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ORIGINAL RESEARCH

Evaluating the Effect of Cryptorchidism on Clinical Stage of Testicular Seminoma

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Objective: To study the effect of cryptorchidism on clinical stage (CS) of testicular seminoma (TS).

Patients and Methods: In the Surveillance Epidemiology and End Results (SEER) database (2006-2016), people with TS were enrolled in our research. Multivariable logistic regression models were constructed to compare the impact of cryptorchidism on CS.

Results: This research was based on the registry information of 12,991 TS patients. All patients with a median age of 36 (13–107) years were pathologically diagnosed with orchiectomy or needle biopsy specimens. Patients with CS I, II, and III TS accounted for 70.68% (n = 9182), 8.30% (n = 1078), and 5.75% (n = 747) of all patients, respectively; still there were 15.27% (n = 1984) of patients whose CS could not be identified or was not available. Among all included patients, 43.45% (n = 5644) of them had normal testis, 2.93% (n = 272) had cryptorchidism, and the primary site of 54.46% (n = 7075) of patients' testis was unavailable. According to our study, patients with cryptorchidism were more likely to suffer advanced CS [OR=1.14, 95% CI (1.01–1.28), p=0.0407]. Furthermore, this effect became more remarkable after adjusting for other factors including age, region, marital status, race, year of diagnosis and laterality [OR=1.23, 95% CI (1.13–1.32), p<0.0001].

Conclusion: According to this study, TS patients with cryptorchidism would be at a higher risk of suffering advanced cancer than patients with normal testis. It demonstrates that surgical correction for cryptorchidism should be timely, and specific management should be conducted on this kind of TS patients.

Keywords: testicular seminoma, cryptorchidism, clinical stage

Introduction

Testicular germ cell tumors (TGCTs) are relatively rare, accounting for only 1% of all cancers in men.[1] However, they represent 11% of the cancers diagnosed in adolescent males and are the most common solid tumors in adult men between the ages of 20 to 35.[2] And pure seminoma accounts for around 50% of all TGCTs.[2]

Cryptorchidism is a very common dysmorphia of the male urogenital system, affecting 2–4% of male infants.[3–5] As we all know, cryptorchidism is one of the risk factors of testicular cancer, with approximately 10% of testicular cancer occurring in this setting.-[1,2,5] Men with a previous history of cryptorchidism have a higher risk of suffering testicular cancers, which appears to be 5–10 times more common than in normal people.[2,6,7]

To our knowledge, there were several studies[1–15] describing the relationship between cryptorchidism and testicular cancer, but no one reported whether cryptorchidism affects the clinical stage of testicular cancer.

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This study aimed to explore the effect of cryptorchidism on clinical stage (CS) of testicular seminoma (TS). We had conducted a study of TS based on the information from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database (2006-2016).

Methods

Study Population

We identified men with testicular seminoma [International Classification of Disease for Oncology (ICD-O-3) code 9061/3] from 2006 to 2016 from cancer registries captured by the Surveillance Epidemiology and End Results (SEER) Program. As shown in Figure 1, tumors containing elements other than seminoma and patients with neoplasms in other sites were excluded. Our study enrolled 12,991 patients, who were stratified based on primary site of testis: normal testis, cryptorchidism and NOS. Data we obtained from the database contained age, region, marital status, race, year of diagnosis, laterality, primary site of testis (with or without cryptorchidism), CS, TNM stage. All patients had AJCC staging assignments. The total available covariates are listed in Table 1.

Independent Variable and Endpoint

In our study, the independent variable of interest was primary site of testis, in other words, whether patients merged cryptorchidism. And the endpoint of this study was clinical stage (CS).

Statistical Analysis

Firstly, we assessed the distribution of baseline characteristics with the use of a two-sample *t*-test and a chi-square test to compare continuous and categorical variables, respectively. Data were presented as median (minimum value – maximum value) for continuous variables and as frequency (%) for categorical variables.

Secondly, multivariable logistic regression models were conducted to compare the impact of different primary site of testis on CS, with adjustment for age, region, marital status, race, year of diagnosis and laterality.

All statistical analyses were performed using Empower Stats (http://www.empowerstats.com, X&Y Solutions, Inc, Boston, MA). A P value <0.05 was considered statistically significant.

