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The Effects of Testicular Cancer Treatment on Health-related Quality of Life

Damon J. Vidrine, Josette E. H. M. Hoekstra-Weebers, Harald J. Hoekstra, Marrit A. Tuinman, Salma Marani, and Ellen R. Gritz

OBJECTIVES   To prospectively describe the effects of adjuvant chemotherapy on health-related quality of life (HRQOL) among men with newly diagnosed non–seminoma germ cell tumors of the testis. Several characteristics of testicular cancer—young age at diagnosis, increasing incidence, and high survival rates—highlight the need for improved understanding of the variables influencing the survivorship experience.

METHODS   Participants (n = 116) were identified and recruited from the genitourinary services of 2 large medical centers—one in the United States and the other in the Netherlands. Baseline assessments were administered after diagnostic orchiectomy but before adjuvant treatment. Participants completed follow-up assessments after the completion of the chemotherapy regimen (or 3 months postdiagnosis for participants on surveillance regimens) and 12 months postdiagnosis. The 36-Item Short-Form Health Survey was used to measure HRQOL.

RESULTS   Findings indicated that men treated with chemotherapy reported significantly more bodily pain, poorer role physical functioning, poorer social functioning, poorer physical health, more fatigue compared with the men who did not receive chemotherapy at the post-treatment assessment. At the time of 12 month follow-up, HRQOL scores did not vary by treatment group, and scores were significantly higher than baseline HRQOL scores. No significant time by treatment group interactions were observed at the 12 month follow-up.

CONCLUSIONS   Results from this study indicate that chemotherapy is associated with only a temporary decrease in HRQOL. Other HRQOL domains, including mental functioning, role emotional, and general health perceptions, were not associated with treatment type at any of the assessment times.   UROLOGY 75: 636–641, 2010. © 2010 Elsevier Inc.

Testicular cancer is the most frequently diagnosed cancer among young men, with approximately 75% of cases occurring among men aged between 20 and 44 years.[1] Incidence estimates vary by world region, but available data suggest that men from Europe and North America have a higher risk than men from other regions.[2] In addition, evidence from numerous countries indicates that the incidence of testicular cancer has been increasing over that past several decades.[3,4] However, effective treatment regimens are available, resulting in 5-year survival rates of >95%.[5] These unique aspects of testicular cancer—the young age at diagnosis, increasing incidence, and high survival rates—highlight

the need for the exploration of health-related quality of life (HRQOL) outcomes in this growing population.

Treatment-related variables have been hypothesized to influence the survivorship experience for men with testicular cancer. Treatment approaches, including orchiectomy, adjuvant chemotherapy, radiation therapy, and retroperitoneal lymph node dissection (RPLND), are typically based on disease stage and tumor histology.[6,7] Each of these approaches is associated with specific treatment-related side effects and late complications and, therefore, may negatively affect HRQOL.[8]

Several studies have attempted to both characterize and identify predictors of quality of life among testicular cancer survivors in the past 25 years, including the seminal work of Gritz et al.[9] Recent comprehensive published data reviews provide an overview of the findings.[10,11] Although several studies have been designed to explore the association between treatment and HRQOL, certain characteristics of these studies create difficulty in ascertaining the true nature of this relationship. For example, most studies have used cross-sectional designs, and numerous psychosocial outcome measures have been administered. Time since diagnosis is also variable among

the participants in these studies, including such diverse groups as newly diagnosed individuals and long-term survivors. Finally, many of these studies were conducted with relatively small samples, undoubtedly because of the rarity of testicular cancer.

Despite these issues with the existing published data, several trends have been fairly consistently observed. Limited evidence suggests that although treatment is associated with a significantly increased risk of certain treatment-related side-effects (eg, fertility, neurotoxicity, and Raynaud's phenomena),[10,12] post-treatment overall quality of life may not be adversely affected by treatment approach.[13-17] In addition, the few prospective studies that have been published suggest that although quality of life is adversely affected during adjuvant chemotherapy and radiation therapy, levels tend to return to baseline after the completion of treatment.[16,18,19] However, several reports suggest that survivors are more likely to experience some adverse outcomes, such as anxiety,[20] chronic fatigue,[21] and sexual dysfunction.[22]

In an effort to advance the understanding of the relationship between testicular cancer treatment and HRQOL, we conducted a prospective study with patients who were newly diagnosed with non–seminoma germ cell tumors (NSGCT) of the testis. Men were recruited from 2 large cancer centers. The purpose of the study was to compare HRQOL outcomes between men who received a treatment regimen consisting of orchiectomy and surveillance with men who received orchiectomy plus adjuvant chemotherapy.

