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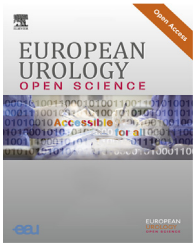

Testis Cancer

Safety of Minimizing Intensity of Follow-up on Active Surveillance for Clinical Stage I Testicular Germ Cell Tumors

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Abstract

Background: We have recommended active surveillance as the preferred management option for clinical stage I (CSI) testicular germ cell tumors (GCTs) since 1980. Over time, the recommended intensity of surveillance has decreased; however, the impact on relapse detection has not been investigated.
Objective: To examine relapse rate, time to relapse, extent of disease, and burden of treatment at relapse across decreasing surveillance intensity over time.
Design, setting, and participants: CSI GCT patients under active surveillance from 1981 to 2021 were included in this study.
Outcome measurements and statistical analysis: Through four major iterations in both nonseminomatous (NSGCT) and seminoma surveillance schedules, visit frequency, blood testing, and imaging have been decreased successively. Low-dose, noncontrast computed tomography (CT) scans were adopted in 2011. Categorical variables and time to relapse were compared using chi-square and Fisher's exact or Kruskal-Wallis test, respectively.
Results and limitations: A total of 1583 consecutive patients (942 with seminoma and 641 with NSGCT) were included. In seminoma, chest x-rays were reduced from 13 to one and CT scans were reduced from 20 to ten. Relapse rate, time to relapse, N or M category, and International Germ Cell Cancer Collaborative Group (IGCCCG) classification did not change. In NSGCT, chest x-rays were reduced from 27 to zero and CT scans were reduced from 11 to five. Relapse rate (from 46.2% to 21.2%, p = 0.002) and the median time to relapse (from 6.54 to 4.47 mo, p = 0.025) decreased. No difference in relapsed disease burden was identified by N, M, and S category or IGCCCG classification. Treatment burden at relapse and GCT cancer

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deaths remained similar for seminoma and NSGCT. Limitations include the retrospective design and large time period covered.

Conclusions: Despite considerable reductions in surveillance intensity, we did not observe an increase in disease extent, treatment burden, or GCT cancer deaths upon relapse. These results support that our current lower-intensity active surveillance schedules are safe for managing CSI GCT.

Patient summary: Our current reduced-intensity surveillance schedules for clinical stage I germ cell tumors appear to be safe.

1. Introduction

The majority of patients with germ cell tumor (GCT) present with clinical stage I (CSI) disease after orchiectomy that is localized to the testicle with no evidence of metastases on serologic, radiographic, or clinical examinations [1]. In these patients, orchiectomy alone is curative in 70% with nonseminomatous germ cell tumor (NSGCT) and in 85% with seminoma [1–3]. Following orchiectomy, management may include active surveillance, adjuvant chemotherapy, radiotherapy, or retroperitoneal lymph node dissection (RPLND), depending on whether the tumor is seminoma or NSGCT, and risk of relapse.

Active surveillance implies monitoring with imaging ± serum tumor markers with no intervention unless relapse occurs. Given that 70–85% of CSI patients are cured with orchiectomy alone, highly effective salvage therapies are available and cancer-specific survival approaches 100%; active surveillance has been adopted universally as a standard of care for seminoma and NSGCT [4,5].

The Princess Margaret Cancer Centre began active surveillance as a management option in CSI NSGCTs and seminomas in 1981. Since inception, our surveillance algorithms have evolved to reflect a growing understanding of the natural history of disease and increased experience providing surveillance care. Specifically, we have a much better understanding of the timing and pattern of relapse in both seminoma [6,7] and NSGCT [8]. Over time the frequency of required hospital visits for blood work, imaging, and follow-up interaction have been reduced progressively.

Reductions in surveillance intensity minimize patient burden, health care system costs, and radiation exposure. Although each revision to our algorithms has been based on analyses of our experience and evolving literature available, the overall safety of minimizing surveillance intensity has not been evaluated formally. Herein, we evaluate whether less intensive surveillance at our institution was associated with change in the incidence of relapse, extent of relapse, and intensity of treatment at relapse.

