Title: Evaluating stage migration of testicular germ cell tumours in Alberta, Canada during the COVID-19 pandemic: a retrospective cohort study

Running Title: Testicular germ cell tumours and COVID-19

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Evaluating stage migration of testicular germ cell tumours in Alberta, Canada during the COVID-19 pandemic: a retrospective cohort study

Abstract:

Background: Testicular germ cell tumours (TGCT) offer a unique perspective on the impact of delays in routine care seeking and diagnostic patterns due to the COVID-19 pandemic. We assessed cancer stage migration of TGCT during the pandemic in a real-world population.

Methods: A retrospective review of all incidental TGCT referrals to Cancer Care Alberta from January 2019-May 2021 was performed. Utilizing a 6-month lag time for seminomas and 3-month lag time for non-seminomas from the initial public health emergency declaration in Alberta (March 12, 2020), we compared the initial stage (III vs I or II) at presentation prior and since the pandemic. Secondary outcomes included risk category, largest tumour dimension, tumour markers, and systemic treatment setting.

Results: Of 220 TGCT patients identified, 166 were pre-pandemic and 54 since the pandemic. In total, 9 (5.4%) pre-pandemic patients presented with stage III disease, compared to 13 (24.1%) since, odds ratio 5.53 (95% confidence interval [CI] 2.21-13.85), p<0.001. Additionally, more patients present with poor risk disease (p=0.004) and median largest tumour dimension increased from 3.6cm (interquartile range [IQR] 2.5-5.5) to 4.7cm (3.4-6.4), p=0.006. No significant differences were observed for any of the other secondary outcomes (p > 0.05).

Interpretation: Despite limited sample size, we observed significant stage migration since the COVID-19 pandemic. Patients should be encouraged to seek timely medical attention, even in the context of public health restrictions to limit unintended health consequences. Healthcare systems must adapt to future increases in cancer burden in the wake of the pandemic.

Introduction:

Since the COVID-19 pandemic, population-based assessments have indicated a decline in the overall rate of reported cancer diagnoses, compared to historical controls (1-4). A reduced number of cancer diagnoses is likely due to delays in cancer detection (5). Disruptions in the healthcare system, including cancer screening programs, surgeries and other routine healthcare services, have made diagnosing cancer more challenging for providers (6-7). Additionally, patients may be more likely to dismiss symptoms, reluctant to seek care even when unwell, or have faced additional barriers in accessing care (8-9). Many cancer care providers are concerned about a pending wave of more advanced diagnoses, and consequently poorer patient outcomes, but direct evidence has been limited (5,12-17).

During the pandemic, an unexpected increase in testicular germ cell tumour (TGCT) patients requiring treatment in the intensive care unit (ICU) was noted, prompting a quality assurance review. TCGT develop and progress more rapidly than many other solid organ malignancies, and changes in staging may be more immediately apparent with delays in presentation (18,19). Progression is even more rapid in non-seminomatous germ cell tumours compared to pure seminomas (19-27). Delays in presentation lead to poorer cancer outcomes, leaving some patients too unwell or less likely to respond to life-prolonging therapy. Although at a reduced rate, cure and long-term survival is still possible even with the most advanced presentations of TGCT. As such, TGCT patients are nearly universally seen and treated by an oncologist, regardless of the severity of their presentation (19,20). Major surgical and urological guidelines have advocated for continued prioritization of TGCT management, even in the context of the pandemic (28-30). We sought to evaluate the presentation and initial treatment of new TCGT diagnoses in Alberta both prior to and since the pandemic. The main objective of this study was to assess for stage migration of TCGT since the onset of the COVID-19 pandemic.

Methods:

Setting

We reviewed all new TCGT referrals to tertiary Cancer Care Alberta sites from January 1, 2019 to May 31, 2021. This timeframe was selected to provide an assessment of TGCT diagnoses both prior to and throughout the COVID-19 pandemic. Cancer Care Alberta is responsible for universal administration of cancer care in the province of Alberta, covering a population of approximately 4.3 million patients and consists of 2 tertiary referral centres, 4 regional cancer centres and 11 community cancer centres. Cancer management follows a tumour group model, where the genitourinary tumour group triages TGCTs. Given the intensity and multidisciplinary nature of TGCT management, virtually all TGCT diagnoses are managed directly by one of the two tertiary referral centres. Each tertiary site provides additional support for the regional and community cancer centres in their geographic area (North and South), including assisting in the triaging and management of less common cancers, including TCGTs, allowing capture of cases not-necessarily managed directly by one of the tertiary centres.