MATERIAL AND METHODS

Study Site and Participants
Participants were recruited from the genitourinary services of 2 university medical centers: the University of Texas MD Anderson Cancer Center (MDACC), Houston, Texas, and University Medical Center Groningen (UMCG), Groningen, the Netherlands. Consecutive patients with NSGCT were identified from daily reviews of clinic schedules. Other eligibility criteria included: (1) age at diagnosis between 18 and 50 years; (2) English speaking and writing at MDACC and Dutch speaking and writing at UMCG; and (3) ability of the patients to give informed consent. Exclusion criteria included: (1) prior neurological disease or injury (eg, brain metastasis and closed head injury); (2) extragonadal germ cell tumor; and (3) major psychiatric illness. The study was reviewed and approved by the institutional review boards of both MDACC and UMCG.

Study Design and Objectives
Participants were recruited to the study after orchiectomy but before beginning adjuvant chemotherapy or a surveillance regimen. At the time of recruitment, socio-demographic, psychosocial, and neurocognitive measures were administered. Participants completed a similar assessment approximately 1 week after the completion of adjuvant chemotherapy, or 3 months after baseline assessment for participants who did not receive adjuvant chemotherapy. A final assessment was completed 12 months after the baseline assessment. In the current study, only

data from the socio-demographic and psychosocial measures were considered.

Measures
Socio-demographic characteristics considered included age at the time of study enrollment, level of education, and marital status. Because of differences in the Dutch and American education systems, the education level was transformed into a 3-category variable. For participants from MDACC, the categories were (1) high-school degree or less, (2) some college, and (3) 4-year college degree or more. Categories for UMCG participants were (1) low-level high school or vocational school or less, (2) midlevel high school or vocational degree, and (3) high-level high school or vocational degree or more.

HRQOL was assessed with the 36-Item Short-Form Health Survey (SF-36) developed at RAND as part of the Medical Outcomes Study. This widely used and well-validated measure yields 8 separate scale scores, including physical function, social function, pain, mental health, energy and/or fatigue, general health perceptions, role limitations because of physical problems, and role limitations because of emotional problems.[23-25]

The Centers for Epidemiologic Studies - Depression was used to assess depressive symptoms and is a well-validated 20-item self-report measure of depression that focuses on affective components, including feeling depressed, hopeless, fearful, or sad. Sound psychometric properties have been established with a wide range of populations, including patient populations.[26] Anxiety was assessed using the state portion of the Spielberger State-Trait Anxiety Inventory, and it is a 20-item scale that provides information about a respondent's current level of anxiety. This well-validated measure has been used widely in various clinical, medical, and general populations.[27]

Medical records were reviewed to confirm tumor pathology and treatment regimen. Additional medical data including disease stage and specific biomarker (ie, alpha-fetoprotein, human chorionic gonadotropin, and lactate dehydrogenase) were also collected from the MDACC participants.

The primary predictor variable of interest in this study was treatment type. At UMCG, all men diagnosed of early stage NSGCT were placed on a surveillance regimen after orchiectomy, whereas men with more advanced NSGCT received 4 cycles of bleomycin, etoposide, and cisplatin (BEP), depending on the Institutional gem Cell Consensus Classification.[28] Adjuvant chemotherapy regimens administered at MDACC were more variable. Although BEP was by far the most common regimen used, the number of cycles varied (ranging from 2 to 4+) based on tumor marker levels and the discretion of the treating physician. For purposes of the current study, treatment type was dichotomized into surveillance or any chemotherapy. In addition, RPLND was included as a covariate in all multivariate analyses.

