	57,510 (8.3)	
Stage			< 0.001
I	13 (3.6)	86,565 (13.5)	
II	30 (8.4)	457,202 (71.3)	
III	9 (2.5)	53,160 (8.3)	
IV	306 (85.5)	44,537 (6.9)	
Gleason grade group			< 0.001
1	3 (7.9)	124,621 (37.0)	
2	4 (10.5)	102,636 (30.5)	
3	3 (7.9)	46,654 (13.9)	
4	4 (10.5)	29,848 (8.9)	
5	24 (63.2)	32,607 (9.7)	
PSA			< 0.001
< 4	110 (41.7)	70,699 (12.1)	
≥ 4, <10	61 (23.1)	348,781 (59.8)	
≥ 10, <20	32 (12.1)	90,926 (15.6)	
≥ 20	61 (23.1)	73,052 (12.5)	

PSA indicates prostate-specific antigen; SCPC, small cell prostate cancer.

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score, and prostate-specific antigen (PSA) level.[5] It is unclear whether the adenocarcinoma staging criteria carry the same clinical value when applied to SCPC patients. Furthermore, it is not well understood whether the limited versus extensive staging system similar to that used in SCLC is feasible for SCPC patients.

Emerging studies have shown a potential link between androgen deprivation therapy (ADT) and the development of neuroendocrine tumors, including small cell cancer of the prostate.[6] However, there has been little clinical or epidemiological data that describes the risk of transformation from adenocarcinoma to a more aggressive type of cancer. In addition, it remains unclear whether SCPC patients with a history of adenocarcinoma have different outcomes than those with de novo SCPC.

In the present study, we utilized the Surveillance Epidemiology and End Result (SEER) database to investigate the incidence and clinical behavior of SCPC.

METHOD

Study Cohort

We obtained publicly available epidemiological data of patients diagnosed with prostate cancer between 2004 and 2016 from the National Cancer Institute SEER database. This database contains high quality data from 18 cancer registries and represents approximately 34.6% of the total US population based on the 2010 census.[7] All patient data are deidentified and available to the public. Thus, IRB approval was not required for the conduct of this study. The International Classification of Disease for Oncology histology codes 8002, 8041, 8042, 8043, and 8044 were used to define small cell carcinoma, and 8140 to identify adenocarcinoma. We analyzed the incidence rate, staging, treatment, overall survival, and disease-specific survival of SCPC.

Staging

Patients were staged using the latest staging criteria available at the time of diagnosis. American Joint Committee on Cancer 6th and 7th editions were used for patients diagnosed in 2004 to 2009 and 2010 to 2016, respectively. Definitions of limited stage and extensive stage are based on the presence of metastasis. Limited stage is defined as disease without any metastasis regardless of local T stage, whereas extensive stage is defined as disease with any type of metastasis, including locoregional lymph node (LN), distant LN, and/or other organs.

Statistical Analysis

The age-adjusted incidence rate was calculated based on the United States standard population in 2000. Trends of incidence over time were analyzed using a linear regression model and quantified using annual percentage change (APC). Survival analysis was performed using the Kaplan-Meier method and the difference between groups was compared using log-rank test. SEER*Stat 8.3.5 (National Cancer Institute, Maryland) and GraphPad Prism 8.1.1 (GraphPad Software, California) were used for the above-mentioned analysis.

RESULTS

Study Cohort Characteristics

We identified a total of 719,655 patients with prostate cancer between 2004 and 2016, including 403 (0.056%) patients with SCPC. The median age at diagnosis was 71 years