Design

We performed a retrospective chart review of all new referrals for TCGTs. Adult patients (>18 years old) with an initial referral for a new diagnosis of TCGT during the study period were included as a convenience sample. Patients referred during the study period and placed on active surveillance who subsequently progressed were included, but treatments upon progression were excluded. Eligible patients were categorized as having a pure seminoma or non-seminoma (including mixed and pure non-seminoma) histology, based on their pathology and tumour markers. Patients were categorized based on date of diagnosis as prior or subsequent to the pandemic. A state of public health emergency for COVID-19 in the province of Alberta was declared on March 12,

2020, with public health restrictions implemented over the course of the following weeks. As potential changes in staging would not be anticipated immediately, we extrapolated from TCGT surveillance guidelines and *a priori* selected a 6-month lag time for seminomas (October 1, 2020) due to their more indolent natural history and 3-month lag time for non-seminomas (July 1, 2020) to serve as the cut-off dates for prior to and during the pandemic (19-27). Baseline presentation and treatment characteristics were collected via chart review. We followed STROBE guidelines for reporting (31).

Data Sources

We reviewed the new patient referrals and consultations of genitourinary tumour group oncologists from January 1, 2019 to May 31, 2021. This list was corroborated by the triage referral records managed by the genitourinary teams at the Cross Cancer Institute and Tom Baker Cancer Centre, and a questionnaire to each of the tumour group oncologists to try and identify all possible patients. The Alberta Cancer Registry was not utilized due to lags in the availability of diagnostic and staging information. The date of diagnosis typically preceded the date of referral and ranged from November 2018 to April 2021. Cancer Care Alberta uses a single electronic medical record system (ARIA MO) at all sites and includes consultation and progress notes, chemotherapy prescriptions, and linkages to province-wide laboratory, pathology, and imaging results. Where appropriate, hospitalization records were reviewed for inpatient chemotherapy records.

Outcomes

TGCT were staged according to the American Joint Committee on Cancer Staging Manual and classified as Stage I, II or III (32). Patients treated with primary chemotherapy were further classified into good, intermediate and for non-seminomatous tumours, poor risk, according to the International Germ Cell Consensus Classification (IGCCC) (30,33,34). The largest tumour dimension was measured radiographically, using first imaging at the time of presentation. Baseline tumour markers pre-orchiectomy including Alpha Fetoprotein (AFP), Beta Human Chorionic Gonadotropin (β-hCG), and Lactate Dehydrogenase (LDH) were collected. If multiple values were available, the values closest to the date of first presentation were used. Systemic treatment setting was defined as either outpatient or inpatient if they were hospitalized, including patients treated in the ICU, based on where the first dose of systemic treatment was administered. Any treatments administered after active surveillance were not considered.

Statistical Analysis

We compared the initial stage (III vs I or II) at presentation prior to and during the pandemic as the primary outcome. Secondary outcomes included differences in largest tumour dimension, and tumour markers (AFP, β-hCG, LDH). Exploratory outcomes included systemic treatment setting for patients with advanced disease (outpatient or inpatient, including ICU), and for patients with stage III/II disease, their IGCCC risk category.

Given the relative rarity of TGCT in Alberta, we present the incidence of seminomas and non-seminomas by stage, in 3-month intervals, with the exception of the beginning and end of the study period (4 months). Additionally, the percentage of stage III tumours in 3-month intervals over this timeframe are presented. We used Chi-square/Fisher's Exact tests (depending on expected cell counts) to compare categorical variables and the Wilcoxon rank signed test to compare continuous variables pre- and since the pandemic. To quantify the odds of being diagnosed with a stage III TGCT during the pandemic compared to pre-pandemic we conducted an unadjusted logistic regression model. A sensitivity analysis was also performed using only a 3-month and only a 6-month lag time for all TGCT cases. All statistical analyses were performed using a 2-sided significance level of 0.05 and R statistical software.

Ethics Approval

This study was reviewed and approved by the Health Research Ethics Board of Alberta - Cancer Committee (HREBA CC-21-0207).