Statistical Analysis
Descriptive statistics (means, medians, and frequencies) were generated for each of the demographic, disease, and treatment-related variables. The effect of treatment type (surveillance vs adjuvant chemotherapy) on the HRQOL outcomes at 3- and 12 month follow-up was assessed with mixed-model ANCOVA (PROC mixed in SAS). Treatment type was modeled as a main effect and baseline value of HRQOL was included as a covariate. No significant predictors of HRQOL outcomes were identified in unadjusted analyses and hence were not included as

Table 1. Baseline characteristics by study site for testicular cancer patients enrolled in the study

Characteristic	The University of Texas MD Anderson Cancer Center, n = 70	University Medical Center Groningen, n = 46
Age, mean (standard deviation)	31.0 (7.4)	27.9 (6.7)
Education, n (%)		
High school or less-US/low-level high school or vocational school or less-Dutch	19 (27.1)	15 (32.6)
Some college-US/mid-level or high degree or vocational degree-Dutch	24 (34.3)	13 (28.3)
4-y college degree or higher-US/high-level high or vocational degree or more-Dutch	27 (38.6)	18 (39.2)
Marital status, n (%)		
Married or living with significant other	41 (58.6)	20 (44.4)
Single	29 (41.4)	25 (55.6)
Race/ethnic affiliation, n (%)		
White	65 (92.9)	4 6(100)
Nonwhite	5 (7.1)	0 (0)
Treatment group, n (%)		
Surveillance	15 (21.4)	12 (26.1)
Adjuvant chemotherapy	55 (78.6)	34 (73.9)
RPLND, n (%)		
No	56 (80.0)	24 (52.2)
Yes	14 (20.0)	22 (47.8)

covariates in the model. The specified approach provides estimates of the treatment effect in terms of differences in baseline-adjusted means to detect the differential effect of the treatment on the groups.

The long-term effects of treatment type were evaluated using longitudinal methods. Specifically, mixed model regression was used to model the average trend over time to analyze the differing patterns of change from baseline to 12 month follow-up between the surveillance and chemotherapy groups. A conditional model was fit to the data to examine differences in trends over time between the surveillance and chemotherapy groups. In addition to the main effects of treatment and time, time by treatment interactions were included as fixed effects in the model to test for differences in average rate of change over time between the 2 groups. The estimated slopes were compared between the treatment groups with Type III tests of fixed effects. The analysis was done with Proc Mixed (SAS) which allows for unbalanced designs, missing data, and different covariance structures. Adjustment for small sample correction was done with the Kenward and Roger method.[29]

All modeling was done first by study site (MDACC and UMCG), and then with the combined sample. In all combined analyses, site was included as a covariate. All analyses were conducted using SAS version 9.1 (SAS Institute, Inc., Cary, NC) and SPSS version 12.0 (SPSS, Inc., Chicago, IL).

RESULTS

A total of 164 eligible men were identified at the 2 sites (100 at MDACC and 64 at UMCG). Of these, 116 men (70 at MDACC and 46 at UMCG; response, 70% and 72%, respectively) consented to participate in the study and completed a baseline assessment. Consent and assessment completion rates were similar at the 2 study sites. At the time of study enrollment, participants from MDACC had a mean (SD) age of 31.0 (7.4) years and approximately two-thirds had completed at least some

college education. Participants from UMCG were slightly younger, with a mean (SD) age of 27.9 (6.7) years, and approximately two-thirds of the Dutch participants reported having a midlevel high school, or vocational degree, or higher level of education. Overall, 52.2% (n = 61) of the participants reported being in a committed relationship, although this proportion was higher among the men from MDACC as compared with those from UMCG (58.6% vs 44.4%). Only 5 participants, all from MDACC, reported non–white race or ethnicity. A full description of the socio-demographic characteristics of the participants can be found in Table 1.

The review of the medical record indicated that the majority (>70%) of men at both recruitment sites received adjuvant chemotherapy after a diagnostic orchiectomy. However, the proportion of men receiving RPLND was only 20% (n = 14) at MDACC as compared with 47.8% (n = 22) at UMCG.

