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A Cross-Sectional Analysis of Testicular Cancer Symptom Recognition and Stage of Diagnosis

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Abstract

There is a need to further explore the relationship between atypical symptom reporting and stage diagnosis to help develop a clearer defined list of possible testicular cancer (TC) symptoms that could assist physicians diagnose the disease earlier. A cross-sectional study was employed to explore possible associations between TC symptom presentation and stage of diagnosis. An original 40-item survey was distributed among 698 TC survivors to determine the potential impact of several risk factors, experiences, and behaviors upon diagnosis. This analysis aimed to explore how certain patient-driven experiences (e.g., symptoms, perceptions, and behaviors) could serve as catalysts for seeking medical care for testicular health concerns. Experiencing hot flashes or having no symptoms had a positive association with later-stage diagnosis while change in shape had a significant negative association with later-stage diagnosis. While the logistic regression model explained relatively low variance in the data ($R^2 = .1415$), it was statistically significant (χ^2 $p < .001$). Pain (odds ratio [OR] = 1.6524, $p < .05$), hot flashes (OR = 5.7893, $p < .01$), and no symptoms experienced (OR = 12.4836, $p < .01$) were all significant predictors of a more advanced stage diagnosis. The concern around uncommon/atypical symptoms are that they are indistinct and do not serve as clear signs that TC is present. However, perhaps in tandem with other more overt symptoms, their discovery can serve in a more confirmatory role for a suspect case. If observed with other uncommonly reported symptoms, these uncommon symptoms could provide another pathway in the TC diagnostic process. Clinical and patient education is warranted to increase awareness of uncommon TC symptoms.

Keywords

testicular cancer, oncology/cancer, symptoms, stage at diagnosis, patient advocacy

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Background

Testicular cancer TC ranks among the most commonly diagnosed neoplasms diagnosed in males 15 to 40 years of age (Raphael et al., 2021). TC treatment is remarkably effective, which is evidenced by a ~95% overall relative 5-year survival rate (Fung et al., 2017). If diagnosed in the early stages of development, the 5-year survival rate is ~99%. When diagnosed with distant metastasis, this rate drops to 73% (Raphael et al., 2021). Survivors of metastatic TC require cisplatin-based chemotherapy and are, therefore, more heavily burdened with lifelong quality of life complications (psychologically and

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physiologically) compared with if they were diagnosed in earlier stages (ArdeshirRouhaniFard et al., 2021; De et al., 2021; Kerns et al., 2018).

Research suggests that TC impact (i.e., rising incidence and/or disparate mortality) is rising throughout the majority of select subsets of males (Burkhamer et al., 2017; Li et al., 2020). For example, Ghazarian et al. (2015) indicate that Latinos will become the demographic subgroup with the highest incidence rate in the United States sometime in the next 10 to 15 years. Black/African Americans, further, have higher proportions of more advanced stage TC diagnoses and mortality in addition to males of lower socioeconomic status (SES) and more rural communities (Adams et al., 2018; Kamel et al., 2016; Markt et al., 2016). This may be attributed to the lack of endorsement of preventive practices (Rovito et al., 2016), such as testicular self-examination (TSE), a historically consistent lack of knowledge about TC symptoms among males (Cronholm et al., 2008; Kuzgunbay et al., 2013; Moore & Topping, 1999; Saab et al., 2019), environmental exposures (De Toni et al., 2019; Kollerud et al., 2020), or any combination of the above.

Despite generally favorable TC treatment outcomes, the substantial contrast in survivorship and quality of life between early- and late-stage cases warrants the need for interventions that promote early detection of TC. A critical component to this process is, at minimum, a modest registration of disease symptoms by the patient. As Saab et al. (2019) indicate, men remain relatively uninformed about testicular disorders, including signs and symptoms of TC. This, Saab et al. continue, lowers their intentions for seeking prompt medical attention for testicular symptoms. Another issue of concern that could affect disease symptom registration among males includes the United States Preventive Services Task Force's (USPSTF) recommendation against testicular examinations to screen for cancer (see Fadich et al., 2018; Rovito et al., 2016). Although the USPSTF states that their recommendations are just that (i.e., recommendations), others report that they have much more influence pertaining to if clinicians decide to advocate for TSE in their clinic or not, which affects if males perform the behavior (Rovito et al., 2018).