2. Patients and methods

2.1. Patient selection

After receiving institutional research ethics board approval, a total of 1580 consecutive CSI patients (641 with NSGCT and 939 with seminoma) managed with non–risk-adapted surveillance at the Princess Margaret Cancer Centre from 1981 to 2020 were identified from our prospectively maintained institutional database. We censored the study cohort on December 31, 2018, to facilitate at least 2 yr of follow-up for all patients, given the median relapse time of 6 mo for CSI NSGCT and 14 mo for CSI seminoma [2]. Relapse was defined as imaging or physical examination evidence of metastases and/or elevated tumor markers. Contralateral primary GCTs and falsely positive patients (possible relapse investigated with no true relapse) were excluded from analysis. The salvage therapies (termed multimodal therapy) utilized were discussed in a multidisciplinary setting for each patient. Patients were staged according to the eighth edition of the TNM staging system with a computed tomography (CT) scan of the chest, abdomen, and pelvis prior to their orchiectomy or directly following it. Tumor markers were drawn both prior to and following orchiectomy.

2.2. Surveillance schedule algorithms

Our follow-up algorithms have been modified over time, and prior versions have been published previously [6,8–16]. Table 1 summarizes the evolution through four iterations of the NSGCT algorithm (Supplementary Table 1) and four iterations of the seminoma algorithm (Supplementary Table 2). For ease of analysis, we have combined NSGCT

Table 1 – Summary of active surveillance schedules

Guideline		Chest x-ray #	CT chest #	CT abdomen #	CT pelvis #	Follow-up (yr)
NSGCT	1st schedule: 1981–1986	27	0	11	11	5
	2nd schedule: 1986–1990	21	0	11	11	5
	3rd schedule: 1990–2010	18	0	6	6	5
	4th schedule: 2010–present	0	5	5[a]	5[a]	5
Seminoma	1st schedule: 1982–2004	13	0	20	20	10
	2nd schedule: 2004–2010	11	0	20	20	10
	3rd schedule: 2011–2017	4	0	10	6	9
	4th schedule: 2017–present	1	0	10[a]	6[a]	9

CT = computed tomography; NSGCT = nonseminomatous germ cell tumor.
[a] CT scans are low dose (55% dose reduction), noncontrast.

iterations #4 and #5, and seminoma iterations #3 and #4, as the changes were minimal and time periods were short. Importantly, starting in 2011, CT scans following initial staging for both seminoma and NSGCT utilized a "low-dose" protocol with the use of oral contrast only, resulting in a 55% reduction in radiation exposure from CT surveillance imaging [17].

2.3. Statistical analysis

Patients were stratified into cohorts by era and surveillance schedule iteration. Separate analyses were done for NSGCT and seminoma. Patients were analyzed as a function of the surveillance iteration in place at the time of their diagnosis. Baseline characteristics, relapse patterns, burden of treatment for relapse, and incidence of second relapse and death were compared between each group.

Chi-square association or Fisher's exact test (as appropriate) was used to compare both categorical treatment variables and relapse rates across all versions of the NSGCT and seminoma surveillance algorithms. Time from the date of orchiectomy to first relapse was compared using the Kruskal-Wallis nonparametric test. Finally, Kaplan-Meier curves were created depicting time to relapse by survival schedule and Cox proportional hazards models were formulated to estimate differences in time to relapse. Results were considered to be significant for $p \leq 0.05$. Statistical analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA), and version 9.4 of the SAS system for Windows (SAS Institute, Inc., Cary, NC, USA).

3. Results

3.1. Nonseminomatous GCT

The 641 NSGCT surveillance patients were grouped into surveillance iteration schedule cohorts as follows: 1981–1986 (n = 52 patients, 8.11%), 1986–1990 (n = 62 patients, 9.67%), 1990–2010 (n = 334 patients, 52.1%), and 2010–present (n = 193 patients, 30.1%). Baseline characteristics were similar across the cohorts, with the exception of the presence of lymphovascular invasion (LVI), which decreased slightly over time (p = 0.03; Table 2).