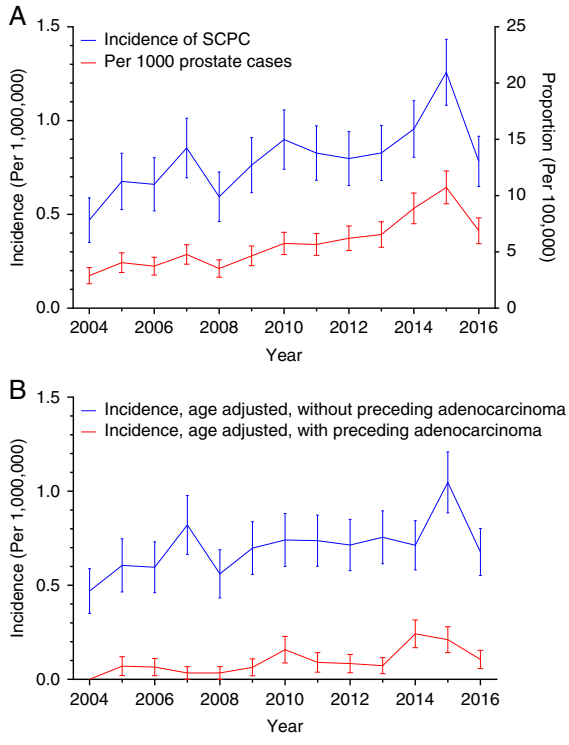

FIGURE 1. A, Incidence trend and proportion of all prostate cancers of SCPC from 2004 to 2016. B, Incidence trend of SCPC stratified by preceding adenocarcinoma. SCPC indicates small cell prostate cancer. full color online

TABLE 2. Characteristics of Limited Stage Versus Extensive Stage SCPC

	n (%)		
	Limited Stage (N = 83)	**Extensive Stage (N = 275)**	***P***
Age			
Median	73	70	0.03
Range	54-96	30-95	
Median survival (mo)	17	9	<0.001
Survival rate			
1 y	56.1	34.4	<0.001
3 y	32.8	5.9	<0.001
5 y	24.2	3.0	<0.001
Multiple primary			
First malignancy	57 (68.7)	212 (77.1)	0.12
Not first malignancy	26 (31.3)	63 (22.9)	
Adenocarcinoma	15 (57.7)	28 (44.4)	
Other cancer	5 (19.2)	14 (22.2)	0.5
Unknown	6 (23.1)	21 (33.3)	
PSA			
<4	21 (39.6)	83 (42.6)	<0.001
≥4, <10	22 (41.5)	35 (17.9)	
≥10, <20	7 (13.2)	22 (11.3)	
≥20	3 (5.7)	55 (28.2)	
Treatment			
Surgery	38 (45.8)	69 (25.1)	<0.001
TURP	26 (31.3)	55 (20.0)	
Prostatectomy	9 (10.8)	10 (3.6)	
Radiation	28 (33.7)	84 (30.5)	0.58
External beam	24 (28.9)	83 (30.2)	
Chemotherapy	35 (42.2)	183 (66.5)	<0.001

PSA indicates prostate-specific antigen; SCPC, small cell prostate cancer; TURP, transurethral resection of the prostate.

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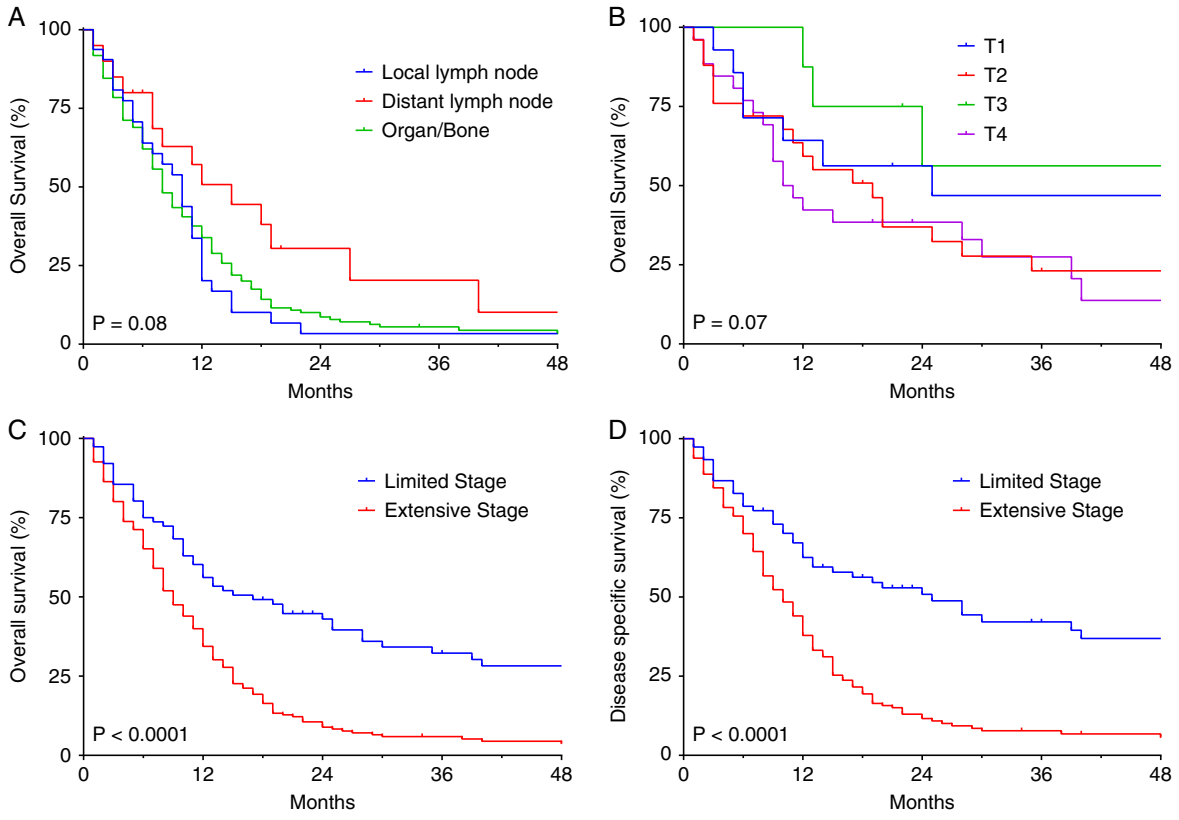