Symptom Presentation

TC usually presents within a diverse classification of symptoms with acute pain in the testes or scrotum, scrotal swelling and heaviness, abdominal pain, and/or a palpable mass being the most commonly reported ones (Baird et al., 2018). TC can present itself as manifestations to other parts of the body or exist asymptomatically. Uncommon symptoms have been recognized, such as back pain, abdominal pain, dyspnea, weight loss, and fatigue (Koo et al., 2020; Shephard & Hamilton, 2018). Night sweats and hot flashes have also been recorded (Koo et al., 2020; Norcross & Schmidt, 1986). Koo et al. (2020), for example, indicated in their study that nearly 10% of TC patients reported having night sweats. Koo et al. (2020) further noted that across all cancers, nearly 25% reported having hot flashes/night sweats. There may be, however, a lack of urgency to seek healthcare services regarding night sweats. Koo et al. (2020) outlined that as 54% of patients with germ cell cancer waited over 1 month after the onset of night sweats to seek medical care, the total for all germ cell tumor patients with symptoms only 25% overall waited >1 month.

Some literature suggests that there is a lack of research regarding a definite and defining list of TC symptoms (Neal et al., 2014), particularly the more uncommon ones. The concern around uncommon or atypical symptoms is that they are inexact and indistinct and not very clear and/or obvious signs that TC is present. For example, given the observable presentation of commonly reported symptoms, Neal et al. (2014) reported that the median time of diagnosis to be 44 days, placing it among the shortest spans of all cancers. Yet, time to diagnosis increased by more than 1 month when symptoms not listed by the National Institute for Health and Care Excellence (NICE) presented (Din et al., 2015; Shephard & Hamilton, 2018).

The above scenario could quite possibly lead to a delay in initial diagnosis, which can lead to worse outcomes (Öztürk et al., 2015). Mian et al. (2021) illustrated this preceding issue within the context of the COVID-19 when delays in diagnosis due to the medical emergencies of pandemic could lead to worse outcomes among those afflicted with cancer. Therefore, there is a need to further explore the relationship between atypical symptom reporting and stage diagnosis to help develop a clearer defined list of possible TC symptoms that could assist physicians diagnose the disease earlier.

Method

Study Design

A cross-sectional study was employed to explore possible associations between TC symptom presentation and stage of diagnosis. An original 40-item survey was distributed among TC survivors to determine the potential impact of several risk factors, experiences, and behaviors upon diagnosis. This analysis aimed to explore how certain patient-driven experiences (e.g., symptoms, perceptions, and behaviors) could serve as catalysts for seeking medical care for testicular health concerns. Specifically, this analysis aimed to highlight the relationship between uncommon symptoms as the primary patient-associated push factor for an individual to seek medical attention.

This project further aimed to explore the relationships and/or possible patterns between symptom presentation and patient characteristics. Ethical approval to conduct this study was granted by the University of Central Florida (IRB reference: SBE-18-13992). The STROBE guidelines (Von Elm et al., 2007) were used to report on this study's findings.

Sampling Methodology

Study participants were recruited via convenience sampling techniques from a national database of TC survivors shepherded by the Testicular Cancer Society. Recruitment was conducted via email and social media channels. The study aimed to recruit any male who was 18+ years of age and had been diagnosed with TC. Exclusion criteria included those who had no previous diagnosis of TC and those who were actively undergoing treatment for TC at the time of data collection. Those currently not in remission were excluded from the study due to the physiological and psychological demands they could be possibly undergoing due to their treatments.

Interested participants were sent/granted access to a Qualtrics (Provo, UT, USA) online survey weblink to obtain access to consenting documentation and the questionnaire. The database is demographically representative of the population parameters of total US TC cases. Informed consent was collected on the first page of the survey where participants reviewed all appropriate study information and then indicated if they desired to proceed forward or not.

In total, 698 TC survivors completed the online survey. Of those, 15 were excluded for indicating they were never diagnosed with TC and 64 for not completing the survey in full, thus leaving 619 participant responses to be included in the final analysis.

Instruments and Measures

The 40-item "Self-Reported Experiences of Prevention and Diagnosis of Testicular Cancer" (SEPD-TC) questionnaire was distributed to assess participants' self-reported experiences of TC diagnosis, treatment, and recovery periods. Participants' perceptions and attitudes toward TSE practice were measured. This survey was developed due to a lack of available instruments that collected the exact information were desired from TC survivors.

The SEPD-TC instrument is comprised of five key domains: (1) demographics and family history, (2) knowledge/awareness of TSE/TC, (3) TSE practice, (4) symptoms, and (5) diagnosis. Symptom-related push factors were measured via a self-reported item inquiring from participants what specific symptoms prompted them to seek health care for their particular concern. Other factors used to assess patient-associated push factors and/or barriers included being medically insured at the time of diagnosis, the type of insurance (if insured) at the time of diagnosis, self-discovery of lump via TSE, annual income, and employment status at the time of diagnosis.

