Compliance and outcome of patients with stage 1 non-seminomatous germ cell tumors (NSGCT) managed with surveillance programs in seven Canadian centres

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Objective: *We evaluate the impact of surveillance programs on the outcome of men with clinical stage 1 NSGCT following orchidectomy.*

Patients and methods: *A retrospective review of 197 patients with a minimum of 2 years follow-up at seven cancer centres was conducted. Histological characteristics of the primary tumor were recorded for each patient. Surveillance protocols consisted of clinical assessments, chest X-rays, serum beta HCG (βHCG), alpha feto-protein (αFP), and abdominopelvic CT. All clinic visits and test completions were tracked. In accordance with each centre's specific surveillance protocol, patient compliance was defined as missing no more than two assessments/year.*

Results: *Overall 5 year survival was 100%. With a median follow-up of 54 months (range: 11-164 months), the relapse rate at 5 years was 29%. The median time to relapse was 6 months (range: 2-135 months). Ninety percent of relapses occurred within 18 months and only two patients relapsed after 5 years. On univariate analysis, only the presence of lymphovascular invasion was predictive of relapse. The first indicator of relapse was: CT alone, 36%; elevated βHCG or αFP, 29%; CXR, 10%; or clinical exam, 7%. Either CT, tumor markers, or CXR detected 90% of all relapses. Although differences in the frequency of assessments between the centres existed, no significant differences occurred in rates of relapse or survival (p>0.07). The mean rate of compliance with clinic visit (which included CXR and tumor markers) was 78% (range: 68.4-94.2%). The mean rate of compliance with CT scanning, was 64.3% (range: 32.2-100%). In the centre with the protocol requiring the least frequent visits, the rates of compliance were observed to be highest.*

Conclusions: *Surveillance remains an effective means of managing stage 1 NSGCT despite variability in protocols and in patients compliance. An abnormal CT was the most frequent identifier of disease relapse, and in combination with tumor markers and CXR, 90% of relapses were detected within 2 years of orchiectomy. Modifications of surveillance protocols to less frequent assessments may be possible and should be subject to prospective evaluation.*

Key Words: testicular neoplasms, surveillance, compliance

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Introduction

Testicular cancer is the most common malignancy in men 18 to 35 years of age and slightly more than half of those diagnosed will have nonseminomatous germ

cell tumors (NSGCT).[1] In the past 2 decades, enhanced clinical staging techniques and the introduction of effective chemotherapy regimens for metastatic disease, have significantly improved the outlook for patients with NSGCT.[2] Conventional treatment of post-orchiectomy stage 1 NSGCT patients has included retroperitoneal lymph node dissection (RPLND), followed by chemotherapy if the nodes are determined pathologically to be involved.[3] In a review of treatment modalities for NSGCT, Lashley and Lowe report that following RPLND there is a low incidence of relapse (6%-14%) and, when combined with the effectiveness of salvage chemotherapy, survival rates approach 100% in many centres.[4] However, RPLND has associated morbidities, such as post-operative complications, recovery time, and possible loss of fertility.[5] As well, it is estimated that 70%-80% of stage 1 patients are cured by orchiectomy alone and any further treatment is unnecessary.[6] Therefore, in order to reduce morbidity while maintaining survival rates, surveillance has been explored as an alternative to initial RPLND.[7]

In Canada, over the past 2 decades, surveillance protocols have been increasingly used in the management of stage 1 NSGCT patients. Although surveillance protocols have some variance between treatment centres, most involve regular clinical assessments, measurement of tumor markers, and imaging of the chest and abdomen. All of these evaluations have been shown to detect relapse, whether alone or in combination with another modality.[8,9] The relapse rate of patients on surveillance ranges from 13% to 37% which is comparable to that of RPLND. The majority of patients relapse within 24 months from orchiectomy.[10,11] Proponents of surveillance emphasize that early detection of recurrence due to the structured schedule of patient evaluations allows for effective treatment of relapse. Surveillance with treatment at relapse has been reported to attain a survival rate of 92% to 100% in patients with stage 1 NSGCT.[3,12,13]

A critical factor in the surveillance approach is the ability to detect early relapses such that effective systemic therapy can be initiated before longterm outcomes can be adversely affected.[7] Consequently, the assessments required in surveillance are frequent. Some patients may find them excessively onerous and consequently, fail to comply with the appropriate tests.[14] We had previously investigated patient compliance with surveillance protocols in a single Canadian centre but were unable to demonstrate whether poor compliance adversely affects overall survival due to the small study population.[15] Other studies have shown that survival is not affected by poor compliance with surveillance protocols.[9,11]