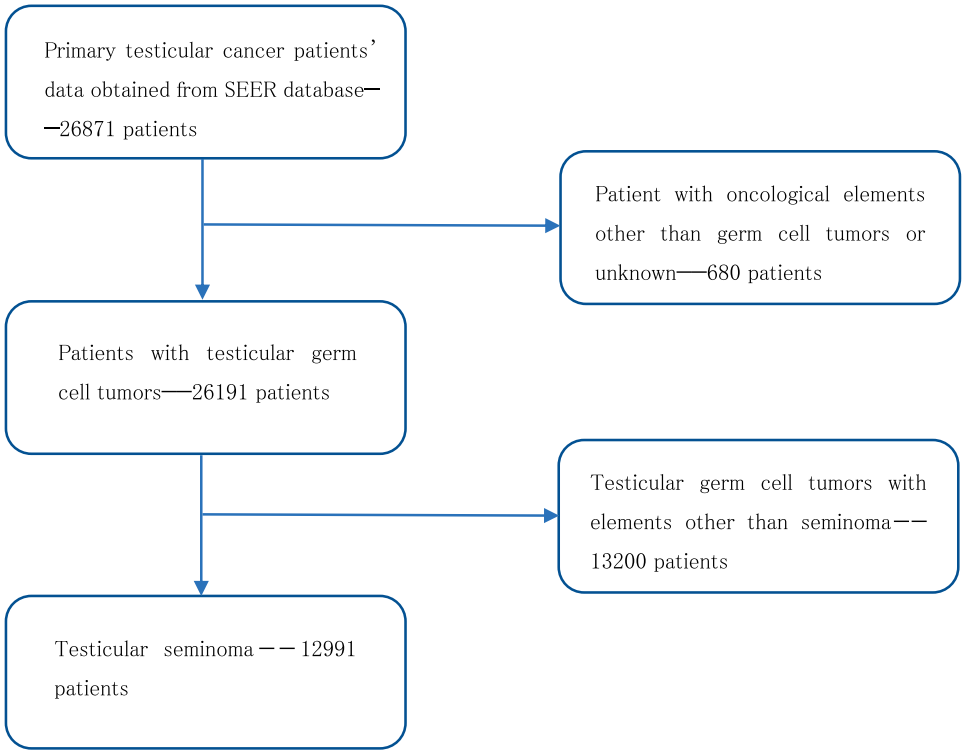

Figure 1 Flowchart of the patients' selection.

Table 1 Baseline Characteristics of 12,991 Patients Stratified Based on Primary Site of Testis

Primary Site of Testis	Normal Testis	Cryptorchidism	Testis, NOS	P value
N	5644	272	7075	
Age	36.0 (14.0–90.0)	36.5 (13.0–71.0)	37.0 (13.0–107.0)	<0.001
Region				<0.001
Pacific Coast	3400 (60.24%)	127 (46.69%)	3382 (47.80%)	
Alaska	16 (0.28%)	0 (0.00%)	13 (0.18%)	
East	1075 (19.05%)	117 (43.01%)	2916 (41.22%)	
Northern Plains	568 (10.06%)	15 (5.51%)	497 (7.02%)	
Southwest	585 (10.36%)	13 (4.78%)	267 (3.77%)	
Marital status				<0.001
Single	2148 (38.06%)	107 (39.34%)	2614 (36.95%)	
Married	2850 (50.50%)	138 (50.74%)	3441 (48.64%)	
Divorced/widowed	328 (5.81%)	16 (5.88%)	435 (6.15%)	
Unknown	318 (5.63%)	11 (4.04%)	585 (8.27%)	
Race				<0.001
White	5066 (89.76%)	226 (83.09%)	6211 (87.79%)	
Black	154 (2.73%)	17 (6.25%)	255 (3.60%)	
Asian/Pacific Islander	221 (3.92%)	22 (8.09%)	283 (4.00%)	
American Indian/Alaska Native	75 (1.33%)	2 (0.74%)	85 (1.20%)	
Unknown	128 (2.27%)	5 (1.84%)	241 (3.41%)	
Year of diagnosis				<0.001
2006	442 (7.83%)	24 (8.82%)	606 (8.57%)	
2007	455 (8.06%)	25 (9.19%)	593 (8.38%)	
2008	460 (8.15%)	20 (7.35%)	677 (9.57%)	
2009	488 (8.65%)	30 (11.03%)	644 (9.10%)	
2010	499 (8.84%)	41 (15.07%)	644 (9.10%)	
2011	407 (7.21%)	30 (11.03%)	725 (10.25%)	
2012	403 (7.14%)	17 (6.25%)	732 (10.35%)	
2013	563 (9.98%)	17 (6.25%)	653 (9.23%)	
2014	681 (12.07%)	28 (10.29%)	622 (8.79%)	
2015	612 (10.84%)	22 (8.09%)	566 (8.00%)	
2016	634 (11.23%)	18 (6.62%)	613 (8.66%)	
Laterality				<0.001
Left	2671 (47.32%)	116 (42.65%)	3264 (46.13%)	
Right	2942 (52.13%)	146 (53.68%)	3657 (51.69%)	
Bilateral	1 (0.02%)	3 (1.10%)	8 (0.11%)	
Only one side – side unspecified	6 (0.11%)	1 (0.37%)	25 (0.35%)	
Paired site, but no information concerning side	24 (0.43%)	6 (2.21%)	121 (1.71%)	