Results:

A total of 220 TGCT patients were included in this study, of which 127 (57.7%) were diagnosed with a pure seminoma and 93 (42.3%) diagnosed with non-seminoma histology. Baseline patient and presentation characteristics stratified by histology are presented in Table 1. Changes in the incidence of TGCT overall and by stage during the COVID-19 pandemic in Alberta are illustrated in Figure 1. The 3-month incidence of TGCT undergoes an initial decline at the onset of the pandemic, followed by a subsequent rise, with a disproportionate amount of stage III disease. Changes in the incidence of TGCT by stage during the COVID-19 pandemic for non-seminoma tumours and pure seminoma tumours are illustrated separately in Figures 2 and 3, respectively.

Prior to the COVID-19 pandemic in Alberta and during the lag period (6 months for pure seminomas and 3 months for non-seminomas) 166 TGCT cases occurred, while 54 cases occurred during the pandemic (after the lag period). Differences in overall stage, systemic therapy treatment setting, IGCCC risk category, largest tumour dimension and tumour markers before and during the COVID-19 pandemic are presented in Table 2. During the pandemic, patients were significantly more likely to be diagnosed with a stage III TGCT ($p < 0.001$), have poor risk disease ($p=0.004$), and to have a larger tumour dimension ($p = 0.006$) compared to the pre-pandemic study period. The odds ratio for diagnosis of a stage III TGCT during the pandemic compared to prior to the pandemic was 5.53 (95% Confidence Interval [CI]: 2.21-13.85, $p<0.001$). A sensitivity analysis was performed using different lag times (i.e. only 3 and only 6 months), however as the results were not meaningfully different, only the original results are presented. The proportion of stage I patients was relatively similar in both periods, and the increase in stage III is largely driven by a decrease in the proportion of stage II disease. There were no significant differences in, systemic therapy treatment setting or any of the pre-orchiectomy tumour markers (all $p > 0.05$). However, there, there were no cases of ICU management in the pre-pandemic period, while two were identified since the pandemic.

Interpretation:

Our population-based assessment of TCGT staging, prior to and during the COVID-19 pandemic and public health emergency, identifies a strong indication of stage migration, with an increased odds ratio of stage III disease. This finding is further corroborated by an increase in poor-risk disease, and in the median largest tumour dimension. Changes in tumour markers were less robust, likely due to the heterogeneity in their utility as a marker of disease burden. Analyses of initial systemic treatment setting were limited by low numbers. However, while no cases of ICU management were identified pre-pandemic, several were identified since the pandemic.

Many studies have warned of an impending wave of more advanced cancer due to public health measures meant to limit the impact of the COVID-19 pandemic (1-8,11-17). A wave of more advanced cancer presentations requires appropriate health systems planning and resource allocation to mitigate. To our knowledge, this is the first study to provide real world evidence of TGCT stage migration associated with the COVID-19 pandemic. While a few others have demonstrated evidence of stage migration in other cancer types, such as lung, bladder and head and neck cancers, these have been limited to single-centre institutions, so this also provides one of the first population-level assessments of stage migration to date (35-37). Although the largest tumour dimension is not a standard TGCT disease metric, it provides a more sensitive measure of disease burden that supports the hypothesis that patients are presenting with more advanced disease. The lack of signal in tumour marker levels is likely a reflection of the heterogeneity of non-seminoma tumours, predominance of stage I disease and the overall limited sample size. Tumour markers can have low sensitivity as predictors of disease severity as the stage and proportion of

different histologic subtypes, has a larger role in varying tumour marker levels than the overall extent of disease at presentation (38).

Most modeling studies have focused on more common cancer types, to try to characterize the greatest impacts of the pandemic on healthcare systems (2,4-8,17,36). However, more common cancers can be impacted by interruptions in screening and access to timely intervention. In contrast, TGCT do not have an organized screening program, so delays in presentation are more likely a reflection of patient education and care-seeking behaviour (11,21-27,39). Such potential mechanisms for observed stage migration are likely relevant for all cancers. Major surgical and uro-oncological groups have advocated for prioritization of TGCT management throughout the pandemic, but messaging to health care providers alone is likely insufficient to reach affected individuals (28-30). TGCT is the most common solid organ cancer in males aged 15-35, a demographic that often has limited interaction with the health system, and may be more prone to avoiding healthcare professional engagement (40,41). Unattached, younger and lower socioeconomic status males may be particularly prone to delays in seeking care and thus poorer cancer outcomes (40-43). Limited or reduced social interactions throughout the pandemic may create even fewer opportunities for these individuals to be encouraged to seek appropriate medical attention. Effective messaging to patients and advocacy groups to identify and address the symptoms of TGCT, is an important step in limiting unintended impacts of the pandemic and public health measures (11,39). Patient advocacy groups and charitable organizations, such as the Testicular Cancer Society, Movember and local organizations, for instance OneBall in Alberta, can play a crucial role in raising awareness since waves of the pandemic may continue for some time.