The use of surveillance as the primary treatment method following orchiectomy has been criticized due to the possibility that non-surgical staging techniques may not detect relapse in all patients. Several factors play a role in the success of surveillance, including effective implementation of follow-up protocols, patient compliance, and predictive determinants for relapse. The optimal frequency of surveillance evaluations has yet to be established and should balance the best possible relapse detection with increased patient compliance. Few studies have evaluated the outcomes of surveillance protocols in multiple treatment centers in order to determine how outcomes are affected by differing protocols. This study addresses some of these factors from the perspective of seven Canadian cancer centers using surveillance to follow post-orchiectomy stage 1 NSGCT patients.

Patients and methods

A retrospective review of 197 patients diagnosed with stage 1 NSGCT was conducted at seven Canadian cancer centers over a 9 month period. All patients had undergone orchiectomy and had histologically confirmed NSGCT. All histological subtypes of NSGCT (embryonal carcinoma, choriocarcinoma, endodermal sinus, malignant teratomas and mixed tumors with seminomatous elements)\l "teratoma" were identified. Those patients in whom lymphovascular invasion was present, were not specifically excluded. In order to verify that all patients had clinical stage 1 disease, chest x-rays and abdominopelvic CT's were normal at baseline, and serum αFP and βHCG were in the normal range within 6 weeks of the orchiectomy.

Following orchiectomy, patients agreed and were placed on a surveillance protocol as previously determined by each center. These protocols consisted of clinical assessments, chest x-ray, serum αFP and βHCG (6-12 in year one; 3-6 in year two) and routine abdominopelvic CT scans (4-6 in year one; 3-4 in year two), with slight variances in the number of these tests between centers. All clinic visits and tests were tracked for all patients.

Case reports were completed at each participating centre using the patient record. If there was no documentation of a particular test result or assessment, it was recorded as "not done". The probability of being

relapse-free over time was calculated using the Kaplan-Meier method. The influence of potential prognostic factors on relapse was assessed using the Cox model. The Chi-square statistic was used to determine if there were differences between the seven centres in the proportion of patients relapsing.

In accordance with each center's specific surveillance protocol, patient compliance was defined as missing no more than two assessments per year. Compliance data was analyzed using descriptive statistics to determine the mean rates of patient compliance with the various components of the surveillance protocol.

Results

The tumor characteristics of all study patients are shown in Table 1. Although the majority had a mixed histology, 34 (17.3%) had pure embryonal tumors. Lymphovascular invasion was present in 18.2% of cases. Transgression of the tunica albuginea was observed in 14.2%.

The median follow-up interval for those who had not relapsed was 54 months with a range of 11-164 months. Overall survival at 5 years was 100%. (Only one death resulting from a motor vehicle accident, occurred in the entire group at 70 months) No treatment or cancer related deaths occurred.

The overall relapse rate at 5 years was 29% (95%CI: 22%, 35%). The median time to relapse was 6 months (range: 2-135 months). Figure 1 Approximately 90% of all relapses occurred within 18 months of orchidectomy. Only two late relapses (> 5 years) occurred, one at 69 and another at 135 months and both patients remain in remission. Relapses were detected through a variety of modalities, either alone or in combination. Table 2 Each one of the tests (CT scan, chest x-ray, tumor markers, clinical exam) was the only mode of relapse detection for some patients. However, CT scans alone were responsible for the detection of the largest number of relapses (36%). When CT findings were combined with tumor marker elevations, the detection rate increased to 79%. The two late relapses were detected by CT scan and clinical exam. One patient was completely asymptomatic and had retroperitoneal adenopathy on CT; the other patient presented with palpable supraclavicular adenopathy. Both patients had complete responses to four cycles of BEP chemotherapy and remain free of disease.

Univariate evaluation of various disease characteristics (histology, invasion) showed that the presence of lymphovascular invasion (Logrank test, p=0.044) and spermatic cord involvement (p = 0.054) were predictive of relapse. Table 3 Multivariable analysis gave similar results.

