Risk Stratification of Pubertal Children and Postpubertal Adolescents with Clinical Stage I Testicular Nonseminomatous Germ Cell Tumors

Nicholas G. Cost,* Jessica D. Lubahn, Mehrad Adibi, Adam Romman, Jonathan E. Wickiser, Ganesh V. Raj, Arthur I. Sagalowsky and Vitaly Margulis

From the Divisions of Urologic Oncology (NGC, JDL, MA, AR, GVR, AIS, VM) and Pediatric Oncology (JEW), University of Texas Southwestern Medical Center, Dallas, Texas, and Division of Urology, University of Colorado School of Medicine (NGC), Aurora, Colorado

Purpose: The COG (Children's Oncology Group) currently recommends surveillance for all children and adolescents with clinical stage I testicular germ cell tumors. However, up to 30% of adults with clinical stage I testicular germ cell tumors harbor occult metastatic disease. In adults with clinical stage I nonseminoma some groups advocate a risk stratified approach. Occult metastases were noted in 50% of patients with features such as lymphovascular invasion or embryonal carcinoma predominance in the orchiectomy. However, to our knowledge there are no data on the impact of high risk features in such pubertal children and postpubertal adolescents.

Materials and Methods: We reviewed an institutional testis cancer database for pubertal children and postpubertal adolescents younger than 21 years. We tested the hypothesis that lymphovascular invasion, or 40% or greater embryonal carcinoma in the orchiectomy specimen, would increase the risk of occult metastases, ie relapse during surveillance or positive nodes on retroperitoneal lymph node dissection.

Results: We identified 23 patients with a median age of 18.6 years (range 7.1 to 20.9) at diagnosis. Of these patients 14 (60.9%) were on surveillance, 9 (39.1%) underwent primary retroperitoneal lymph node dissection and none received initial chemotherapy. Seven patients (30.4%) had occult metastatic disease. High risk pathological features were found in the orchiectomy specimen in 12 patients (52.2%), including all 12 (52.2%) with 40% or greater embryonal carcinoma and 3 (13.0%) with lymphovascular invasion. Seven patients (58.3%) with high risk features had occult metastatic disease vs none (0%) without high risk features (log rank $p = 0.031$).

Conclusions: Approximately half of pubertal children and postpubertal adolescents with high risk clinical stage I testicular germ cell tumors harbor occult metastatic disease. These results may be useful when discussing prognosis and treatment with patients and families.

Key Words: testis; neoplasms, germ cell and embryonal; neoplasm metastasis; adolescent; puberty

Abbreviations and Acronyms

CS1 = clinical stage I
EC = embryonal carcinoma
GCT = germ cell tumor
LN = lymph node
LVI = lymphovascular invasion
NSGCT = nonseminomatous GCT
RPLND = retroperitoneal LN dissection
T-GCT = testicular GCT
TMNS = TNM-serum marker

Accepted for publication August 16, 2013.
Study received institutional review board approval.

* Correspondence: Division of Urology, University of Colorado School of Medicine and the Children's Hospital Colorado, 13123 East 16th Ave., B 463, Aurora, Colorado 80045 (telephone: 720-777-5084; FAX: 720-777-7370; e-mail: nicholas.cost@childrenscolorado.org).

TESTICULAR germ cell tumors can develop from infancy to adulthood and they are the most common solid tumor in postpubertal males from ages 15 to 39 years.[1,2] Most of these patients present with CS1 disease, defined as absent radiological or biochemical evidence of metastatic

0022-5347/14/1915-1485/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2013.08.047
Vol. 191, 1485-1490, May 2014
Printed in U.S.A.

disease. Recent data estimated that 70% to 80% of prepubertal children and 50% to 60% of adolescents with T-GCTs have CS1 disease.[3–5] In contrast, approximately 40% to 50% of adults with NSGCT present with CS1 disease.[6] Data from previous studies of prepubertal boys show a 20% recurrence rate for universal surveillance of stage I disease.[3] Similarly, approximately 30% of adults with CS1 NSGCT are under staged and will experience relapse on surveillance or have positive LNs on primary RPLND.[7,8] These 30% with relapse during surveillance require post-relapse chemotherapy with its associated risks of cardiovascular disease and secondary malignancy, and they may require post-chemotherapy surgery.

