Community-based surveillance in clinical stage I germ cell tumors

James Perkins, MD,[1] Michael J. Guarino, MD,[2] and Nicholas J. Petrelli, MD[3]

[1]Department of Internal Medicine, The Helen F Graham Cancer Center, Christiana Care Health System; [2]Medical Oncology Hematology Consultants, PA, Pharmaceutical Clinical Trials, The Helen F Graham Cancer Center, Christiana Care Health System; [3]The Helen F Graham Cancer Center, Christiana Care Health System, Newark, Delaware

Purpose: To show successful treatment of testicular cancer in a community-based setting by following established national guidelines and a multidisciplinary approach that includes postorchiectomy surveillance.

Methods: The Christiana Care Health System Oncology Data Base and records of treating physicians at the Helen F. Graham Cancer Center were analyzed for patients diagnosed with clinical stages I, II, and III testicular cancer from November 1, 1995, to January 27, 2005.

Results: Relative survival rates for 136 testicular cancer patients diagnosed and/or treated at the Christiana Care Helen F. Graham Cancer Center from 1995 to 2005 were 98.5% for stages I and II seminomas and nonseminomas and 92.8% for stage III disease. Surveillance following orchiectomy was the primary mode of management for 35 of 38 patients (92%) with clinical stage I nonseminomatous disease. Six of 35 patients (17%) relapsed between 3 and 46 months after initial treatment. Of the 72 patients (85%) with clinical stage I seminomatous disease, 17 (25%) underwent surveillance, and 1 patient, who is still living, relapsed at 15 months.

Conclusion: We demonstrate that at a National Cancer Institute-selected community cancer center, the survival rate of patients with testicular cancer is excellent and consistent with SEER-reported rates. Our findings support surveillance as a viable treatment of clinical stage I germ cell tumors.

Controversy continues over the optimal treatment of early-stage, nonseminomatous germ cell testicular cancer (NSGCT). Established strategies include surveillance, chemotherapy, and nerve-sparing retroperitoneal lymph node dissection (RPLND). A 10-year retrospective study of 136 testicular cancer patients diagnosed and/or treated at the Christiana Care Helen F. Graham Cancer Center shows the benefits of a multidisciplinary approach, which combines postsurgery surveillance and adjuvant chemotherapy for NSGCT without RPLND.

Background

Testicular cancer accounts for 1% of all cancers in men, diagnosed most commonly between the ages of 15 and 35. In 2010, the American Cancer Society estimated 8,480 new cases of testicular cancer and 350 deaths from this disease in the United States.[1] Although the incidence of testicular cancer is on the rise, it is nearly 100% curable if found and treated early.

Germ cell tumors of the testis account for 94% of testicular tumors and are most often defined as either seminomas or nonseminomas.[2] For clinical stages I and II cancers, treatment starts with inguinal orchiectomy to remove the affected testicle through an incision in the groin. Seminomas represent roughly 60% of germ cell testicular cancers. National Comprehensive Cancer Network (NCCN) guidelines[3] state radiation therapy post orchiectomy as a standard of care for these stage I radiosensitive tumors. However, surveillance has become an accepted alternative to radiation therapy within the past 15 years, with reported cure rates of 80% for surveillance alone. Chemotherapy is also a recommended adjuvant treatment option.

Approximately three quarters of patients who have NSGCT have clinical stage I disease at diagnosis.[4] NCCN guidelines for stage I nonseminomatous disease include postorchiectomy surveillance, chemotherapy with 2 cycles of bleomycin, etoposide, and platinum (BEP) or nerve-sparing RPLND.[3]

Manuscript received July 20, 2011; accepted November 22, 2011.
Correspondence: Michael Guarino, MD, Medical Oncology Hematology Consultants, PA, 4701 Ogletown Stanton Road, Newark, DE 19713; e-mail: mguarino@cbg.org.
Disclosures: The authors have completed and submitted ICMJE Forms for Disclosure of Potential Conflicts of Interest and none were reported.