Results

A total of 12,991 TS patients were included in our study. All patients were diagnosed pathologically through surgery or needle biopsy. The participants were 13–107 years old, with a median age of 36 years. Among all patients, 43.45% (n = 5644) of them had normal testis, 2.93% (n = 272) had cryptorchidism, and the primary site of 54.46% (n = 7075) patients' testis was unavailable. Details of the baseline information were tabulated in Table 1 and were stratified according to primary site of testis.

According to the AJCC staging system, patients were categorized as followed: 9182 (70.68%) with CS I, 1078 (8.30%) with II, 747 (5.75%) with III, and the information was not available in 1984 (15.27%) patients.

As reported in Table 2, in patients with cryptorchidism, CS I, II, and III TS accounted for 60.29% (n=164), 14.71% (n = 40), and 10.29% (n =28) respectively; still, there were

Table 2 Clinical Stage of Different Group Patients

Clinical Stage	Primary Site of Testis			P value
	Normal Testis	Cryptorchidism	Testis, NOS	
I	3995 (70.78%)	164 (60.29%)	5023 (71.00%)	<0.001
II	485 (8.59%)	40 (14.71%)	553 (7.82%)	
III	299 (5.30%)	28 (10.29%)	420 (5.94%)	
NA	865 (15.33%)	40 (14.71%)	1079 (15.25%)	

14.71% (n = 40) patients whose CS could not be identified or was not available. And proportion of CS I, II, III and unknown CS were 70.78% (n=3995), 8.59% (n=485), 5.30% (n=299) and 15.33% (n=865), respectively, in patients with normal testis. The component ratio was also intuitively presented in Figure 2.

Results of the multivariate logistic regression model showed that cryptorchidism involved advanced CS [OR=1.14, 95% CI (1.01–1.28), p=0.0407] (Table 3). Furthermore, after adjusting for other factors including age, region, marital status, race, year of diagnosis and laterality, this effect became even more remarkable [OR=1.23, 95% CI (1.13–1.32), p<0.0001] (Table 3).

Discussion

The association between cryptorchidism and testicular cancer has been well documented very long before. As far back as 1924, Hobday[9] had found testicular cancer occurring more frequently in undescended testicles than in those normally placed.

Along with more and more studies published,[1,3–16,9–15] cryptorchidism is already an accepted morbidity risk factor for testicular cancer. Batata et al[13] found 13 out of 14 uncorrected cryptorchid patients between 1934 and 1975 developed TGCT in their abdominal testes. The incidence of testicular cancer for adults with cryptorchidism in childhood is reported to be 5–10 times greater than normal.[3,7,16] And it has been shown that 10% of men who develop testicular cancer, have a history of cryptorchidism or merge cryptorchidism in the meantime.[1,3,6] Moreover, there is an increased risk of testicular cancer occurrence in bilateral as opposed to unilateral cryptorchidism.[6]

The possible mechanism in which cryptorchidism increases the incidence risk of testicular cancer may embody in following aspects: (1) Heat: A study conducted by Cortes et al[10] showed that an abdominal testis presents a greater risk for TGCT than an inguinal testis. (2) Maternal hormone patterns: Holl et al[18] found that high dehydroepiandrosterone (DHEAS) levels in mothers were associated with a significantly decreased risk of TGCT in the offspring, whereas mothers with high androstenedione levels conferred an increased risk of TGCT to their offspring. (3) It is more difficult to be early discovered malignant transformation for an abdominal testis than a normal one, for most patients feel no pain. And clinical stage has progressed when diagnosed.