FIGURE 2. A, Overall survival of extensive stage SCPC stratified by type of metastasis. B, Overall survival of limited-stage SCPC stratified by local T stage. C, Overall survival of SCPC stratified by limited-versus-extensive stage. D, Disease-specific survival of SCPC stratified by limited-versus-extensive stage. SCPC indicates small cell prostate cancer. full color online

(range, 30 to 96 y). Of the 403 patients, 310 had SCPC as their first malignancy. The remaining 93 patients had at least one other malignancy before SCPC, including 48 patients who had adenocarcinoma of the prostate preceding SCPC. In comparison to patients with adenocarcinoma (Table 1), SCPC patients were older at the time of diagnosis (71 vs. 66 y), presented at later stage (stage IV 85.5% vs. 6.9%), more likely to have Gleason grade group 5 (63.2% vs. 9.7%), and were more likely to have a normal PSA (41.7% vs. 12.1%); a greater proportion of SCPC patients also had at least one other malignancy preceding the diagnosis of SCPC (23.1% vs. 8.3%). The majority of SCPC patients presented in stage IV (85.5%), whereas most patients with prostatic adenocarcinoma presented in stage II (71.3%).

At the end of the follow-up period, 345 SCPC patients had died, including 290 whose deaths were attributable to prostate cancer. The median overall survival was found to be 9 months, and the 5-year survival rate was 8.2%.

Incidence Trend of SCPC

Overall, the age-adjusted incidence of SCPC is 0.81 per 1,000,000 person-years for the duration of the study period. An increase in the age-adjusted incidence of SCPC from 0.47 in 2004 to 0.783 in 2016 was observed, corresponding to an APC of 4.52% (Fig. 1A, $P<0.05$). The percentage of SCPC in all types of prostate cancer increased by 2.4-fold from 2.9 per 100,000 in 2004 to 6.9 per 100,000 in 2016 (Fig. 1B, $P<0.001$). In patients with a history of prostate adenocarcinoma, the age-adjusted annual incidence of SCPC increased from 0 in 2004 to 0.07 in 2005 and 0.106 in 2016, corresponding to an APC of 12.65% (Fig. 1B, $P<0.05$). In contrast, in patients without a history of prostate adenocarcinoma, the age-adjusted incidence rate increased from 0.47 in 2004 to 0.677 in 2016, corresponding to an APC of 3.2% (Fig. 1B, $P<0.05$).