The median follow-up was 5.30 yr (interquartile range [IQR]: 3.57–9.50 yr). Between 1981 and the present schedule, the number of surveillance CT scans was incrementally reduced from 11 to 5, and chest x-rays were reduced from 27 to zero. After 2011, all CT scans were low dose and non-contrast. The modeled cumulative radiation dose decreased from 156.7 to 52.7 mSv from the initial to the most recent schedule. Throughout all cohorts, relapse occurred in 165 patients (25.7%), with a median time to relapse of 6.30 mo (1.90–331.9 mo).

Over time, relapse rate decreased from 46.2% in the 1981–1986 era to 21.2% in the 2010–present era (p < 0.001; Table 3). Time to relapse by surveillance schedule is depicted in Supplementary Fig. 1. Time from orchiectomy to relapse was also shortened (from 6.54 to 4.47 mo from the 1981–1986 to the present era, p = 0.025). The modality identifying relapse differed significantly across schedules (p = 0.002). Specifically, the proportion of relapses identified by tumor markers decreased (from 60.9% to 26.8% in the present era) and the proportion identified by imaging increased (from 26.1% to 56.1% in the present era).

Importantly, no difference was noted in the burden of disease at relapse over time, as depicted by the N (p = 0.4), M (p = 0.3), and S (p = 0.1), stage and International Germ Cell Cancer Collaborative Group (IGCCCG) classification (p = 0.3). While no change was seen in the burden of relapse therapy, increasing use of chemotherapy was noted, although this may be confounded by the early use of radiation for NSGCT relapses, a practice stopped in 1986.

The incidence of second relapse remained similar across the surveillance schedules, ranging from 17.1% to 20.8%. There were five testis cancer deaths (3.29% of total relapsed patients and 0.78% of total patients on surveillance), two in the 1981–1986 schedule and three in the 1990–2010 schedule.

3.2. Seminoma

The 942 stage I seminoma patients were grouped into four iterations of surveillance schedules as follows: 1982–2004 (n = 416 patients, 44.2%), 2004–2010 (n = 241 patients, 25.6%), 2011–2017 (n = 248 patients, 26.3%), and 2017–present (n = 37, 3.93%) eras. The median follow-up was 8.37 yr (IQR: 4.49–10.19 yr). Baseline characteristics were similar across all surveillance schedule versions except age

Table 2 – NSGCT patient baseline characteristics

Patient characteristics	Nonseminomatous germ cell tumor patients (N = 641)				
	1981–1986 (N = 52)	1986–1990 (N = 62)	1990–2010 (N = 334)	2010–present (N = 193)	p value
Age at orchiectomy (yr), mean (SD)	29.3 (10.5)	29.5 (7.3)	29.6 (8.3)	30.0 (9.7)	0.81
Right-sided primary, n (%)	30 (57.69)	32 (51.61)	183 (54.79)	96 (49.74)	0.63
pT stage, n (%)					0.05
T1	37 (71.15)	38 (61.29)	259 (77.54)	143 (74.09)	
T2	15 (28.85)	22 (35.48)	71 (21.26)	50 (25.91)	
T3	0	2 (3.23)	2 (0.60)	0	
T4	0	0	2 (0.60)	0	
TIS	0	0	0	0	
TX	0	0	0	0	
Stage at presentation, n (%)					0.05
Stage 1A	037 (71.15)	038 (61.29)	259 (77.54)	143 (74.09)	
Stage 1B	015 (28.85)	024 (38.71)	075 (22.46)	050 (25.91)	
LVI present, n (%)	15 (34.88)	23 (38.98)	69 (22.40)	49 (26.20)	0.03*
Pure EC pathology, n (%)	013 (25.00)	010 (16.13)	047 (14.16)	025 (12.95)	0.17
Both LVI and pure EC, n (%)	5 (9.62)	7 (11.29)	17 (5.09)	14 (7.25)	0.23

EC = embryonal carcinoma; LVI = lymphovascular invasion; NSGCT = nonseminomatous germ cell tumor; SD = standard deviation.
* The asterisk symbol denotes significance.