Commun Oncol 2012;9:15-19
doi:10.1016/j.cmonc.2011.11.003

TABLE 1 Summary of treatments for seminomatous germ cell tumors

AJCC stage	Treatment (No. of patients)	No. of patients alive at 5 years	No. of patients lost to follow-up (months)	No. of patients who died with disease
I	Surveillance (17)	16	1 (59)	0
I	Radiation therapy (54)	51	3 (3, 58, 59)	0
I	Chemotherapy (1)	1	0	0
II	Radiation therapy (6)	6	0	0
II	Chemotherapy (3)	3	0	0
III	Chemotherapy (4)	4	0	0

AJCC = American Joint Committee on Cancer

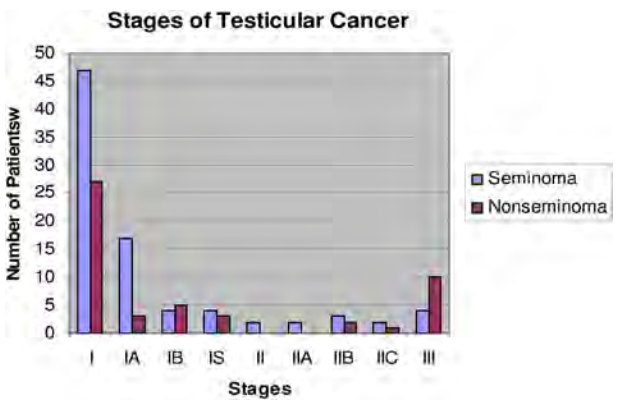

FIGURE 1 The number of patients by stage of seminomatous and nonseminomatous testicular cancer treated and or diagnosed at Christiana Care Health System from 1995 to 2005. Source: Christiana Care Health System Oncology Data Base. (Staging uses the American Joint Committee on Cancer [AJCC] stages.)

Regardless of the approach taken, cure rates are close to 100% for patients with early-stage nonseminomatous germ cell tumors.[4]

Retroperitoneal lymph node dissection is one option for treatment of early-stage nonseminomatous disease. In this article, we demonstrate that at a National Cancer Institute-selected community cancer center, the survival rate of patients with testicular cancer is excellent and consistent with Surveillance, Epidemiology, and End Results (SEER)-reported rates.[2] As a result, patients, particularly those with clinical stages I and II nonseminomas, need not undergo RPLND and its potential side effects. Furthermore, findings from our study support surveillance as a viable treatment of seminomas (Table 1).

Scope of study

This was a retrospective study of 136 testicular cancer patients diagnosed and/or treated at the Christiana Care Helen F. Graham Cancer Center from 1995 to 2005.

Staging was based on the American Joint Committee on Cancer (AJCC) Stages.[5] Patients were treated according to established NCCN guidelines[3] for clinical stages I, II, and III seminomatous or nonseminomatous disease (Figure 1). Of particular interest are results for patients with early-stage (clinical stage I), NSGCT who were followed post orchiectomy with standard surveillance and, in relatively few cases, were given adjuvant chemotherapy. Among this group, the 5-year relative survival rate was 95.2%. One patient, who had clinical stage I nonseminomatous disease, was treated with RPLND.

Methods

Data from the tumor registry at Christiana Care Health System and private office records of treating physicians at the Helen F. Graham Cancer Center were analyzed for 136 men diagnosed with clinical stages I, II, and III testicular cancer from November 1, 1995, to January 27, 2005. All patients presented during this time period are reported.

We used a Microsoft Excel spreadsheet to compile relevant data, such as germ cell tumor type, age at initial presentation, stage at initial presentation, treatment, time to disease relapse, whether the patient was living or deceased, and duration of life after diagnosis. The study was performed with investigational review board (IRB) approval and in a blinded manner with respect to patient identity. All patient identifiers were kept confidential, and no single patient could be identified from the data. Survival rates were calculated from the Christiana Care Oncology Data Base using Rocky Mountain Software. Decisions concerning treatment were made with multidisciplinary input from medical and radiation oncologists and urologists as part of a tumor board.

Results

In our study, 85 of 136 patients (63%) were diagnosed with seminomatous germ cell tumors (SGCTs); 72 of 85 (85%) had clinical stage I disease. Surveillance was employed in 17 patients (25%) with clinical stage I seminomatous disease, and 1 patient, who is still living, relapsed at 15 months. These findings are in contrast to relapse rates reported from 6% to 24% in some studies and disease recurrence reported from 12 to 18 months to as late as 10 years.[4] In our study, 74% of clinical stage I and 67% of clinical stage II patients with seminomas underwent radiation therapy. Among this group, only one patient with clinical stage IIB disease relapsed following radiation therapy, and this patient is still alive.