The Limited-Versus-Extensive Staging System

A total of 358 SCPC patients with known metastatic status were stratified according to the limited and extensive disease staging system: 83 (23.2%) patients were found to have limited-stage disease, whereas 275 (76.8%) patients had extensive stage disease (Table 2). In addition, 45 patients had incomplete staging information were excluded from further analysis. Patients with extensive stage disease were younger in age (70 vs. 73 y, $P=0.03$) and were more likely to have PSA above 20 (28.2% vs. 5.7%, $P<0.001$). In both groups, a similar proportion of patients had SCPC as their first malignancy (77.1% vs. 68.7%, $P=0.12$). In those who had at least one other malignancy preceding SCPC, a similar proportion of patients had adenocarcinoma of the prostate before SCPC (44.4% vs. 57.7%, $P=0.5$). With regard to cancer therapy, patients with limited-stage disease were more likely to undergo surgical treatment (mostly transurethral resection of the prostate [TURP] and prostatectomy) in comparison to those with extensive stage disease (45.8% vs. 25.1%, $P<0.001$). Patients with extensive stage disease were more likely to receive chemotherapy relative to those with limited-stage disease (66.5% vs. 42.2%, $P<0.001$). A similar proportion of patients from both groups received radiation.

There were no significant differences in outcome among patients who had limited-stage disease with different T stages

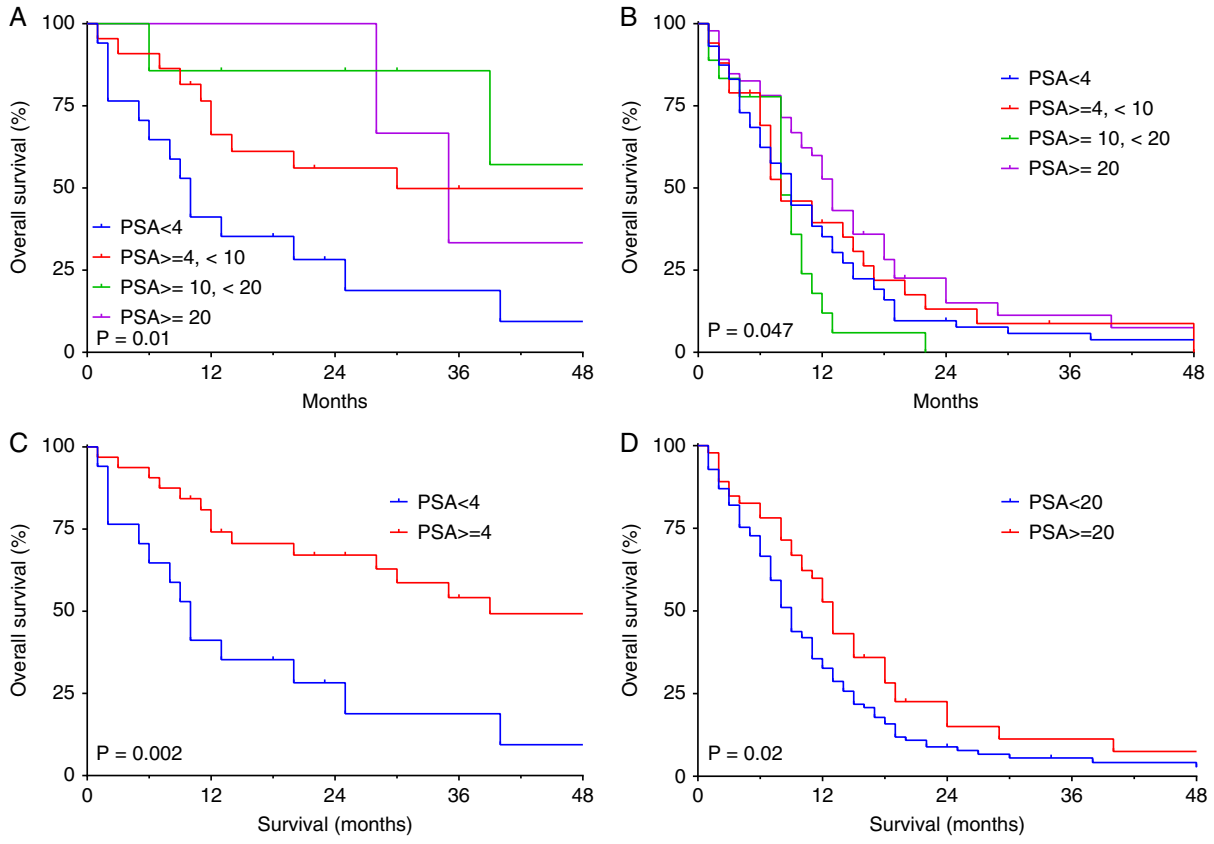

FIGURE 3. A, Overall survival of limited-stage SCPC stratified by PSA level. B, Overall survival of extensive stage SCPC stratified by PSA level. C, Overall survival of limited-stage SCPC stratified by PSA level <4 and ≥4. D, Overall survival of extensive stage SCPC stratified by PSA level <20 and ≥20. PSA indicates prostate-specific antigen; SCPC, small cell prostate cancer. full color online