TGCT carry the lowest mortality rate amongst the top 20 solid-organ malignancies in males, with an estimated 5-year overall survival rate of 97% and are thus treated far more aggressively than virtually all other solid-organ malignancies, given their responsiveness to systemic therapy. Aggressive treatment can have severe immediate and potential long-term toxicities for patients, and increased treatment due to stage migration can have major consequences. Despite the curative-intent nature of even advanced TGCT treatment, outcomes are also poorer with more extensive disease, with 5-year relative survival decreasing from >95% with Stage I and II down to 67% with poor risk disease (33-34). Outcomes for TGCT patients managed in the ICU have even poorer outcomes with 6-month mortality rates as high as 63.3% (19). Time and longer follow-up are required to evaluate if poorer outcomes have resulted from the pandemic. Regardless, patients with more advanced TGCT are more likely to receive treatment, even when unwell enough to require ICU management. Even a single case of ICU management may have marked health resource implications, particularly in the context of COVID-19 when ICU beds are in high demand. Mitigating TGCT presentations that require ICU-level care should remain a priority.

Limitations

This study is limited by its retrospective, observational nature, so the stage migration observed is only associated with the pandemic. The methods used to identify TGCT cases in this study are traditionally less robust than data from the cancer registry to ensure complete population capture, but the multidisciplinary nature of TGCT management in the province of Alberta and low baseline incidence makes it unlikely that any new cases would not have received appropriate tertiary cancer centre involvement. The necessity of convenience sampling and the low total number of cases limited our ability to evaluate important subgroups. The impact of specific public health measures and changes throughout various pandemic waves are unclear, but the signal for stage migration remains strong enough to warrant attention.

Conclusion

The presence of stage migration in TGCT associated with the COVID-19 pandemic emphasizes the need for increased resource allocation to mitigate and manage an anticipated rise in advanced cancer presentations. Patients should be encouraged to seek medical attention for cancer-associated symptoms, particularly for cancers that lack robust screening programs. TGCT management should remain a priority, even amidst a global pandemic.

Availability of Data.

Primary or supplementary data may be made available upon request from the corresponding author. Due to privacy concerns, data may only be shared in aggregate and any data categories that may include cell counts of <5 will be reported as such.

Table 1. Baseline patient and presentation characteristics stratified by histology

Variable	Seminoma (n = 127)	Non-seminoma (n = 93)
Age		
Median (IQR)	39.5 (33.0-47.5)	33.1 (28.0-39.7)
Histology		
Seminoma	127 (100.0%)	35 (37.6%)
Embryonal	-	66 (70.9%)
Yolk Sac	-	43 (46.2%)
Choriocarcinoma	-	11 (11.8%)
Teratoma	-	47 (50.5%)
Other	-	6 (6.5%)
T Stage		
1	78 (61.4%)	47 (50.5%)
2+	45 (35.4%)	30 (32.2%)
0/Unknown	4 (3.1%)	16 (17.2%)
N Stage		
0	100 (78.7%)	56 (60.2%)
1	7 (5.5%)	7 (7.5%)
2	10 (7.9%)	13 (14.0%)
3	10 (7.9%)	17 (18.3%)
M Stage		
0	121 (95.3%)	77 (82.8%)
1	6 (4.7%)	16 (17.2%)
Stage		
I	100 (78.7%)	55 (59.1%)
II	21 (16.5%)	22 (23.7%)
III	6 (4.7%)	16 (17.2%)

Treatment location		
TBCC	58 (45.7%)	37 (39.8%)
CCI	67 (52.8%)	50 (53.8%)
Other	2 (1.5%)	6 (3.7%)
Orchiectomy		
Yes	124 (97.6%)	81 (87.1%)
Upfront Radiation		
Yes	7 (5.5%)	<5 (<5.4%)
Systemic Therapy		
Yes	19 (15.0%)	34 (36.6%)