NCCN guidelines include chemotherapy with carboplatin as an option for clinical stage I SGCTs.[3] In our study, one patient with clinical stage I seminomatous disease underwent adjuvant chemotherapy with carboplatin, with no disease recurrence during the study period. Of the patients with clinical stage II disease, 6 of 9 patients (67%) were treated with radiation therapy, and the remaining 3 patients (33%) received chemotherapy consisting of 3 cycles of BEP, as recommended by the NCCN. None of these patients experienced recurrence of disease. The 5-year survival rate was 98.5% for clinical stages I and II seminomas and nonseminomas and 92.8% for clinical stage III disease.

TABLE 2 Summary of treatments for nonseminomatous germ cell tumors

AJCC stage	Treatment (No. of patients)	No. of patients alive at 5 years	No. of patients lost to follow up (months)	No. of patients who died with disease (months)
I[1]	Surveillance (35)	30	2 (2, 2)	1 (26)
I	Chemotherapy (2)	2	0	0
I	RPLND (1)	1	0	0
II	Chemotherapy (2)	2	0	0
II	RPLND (1)	1	0	0
III	Chemotherapy (10)	8	1 (46)	1 (41)

RPLND = retroperitoneal lymph node dissection
[1] One patient died at 41 months without disease. One patient died at 17 months without disease

Patients ranged in age from 17 to 77 years, with a median age of 35. At the 5-year point, 123 patients were alive and disease free; 9 were lost to follow-up. A total of 4 patients died during the study. Two died with testicular cancer, and none died of testicular cancer or its treatment.

Surveillance

As in other studies reported in the literature, most of the NSGCT patients in our study were diagnosed with clinical stage I disease (38 of 52 patients, 75%; Table 2). Surveillance following orchiectomy was the primary mode of management for 35 of 38 patients (92%). The relapse rate for observed patients was 17% (6 of 35 patients), ranging from 3 to 46 months after initial treatment.

The NCCN guidelines include surveillance as an option for compliant patients with stage IA nonseminomas.[3] Of the 35 patients who underwent surveillance in our study, 31 were diagnosed with clinical stage IA disease. One patient from this group died disease free at 17 months. Surveillance was employed in four patients with clinical stage IB disease. Among this group, one patient relapsed and died with disease at 26 months.

Retroperitoneal lymph node dissection

One patient with clinical stage IB disease diagnosed with embryonal carcinoma underwent successful RPLND. Two commonly reported risk factors for occult metastases are lymphovascular invasion and embryonal carcinoma. Reported rates of relapse for patients with embryonal carcinoma predominance are between 30% and 80%.[4] If the germ cell tumor is pure embryonal carcinoma, as was the case for this patient, the risk for relapse is theoretically higher.

Adjuvant chemotherapy

Recommended chemotherapy post orchiectomy instead of nerve-sparing RPLND is 2 cycles of BEP for patients with clinical stage I disease. In our study, 3 of 38 patients (8%) with NSGCT clinical stage I received adjuvant chemotherapy; one patient relapsed at 7 months but was still living 5 years after the study.

Clinical stage II treatment

NCCN guidelines recommend treatment with RPLND or chemotherapy for clinical stage II nonseminomatous disease (defined as having possible elevated tumor markers with regional lymph node involvement).[3] Chemotherapy consists of 3 cycles of BEP or 4 cycles of EP (etoposide/cisplatin). In our study, 3 of 51 patients (6%) with NSGCT had clinical stage II disease, and 2 were treated with chemotherapy. One patient from this group underwent successful RPLND. No patients from this group relapsed or died from their disease.

Clinical stage III treatment

Ten patients with NSGCT had clinical stage III disease. All received chemotherapy. Nine are still living, and one patient died with the disease.

Five-year survival rates

The 5-year survival rates in our study are consistent with reported rates for early-stage testicular cancer. The Christiana Care Health System Oncology Data Base shows the following 5-year survival rates for seminomas: clinical stage I, 100%; clinical stage II, 100%; clinical stage III, 100%; clinical stages I–III combined, 100%. For nonseminomas, the following 5-year survival rates were shown: clinical stage I, 92.1% (8.6%); clinical stage II, 100%; clinical stage III, 90% (18.6%); clinical stages I–III

combined, 92.2% (7.4%). The median follow-up is 9.3 years, with an interquartile range of between 7.1 and 11.7 years.

Discussion

Is surveillance a viable option for seminomas?