(Fig. 2A, $P=0.07$). Similarly, patients with extensive stage disease involving locoregional LN, distant LN, and solid organ (including bone) metastases had a similar survival (Fig. 2B, $P=0.08$). Overall, patients with localized disease had significantly better overall survival (17 vs. 9 mo, $P<0.0001$, Fig. 2C) and disease-specific survival (25 vs. 10 mo, $P<0.0001$, Fig. 2D) compared with patients with extensive disease SCPC.

On the basis of disease stage, 21 (39.6%) patients with limited-stage SCPC and 83 (42.6%) with extensive disease SCPC had a normal PSA at presentation, respectively. However, a higher proportion of patients with extensive stage SCPC had PSA ≥ 20 as compared with patients with limited-stage disease (28.2% vs. 5.7%). In both groups, PSA levels are associated with patient outcome (Figs. 3A, B). Specifically, in patients with limited-stage disease, those with PSA < 4 had a worse overall survival compared with those with PSA ≥ 4 (10 vs. 39 mo, $P=0.02$, Fig. 3C). Similarly, in patients with extensive stage disease, those with PSA < 20 had a worse overall survival than those with PSA ≥ 20 (9 vs. 13 mo, $P=0.002$, Fig. 3D).

Upon comparing outcome of SCPC patients with and without prior history of malignancies, there was no significant difference in overall survival between SCPC patients with no prior malignancy and those with a history of prostate adenocarcinoma or other malignancies (Figs. 4A, B).

The impact of treatment modalities on outcome was also evaluated. In this relatively small sample set, there was no significant benefit in overall survival for patients with limited-stage disease who underwent TURP or prostatectomy (13 vs. 20 mo, $P=0.68$, Fig. 5A), external beam radiation (20 vs. 12 mo, $P=0.62$, Fig. 5C) or chemotherapy (24 vs. 12 mo, $P=0.68$, Fig. 5E). Patients with extensive stage disease who had chemotherapy had significantly improved survival as compared with those who were treated with other therapies (11 vs. 3 mo, $P<0.001$, Fig. 5F). Treatment with TURP or prostatectomy (8 vs. 9 mo, $P=0.44$, Fig. 5B) or external beam radiation (9 vs. 9 mo, $P=0.1$, Fig. 5D) conferred no survival benefit for patients with extensive stage disease.

A multivariate analysis was performed to rule out possible confounding factors including age and treatment modalities given that many patients received > 1 type of treatment. The results of the multivariate analysis mirrored the univariate analysis, showing that improvement in survival was limited to patients with extensive stage disease who had undergone chemotherapy (Table 3, hazard ratio: 0.52, $P<0.001$).

DISCUSSION

In this study, we analyzed the incidence, outcome, and prognostic factors of SCPC by utilizing a population-based registry. SCPC is a rare histologic type of prostate cancer that continues to have dismal outcomes. On the basis of the degree of metastasis, SCPC can be divided into limited and extensive stage disease. Extensive stage disease is associated with inferior survival compared with limited-stage disease. Furthermore, patients with limited-stage disease have similar overall survival regardless of their local T stage and patients with extensive

