A refined risk stratification scheme for clinical stage 1 NSGCT based on evaluation of both embryonal predominance and lymphovascular invasion


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Background: Active surveillance is an increasingly accepted approach for managing patients with germ-cell tumors (GCTs) after an orchiectomy. Here we investigate a time-to-relapse stratification scheme for clinical stage 1 (CS1) nonseminoma GCT (NSGCT) patients according to factors associated with relapse and identify a group of patients with a lower frequency and longer time-to-relapse who may require an alternative surveillance strategy.

Patients and methods: We analyzed 266 CS1 GCT patients from the IRB-approved DFCI GCT database that exclusively underwent surveillance following orchiectomy from 1997 to 2013. We stratified NSGCT patients according to predominance of embryonal carcinoma (EmbP) and lymphovascular invasion (LVI), using a 0, 1, and 2 scoring system. Cox regression and conditional risk analysis were used to compare each NSGCT group to patients in the seminomatous germ-cell tumor (SGCT) category. Median time-to-relapse values were then calculated among those patients who underwent relapse. Relapse-free survival curves were generated using the Kaplan–Meier method.

Results: Fifty (37%) NSGCT and 20 (15%) SGCT patients relapsed. The median time-to-relapse was 11.5 versus 6.3 months for the SGCT and NSGCT groups, respectively. For NSGCT patients, relapse rates were higher and median time-to-relapse faster with increasing number of risk factors (RFs). Relapse rates (%) and median time-to-relapse (months) were 25%/8.5 months, 41%/6.8 months and 78%/3.8 months for RF0, RF1 and RF2, respectively. We found a statistically significant difference between SGCT and patients with one or two RFs ($P < 0.001$) but not between SGCT and NSGCT RF0 ($P = 0.108$).

Conclusion: NSGCT patients grouped by a risk score system based on EmbP and LVI yielded three groups with distinct relapse patterns -and patients with neither EmbP nor LVI appear to behave similar to SGCT.

Key words: nonseminoma germ-cell tumor, clinical stage 1, relapse, embryonal predominance, lymphovascular invasion, active surveillance

introduction

Germ-cell tumors (GCTs) account for 95% of malignant tumors of the testicle and are the most common solid tumor in men ages 15–34 years [1]. CS1 seminoma and nonseminomatous germ-cell tumor (NSGCT) have different propensities for relapse [2–4] and 54% of NSGCTs present with clinical stage 1 (CS1) disease defined as no tumor marker (TM) elevation or radiographic evidence of disease beyond the scrotum [5, 6].

Orchiectomy cures ~70% of NSGCT CS1 patients as 30% have occult metastasis and relapse [2]. The management options for CS1 NSGCT are nerve-sparing retroperitoneal lymph node dissection (RPLND), adjuvant chemotherapy and surveillance [6] with cure rates of 99% as salvage therapy cures nearly all patients who relapse on surveillance [1]. Seminomatous germ-cell tumors (SGCTs) present as CS1 in 75% of the cases and orchietomy cures ~85% of these patients [3, 4]. The postorchietomy management options for seminoma are adjuvant chemotherapy, adjuvant external beam radiation and surveillance with cure rates approximating 100% regardless of initial management [7].

Active surveillance entails the periodic assessment of TMs, CT of the abdomen and pelvis, and chest imaging in postorchietomy
patients, reserving additional treatment of those who relapse. Surveillance has been deemed an effective management strategy for CS1 GCTs even in patients with high-risk (~50%) chance of relapse, given the morbidity associated with primary RPLND or adjuvant chemotherapy given avoidance of overtreatment of those cured with orchietomy alone and availability of successful salvaged therapy [5, 8]. Recent modeling research has shown that surveillance does not compromise life expectancy for patients with either SGCT or NSGCT [9].

Surveillance guidelines for diagnostic imaging are more intense for NSGCT than for seminoma patients given that the former has a higher risk of recurrence and a shorter time-to-relapse. Different pathological features identify NSGCT patients with higher risk of relapse with lymphovascular invasion (LVI) being regarded as the most consistent independent predictive factor of relapse [10, 11]. A high component of embryonal carcinoma is another factor reported to be associated with risk of relapse [11, 12].

Given the benefits of active surveillance, strategies that reduce ionizing radiation exposure while preserving the outcome benefits of surveillance could improve the care of these patients. One potential strategy is to stratify NSGCTs patients according to a risk factor (RF) scoring system that optimizes surveillance frequency for those with a low-risk and delayed time-to-relapse. In the present study, we carried out a retrospective survey to establish a time-to-relapse model in the first 2 years of surveillance for CS1 NSGCT patients according relapse-associated RFs, with particular emphasis on the first 6 months.