Our findings support surveillance as a viable treatment for clinical stage I germ cell tumors. However, given the excellent outcomes (recurrence rates of between 3% and 4%), it remains likely that most patients with early-stage SGCTs will be treated up front with radiation therapy.[6] Nevertheless, long-term risks such as secondary malignancies remain a concern, as do more immediate side effects such as nausea, fatigue, and diarrhea. Nor can we ignore the financial burden of recurrent disease.[6,7] In our study, most of the patients with early-stage SGCT (70%) were treated successfully with radiation therapy and had a low recurrence rate (2%).

In the past 20 years, postorchiectomy surveillance has become another widely practiced treatment option for clinical stage I seminomas. Notable are the 80% to 85% of patients with seminomas who are cured with orchiectomy alone and who need not be subjected to overtreatment with radiation.[6]

The recurrence rate with surveillance for clinical stage I seminomas is reported to be as high as 21%.[4] In our study, the recurrence rate was substantially lower (5%) for patients with clinical stage I disease undergoing surveillance. Interestingly, when surveillance is employed as a management option, de Wit and Fizazi expressed concern for late-term relapse beyond 5 years.[6] However, in our study, only one patient who underwent surveillance relapsed at 15 months, and that patient was still living at 10 years post study.

When is RPLND a better option for nonseminomas?

The majority of patients with clinical stage I NSGCT are cured with orchiectomy alone. However. 25% to 30% of patients with early-stage nonseminomas will have occult metastases and will relapse in the absence of additional treatment.[4,6,8] Currently, these patients are being managed by either surveillance or nerve-sparing RPLND. Results from prospective randomized trials comparing RPLND and surveillance alone for treatment of clinical stage I NSGCT are as yet unavailable, but studies by Foster and others around the world have shown that the chance for cure is essentially the same—99%—with either method of management.[9]

Arguments in favor of nerve-sparing RPLND seem to offer the advantage of more accurate staging for this group, potentially sparing them the toxicities of drug overtreatment or the psychological burden of surveillance. Of equal concern is the higher probability of understaged patients requiring postchemotherapy RPLND, a procedure with higher morbidity than primary RPLND. Although complications associated with RPLND are relatively infrequent when performed by experienced surgeons, mean hospital stays of 2.8 days and problems such as anejaculation, small bowel obstruction, ventral hernia, and chylous ascites cannot be discounted.[10]

Successful chemotherapy to treat advanced disease has led to its use as adjuvant therapy for earlier stage germ cell tumors to improve outcomes. The use of adjuvant chemotherapy for clinical stage I nonseminomas was evaluated in a study by Albers et al, who compared RPLND with 1 course of BEP for those with stage I nonseminomas.[11] After a median follow-up of 4.7 years, 2 recurrences were observed in the chemotherapy group versus 15 in those that had undergone RPLND.[11]

From the results of this study, it would be safe to say that for high-risk patients who are candidates for adjuvant treatment, chemotherapy is an option. In our study, three patients (8%) with clinical stage I NSGCT received adjuvant chemotherapy. Among patients with clinical stage II disease, two of three were treated with primary chemotherapy, with no recurrence or death in this group during the study period.

In support of surveillance, there is evidence to suggest that the majority of patients with clinical stage I NSGCT (65% to 70%) would be overtreated if subjected to more than surveillance alone.[4,6,8] Furthermore, in their review of RPLND, Jacobsen et al noted that 70% to 75% of patients with clinical stage I disease have no evidence of tumor involvement of retroperitoneal lymph nodes after undergoing staging through RPLND. Of these patients, the authors submit that 90% will never experience a relapse of their disease.[10] Thus, it can be argued that surveillance would spare the majority of patients with clinical stage I NSGCT unnecessary abdominal surgery and chemotherapy.

In their study of Swedish and Norwegian patients with clinical stage I NSGCT (the SWENOTECA project), Tandstad et al demonstrated that a risk-adapted approach in patients with clinical stage I nonseminomatous disease is an effective strategy.[12] It has been argued that lymphovascular tumor invasion is a prognostic indicator of potential relapse.[4]

The SWENOTECA study divided patients into two groups: those with evidence of vascular tumor invasion post orchiectomy and those with no evidence of vascular tumor invasion. Patients without vascular tumor invasion were managed by either surveillance or 1 course of adjuvant chemotherapy with cisplatin, vinblastine, and bleomycin (CVB). Patients with evidence of vascular tumor

invasion were managed by either surveillance or 2 courses of CVB.