Health-Related Quality of Life at 3- and 12 Month Follow-Up by Treatment Group

HRQOL outcomes, expressed as baseline adjusted mean scores of the 8 SF-36 scales (ie, bodily pain, role physical, social functioning, general health, mental health, physical health, role emotional, and vitality), at the 3 month follow-up are displayed in Table 2. In general, HRQOL was poorer for men in the chemotherapy than for men in the surveillance group. Specifically, findings from the combined sample models indicated that men treated with chemotherapy reported significantly more bodily pain, poorer role physical functioning, poorer social functioning, poorer physical health, and more fatigue as compared with the men who did not receive chemotherapy. Findings from the MDACC and UMCG site-specific analyses

Table 2. Adjusted mean (standard error) health-related quality of life scores at 3-month follow-up*

	MD Anderson Cancer Center		University Medical Center Groningen		Combined Sample	
	Surveillance (n = 11)	Chemotherapy (n = 49)	Surveillance (n = 12)	Chemotherapy (n = 28)	Surveillance (n = 23)	Chemotherapy (n = 77)
Bodily pain	87.2 (7.5)	68.9 (3.5)**	88.3 (7.3)	73.1 (4.8)	87.2 (5.2)	71.0 (2.9)***
Role physical	78.1 (13.0)	39.6 (6.2)***	81.5 (8.8)	15.1 (5.7)****	80.5 (8.0)	28.5 (4.5)****
Social functioning	83.3 (7.4)	70.9 (3.5)	82.3 (6.4)	64.7 (4.2)**	82.5 (4.9)	67.8 (2.7)***
General health	69.3 (4.4)	68.8 (2.1)	73.8 (3.6)	61.7 (2.4)***	72.1 (2.9)	66.0 (1.6)
Mental health	74.6 (4.6)	75.3 (2.6)	78.3 (2.6)	73.7 (1.7)	76.5 (2.7)	74.8 (1.5)
Physical health	87.8 (7.1)	76.9 (3.4)	89.9 (5.9)	70.4 (3.8)***	88.4 (4.7)	74.2 (2.6)***
Role emotional	82.2 (11.6)	70.7 (5.5)	70.3 (13.4)	60.3 (8.8)	76.5 (8.6)	65.4 (4.8)
Vitality	60.7 (6.0)	52.0 (2.9)	70.0 (4.4)	56.3 (2.9)**	65.3 (3.8)	54.1 (2.1)**

* Follow-up scores adjusted for baseline scores.
** $P < .05$.
*** $P < .01$.
**** $P < .001$.

Table 3. Adjusted mean (standard error) health-related quality of life scores at 12-month follow-up*

	MD Anderson Cancer Center		University Medical Center Groningen		Combined Sample	
	Surveillance (n = 9)	Chemotherapy (n = 43)	Surveillance (n = 12)	Chemotherapy (n = 28)	Surveillance (n = 21)	Chemotherapy (n = 71)
Bodily pain	90.3 (5.7)	87.7 (2.6)	86.9 (3.9)	95.0 (2.5)	87.5 (3.4)	91.2 (1.9)
Role physical	91.3 (9.3)	87.9 (4.2)	78.8 (9.5)	84.4 (6.2)	85.0 (6.5)	85.8 (3.6)
Social functioning	91.7 (4.9)	87.5 (2.2)	87.1 (4.5)	89.0 (2.9)	88.9 (3.3)	88.0 (1.8)
General Health	74.3 (5.4)	77.4 (2.5)	68.9 (4.5)	75.2 (2.8)	71.8 (3.5)	76.5 (1.9)
Mental health	80.6 (3.7)	79.2 (1.7)	76.0 (3.4)	81.0 (2.2)	78.0 (2.5)	79.9 (1.4)
Physical health	97.5 (4.7)	91.6 (2.2)	91.0 (4.4)	92.6 (2.9)	93.4 (3.2)	92.0 (1.8)
Role emotional	87.8 (9.7)	84.7 (4.4)	89.2 (7.2)	92.7 (4.7)	88.4 (5.9)	88.5 (3.3)
Vitality	69.6 (4.7)	66.7 (2.1)	67.1 (5.2)	71.8 (3.4)	67.8 (3.4)	69.0 (1.9)

* Follow-up scores adjusted for baseline scores.
** $P < .05$.
*** $P < .01$.
**** $P < .001$.

indicated very similar trends, although not all differences reached the level of statistical significance, most likely due to limited power. No significant differences by treatment group were observed in the HRQOL domains of mental health or role emotional functioning.