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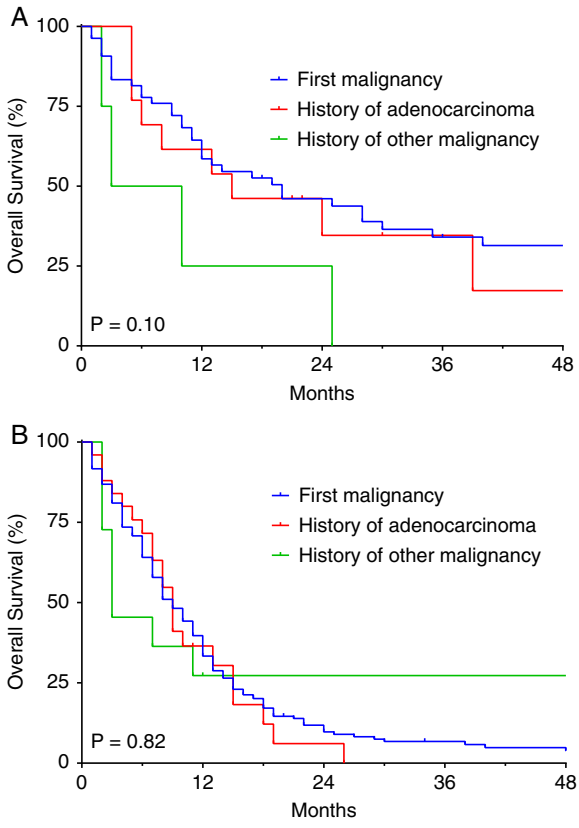

FIGURE 4. A, Overall survival of limited-stage SCPC stratified by preceding malignancies. B, Overall survival of extensive stage SCPC stratified by preceding malignancies. SCPC indicates small cell prostate cancer. full color online

stage disease had a similar outcome regardless of their degree of metastasis.

An increasing incidence of SCPC was observed in our study, which is consistent with the current body of literature. Advancement of histologic techniques and promotion of disease awareness has likely led to an increase in diagnosis.[8] There is some evidence that novel ADT is directly linked to treatment-related neuroendocrine prostate cancer including SCPC. Neuroendocrine tumors are hormone refractory, though androgen receptor (AR) signaling can still occur through AR gene amplification and intratumoral androgen production, among other mechanisms.[5] Studies suggest that prostatic adenocarcinoma in the setting of ADT exhibits overexpression of aurora kinase A and n-MYCN genes, which are specific to neuroendocrine tumors.[6] Neuroendocrine differentiation is also thought to act as a mechanism of resistance to therapy. The increasing use of second-generation androgen signaling inhibitors including abiraterone, enzalutamide, and apalutamide in prostate adenocarcinoma might contribute to the rising incidence of SCPC as noted in our study.[9]

Our analysis demonstrated superior overall survival in patients with limited-stage SCPC relative to those with extensive stage SCPC. A previous study has investigated neuroendocrine tumors of the prostate, including SCPC, and concluded that the presence of metastasis is associated with inferior overall survival.[10] However, previous studies that utilized the National Cancer Database (NCDB) drew somewhat different conclusions with regard to SCPC. A study by Weiner et al[11] of 287 patients with localized SCPC concluded that advanced T stage higher than cT3 was associated with worse survival in men who received local therapy. Our study, however, revealed that patients with limited-stage disease had similar overall survival despite local T stage. Furthermore, a study by Cohen et al[12] of 379 patients with metastatic SCPC suggested that patients with distant metastasis had worse survival as compared with those with regional metastasis. In contrast, all patients with metastatic SCPC in our study had similar overall survival regardless of the type of metastasis. There might be several reasons for these differences. First, the sampling strategies of the SEER database and the National Cancer Database are quite different.[13] Every SEER registry requires all hospitals in its geographical area to report all cancer diagnosis, providing a patient sample closely resembles the general population. While the NCDB only includes cases reported by Commission on Cancer accredited hospitals which represent about one third of all hospitals nationwide, resulting in a different patient population being selected. Secondly, the time frame for the NCDB-based studies (1998 to 2011) was earlier than for our study (2004 to 2016). While there have been only minor changes in staging criteria over the specified time period, advances in imaging techniques and other staging studies have provided the opportunity for more precise staging of prostate cancer. This is reflected by the presence of metastases at diagnosis in 75.5% of patients with extensive stage disease in our study, in contrast to 56.9% of patients in the earlier NCDB cohorts. Third, while the survival difference associated with T stage in limited-stage patients are only observed in those who received localized therapy, compared with the NCDB cohort, a smaller number of limited-stage patients in our cohort received local treatment: 8.4% versus 13.2% for radical prostatectomy and 33.7% versus 46.0% for radiation.