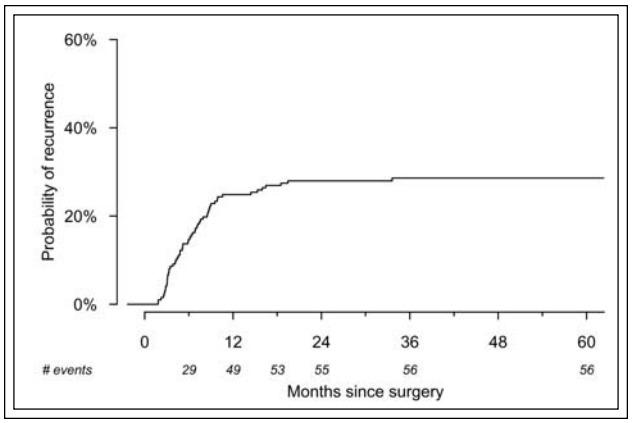

Figure 1. Probability of recurrence curve and method used to detect the recurrence.

TABLE 1. **Tumor characteristics in patient population**

Characteristic	**Value**	**%**
N	197	~
Mean age (range)	30.3 (14-63)	~
Histology		
Mixed	116	58.9
Teratoma	45	22.8
Embryonal	34	17.3
Choriocarcinoma	1	0.5
Endodermal sinus	1	0.5
Invasion		
Lymphovascular	36	18.2
Tunica albuginea	28	14.2
Spermatic cord	9	4.6
Epididymis	9	4.6

TABLE 2. **Methods of relapse detection**

Method	**Number**	**%**
CT scan	21	36
Tumor markers	17	29
Chest x-ray	6	10
Clinical exam	4	7
CT scan + tumor markers	8	14
CT scan + chest x-ray + tumor markers	2	3

TABLE 3. **Cox regression analyses for relapse**

Prognostic Factor	p
Lymphovascular invasion	0.026
Spermatic cord involvement	0.05
Epididymal involvement	0.71
Tunica vaginalis involvement	0.33
Embryonal cell element	0.40

TABLE 4. **Compliance by centre**

Treatment centre	n	% Relapse	% Compliance
A	34	26	71
B	31	42	87
C	37	41	78
D	19	11	68
E	25	36	72
F	16	12	81
G	35	23	94

Clinic visits always included physical exam, chest x-ray and tumor markers evaluation. The median compliance rate with clinical visits was 79% (range: 68%-94%). Table 4 Additionally, the mean rate of compliance for CT was 64% (range: 32%-100%).

Overall compliance was the highest at Centre G where the surveillance protocol required the least frequent follow-up visits (94%). This center also reported 100% patient compliance with CT scans, which were required every 4 months, instead of every 2 or 3 months, as in the other centers. Although differences existed in the frequency of surveillance assessments between centers, no significant differences occurred in rates of relapse. (p=0.077)

Discussion

A substantial proportion of stage 1 NSGCT patients would be expected to relapse as clinical staging will fail to identify patients with occult metastatic disease. Relapse rates with surveillance range from 13%-37% and usually occur within 2 years of the orchiectomy.[2,12,14] The relapse rate of 29% in this study compares favorably with previous reports. The relapse rate would only be acceptable if no negative impact on survival could also be demonstrated. In this series, the disease free survival was 100%. This finding compares favorably with the survival of patients initially managed with orchiectomy and RPLND and is achieved without the accompanying morbidities of the RPLND.[9] Therefore, relapse detection and survival do not appear to be compromised through the use of surveillance protocols.

All patients who relapsed received 3 – 4 cycles of BEP chemotherapy. Adjuvant chemotherapy was not considered to be an option for patients with stage 1 NSGCT during the time when the study was conducted. Although surveillance may provide a potential advantage over adjuvant chemotherapy in reducing the amount of chemotherapy required overall, the issue is beyond the scope of this study. However, an important cost consideration in the utilization of surveillance is the requirement for frequent clinical and radiological assessments which are necessarily extended to 5 years and beyond.

Given that clinical staging with CTs and chest x-rays is less sensitive than surgical staging, surveillance protocols make use of multiple evaluation modalities to detect early relapses. Previous studies have shown that all commonly employed surveillance methods are able to detect relapse in some patients and that CT is consistently the most sensitive.[3,9] Similarly, this study confirms that CT scanning was most frequently the sole method of relapse detection. Tumor markers were also an important means of early detection and when combined with CT scan, doubled the detection rate to 79%. Other studies have found that chest x-rays did not independently detect relapse and recommended that this test could be removed from the surveillance protocol.[3,16] However, in this study, 10% of relapses were discovered on chest x-ray alone. Although the physical examination also appears to have a very limited role, the two late relapses were identified by utilizing the physical assessment and should remain in the surveillance protocols. The inclusion of the physical exam also helps to ensure that patients have the x-rays done and tumor markers drawn.