Table 3 – NSGCT patient characteristics at relapse

Schedule iteration	1981–1986 (*n* = 52)	1986–1990 (*n* = 62)	1990–2010 (*n* = 334)	2010–present (*n* = 193)	*p* value
Number relapsed, *n* (%)	24 (46.2)$_{1,2}$	20 (32.3)	80 (24.0)$_{1}$	41 (21.2)$_{2}$	0.002*
Time from orchiectomy to relapse (mo), median (range)	6.54 (2.67-21.13)	6.89 (3.10-331.90)$_{1}$	7.37 (1.90-76.63)$_{2}$	4.47 (2.10-64.50)$_{1,2}$	0.025*
N at relapse, *n* (%)					0.425
N0	7 (29.2)	5 (25.0)	16 (20.0)	9 (22.0)	
N1	7 (29.2)	6 (30.0)	39 (48.8)	21 (51.2)	
N2	9 (37.5)	7 (35.0)	23 (28.8)	11 (26.8)	
N3	1 (4.2)	2 (10.0)	2 (2.5)	0	
M at relapse, *n* (%)					0.341[a]
M0	20 (83.3)	15 (75.0)	61 (76.3)	26 (63.4)	
M1a	4 (16.6)	5 (25.0)	16 (20.0)	15 (36.6)	
M1b	0	0	3 (3.8)	0	
S at relapse, *n* (%)					0.170[a]
S0	7 (29.2)	5 (25.0)	36 (45.0)	15 (36.6)	
S1	17 (70.8)	14 (70.0)	37 (46.3)	26 (63.4)	
S2	0	1 (5.0)	6 (7.5)	0	
S3	0	0	1 (1.3)	0	
IGCCCG class, *n* (%)					0.291[a]
Good	24 (100)	19 (95.0)	71 (88.8)	41 (100)	
Intermediate	0	1 (5.0)	5 (6.3)	0	
Poor	0	0	4 (0.5)	0	
Modality identifying relapse, *n* (%)					0.003[a,*]
Imaging	6 (26.1)$_{1}$	6 (30.0)	44 (55.0)	23 (56.1)$_{1}$	*
Tumor markers	14 (60.9)$_{1,2}$	12 (60.0)$_{3}$	22 (27.5)	11 (26.8)$_{2}$	*
Imaging + tumor markers	2 (8.7)	0	12 (15.0)	7 (17.1)	
History/physical examination	1 (4.3)	2 (10.0)	2 (2.5)	0	
Positive modality at relapse, *n* (%)					
Tumor markers	17 (70.8)	15 (75.0)	44 (55.0)	27 (65.9)	
CT A/P	17 (70.8)	15 (75.0)	65 (81.3)	31 (75.6)	
CXR	3 (12.5)	1 (5.0)	10 (12.5)	0	
CT T	1 (4.17)	3 (15.0)	14 (17.5)	14 (34.2)	
History/physical examination	6 (25.0)	7 (35.0)	9 (11.3)	2 (4.8)	
Modes of therapy required, *n* (%)					0.136[a]
Single	12 (50.0)	6 (30.0)	19 (24.4)	12 (30.0)	
Multimodal	12 (50.0)	14 (70.0)	59 (75.6)	28 (70.0)	
First therapy, *n* (%)					<0.001 [a,*]
Chemotherapy	12 (50.0)	13 (65.0)	44 (56.4)	28 (70.0)	
RPLND	6 (25.0)	7 (35.0)	33 (42.3)	9 (22.5)	
Other surgery[b]	0$_{1}$	0	1 (1.3)	3 (7.5)$_{1}$	*
Radiation	6 (25.0)$_{1,2}$	0	0$_{1}$	0$_{2}$	*
Second relapse, *n* (%)	5 (20.8)	4 (20.0)	15 (18.8)	7 (17.1)	0.971[a]
Deaths	2 (3.9)	0	3 (0.9)	0	0.254[a]

A/P = abdomen/pelvis; CT = computed tomography; CT T = CT of the thorax; CXR = chest x-ray; IGCCCG = International Germ Cell Cancer Collaborative Group; NSGCT = nonseminomatous germ cell tumor; RPLND = retroperitoneal lymph node dissection.
Subscript numbers 1, 2, and 3 indicate statistically significant difference between marked schedules (Bonferroni corrected). The asterisk symbol denotes significance.
[a] Fisher's exact test.
[b] One cranial resection for brain metastases, one pelvic lymph node dissection, and two scrotectomies.