SCPC is generally a non-PSA producing tumor, though a subset of patients has fluctuations in their PSA level, likely due to either the interactions between the cancerous tissue and normal prostate tissue, or the presence a mixed histology. In our cohort, patients with extensive stage disease are more likely to have a PSA level higher than 20, suggesting a positive correlation between tumor burden and PSA level and makes the hypothesis of mixed histology more likely. Furthermore, our analysis showed better overall survival in limited-stage patients with PSA $\geq$ 4 and extensive stage patients with PSA $\geq$ 20, compared with their counterpart with lower PSA. This paradoxical relationship between PSA and outcome can also be explained by the presence of PSA-secreting androgen-dependent disease, which confers a less aggressive disease course thus better prognosis. Further research into the possible mechanisms dictating this observed survival benefit is needed. Furthermore, given the lack of clear association between disease burden and PSA level in SCPC patients, PSA could not be reliably used to monitor disease progression in SCPC. Further studies are warranted to clarify the role of neuroendocrine tumor markers including Chromogranin A, neuron-specific enolase, and pro-gastrin-releasing peptide in SCPC patients.[14,15]

There is much ambiguity associated with the management of SCPC, and an algorithmic approach to SCPC management is yet to be established. The National Comprehensive Cancer Network (NCCN) guidelines encourage modeling SCPC management according to NCCN guidelines for SCLC due to similarities in the histology and disease progression pattern of these 2 diseases.[16] Our study confirmed the value of chemotherapy in management of extensive stage SCPC, but not in localized stage SCPC. This is in line with previous NCDB-based studies.[11,12] In regard to localized therapy, including surgery and radiation therapy, previous studies reported survival benefit of localized therapy in limited-stage disease, but