**patients and methods**

We identified 266 patients from the IRB-approved Dana-Farber Cancer Institute (DFCI) GCT database with CS1 disease who were managed with surveillance between 1997 and 2013. Clinical and pathological data collected included: age at orchietomy, orchietomy histology, level of preoperative TMs, presence/absence of LVI, embryonal predominance (EmbP), as well as postorchietomy management information for the first 2 years and grouped by 3-month intervals. These included: number of AP-CTs (abdomino-pelvic computerized tomography excluding initial staging scan), TMs and follow-up visits. The Genitourinary Pathology Division of Brigham and Women’s Hospital/DFCI carried out central pathology review before treatment recommendations, in accordance with institutional policy. A tumor was considered embryonal predominant if this component was present at a level larger than any other histologic type present on the sample. The frequency of surveillance with CT-AP, chest X-ray and TMs was decided by the treating physicians and in essence followed NCCN guidelines at relevant times [13].

The primary end point in this study was time-to-relapse from date of orchietomy. To assess the relapse-predictive nature of our proposed model, we calculated hazard ratios (HRs) using the Cox regression proportional hazards model. A value of $P < 0.05$ was deemed statistically significant for multivariate modeling. Relapse-free survival (RFS) rates and incidence rates were calculated using the Kaplan–Meier method and conditional risk analysis was carried out using varying times of origin ($t_0$) at 0, 6, 12 and 18 months. Median time-to-relapse values were calculated after Cox regression among patients who relapsed. Finally, for model diagnostic purposes, the proportionality assumption was tested using Schoenfeld’s scaled residuals and data goodness-of-fit was assessed using Cox-Snell residuals.

**results**

**patient characteristics**

The cohort consisted of 135 patients with NSGCT and 131 patients with seminoma ($n = 266$). Patient characteristics are described in Table 1. For NSGCT patients, there was no difference between LVI+ and LVI− in age, median follow-up time, median time-to-first surveillance scan, or surveillance metrics.
(15%) SGCT patients relapsed. The median time-to-relapse was 11.5 versus 6.3 months for the SGCT and NSGCT groups, respectively. For NSGCT, relapse incidence was highest in the first 6-month interval (48% of all relapses) and the rate then progressively declined (26% more by year 1; 12% more by year 2). For SGCT, relapse incidence was highest in the second 6-month interval (30% versus 20% during the first 6 months), and then declined (15% more by year 2). Seven of 50 (14%) relapses took place after 2 years for NSGCT, compared with 7 of 20 (35%) relapses for seminomas. Of the 85 NSGCT patients who had not relapsed by year 5, 2.6% (2 of 85) subsequently relapsed. Of the 114 SGCT patients who had not relapsed by year 5, 2.6% (2 of 114) subsequently did.

For NSGCT patients, relapse rates were higher and median time-to-relapse faster with increasing number of RFs: relapse rates (%) and median time-to-relapse (months) were 25%/8.5 months, 41%/6.8 months and 78%/3.8 months for RF0, RF1 and RF2, respectively. Regarding disease-risk category at relapse, 94% of the 50 NSGCT relapses were classified as good-risk, while intermediate and poor-risk disease was found in two and one patients, respectively—13 of the 14 RF2 patients who relapsed had good-risk metastatic disease and one had intermediate-risk disease. All RF2 relapses occurred before 24 months. Of the 20 SGCT patients who relapsed, only one of 20 did not present with good-risk disease.

**discussion**

GCT worldwide incidence has more than doubled in the last 40 years, especially in industrialized countries [14]. The advent of successful salvage therapy, as well as the morbidity associated with other postoperative management options, has made active surveillance an acceptable management strategy [5]. In order to decrease the potential lifetime attributable risk of cancer incidence, modern surveillance regimens obtain fewer CTs, employ techniques aimed at limiting radiation to the minimum necessary for diagnostic purposes, or avoid altogether (i.e. MRI). The widespread implementation MRI surveillance may be limited by the availability of appropriately experienced radiologists required to achieve the same sensitivity as CTs, and is the subject of an ongoing study [15].

Even with these modality improvements, active surveillance is associated with significant radiation exposure, which is particularly relevant for the young GCT population. The safety of decreasing the number of surveillance AP-CT scans for CS1 NSGCT patients was demonstrated by the Medical Research Center...
Table 4. Relapse incidence and relapse-free survival