(p = 0.023), pT stage (p = 0.006), and the simultaneous presence of tumor size ≥4 cm and rete testis invasion (p = 0.016; Table 4).

Between 1982 and the present schedule, the number of recommended surveillance chest x-rays was reduced from 13 to 1 and the number of CT scans from 20 to 10, with only abdominal CT scans being performed after year 3 (four of ten CT scans). Similar to NSGCT, after 2011 all surveillance CT scans were low dose, oral contrast alone. The modeled cumulative radiation dose decreased from 281.3 to 58.1 mSv from the initial to the most recent schedule. After 2010, tumor markers were no longer measured routinely.

Relapse occurred in 159 patients (16.9%) with a median time to relapse of 13.25 mo (2.30–133.28 mo). Over time, although relapse rate (p = 0.6; Table 5) and time to relapse (p = 0.2) did not change significantly, there was a trend toward fewer relapses and earlier relapse detection. Increasingly, relapse was detected with imaging alone (p = 0.016). Time to relapse by surveillance schedule is depicted in Supplementary Fig. 2.

Importantly, there was no difference in the N (p = 0.3) or M (p = 0.4) category, or in IGCCCG risk (p = 0.8) at relapse over time. In the modern cohorts (2011–2017 and 2017–present), all men had good-risk disease at relapse. Although more men appeared to relapse with higher S stage (p = 0.003), the majority remained S1.

Treatment burden upon relapse did not increase with time (p = 0.9), with the majority being cured with unimodal therapy (88.9% in 1985–2004, 84.6% in 2004–2010, 88.6% in 2011–2017, and 100% in 2017–present). Radiation was used less frequently (reduced from 79.0% to 45.7% and 50.0%, p = 0.003) in modern cohorts.

The incidence of second relapse remained low, ranging from 11.1% to 12.8% across all cohorts. In total, there were

Table 4 – Seminoma patient baseline characteristics

Patient characteristics	Seminoma tumor patients (*N* = 942)				
	1982–2004 (*N* = 416)	2005–2010 (*N* = 241)	2011–2017 (*N* = 248)	2017–Present (*N* = 37)	*p* value
Age at orchiectomy (yr), mean (SD)	36.1 (9.2)	37.8 (9.8)	35.2 (9.8)	36.6 (7.3)	0.023*
Right-sided primary, *n* (%)	215 (51.68)	126 (52.28)	119 (47.98)	020 (54.05)	0.73
pT stage, *n* (%)					<0.01*
T1	297 (71.39)	209 (86.72)	218 (87.90)	30 (81.08)	
T2	69 (16.59)	24 (9.96)	27 (10.89)	7 (18.92)	
T3	8 (1.92)	5 (2.07)	0	0	
T4	1 (0.24)	0	0	0	
TIS	0	2 (0.83)	1 (0.40)	0	
TX	41 (9.86)	1 (0.41)	2 (0.81)	0	
Tumor ≥4 cm, *n* (%)	153 (36.78)	106 (43.98)	088 (35.48)	014 (37.84)	0.21
RTI present, *n* (%)	126 (46.84)	101 (47.87)	117 (51.54)	19 (57.58)	0.54
RTI and ≥4 cm, *n* (%)	051 (12.26)	050 (20.75)	047 (18.95)	008 (21.62)	0.02*

RTI = rete testis invasion; SD = standard deviation.
* The asterisk symbol denotes significance.