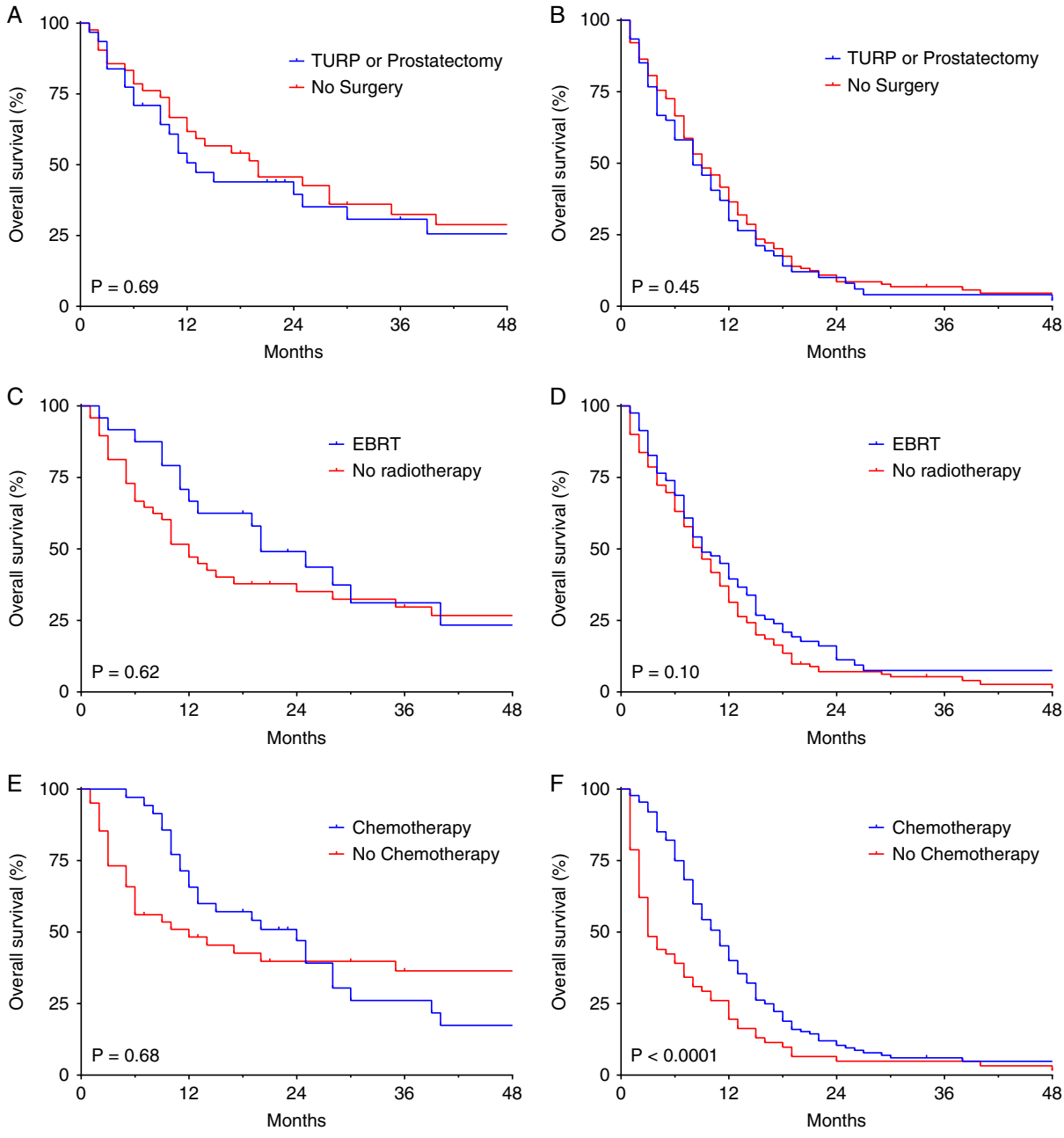

FIGURE 5. A, C, and E, Overall survival of limited-stage SCPC stratified by surgery (A), radiation (C), and chemotherapy (E). B, D, and F, Overall survival of extensive stage SCPC stratified by surgery (B), radiation (D), and chemotherapy (F). SCPC indicates small cell prostate cancer. TURP indicates transurethral resection of the prostate. EBT indicates external beam radiotherapy. full color online

not in extensive stage disease.[11,12] However, in our study, we did not find survival difference between those who received local therapy and those who did not. This could be due to a significant higher proportion of patients with T4 stage disease in our cohort (33.8% vs. 16.0%) who are less likely to benefit localized therapy.

Currently, combination chemotherapy with etoposide and cisplatin are treatments of choice in SCPC.[5,17] A phase II study of patients with metastatic SCPC treated with doxorubicin, etoposide, and cisplatin revealed that addition of doxorubicin to the conventional regimen resulted in more adverse events without improvement in outcomes.[18] There are currently ongoing clinical trials that may further shape the treatment of SCPC. Shimomura et al demonstrated a decrease in neuroendocrine markers in 5 out of 7 cases after everolimus treatment.[15] A phase II multi-institutional trial of 60 patients with SCPC or prostate cancer with neuroendocrine features treated with alisertib (Aurora Kinase A inhibitor) revealed a median overall survival of 9.5 months in response to therapy.[19] Another ongoing clinical trial of avelumab treatment for 18 participants with neuroendocrine prostate cancer may also introduce a new modality of treatment as part of an algorithmic approach to contain the spread of lethal SCPC.[20]

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TABLE 3. Multivariate Analysis of Treatment of SCPC Patients Stratified by Disease Stage

	Limited Stage			Extensive Stage		
	HR	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age (each year)	1.05	1.01-1.08	0.004	1.02	1.01-1.03	0.002
Surgery						
No surgery	Ref	Ref	Ref	Ref	Ref	Ref
TURP	1.52	0.85-2.73	0.16	1.07	0.78-1.47	0.68
Prostatectomy	0.56	0.20-1.54	0.26	0.69	0.34-1.40	0.30
Radiation						
No/unknown	Ref	Ref	Ref	Ref	Ref	Ref
External beam	0.98	0.50-1.93	0.96	0.79	0.59-1.06	0.11
Chemotherapy						
No/unknown	Ref	Ref	Ref	Ref	Ref	Ref
Yes	0.75	0.41-1.37	0.75	0.52	0.39-0.68	< 0.001

CI indicates confidence interval; HR, hazard ratio; Ref, reference; SCPC, small cell prostate cancer; TURP, transurethral resection of the prostate.

SCPC remains an aggressive disease, and our study sheds light on its epidemiologic and clinical features. We partially controlled for the inherent biases of a retrospective study by having a large sample size. However, information bias and selection bias cannot be completely controlled. Furthermore, an inherent fallacy of using a cancer registry-based data is that the impact of missing data or inconsistency in data collection cannot be assessed.[21] It is known that the SEER database is not an optimal tool for analyzing the impact of treatment because treatment information is, oftentimes, not correctly captured. Prospective studies are warranted to further clarify the optimal management approach and explore new treatment options for this condition.

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