Results from the mixed-model regressions with the 12 month HRQOL outcomes are presented in Table 3. These findings indicated that treatment group was not significantly associated with any of the SF-36 scale scores.

Health-Related Quality of Life Outcomes by Treatment Group Over Time

Fixed effect coefficients, standard errors, and *P* values from the mixed models generated to examine the effects of treatment group on the SF-36 HRQOL scale scores over time are presented in Table 4. The final models were fit using the conditional model with main effects of treatment condition and time, along with treatment by time interaction terms. The coefficients of treatment by time terms provided estimates of the average rate of change from baseline to month 12 for the surveillance and chemo groups. Findings from the combined sample analyses revealed a significant main effect for time, with 12 month HRQOL scale scores significantly higher than

baseline in both the surveillance and chemo groups on all outcomes except in the general health domain. No statistically significant time by treatment interactions for any of the HRQOL outcomes were observed. A comparison between the MDACC and UMCG samples revealed similar trends.

COMMENT

Findings from this study indicated that as compared with men placed on surveillance regimens, men who received adjuvant chemotherapy for NSGCT experienced a statistically significant decrease in multiple dimensions of HRQOL (ie, physical health, role physical, bodily pain, social functioning, and fatigue) in the period soon after the completion of treatment. However, no significant differences were observed at the time of 12 month follow-up. Specifically, our results suggest that chemotherapy is associated with only a temporary decrease in HRQOL. Also, of note was the finding that HRQOL increased over the course of the year-long follow-up period. HRQOL scores at the time of the 12 month follow-up were significantly higher than baseline scores, regardless of treatment group.

Table 4. Rate of change (estimated slope) in health-related quality of life scores from baseline to 12-month follow-up

	MD Anderson Cancer Center		University Medical Center Groningen		Combined Sample	
	Fixed Effect of Time (SE)	P	Fixed Effect of Time (SE)	P	Fixed Effect of Time (SE)	P
Bodily pain	14.3 (2.4)	<.0001	14.3 (2.5)	<.0001	14.3 (1.7)	<.00001
Role physical	23.1 (4.0)	<.0001	25.7 (4.2)	<.0001	24.2 (2.9)	<.0001
Social functioning	10.3 (2.1)	<.0001	7.7 (2.5)	.0023	9.2 (1.6)	<.0001
General Health	1.1 (1.5)	.4745	2.9 (1.9)	.1317	1.9 (1.2)	.1172
Mental health	4.7 (1.2)	.0009	4.9 (1.3)	.0004	4.9 (1.0)	<.0001
Physical health	3.9 (1.9)	.0430	4.6 (2.4)	.0520	4.2 (1.5)	.0049
Role emotional	9.9 (3.2)	.0026	12.1 (4.3)	.0059	10.9 (2.7)	<.0001
Vitality	4.6 (1.7)	.0088	3.9 (2.2)	.0730	4.3 (1.3)	.0017

Other attempts to investigate the relationship between testicular cancer treatment and HRQOL outcomes have yielded conflicting findings. Several reviews published in recent years clearly document the various side effects associated with cisplatin-based regimens typically used for the treatment of NSGCT.[8,10,11] Common side effects include cardiovascular toxicity, increased risk of second malignancy, infertility, ototoxicity, neurotoxicity, and gastrointestinal toxicity. However, existing evidence indicates that side effects are associated with poorer HRQOL, but treatment-type is not necessarily associated with HRQOL. For example, Mykletum et al[30] conducted a large cross-sectional study of more than 1400 testicular cancer survivors and approximately 2700 controls. Their findings indicated that at an average of 11 years from diagnosis, treatment type was not associated with HRQOL. Side effects, however, were associated with HRQOL scores. Somewhat surprisingly, their results also indicated that treatment type was not related to the side effects. Similar results have also been reported from smaller cross-sectional studies of testicular cancer survivors.[13,15]

