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Contemporary Treatment Patterns and Outcomes for Clinical Stage IS Testicular Cancer

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Abstract

Background: Controversy exists regarding the optimal management strategy for clinical stage IS seminomatous (SGCT) and nonseminomatous germ cell tumors (NSGCT) of the testis.
Objective: To assess contemporary treatment patterns and outcomes for clinical stage IS testicular cancer.
Design, setting, and participants: Using the National Cancer Data Base (2004–2012), we identified 1362 patients with clinical stage IS SGCT and NSGCT of the testis, treated with either adjuvant treatment (AT) or observation.
Outcome measures and statistical analysis: We calculated the annual percent change (APC) to assess treatment trends. Inverse probability of treatment weighting (IPTW)-adjusted Kaplan-Meier curves and Cox regression analyses were used to compare overall survival (OS) between AT and observation groups. Analyses were stratified by histologic type.
Results and limitations: Overall, there were 581 (43%) and 781 (57%) men with SGCT and NSGCT, respectively. Among men with SGCT, the use of AT decreased over the study period (APC = –2.7, 95% confidence interval [CI]: –4.4, –1.1, $p = 0.001$). The 5-yr IPTW-adjusted rates of OS were 99% and 97% in the AT and observation groups, respectively (hazard ratio = 0.36, 95% CI: 0.12, 1.14, $p = 0.08$). Among men with NSGCT, the use of AT remained stable over the study period (APC = +0.8, 95% CI: –0.7, +2.2, $p = 0.29$). The 5-yr IPTW-adjusted rates of OS were 97% and 95% in the AT and observation groups, respectively (HR = 0.66, 95% CI: 0.27, 1.61, $p = 0.36$). Limitations include the lack of full treatment details and cancer-specific survival information.
Conclusions: Trends in the use of AT for significantly decreased over time for SCGT, while it remained stable for NSGCT. Nonetheless, we report 5-yr OS rates of ≥95% for both histologies without any significant benefit with the use of AT. Further studies are warranted to confirm these findings.
Patient summary: We evaluated treatment trends and outcomes for stage IS testicular cancer. We found that treatment changed over time for seminoma and remained stable for nonseminoma; there was no significant survival benefit in the use of adjuvant treatment versus observation for both seminomatous and nonseminomatous germ cell tumors.

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1. Introduction

Testicular cancer is the most common malignancy in men aged 15–35 yr. The vast majority of testicular cancer patients present with clinical stage I germ cell tumor (GCT), defined as disease limited to the testis with negative postorchiectomy serum tumor markers [1]. Prognosis for those with clinical stage I testicular GCT is excellent, as cure rates have been shown to be as high as 98% [2]. Rarely, testicular GCT patients exhibit persistent elevation of serum tumor markers following orchiectomy despite negative radiographic evidence of metastases; this is referred to as having clinical stage IS disease [3].

For individuals with clinical stage IS seminomatous GCT (SGCT) of the testis, primary adjuvant radiation therapy has been the treatment of choice for many decades, particularly before the advent of effective cisplatin-based salvage chemotherapy. However, these patients have been systematically excluded from all randomized controlled trials evaluating the role of adjuvant radiation- or chemotherapy for clinical stage I disease, including the MRC TE19/EORTC 30982 study [4–6]. As such, per current National Comprehensive Cancer Network (NCCN) guidelines, men with clinical stage IS SGCT of the testis require repeat evaluation of serum tumor markers and imaging studies, with postorchiectomy treatment using preferentially upfront chemotherapy only if serum tumor markers persist [3] and/or significant extratesticular disease is identified on subsequent imaging studies.

For individuals with clinical stage IS nonseminomatous GCT (NSGCT) of the testis, upfront chemotherapy has been widely used over the past decades. On the basis of small observational reports [7–10], either four cycles of etoposide/cisplatin or three cycles of bleomycin, etoposide, and cisplatin can be considered to treat these patients. Accordingly, current NCCN guidelines recommend immediate postorchiectomy treatment with upfront chemotherapy for clinical stage IS NSGCT of the testis [3].