Table 5 – Seminoma patient characteristics at relapse

Schedule iteration	1982–2004 (*n* = 416)	2004–2010 (*n* = 241)	2011–2017 (*n* = 248)	2017–present (*n* = 37)	*p* value
Number relapsed, *n* (%)	81 (19.5)	39 (16.2)	35 (14.1)	4 (10.8)	0.221
Time from orchiectomy to relapse (mo), median (range)	15.52 (2.66–133.28)	13.02 (3.29–113.46)	14.40 (2.30–60.13)	9.46 (5.98–12.76)	0.639
N at relapse, *n* (%)					0.302[a]
N0	0	1 (2.5)	0	0	
N1	43 (53.1)	22 (56.4)	14 (40.0)	3 (75.0)	
N2	32 (39.5)	13 (33.3)	18 (48.6)	0	
N3	6 (7.4)	3 (7.7)	4 (11.4)	1 (25.0)	
M at relapse, *n* (%)					0.404[a]
M0	78 (96.3)	36 (92.3)	31 (88.6)	4 (100)	
M1	3 (3.7)	3 (7.7)	4 (11.4)	0	
S at relapse, *n* (%)					0.003[a,*]
S0	46 (56.8)$_1$	24 (61.5)$_2$	9 (25.7)$_{1,2}$	3 (75.0)	*
S1	18 (22.2)$_1$	8 (20.5)$_2$	18 (51.4)$_{1,2}$	0	*
S2	5 (6.2)	4 (10.3)	7 (20.0)	1 (25.0)	
S3	1 (1.2)	0	0	0	
Unknown	11 (13.6)	3 (7.7)	1 (2.9)	0	
IGCCCG class, *n* (%)					0.827[a]
Good	78 (96.3)	38 (97.4)	35 (100)	4 (100)	
Intermediate	3 (3.7)	1 (2.6)	0	0	
Modality identifying relapse, *n* (%)					0.016[a,*]
Imaging	77 (95.1)$_1$	31 (79.5)$_1$	29 (82.9)	4 (100)	*
Tumor markers	1 (1.2)	0	0	0	
Imaging + tumor markers	1 (1.2)$_{1,2}$	6 (15.4)$_1$	6 (17.1)$_2$	0	*
History/physical examination	2 (2.5)	2 (5.1)	0	0	
Positive modality at relapse, *n* (%)					
Tumor markers	24 (29.6)$_1$	12 (30.8)$_2$	25 (71.4)$_{1,2}$	1 (25.0)	
CT A/P	64 (79.0)$_{1,2}$	38 (97.4)$_1$	35 (100)$_2$	4 (100)	
CXR	1 (1.2)	1 (2.6)	0	0	
CT T	3 (3.7)	3 (7.7)	4 (11.4)	0	
History/physical examination	6 (7.4)	3 (7.7)	0	0	
Modes of therapy required, *n* (%)					0.859[a]
Single	72 (88.9)	33 (84.6)	31 (88.6)	4 (100)	
Multimodal	9 (11.1)	6 (15.4)	4 (11.4)	0	
First therapy, *n* (%)					0.003[a,*]
Radiation	64 (79.0)$_1$	29 (74.4)	16 (45.7)$_1$	2 (50.0)	
Chemotherapy	17 (21.0)$_1$	8 (20.5)	17 (48.6)$_1$	2 (50.0)	
RPLND	0	1 (2.6)	2 (5.7)	0	
Other surgery[b]	0	1 (2.6)	0	0	
Second relapse, *n* (%)	9 (11.1)	5 (12.8)	4 (11.4)	0	0.967[a]
Deaths	5 (6.20)	1 (2.6)	0	0	0.502[a]

A/P = abdomen/pelvis; CT = computed tomography; CT T = CT of the thorax; CXR = chest x-ray; IGCCCG = International Germ Cell Cancer Collaborative Group; NSGCT = nonseminomatous germ cell tumor; RPLND = retroperitoneal lymph node dissection.
Subscript numbers 1 and 2 indicate statistically significant difference between marked schedules (Bonferonni corrected). The asterisk symbol denotes significance.
[a] Fisher's exact test.
[b] Thoracic laminectomy.

six testis cancer deaths (3.77% of total relapsed patients and 0.64% of total patients on surveillance). However, five of six deaths occurred in the 1982–2004 cohort with only one in the 2004–2010 cohort, and none since.