<table>
<thead>
<tr>
<th>Groups</th>
<th>Total relapses (rate)</th>
<th>Cumulative relapse incidence</th>
<th>Risk classification status at relapse</th>
<th>Relapse after first-line chemotherapy</th>
<th>Death secondary to GCT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>6 months</td>
<td>1 year</td>
<td>2 years</td>
<td>5 years</td>
</tr>
<tr>
<td>Full cohort (n = 266)</td>
<td>70/266 (26%)</td>
<td>28/70 (40%)</td>
<td>47/70 (67%)</td>
<td>56/70 (80%)</td>
<td>65/70 (93%)</td>
</tr>
<tr>
<td>SGCT (n = 131)</td>
<td>20/131 (15%)</td>
<td>4/20 (20%)</td>
<td>10/20 (50%)</td>
<td>13/20 (65%)</td>
<td>17/20 (85%)</td>
</tr>
<tr>
<td>NSGCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All (n = 135)</td>
<td>50/135 (37%)</td>
<td>24/50 (48%)</td>
<td>37/50 (74%)</td>
<td>43/50 (86%)</td>
<td>48/50 (96%)</td>
</tr>
<tr>
<td>RF0 (n = 76)</td>
<td>19/76 (25%)</td>
<td>7/19 (37%)</td>
<td>11/19 (58%)</td>
<td>14/19 (74%)</td>
<td>17/19 (89%)</td>
</tr>
<tr>
<td>RF1 (n = 41)</td>
<td>17/41 (41%)</td>
<td>9/17 (53%)</td>
<td>11/17 (65%)</td>
<td>14/17 (82%)</td>
<td>17/17 (100%)</td>
</tr>
<tr>
<td>RF2 (n = 18)</td>
<td>14/18 (78%)</td>
<td>0/0 0.00</td>
<td>0.25 0.50</td>
<td>0.75 1.00</td>
<td>Relapse-free survival rate</td>
</tr>
</tbody>
</table>

SGCT, seminomatous germ-cell tumor; NSGCT, nonseminomatous germ-cell tumor; LVI, lymphovascular invasion; EmbP, embryonal predominance; RF0, LVI− and EmbP−; RF1, LVI or EmbP+; RF2, LVI+ and EmbP+; HR, hazard ratio; CI, confidence interval.

Table 5. Patterns of relapse

<table>
<thead>
<tr>
<th>Groups</th>
<th>Median time-to-relapse (months)</th>
<th>Risk classification status at relapse</th>
<th>Relapse after first-line chemotherapy</th>
<th>Death secondary to GCT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7.5</td>
<td>66/70 (95%)</td>
<td>7/70 (10%)</td>
<td>3/266 (1%)</td>
</tr>
<tr>
<td>SGCT (n = 131)</td>
<td>11.5</td>
<td>19/20 (95%)</td>
<td>17/20 (100%)</td>
<td>1/131 (1%)</td>
</tr>
<tr>
<td>NSGCT</td>
<td>6.3</td>
<td>47/50 (94%)</td>
<td>5/50 (10%)</td>
<td>2/135 (1%)</td>
</tr>
<tr>
<td>All (n = 135)</td>
<td>8.5</td>
<td>17/19 (90%)</td>
<td>17/19 (100%)</td>
<td>1/135 (1%)</td>
</tr>
<tr>
<td>RF0 (n = 76)</td>
<td>6.8</td>
<td>17/17 (100%)</td>
<td>17/17 (100%)</td>
<td>1/135 (1%)</td>
</tr>
<tr>
<td>RF1 (n = 41)</td>
<td>3.8</td>
<td>13/14 (93%)</td>
<td>13/14 (93%)</td>
<td>1/135 (1%)</td>
</tr>
</tbody>
</table>

SGCT, seminomatous germ-cell tumor; NSGCT, nonseminomatous germ-cell tumor; GCT, germ-cell tumor; LVI, lymphovascular invasion; EmbP, embryonal predominance; RF0, LVI− and EmbP−; RF1, LVI or EmbP+; RF2, LVI+ and EmbP+; HR, hazard ratio; CI, confidence interval.

Figure 1. Kaplan–Meier relapse-free survival estimates.
Council (MRC) randomized, controlled trial which randomized 400 patients to CT imaging at either 3 and 12 or 3, 6, 9, 12 and 24 months postorchiectomy [16]. It showed that there was no appreciable increased risk of patients relapsing with intermediate- or poor-prognosis disease in the 2 versus 5 scans when patients were also surveyed with frequent plain chest radiographs and blood TMs. The currently employed surveillance regimen leads to significant radiation exposure with as many as 12 AP-CTs within the first 5-year period for NSGCT patients [13]. This number of CT scans typically leads to radiation exposure surpassing the established 5-year 100 mSv cumulative radiation exposure limit. Aiming to minimize the radiation exposure burden associated with active surveillance, we sought to identify low-risk NSGCT patient subsets whose relapse risk would not be affected by less frequent CT scanning.