However, as underlined by the most recent European Association of Urology guidelines, any form of adjuvant treatment (AT) following radical inguinal orchiectomy for clinical stage IS disease remains controversial, given the low level of evidence available in the literature [11]. Against this backdrop, we aimed to evaluate practice patterns and compare overall survival (OS) between patients who received AT or observation for clinical stage IS SGCT and NSGCT of the testis using the National Cancer Database (NCDB).

2. Material and methods

2.1. Data source

Established in 1989 by the Commission on Cancer of American Cancer Society and the American College of Surgeons, the NCDB includes all patients seen at one of the 1500 participating Commission on Cancer-accredited institutions for initial diagnosis and/or first course of treatment. The dataset captures over 70% of incident cancer cases in the US, comprising more than 29 million unique patients [12]. Trained data abstractors use standardized methodology (http://www.facs.org/cancer/coc/fordsmanual.html) to collect demographic and clinical data including tumor type, stage, grade, as well as initial treatment. The study was approved by the institutional review board at Dana-Farber Cancer Institute.

2.2. Study population

From a population of 50 046 men diagnosed with testicular cancer between 2004 and 2012 (International Classification of Diseases-O-3 codes C62.0, C62.1, C62.9), we identified 41 391 individuals ≥18 yr treated with radical inguinal orchiectomy for primary testicular SGCT or NSGCT. Only those who further received any form of AT or observation for clinical American Joint Committee on Cancer stage IS disease were considered ($n = 1373$). Individuals with missing survival time were subsequently excluded ($n = 11$); the final study population included 1362 patients (Fig. 1). Given the clinical heterogeneity between testicular SGCT and NSGCT, the study population was further dichotomized according to histologic type for all analyses.

2.3. Definition of treatment groups according to histologic type

For testicular SGCT, postorchiectomy AT was defined as the receipt of chemotherapy or radiation therapy, while for testicular NSGCT, this included chemotherapy or retroperitoneal lymph node dissection (RPLND). Given that NCDB reports only first-line therapy [13], receipt of chemotherapy, radiation, or RPLND as planned postorchiectomy management were categorized as adjuvant treatment. Patients who did not receive AT following radical inguinal orchiectomy were coded as undergoing observation for both tumor types.

2.4. Other covariates

We extracted patient-level variables including age at diagnosis, race, baseline Charlson Comorbidity Index, and insurance status. Household income and education level were estimated from county of residence. Facility-level variables included travel distance and hospital volume. Finally, we extracted tumor-level variables including pT stage as well as tumor size for SGCT and lymphovascular invasion for NSGCT. Missingness in these covariates ranged from 1.0% to 3.2%.

2.5. Statistical analyses

All analyses were conducted separately for testicular SGCT and NSGCT. First, we performed multiple imputation using chained equations to handle missing data in the covariates [14]. We generated 15 imputed datasets using sequential regression. In all subsequent analyses, Rubin's rules were applied to summarize the effect estimates and variances from the 15 different analyses across multiple imputed datasets [15]. We then plotted treatment trends over time for clinical stage IS SGCT and NSGCT of the testis. Annual percent change (APC) in the delivery of AT versus observation was calculated using linear regression. In addition, we assessed APC in the delivery of adjuvant chemotherapy versus radiation therapy for testicular SGCT, and adjuvant chemotherapy versus RPLND for testicular NSGCT.

We compared covariates between patients who received AT versus observation using the standardized differences approach [16]. Imbalance was defined as a difference greater than 10%.

Finally, to compare OS between patients who received AT versus observation, measured differences in baseline characteristics were controlled for with inverse probability of treatment weighting (IPTW)-adjusted Kaplan Meier and Cox regression analyses [17–19]. Specifically, multivariable logistic regression models predicting the receipt of AT versus initial observation were used to separately weight each testicular SGCT and NSGCT patient with the aim of balancing out observable

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