Abbreviations: CCI = Cross Cancer Institute; IQR = interquartile range; TBCC = Tom Baker Cancer Centre

Table 2. Difference in overall stage, systemic therapy setting, largest tumour dimension, and pre-orchiectomy markers before (including 6-month lag for seminomas and 3 months for non-seminomas) and during the COVID-19 pandemic

Variable	Pre-COVID Period[1] (n = 166)	COVID Period (n = 54)	P-value
Stage			< 0.001[2]
I	116 (69.9%)	39 (72.2%)	
II	41 (24.7%)	2 (3.7%)	
III	9 (5.4%)	13 (24.1%)	
IGCCC Risk Category			0.004[3]
Good	38 (76.0%)	5 (33.3%)	
Intermediate	7 (14.0%)	6 (40.0%)	
Poor	2 (4.0%)	4 (26.7%)	
Missing	3 (6.0%)	0 (0.0%)	
Systemic therapy setting			0.48[3]
Outpatient	32 (76.2%)	9 (64.3%)	
Inpatient/ICU	10 (23.8%)	3 (21.4%)	
ICU	0 (0.0%)	2 (14.3%)	
Largest tumour dimension			0.006[4]
Mean (SD)	4.6 (3.8)	5.9 (4.7)	
Median (IQR)	3.6 (2.5-5.5)	4.7 (3.4-6.4)	
Missing (%)	0 (0.0)	0 (0.0)	
Pre-orchiectomy LDH			0.83[4]
Mean (SD)	307.2 (418.9)	258.6 (174.4)	
Median (25th-75th percentiles)	193.0 (169.5-311.0)	200.5 (171.2-239.5)	
Missing (%)	39 (23.4%)	12 (22.2%)	
Pre-orchiectomy Beta-HCG			0.25[4]
Mean (SD)	1563.0 (18580.1)	12925 (83584.2)	
Median (25th-75th percentiles)	5.0 (1.0-11.0)	5.0 (3.0-21.0)	

Missing (%)	13 (7.8%)	9 (16.7%)	
Pre-orchiectomy AFP			0.19[4]
Mean (SD)	680.9 (5818.0)	94.0 (449.7)	
Median (25th-75th percentiles)	3.6 (2.0-6.0)	2.9 (2.0-5.7)	
Missing (%)	15 (9.0%)	7 (13.0%)	

[1]Includes 6-month lag period for seminomas and 3 month lag period for non-seminomas
[2]P-value from Chi-square test
[3]P-value from Fisher's exact test
[4]P-value from Wilcoxon rank sum test
Abbreviations: AFP = Alpha Fetoprotein; HCG = Human Chorionic Gonadotropin; ICU = intensive care unit; LDH = Lactate Dehydrogenase; SD = standard deviation