Although findings from the more rigorously designed cross-sectional studies suggest that treatment type may not be an important factor in the long term quality of life of testicular cancer survivors, findings from prospective studies are required to more definitively address this research question. To our knowledge, however, very few prospective studies have been conducted. Fossa et al[16] conducted one of the few studies using data collected from patients enrolled in a clinical trial conducted through the European Organization for Research and Treatment of Cancer. In this study, the authors compared HRQOL outcomes among men treated with 4 different chemotherapy regimens. Very similar to our findings, Fossa et al observed that HRQOL scale scores dropped during and immediately after chemotherapy administration, but fully recovered by the time of 12- and 24 month follow-ups. Their results also indicated that treatment type had no effect on HRQOL scores. Because all the men in the trial were treated with very similar regimens (3 cycles of BEP vs 3 cycles of BEP plus one cycle of etoposide and cisplatin delivered over 3 or 5 days), the failure to observe treatment group differences is not overly surprising. Trask et al also published results from a small pilot trial

designed to prospectively explore HRQOL among men with newly diagnosed testicular cancer. Similar to the other findings, the authors found that HRQOL drops during and immediately after chemotherapy, but tends to recover to baseline levels by 8 months postbaseline. Because this study was a pilot investigation, no comparison groups were available.

Our attempt to investigate the relationship between treatment and HRQOL among men with testicular cancer offers several important contributions. First, we used a prospective study design, with pre-chemotherapy assessment, a postchemotherapy (or 3 months postbaseline for the participants in the surveillance group) follow-up, and 12 month follow-up. Second, unlike other prospective studies of HRQOL outcomes, we included men receiving chemotherapy and men who were followed up with a surveillance regimen. Therefore, our study was able to offer a more direct assessment of the short-term effects of chemotherapy than the previous efforts. In addition, the present study recruited men from cancer centers located in 2 diverse sites—Houston, Texas, and Groningen, the Netherlands. Despite possible socio-cultural differences between these 2 locations, we observed an almost identical pattern in HRQOL scale scores.

The prospective study design and the inclusion of a surveillance-only treatment group were important strengths of the current study. However, several limitations should be considered when interpreting the findings. First, the men receiving chemotherapy at MDACC were placed on various regimens, ranging from 2-7 cycles. Therefore, our approach which involved grouping all men who received chemotherapy into the same category did not allow a true dose–response assessment of the effects of chemotherapy. To partially address this problem, we performed exploratory analyses (not presented) with the MDACC sample in which various categories of chemotherapy (based on number of cycles received) were used. These exploratory analyses yielded consistent findings. That is, regardless of the operational definition of the chemotherapy group, men who receive chemotherapy experience a significant decrease in HRQOL scores immediately after treatment completion (compared with men who do not receive chemotherapy), but HRQOL scores recover to levels above the baseline scores at the

time of 12 month follow-up. The lack of a primary RPLND group may have also limited our ability to separate surgical- and chemotherapy-related effects.

Another limitation was the unavailability of complete medical data, including detailed staging and biomarker levels from participants at the UMCG site. However, exploratory analyses (not presented) using the detailed staging and tumor marked data available from the MDACC participants indicated that these variables were not significant predictors of the post chemotherapy drops in HRQOL scores after treatment group was included in the models, nor were they predictive of 12-month outcomes.

A final limitation of note involves the measure of HRQOL used in this study—the SF-36. Although this is a widely used and well-validated measure of generic HRQOL, is was not designed to tap all functional domains that may have been affected by testicular cancer treatment. Therefore, the use of a testicular cancer-specific measure may have provided more insight about the long-term effects of treatment.

In conclusion, our results confirm the finding that men treated with chemotherapy experience a significant, but temporary drop in HRQOL. These findings may be helpful both to patients with newly diagnosed NSGCT and to clinicians. Specifically, clinicians may be able to better inform the patients about the expected decline in HRQOL associated with chemotherapy, while offering reassurance about the temporary nature of these declines.

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