Consequently, management of the CS1 population is controversial, given that a third of cases are under staged and yet universal adjuvant therapy results in a significant overtreatment rate. This led to previous investigation of risk stratification in adults with CS1 NSGCT and identification of factors that increase the likelihood of harboring occult metastatic disease. Such analysis established that LVI and a higher percent component (40% or greater to 50%) of EC in the orchiectomy specimen are high risk features. The reported rate of occult metastasis with LVI and EC predominance varies from 45% to 90% and 30% to 80%, respectively.[9]

Potential treatment options for patients with CS1 NSGCT include surveillance, primary RPLND or limited cycle adjuvant chemotherapy. The COG recommends surveillance for all prepubertal patients with stage I due to the low incidence of occult metastasis in children (approximately 20%) and the fact that salvage is uniformly achieved in those with relapse on surveillance.[3] For the pubertal child and postpubertal stage I adolescent with T-GCT there are limited data to support treatment according to the pediatric or adult guidelines. The effect of the mentioned high risk features on relapse is also unclear in this population. Such data would be clinically useful when discussing surveillance with patients and families. These data may also provide a rationale for risk adapted strategies that include adjuvant therapy for those at especially high risk.

MATERIALS AND METHODS

Study

Population. After obtaining institutional review board approval we reviewed a prospectively maintained institutional database of patients with T-GCT. This database includes all patients seen at a tertiary referral center from 1996 to 2012 with an ICD-9 code for testicular cancer (186). Primary study inclusion criteria were pubertal males, Tanner stage II or greater (as coded by the treating physician) and patients younger than 21 years with CS1 T-NSGCT. All study patients were offered surveillance, primary RPLND or primary limited cycle chemotherapy. For subanalysis of age groups we included patients from the same database who were older than 21 years with CS1 NSGCT. Those with nonGCT testicular tumors or GCTs arising in a dysgenetic or intersex gonad were excluded from analysis.

Design. The charts of patients who met study criteria were retrospectively reviewed to extract data points, including demographics, pubertal status and Tanner stage,[10] orchiectomy pathology/histology, percent components of various histology, AJCC (American Joint Committee on Cancer) 7th edition TNMS stage and stage group,[11] surgical history, chemotherapy for T-GCT (yes or no), further surgery for T-GCT, followup duration, presence or absence of recurrence, disease progression or death and time to each of these events.

Definitions

T-GCTs were defined as primary testicular tumors with a certain histology, that is pure seminoma vs nonseminoma, which includes pure nonseminoma (yolk sac tumor, EC, teratoma and choriocarcinoma) and mixed nonseminoma. All cases were staged using the AJCC 7th edition TNMS stage and stage grouping. Study groups were defined as pubertal children who were Tanner stage II or greater and postpubertal adolescents younger than 21 years. Patients were considered adults when they were 21 years or older. Occult metastatic disease was considered 1) any increase in serum tumor markers (α-fetoprotein or β human chorionic gonadotropin) after initially coming to normal levels after orchiectomy while on surveillance, 2) any new metastasis detected radiologically during surveillance or 3) positive LNs found at primary RPLND. Time to metastasis was coded as time from the date of orchiectomy to the date of marker recurrence, radiological detection of metastasis or the date of RPLND revealing the positive LN. Patients were censored at the last recorded visit in the medical chart.

Study Objectives

The primary objective was to determine the percent of pubertal children and postpubertal adolescents with CS1 NSGCT who had the high risk pathological features of LVI and/or 40% or greater EC. The clinical hypothesis to be tested was that patients with one of these high risk features were more likely to harbor occult metastatic disease than those without high risk pathological features. Secondary objectives included 1) determining overall survival in the study cohort, 2) comparing characteristics of study patients with and without occult metastatic disease, and 3) comparing metastasis-free survival in pubertal and adolescent patients to that in adult patients.

Data Analysis

Demographic and clinical data were analyzed using nonparametric methods with the chi-square or Fisher exact test for categorical data and the Mann-Whitney U or Kruskal-Wallis test for continuous data. Time to event data were used to construct Kaplan-Meier curves for metastasis-free survival and overall survival. These curves