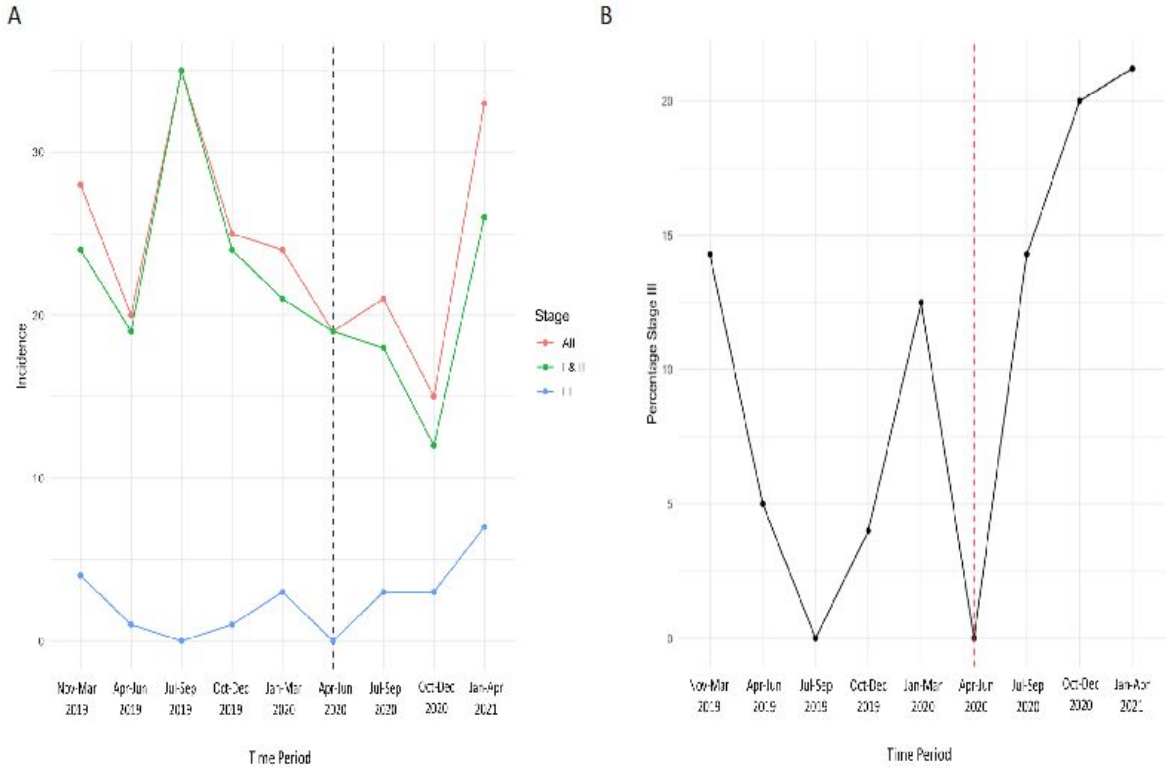

Figure 1. Changes in the incidence of testicular cancer overall and by stage during the COVID-19 pandemic in Alberta. **(A)** Changes in the incidence of testicular cancer overall and by stage in 3-month periods. The black dotted line represents the start of the COVID-19 pandemic in Alberta and a 3-month lag period. **(B)** The proportion of stage III testicular cancers diagnosed in Alberta in 3-month periods. The red dotted line represents the start of the COVID-19 pandemic in Alberta and a 3-month lag period.