Stage of diagnosis was operationalized by one question that inquired at which stage of cancer was the participant originally diagnosed. The type of TC (either seminoma or nonseminoma) was measured via self-report in response to a prompt with what type of cancer were they diagnosed with by their attending medical professional. Race, ethnicity, education, marital status at the time of diagnosis, sexual orientation, along with other demographic variables, were controlled for as covariates.

Face and content validity of the survey were established through a series of peer conferencing and deliberation techniques among a total of three members of the research team. This panel of experts independently performed a systematic search of the literature and highlighted key domains of survivors of TC wellness, inclusive of TSE practice. This panel then conferred with each other in a series of meetings to establish the core structure of the survey. Within the subset of continuous variables, sufficient levels of internal consistency were reported among primary composite variables (Cronbach's α range = .7246–.8411). Validation analyses of the SEPD-TC are ongoing.

Analytical Plan

The current analysis performed included a set of bivariate Spearman's rho correlation analyses to assess individual relationships with self-reported symptoms that prompted health care seeking and later-stage diagnosis. This analysis preceded multiple ordered logistic regressions to assess the relationship of certain factors with later-stage diagnosis controlling for all factors. A secondary analysis of bivariate Spearman's rho correlation analyses was conducted to assess type of TC (seminoma or nonseminoma) with symptoms prompting health care seeking. Other correlations between demographic factors were not explored in this current study. These analyses were best fit to this study's data due to the nature of its cross-sectional methodology.

Variations of the regression model assessed the impact of modifying variables that were observed. All models were assessed at the 95% confidence interval. Variation inflation factors (VIFs) determined the presence of multicollinearity; a VIF greater than 3 was considered to be not significant (or findings inconclusive) and was not reported in this study.

Results

Demographic Overview

Table 1 highlights the demographic makeup of the study participants. The majority of study participants were White/Caucasian, married, and had more than high school education. The mean age was ~40. These numbers are a deviation from the prevalence of TC among males. Notably, younger males and minority races/ethnicities were underrepresented in the sample.

Primary Analyses

Participants responded to the question of what symptoms prompted them to make a clinical visit. Table 2 highlights the frequency of participant symptoms that helped spur them to visit a physician for their testicular health concern, as well as what stage each participant was diagnosed with TC. The sample size of stage diagnosis reflects slightly smaller values as some participants did not answer the stage question or did not know their exact stage.

Spearman's rho correlation analyses indicated the strength and significance of relationship between reported symptoms and stage diagnosis. The only nonsignificant association was with reported pain in the testicle. Experiencing hot flashes and having no symptoms had a positive association with later-stage diagnosis while change in shape had a significant negative association with later-stage diagnosis.

Results of the ordered logistic regression are shown in Table 3. While the model explained relatively low variance in the data (pseudo $R^2 = .1415$), it was statistically significant (χ^2 probability $< .001$). Pain (odds ratio [OR] $= 1.6524$, $p < .05$), hot flashes (OR $= 5.7893$, $p < .01$), and no symptoms experienced (OR $= 12.4836$, $p < .01$) were all significant predictors of a more advanced stage diagnosis. Other covariates of the model included race/ethnicity, age, sexual orientation, educational achievement, marital status at the time of diagnosis, employment status at the time of diagnosis, income at the time of diagnosis, insured status at the time of diagnosis, and TC type (nonseminoma vs. seminoma), none of which were significant predictors of stage diagnosis.

Discussion

This study addressed TC patient-associated push factors (i.e., symptoms) that prompted them to visit their clinician about their testicular health concern prior to diagnosis. We explored four predictive variable effects upon stage of diagnosis, including more common symptoms (e.g., change in testicle shape) and less common ones (e.g., pain, hot flashes, and no symptoms). This discussion will examine each of the

Table 1. Participant Demographics.