4. Discussion

In this study, we evaluated whether successive reductions in the intensity of active surveillance for our CSI patients over four decades were associated with delayed relapse identification and subsequent worse outcomes. For both seminoma and NSGCT, we observed no significant change in the incidence or severity of relapse detected, the burden of treatment upon relapse, or the outcomes after relapse. This suggests that our reduced intensity schedules are appropriate for ongoing use in active surveillance.

Our series of 1583 CSI patients with adequate long-term follow-up represents the largest reported surveillance cohort from a single institution. Our experience indicates that active surveillance is a safe and effective strategy for patients with CSI GCT. Overall, we identified a relapse rate of 25.7% (165) and 16.9% (159), and successful salvage in all but five (0.78%) and six (0.64%) patients with seminoma and NSGCT, respectively. Our findings are consistent with other published data that have reported 5-yr recurrence rates of 14–20% and 13–32%, and mortality rates of 0–1.4% and 0–3% for CSI NSGCT and seminoma, respectively [18].

There is worldwide variation in the recommended active surveillance protocols due to the lack of comparative data [2,4,18]. Over time, we have continuously evaluated the surveillance program and have successively modified our schedules to minimize visit frequency, blood draw, radiation exposure, and cost. Table 6 compares imaging in the current version of the American Urological Association, National Comprehensive Cancer Network, and European Association of Urology guidelines for CSI NSGCT and seminoma with our current algorithms [19–21]. Notably, following institutional evaluation, we have minimized or entirely removed chest radiography from seminoma and NSGCT surveillance schedules, respectively [22]. In NSGCT, chest radiography was replaced by low-dose chest CT, as we have previously identified 12% of relapses occurring in the lung, mediastinal, or supraclavicular regions, and believe that utilizing a single imaging modality for surveillance imaging may increase adherence [8].

In examining our data, we noticed a decreased relapse rate in the modern cohorts for NSGCT and a similar trend in seminoma (Tables 3 and 5). At first glance, this may raise concerns that reduced intensity surveillance is missing relapses. However, in the case of NSGCT, the time from orchiectomy to relapse detection was significantly shorter and a similar trend was observed in seminoma. This would suggest that we are not introducing delays in relapse detection with reduced surveillance intensity. In further support of this, the extent of disease at relapse was unchanged over time. Therefore, we surmise that the reduced relapse rate in the modern cohort may be due to improved upfront identification of patients with borderline retroperitoneal lymphadenopathy who had stage II disease at diagnosis and thus eliminate such patients from the modern cohort, reducing relapse rate. Improvement in CT imaging over this time period, such that earlier identification of stage II patients occurred, may also have contributed to the lower relapse rates seen in more recent patients. Finally, median relapse time is markedly reduced in modern cohorts, suggesting that decreased available follow-up may contribute to the decreasing relapse rates as well.

We observed, over time, that lower relapse rates were detected by tumor markers and more with imaging. This is likely a product of decreased frequency of tumor marker assessment in our schedules and the eventual omission of tumor markers in seminoma surveillance after 2010. The S category and IGCCCG classification at relapse did not change with time, suggesting that our iterative changes did not lead to missing marker-based relapses or worse disease burden at the time of relapse. The utility of serum tumor marker surveillance for CSI seminoma has previously been called into question and has been dropped from several surveillance guidelines [6,23,24].

One of the main criticisms of active surveillance has been the radiation exposure associated with diagnostic imaging. Indeed, modeling of cumulative radiation dose from the earliest to the modern versions of the NSGCT and seminoma schedules demonstrated considerable decreases in radiation dosing from 156.7 to 52.7 mSv and from 281.3 to 58.1 mSv for NSGCT and seminoma, respectively. These decreases reflect the inclusion of low-dose CT scans and minimization of chest x-rays [22]. Our study is the first institutional policy to demonstrate that these impressive reductions can be achieved while still maintaining surveillance safety.