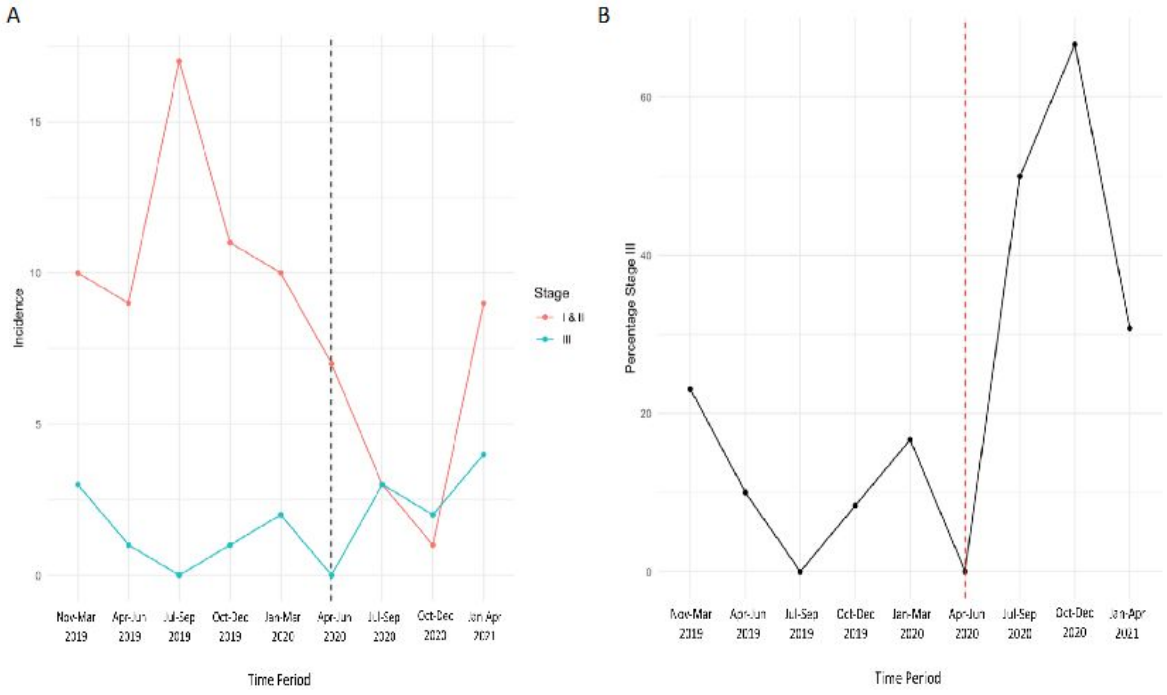

Figure 2. Changes in the incidence of non-seminoma testicular cancer by stage during the COVID-19 pandemic in Alberta. **(A)** Changes in the incidence of non-seminoma testicular cancer by stage in 3-month periods. The black dotted line represents the start of the COVID-19 pandemic in Alberta and a 3-month lag period. **(B)** The proportion of stage III pure seminoma testicular cancers diagnosed in Alberta in 3-month periods. The red dotted line represents the start of the COVID-19 pandemic in Alberta and a 3-month lag period.

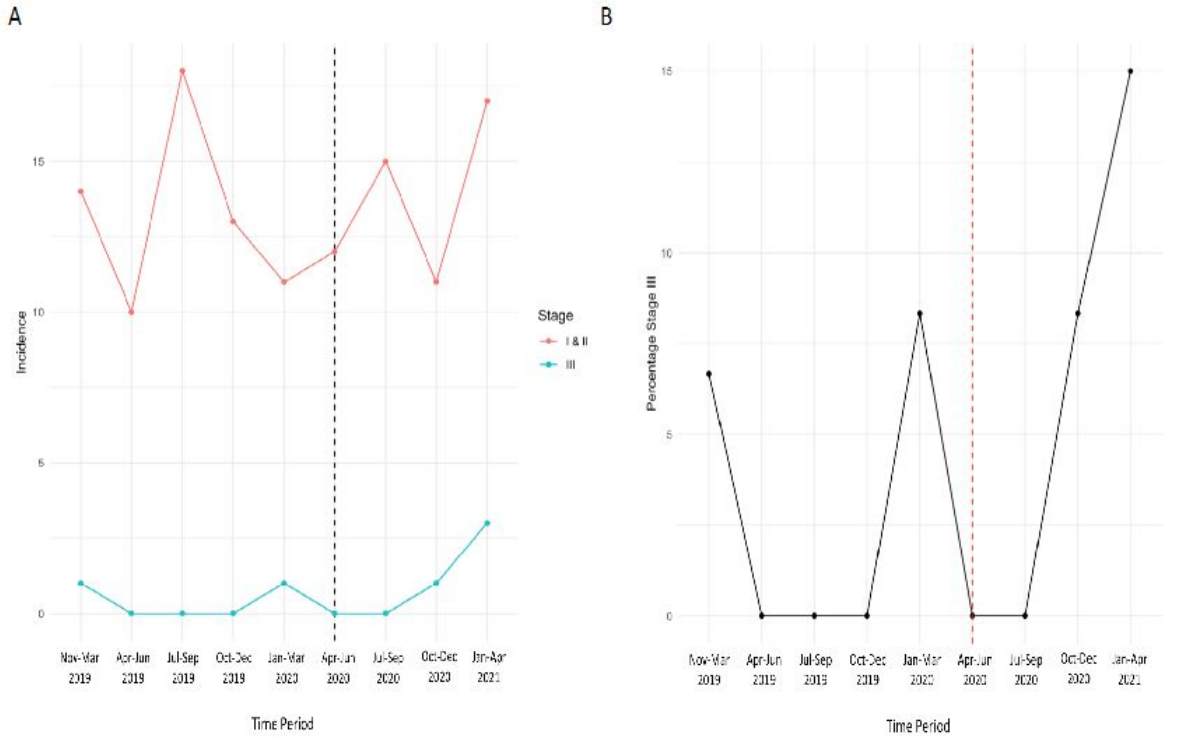

Figure 3. Changes in the incidence of pure seminoma testicular cancer by stage during the COVID-19 pandemic in Alberta. **(A)** Changes in the incidence of pure seminoma testicular cancer by stage in 3-month periods. The black dotted line represents the first 3-month period of the COVID-19 pandemic in Alberta. **(B)** The proportion of stage III pure seminoma testicular cancers diagnosed in Alberta in 3-month periods. The red dotted line represents the first 3-month period of the COVID-19 pandemic in Alberta.

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