Results showed that more than 85% of patients without vascular tumor invasion were successfully managed by surveillance alone. In addition, approximately 50% of the patients with vascular tumor invasion also were successfully managed with surveillance alone.[12] As Nichols and Kollmannsberger succinctly concluded about this trial—the world's largest combined study of primary nonsurgical management of clinical stage I testicular nonseminomas—fewer than 5% of patients underwent RPLND without a high incidence of late relapse, unmanageable teratoma, or any cancer-related death.[13]

With surveillance, early-stage NSGCT remains a highly curable disease, provided patients have strict follow-up so that relapses can be treated in a timely manner. Perhaps the successful outcomes experienced by patients in our study who underwent surveillance post orchiectomy can be attributed in part to the multidisciplinary approach to treatment and patient care at the Christiana Care Helen F. Graham Cancer Center. As a National Cancer Institute community cancer center, our unique model of care delivered in the setting of multidisciplinary disease centers is most pertinent to this discussion. This model brings specialists from every related discipline together with patients and family members in a team approach to treatment, which promotes and facilitates compliance.

Conclusion

Our study supports the successful implementation of NCCN guidelines in the treatment of testicular cancer in a community-based setting. The predominance of positive outcomes across a 10-year period confirms the relevance of current guidelines for treating both seminomatous and nonseminomatous testicular cancers diagnosed among an unselected, nonexclusive, and diverse community of patients. The study shows that at a National Cancer Institute-selected community cancer center, the survival rate of patients with testicular cancer is excellent and consistent with SEER-reported rates. Our findings also support surveillance as a viable treatment for clinical stage I germ cell tumors. Future, similar studies have much to contribute to the continuing evolution of best practices in cancer medicine and their implementation and evaluation among community hospital populations.

Acknowledgments

The authors thank Lois Torgerson, MS, and Cecilia Touchstone for their assistance in writing this manuscript, and Robert McBride, director of the data center at the Christiana Care Health System Oncology Data Center.

References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin*. 2010;60:277-300.

2. SEER database. National Cancer Institute. http://seer.cancer.gov/statfacts/html/testis.html. Accessed December 2, 2011.

3. NCCN Clinical Practice Guidelines in Oncology Testicular Cancer Version 1.2011. *National Comprehensive Cancer Network*. http://www.nccn.org/professionals/physician_gls/pdf/testicular.pdf. Accessed December 2, 2011.

4. Tan A, Gilligan T. Controversies in the management of early-stage germ cell tumors. *Curr Oncol Rep*. 2009;11:235-243.

5. AJCC: Testis. In: AJCC Cancer Staging Manual, 7th ed, Edge SB, Byrd DR, Compton CC, et al (eds): New York, NY: Springer; 2010:471.

6. de Wit R, Fizazi K. Controversies in the management of clinical stage I testis cancer. *J Clin Oncol*. 2006;24:5482-5492.

7. Pectasides D, Pectasides E, Constantinidou A, Aravantinos G. Stage I testicular seminoma: management and controversies. *Crit Rev Oncol Hematol*. 2009;71:22-28.

8. Choueiri TK, Stephenson AJ, Gilligan T, Klein EA. Management of clinical stage I nonseminomatous germ cell testicular cancer. *Urol Clin North Am*. 2007;34:137-148.

9. Foster R, Bihrle R. Current status of retroperitoneal lymph node dissection and testicular cancer: when to operate. *Cancer Control*. 2002;9:277-283.

10. Jacobsen NE, Foster RS, Donohue JP. Retroperitoneal lymph node dissection in testicular cancer. *Surg Oncol Clin N Am*. 2007;16:199-220.

11. Albers P, Siener R, Krege S, et al. Randomized phase III trial comparing retroperitoneal lymph node dissection with one course of bleomycin and etoposide plus cisplatin chemotherapy in the adjuvant treatment of clinical stage I nonseminomatous testicular germ cell tumors: AUO trial AH O1/94 by the German Testicular Cancer Study Group. *J Clin Oncol*. 2008;26:2966-2972.

12. Tandstad T, Cohn-Cedermark G, Dahl O, et al. Long-term follow-up after risk-adapted treatment in clinical stage 1 (CS1) nonseminomatous germ cell testicular cancer (NSGCT) implementing adjuvant CVB chemotherapy. A SWENOTECA study. *Ann Oncol*. 2010;21:1858-1863, 2010.

13. Nichols CR, Kollmannsberger C. Vox populi: using community-based studies to determine best management of early-stage nonseminoma. *J Clin Oncol*. 2009;27:2114-2116.