Demographic variable	% value
Race/ethnicity	
Caucasian/White	566 (91.46%)
African American/Black	3 (0.49%)
Asian/Pacific Islander	15 (2.46%)
American Indian/Alaska Native	2 (0.33%)
Non-White Hispanic	20 (3.28%)
Other	12 (1.97%)
Age	$\overline{x} = 40.18$ ($SD = 10.6$; range = 18–69)
Educational achievement	
Did not finish high school	10 (1.65%)
High school diploma/GED	133 (21.95%)
Technical school	61 (10.07%)
2-year associate's degree	62 (10.23%)
4-year bachelor's degree	185 (30.53%)
Master's degree	103 (17.00%)
Doctoral degree	34 (5.61%)
Other	18 (2.97%)
Sexual orientation	
Heterosexual	541 (89.42%)
Homosexual	46 (7.60%)
Bisexual	3 (0.50%)
Prefer not to say	7 (1.16%)
Marital status at the time of diagnosis	
Married	352 (57.99%)
Widowed	1 (0.16%)
Divorced	29 (4.78%)
Separated	6 (0.99%)
Never married	219 (36.08%)
Employment status at the time of diagnosis	
Unemployed	37 (6.73%)
Part-time employed	42 (7.64%)
Full-time employed	414 (75.27%)
Other	57 (10.36%)
Income at the time of diagnosis	
0–US$19,999	107 (19.89%)
US$20,000–US$39,999	130 (24.16%)
US$40,000–US$59,999	103 (19.14%)
US$60,000–US$79,999	71 (13.20%)
US$80,000–US$99,999	45 (8.36%)
US$100,000 or higher	82 (15.24%)
Medically insured status at the time of diagnosis	
Yes	470 (85.61%)
No	79 (14.39%)
Testicular cancer type	
Seminoma	282 (49.47%)
Nonseminoma	228 (40.00%)
Other	60 (10.53%)
Testicular cancer stage (simplified)	
Stage 1	259 (53.40%)
Stage 2	113 (23.30%)
Stage 3	113 (23.30%)

Note. GED = general educational development.

Table 2. Reported Symptoms and Stage Diagnosis Analyses.

Participant Response	Change in shape	Pain	Hot flash	No symptoms
No	185 (32.5%)	317 (55.7%)	530 (93.1%)	511 (89.8%)
Yes	384 (67.5%)	252 (44.3%)	39 (6.9%)	58 (10.2%)
Stage	**Change in shape**	**Pain**	**Hot flash**	**No symptoms**
1	200	117	9	9
2	71	56	8	11
3	48	44	17	30
Spearman (*p* value)	−.2938 (<.001)	−.0298 (.5159)	.1753 (<.001)	.2894 (<.001)

Table 3. Ordered Logistic Regression*.

Observations	450	
Probability of χ^2	<.0001	
Pseudo R^2	.1415	
	OR (95% CI)	*p* value
Change in shape	0.81 [0.47, 1.42]	.467
Pain	1.65 [1.02, 2.67]	.040
Hot flash	5.79 [2.34, 14.32]	.001
No symptoms	12.48 [5.02, 31.05]	.001

Note. CI = confidence interval.
*The following covariates were included in the model: age, race/ethnicity, educational achievement, sexual orientation, marital status at the time of diagnosis, employment status at the time of diagnosis, income at the time of diagnosis, insured status at the time of diagnosis, and TC type (nonseminoma vs. seminoma).

preceding experiences to determine their potential influence in TC staging process.

Regarding change in shape, no significant association of risk was found between staging and symptom experience. Our previous research demonstrated a significant correlation between feeling shape/feel differences of the testicle before diagnosis ($r = -.2938$) and later-stage diagnosis (Rovito et al., 2022). Öztürk et al. (2015), on the contrary, did not report significant associations between a change in the testicle and stage at diagnosis, which indicates some evidence of effect heterogeneity. When it came to predictive risk, difference in testicular shape and feel was unremarkable in this current study. More research is needed on this topic to verify the influence of discerned testicular shape and feel differences with stage at diagnosis.

In terms of self-reported pain, the results are mixed within the existing literature with only some studies vaguely discussing pain and stage at diagnosis. Wilson and Cooksey (2004) indicated that nearly a quarter of their sample presented with testicular pain. However, pain was not significantly associated with a particular histological subtype of neoplasm or stage of disease. Interestingly, those TC patients who presented with testicular pain were more likely to experience recurrence than those reporting no pain (16% compared with 2.6%). Shephard and Hamilton (2018) indicated that when testicular lumps were combined with pain, there was a positive predictive value of ~10%. Wymer et al. (2017) discussed how patients who received nonguideline-directed care (i.e., non-National Comprehensive Cancer Network treatment guidelines) were more likely to report pain (19% vs. 13%) compared with those presenting with a change in testicular shape. Öztürk et al. (2015), however, reported a lack of any significant effect of testicular pain upon patient delay. Furthermore, they indicate that patient-reported testicular pain had no effect upon physician referral times. This current study's results suggest otherwise. We found a significant effect pertaining to testicular pain where those who had a later-stage diagnosis had 65% higher odds of reporting pain then those who had earlier stage diagnoses. Interestingly, our survey indicated that 47% of guys report pain being their driving factor, while historically only 20% of patients present with scrotal pain (Scottish Intercollegiate Guidelines Network [SIGN], 2011).