We selected LVI and EmbP to be the main constituents of the NSGCT risk score given that several prior reports have shown that EmbP and LVI together portend a higher risk of relapse than either one alone, although EmbP’s prognostic significance is still actively debated [12, 17, 18]. The EmbP definition avoids the exclusion of patients with substantial embryonal cell cancer which may still lead to an increased risk of recurrence (30–40%) [19] as the alternate definition (>50% cutoff value) fails to incorporate cases in which the embryonal component predominates such as mixed tumors with multiple tissue subtypes with 40%/30%/30% distributions. Additionally, by assessing EmbP in conjunction with LVI, avoidance of an effect of LVI status upon 40%/30%/30% distributions. Additionally, by assessing EmbP in incorporation cases in which the embryonal component predominates such as mixed tumors with multiple tissue subtypes with 40%/30%/30% distributions. Additionally, by assessing EmbP in conjunction with LVI, avoidance of an effect of LVI status upon EmbP status might be avoided [12].

Both the LVI+/LVI− and EmbP+/EmbP− had similar follow-up time intervals, days to first surveillance scan and number of AP-CTs, TMs and visits. Furthermore, the relapse rates obtained in our study are consistent with what has been previously reported for SGCT [20] and NSGCT [6].

We found that the RF score was proportional to relapse rate, incidence rate and cumulative incidence but inversely proportional to RFS and median time-to-relapse. It is of note that we found the RFS for SGCT and NSGCT with neither EmbP nor LVI (RF0) were similar. Cox regression analysis confirmed that their RFS functions were not statistically different at all time points (including \( t_0 = 0 \) months). Conditional risk analysis revealed that the absolute and relative relapse probability for all groups was highest during the first 6-month period and progressively decreased thereafter. However, analysis beyond the 1-year time point should be carefully interpreted due to the small sample sizes (particularly on the RF1/RF2) and the resulting loss of statistical power.

Recent work by Kollmannsberger et al. suggests the plausibility of optimizing surveillance schedules by risk-stratifying patients by LVI status [21]. Our study offers an opportunity to further refine these schemes by showing that EmbP may be predictive of relapse when considered in conjunction with LVI. Although this retrospective study is not intended to change practice, it aims to support a prospective evaluation of these findings along with cranio-caudal lymph node assessment, as well as other potential novel pathologibal/ molecular biomarkers and their influence on relapse occurrence and timing.

In summary, we found that the risk stratification of NSGCT patients into a risk score system based on EmbP and LVI yielded three groups with significantly different RFS functions. The lowest risk group (RF0) behaved similarly to SGCT in terms of time-to-relapse for all recorded time points, while RF1 and RF2 joined them at 12 and 18 months, respectively. Our work supports the notion that the surveillance regimen for NSGCT RF2 may be optimized to resemble that of SGCT patients. Additionally, it is consistent with Kollmannsberger’s study but supports utilizing EmbP and LVI status to further risk-stratify patients in order to optimize surveillance regimens.

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disclosure
The authors have declared no conflicts of interest.

references
A randomized phase III trial of oral S-1 plus cisplatin versus docetaxel plus cisplatin in Japanese patients with advanced non-small-cell lung cancer: TCOG0701 CATS trial


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Background: Platinum-based two-drug combination chemotherapy has been standard of care for patients with advanced nonsmall-cell lung cancer (NSCLC). The primary aim was to compare overall survival (OS) of patients with advanced NSCLC between the two chemotherapy regimens. Secondary end points included progression-free survival (PFS), response, safety, and quality of life (QoL).

Patients and methods: Patients with previously untreated stage IIIIB or IV NSCLC, an Eastern Cooperative Oncology Group performance status of 0–1 and adequate organ function were randomized to receive either oral S-1 80 mg/m²/day on days 1–21 plus cisplatin 60 mg/m² on day 8 every 4–5 weeks, or docetaxel 60 mg/m² on day 1 plus cisplatin 80 mg/m² on day 1 every 3–4 weeks, both up to six cycles.

Results: A total of 608 patients from 66 sites in Japan were randomized to S-1 plus cisplatin (n = 303) or docetaxel plus cisplatin (n = 305). OS for oral S-1 plus cisplatin was noninferior to docetaxel plus cisplatin [median survival, 16.1 versus 13.1 months; hazard ratio (HR) for death, 0.88; 95% confidence interval (CI), 0.71–1.10; P = 0.28]. PFS was longer for S-1 plus cisplatin than for docetaxel plus cisplatin (median PFS, 4.8 versus 3.6 months; HR, 0.69; 95% CI, 0.56–0.85; P < 0.001). There was no significant difference in the median duration of response between the two arms (3.9 months for S-1 plus cisplatin versus 5.0 months for docetaxel plus cisplatin; HR, 1.12; 95% CI, 0.76–1.63; P = 0.58). The safety profile was similar in the two groups, although neutropenia was more frequent in the S-1 plus cisplatin group (84% vs 77%).

Conclusion: Oral S-1 plus cisplatin resulted in noninferior OS compared with docetaxel plus cisplatin. This regimen was associated with improved PFS and a less frequent occurrence of neutropenia.