Although most testicular cancers in men with a history of maldescent occur on the ipsilateral side, approximately 5% to 10% occur in the contralateral testis.[17] In our study, 3 of 272 patients with cryptorchidism had bilateral TS. The reason why testicular cancers occur in the normal side probably because cryptorchidism is not the only risk factor. Apart from that, gonadal dysgenesis, injury, hormones, genetic factors, chemical carcinogens, orchiatrophy, testicular microlithiasis and even birth weight and length are identified as risk factors.[1,17] So among part of men with cryptorchidism, although the contralateral testicles

Table 3 Multivariable Logistic Regression Analysis for CS

Primary Site of Testis	Non-Adjusted Model		Adjusted Model	
	OR (95% CI)	P value	OR (95% CI)	P value
Normal testis	0		0	
Cryptorchidism	0.14 (0.01, 0.28)	0.0407	0.23 (0.13, 0.32)	<0.0001
Testis, NOS	0.00 (−0.04, 0.04)	0.8906	0.04 (0.01, 0.07)	0.0110

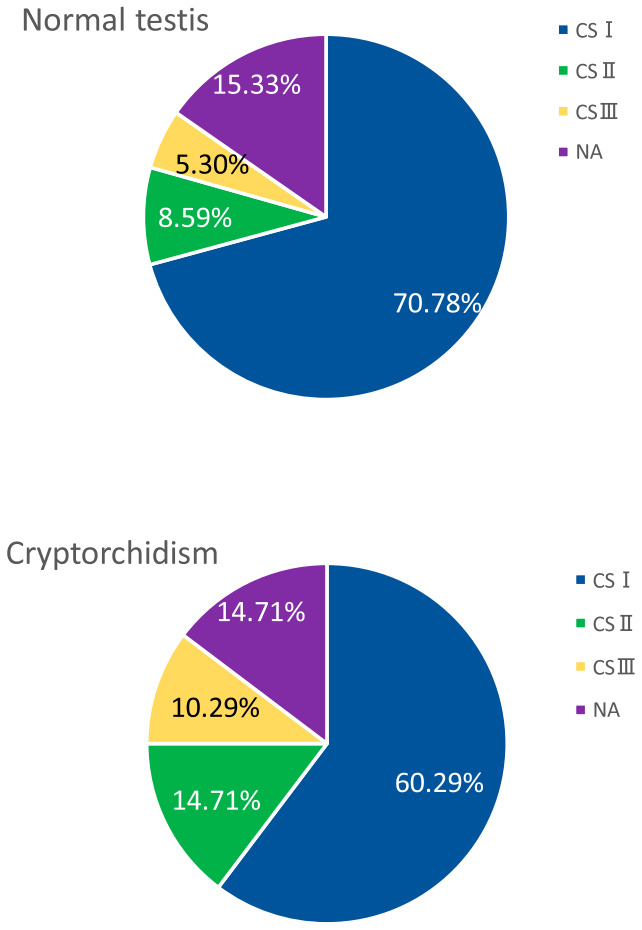

Figure 2 Clinical stage in patients with normal testis and cryptorchidism.

descend normally, other risk factors could cause the occurrence of testicular cancers.

Several studies had explored correlation between the age of surgery and risk of testicular cancer. Pettersson et al[16] studied almost 17,000 cryptorchidism patients who received surgery with the average age of 8.6 years between 1964 and 1999. Among them, 56 individuals developed testicular cancer. The incidence rate of those who had corrective surgery before the age of 13 was 2.23%, while that of those received surgery after 13 was 5.4%. However, a study that Hack et al[15] performed did not find a similar result, which showed that the occurrence risk of testicular cancer was somewhat higher in patients with cryptorchidism even after early surgical correction.

Although it is common knowledge that cryptorchidism increased the incidence of testicular cancer, no study reported whether cryptorchidism affects the CS of testicular cancer yet. As was reported in our study, advanced CS accounted for a greater proportion in patients with cryptorchidism while comparing with those with normal testis. The risk of advanced CS in patients with cryptorchidism was 1.14 fold of those who had normal testis, and became 1.23 fold after removing the effect of other factors including age, region, marital status, race, year of diagnosis and laterality.

This is the first study reporting the effect of cryptorchidism on clinical stage of testicular seminoma. Our findings presented TS patients with cryptorchidism would be more likely to have a higher CS than patients with normal testis. What is more, it based on a large and multiracial scope. Moreover, the availability of multiple clinical variables was its another advantage.

There are still some limitations of our study. Due to its retrospective nature, not all clinical data were collected in SEER database, which is the common defect in any observational studies. In addition, there may exist some measurement bias and potential confounders. However, since the sample size of this study was large, the results would be still significant even if there existed these limitations.

Conclusion

According to this study, TS patients with cryptorchidism would be at a higher risk of suffering advanced cancer than patients with normal testis. It demonstrates that surgical correction for cryptorchidism should be timely, and specific management should be conducted on this kind of TS patients.

Ethics Statement

The data in our study were acquired from the SEER database, which was an open access database and there is no ethical approval needed.

Author contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors have no conflicts of interest to declare.

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