One final thought on pain deals with the source of pain. We need to be diligent about differentiating testicular pain and pain in the back/pelvis as the latter tends to be associated with later stages (Shephard & Hamilton, 2018; Vural, 2018). Although Öztürk et al. (2015) and Shephard and Hamilton (2018) hint on this differentiation (i.e., testicular vs. groin pain), future research needs to specifically clarify from what source are the patients experiencing pain, if any.

The literature on hot flashes/flushes/night sweats is very limited. Sommerhalder and Blondin's (2017) case report offer description of a man with advanced TC presenting with night sweats as one of the symptoms. Similarly, Zeitjian et al. (2019) outline in their case report a detailed description of one of their patients who reported having persistent night sweats before being prompted to get checked for a potential testicular health issue. Dick et al. (2010) discuss hot flashes/flushes/night sweats in

the context of sarcoidosis case studies being mistaken for TC. As for asymptomatic cases of TC, we found no studies directly discussing or analyzing a lack of symptoms and stage at diagnosis.

Interestingly, employment status at the time of diagnosis, income at the time of diagnosis, and insured status at the time of diagnosis were not statistically significant predictors. This possibly indicates that those in higher paying jobs with insurance, which is usually predicated by the individual having higher education status, have no impact on disease stage at presentation at least in this sample. This stands in stark contrast to conventional wisdom where more access usually equates to more favorable outcomes. This finding could be an anomaly for this study or indicative of something more complex regarding TC insomuch that improved access does not manifest better outcomes. In other words, males are being diagnosed at similar stages regardless of their access. Whether or not this speaks to a general ignorance of TC and its symptoms in the larger male population or something more provider-based has yet to be determined. Future research needs to investigate these factors further, particularly considering the lack of representativeness with this sample and the lower sample sizes of some comparative demographic subgroups.

This current study is the first of its kind to address hot flashes/flushes/night sweats with a more rigorous design concept beyond the confines of a case study/case series. Furthermore, this is the first study, according to the current knowledge of these authors, to directly analyze the lack of symptom presentation and stage at diagnosis for TC. We identified a significant association, although weak, between hot flash symptom reporting and later-stage diagnosis and a weak-moderate association between no symptoms and staging. Furthermore, those who were diagnosed at a later TC stage were approximately 6 times more likely to report hot flashes/flushes/night sweats and more than 11 times more likely to report no symptoms than those diagnosed at an earlier stage.

Limitations

Despite the large sample size, the numbers of those reporting symptoms like hot flashes, pain, and no symptoms were small, which may have mollified our overall conclusions. The larger ORs and CIs for hot flashes, and especially no symptoms, are indicative of this influence. Though there is likely some predictive value of these variables regarding later-stage diagnosis, we cannot confidently comment on these effects' power. Issues of representativeness among the sample could also affect the study's external validity.

Self-reported data from the SEPD-TC are suspect to recall bias and to issues of reliability and validity, despite initial analyses on instrument quality. However, preliminary psychometric analyses indicated acceptable levels of both reliability and validity. Further validation is needed.

We did not explore some potentially influential variables in the study, most importantly, time from symptom recognition to time of diagnosis. This temporal relationship is critical to identify so as to help establish more of a causal chain of events.

Conclusion

In summary, having no symptoms or hot flashes/flushes/night sweats is associated with a later stage diagnosis, which is clinically sound. If an individual does not present with symptoms, then they would likely present with more advanced disease. Conversely, if they notice a change in shape of the testicle, that will "push" an individual to seek medical care sooner rather than later.

The concern around uncommon or atypical symptoms is that they are inexact and indistinct. They are not very clear and/or obvious signs that TC is present. Perhaps in tandem with other more overt symptoms, however, they can serve as more confirmatory variables for a suspect case or, if observed with other uncommonly reported symptoms, that it could serve as a viable option for the diagnostic process to consider TC as a possible prognosis.

There is not enough evidence to corroborate or refute findings from this study, particularly findings relating to hot flashes and/or asymptomatic TC, which undergirds the novelty of this study. What is presented here is a more novel symptom that "drove patients to see their doctor" and not simply a symptom in the cascade. If true, hot flash symptom education can be used to help decrease patient interval for seeking care. This would be better confirmed in further research in actively diagnosed patients. Finally, with proper professional education, the use of these symptoms in a standard examination of suspect cases can perhaps lessen the threshold for ordering a scrotal ultrasound/tumor markers and possibly hypogonadism evaluations.

Declaration of Conflicting Interests

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