Table 6 – Comparison of current guideline recommendations of total surveillance imaging for CSI NSGCT and seminoma

Guideline		Chest x-Ray #	CT chest #	CT abdomen #	CT pelvis #
NSGCT	PMCC	0	5[a]	5[a]	5[a]
	AUA	5–9	0	5–9	5–9
	NCCN	6–9	0	5–9	5–9
	EAU	4–6	0	5–7	5–7
Seminoma	PMCC	1	0	10[a]	6[a]
	AUA	0	0	7–12	7–12
	NCCN	0	0	7–8	7–8
	EAU	0	0	6	6

AUA = American Urological Association; CT = computed tomography; EAU = European Association of Urology; NCCN = National Comprehensive Cancer Network; NSGCT = nonseminomatous germ cell tumor; PMCC = Princess Margaret Cancer Centre.
[a] CT scans are low dose (55% dose reduction), noncontrast.

Ongoing attempts to reduce radiation exposure further are being tested. Recently, the Medical Research Council completed the Trial of Imaging and Surveillance in Seminoma Testis (TRISST-MRC TE24) study. This trial randomized 669 CSI seminoma patients to either CT or magnetic resonance imaging (MRI) and to either three or seven scans over a 5-yr period [25]. Early results presented in abstract form only suggest that MRI imaging was noninferior to CT scans and a three-scan schedule was noninferior to a seven-scan schedule. It should be noted the primary endpoint was detection of stage ≥IIC relapses. In our cohort, these larger relapses comprised only 10% of seminoma relapses. Thus, it is possible that MRI and/or the three-scan schedule introduces delays, but, by only looking at larger nodal relapses, it is still unclear whether smaller relapses may be left undetected until later or missed altogether on imaging. Regardless, as the TRISST data have been finalized and other data emerge, it may be suggested that ionizing radiation exposure can be reduced further.

Another criticism of active surveillance is that when relapse occurs, the amount of treatment and the toxicity from that treatment are significantly greater than if all patients were treated with upfront adjuvant therapy [26,27]. If lowering the intensity of surveillance schedules led to delayed relapse detection and worse disease burden, this would strengthen arguments against surveillance and favor adjuvant treatment. However, in prior publications, we have shown that when surveillance relapse is managed with regional therapies when appropriate (ie, radiation for seminoma relapse and RPLND for NSGCT relapse), the total treatment burden is no worse than adjuvant strategies [8,15]. To this end, complications of surgery, radiation, and long-term side effects of adjuvant chemotherapy (cardiotoxicity and secondary neoplasms) are additionally avoided [28]. In the current study, we observed no increased burden of disease or its treatment at relapse with reduced surveillance intensity.

Future directions include further reduction in surveillance intensity, improvement of patient experience including virtual care, and evaluation of prognostic biomarkers at diagnosis and relapse. We have an ongoing randomized trial of asynchronous virtual care (using our WATChmAN platform) versus standard in-person surveillance (NCT03360994). On the biomarker front, serum or plasma miRNA, in particular miR-371a-3p, appears promising [29]. Our initial study suggests that while miR-371a-3p appears not to be able to serve as a prognostic biomarker, it may serve as an earlier means to identify relapse on surveillance [30]. With further studies, this could translate to reduced surveillance imaging requirements and reduced disease burden at relapse.

This study has limitations. First, the retrospective design does not provide direct comparisons of high- versus low-intensity surveillance. Second, there were a limited number of events in the most recent seminoma schedule iteration, which limits our ability to compare with the most recent cohort. Third, as the study covers a period of four decades, there may be unmeasured differences in imaging technology, laboratory assays, or patient selection over time, which introduce a cohort effect. For example, as initial schedules occurred when CT imaging was in its infancy, concerns of intra- and interobserver reliability may partially explain relapse rate differences seen compared with modern cohorts. Finally, our data are unable to address potential decreased schedule compliance or decreased ability to detect survivorship issues due to less intense follow-up.

5. Conclusions

In our four-decade single-center CSI GCT active surveillance experience, reduced surveillance schedule intensity did not significantly change the incidence, severity, burden of treatment, or outcomes at relapse. Thus, we feel that our reduced intensity schedules remain safe and adequate to offer to all patients with CSI testicular GCTs.

***Author contributions*:** Robert J. Hamilton had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Hamilton.
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Drafting of the manuscript: Gariscsak, Hamilton.
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Statistical analysis: Gariscsak, Atenafu.
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Appendix A. Supplementary data

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