The relapse rates have been shown to be dependant upon the presence or absence of a number of prognostic factors. Lymphovascular invasion alone has been consistently reported as predictive of relapse patients.[17,18] Klepp et al found that the presence of lymphovascular invasion was the strongest predictor for relapse on multivariate analysis.[19] In our study, lymphovascular invasion similarly appeared to be an important determinant for relapse.

Freedman et al had identified four pathological characteristics which predicted relapses: vascular

invasion, lymphatic invasion, absence of yolk sac elements and presence of undifferentiated tumour.[20] An index which incorporated these factors was constructed in order to identify high risk patients. Read et al applied the index to a cohort of 373 patients on surveillance post-orchiectomy.[21] The retrospective nature of the study meant that we did not have complete information to assess Read's index. In particular, we had no information about the presence or absence of undifferentiated tumor. Eight individuals had all of the remaining three factors (vascular invasion, lymphatic invasion, and absence of yolk sac elements). Two recurred, one at 3.1 months and the other at 33.6 months post orchiectomy.

Furthermore, several studies have consistently reported that the presence of embryonal histology is an independent adverse prognostic feature and is associated with higher relapse rates.[3,15,21] We did not confirm this observation in this series. However, in the seven patients with both embryonal cell features and lymphovascular features present, the relapse rate at 5 years was 43%. In a series of Pont et al, 17 of 18 patients with embryonal cell histology had demonstrable vascular invasion raising the possibility that these factors are linked.[22] In two prospective studies of surveillance and adjuvant chemotherapy, the relapse rate at 2 years for patients who did not have lymphovascular was 14-15%.[18,23]

The optimal schedule for surveillance has yet to be determined prospectively. Differences in the frequency of follow-up procedures are variable between centers. In this study, comparisons of outcomes between seven different centres with some minor variations in surveillance schedules, was possible. The differences in surveillance protocols had no significant effect on relapse rates or survival. This is similar to results reported by Freedman et al, where the variations in surveillance protocols between centers taking part in the study did not influence timing or extent of disease at relapse.[20] Thus, those centres with less intensive protocols achieved similar results to those that require patients to be followed more frequently. This has led some to suggest that reducing the frequency of surveillance visits may be more attractive to patients while resulting in similar outcomes.[9,14,15]

In order for a surveillance protocol to be successful in detecting relapse, patients must comply with the schedule of evaluations. This has proven to be a challenge with this cohort of patients due to the fact that it is generally composed of young men who are socially mobile.[4,14] As well, institutional difficulties including access to and waiting times for CT scans, can affect compliance with protocols.[11] Although non-compliance would suggest that patient outcomes respond accordingly, the seven centers in this study reported a range of compliance rates (68%-94%), which did not seem to affect relapse rate or survival. This is similar to results reported by Colls, who found that 30 of 248 patients (12%) were non-compliant with clinic attendance; of these, 6 (20%) subsequently relapsed.[9] Only one patient died from disease having refused treatment.

Compliance rates will be influenced by the frequency of assessments. Although it seems that compliance may not play a significant role in the success of surveillance, some argue that poor compliance may result in a greater chance that relapse is detected at a more advanced stage of disease with a potentially worse prognosis.[14] In protocols with more intensive schedules, the possibility of missing several tests is increased and therefore the potential for non-compliance is greater. On the other hand, the ability to detect relapses is enhanced by the more frequent assessments. Our findings were illustrative in that the centre with the less intensive program, had the highest compliance rate. Yet, the overall outcome was the same as those centres with the more intense surveillance schedule. However, before making any recommendations towards less frequent assessments, a randomized prospective trial should be performed and is the subject of an on-going international trial conducted by the Medical Research Council of the UK.

Surveillance remains as an important management option for selected patients with stage 1 NSGCT with very favorable long-term survival. Differences in the frequency of assessments did not appear to impact on outcomes. In this study, most relapses were detected with a combination of abdominopelvic CT scans and serial tumor marker evaluations. Although the optimal follow-up schedule has yet to be established, less frequent assessments may be potentially utilized without jeopardizing long-term outcome; however, this hypothesis should be subject to a randomized control study before widespread implementation. □

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