ELSEVIER

Urologic Oncology: Seminars and Original Investigations 37 (2019) 183.e17−183.e24

UROLOGIC ONCOLOGY

Clinical-Testis cancer

# Delivery of chemotherapy for testicular cancer in routine practice: A population-based study

Safiya Karim, M.D.[a], Xuejiao Wei, MSc[b], Michael J. Leveridge, M.D.[c,d], David Robert Siemens, M.D.[c,d], Andrew G. Robinson, M.D.[b,d], Philippe L. Bedard, M.D.[f], Christopher M. Booth, M.D.[b,d,e,*]

[a] *Department of Oncology, Tom Baker Cancer Centre, University of Calgary, Calgary, Canada*
[b] *Division of Cancer Care and Epidemiology, Queen's Cancer Research Institute, Kingston, Canada*
[c] *Department of Urology, Queen's University, Kingston, Canada*
[d] *Department of Oncology, Queen's University, Kingston, Canada*
[e] *Department of Public Health Sciences, Queen's University, Kingston, Canada*
[f] *Division of Medical Oncology & Hematology, Department of Medicine, Princess Margaret Cancer Centre, University of Toronto, Toronto, Canada*

Received 19 September 2018; received in revised form 15 October 2018; accepted 26 October 2018

**Abstract**

**Introduction:** Maintenance of chemotherapy dose intensity is a cornerstone of management in testicular germ cell tumors. We describe chemotherapy delivery and outcomes of patients in routine practice.

**Methods:** The Ontario Cancer Registry was linked to electronic records of treatment to identify patients diagnosed with testicular cancer treated with orchiectomy and chemotherapy from 2005 to 2010. We describe chemotherapy delivery and dose intensity. Overall survival was measured from the start of chemotherapy.

**Results:** During the study period, 552 new cases of testicular cancer were treated with orchiectomy and chemotherapy; drug/regimen details were available for 475 (86%) cases. The study population included 324 patients with nonseminoma and 151 with seminoma. The majority of patients were treated with bleomycin, etoposide, and cisplatin (BEP) (83%, 394/475) or etoposide and cisplatin (EP) (6%, 30/475); 89% (379/424) received 3 to 4 cycles of treatment. Thirty two percent of all BEP patients (125/394) had at least 1 dose omission of bleomycin; this rate increased to 51% of patients treated with BEP × 4. Eight percent (33/397) of evaluable BEP/EP patients had a dose reduction/omission of cisplatin and 21% (82/397) had a dose delay of >6 days. Among the BEP/EP cases, 44% (174/397) had reduced chemotherapy dose intensity. Five-year overall survival for all cases was 95%.

**Conclusions:** Almost half of patients treated with BEP/EP chemotherapy in routine practice have some form of reduced chemotherapy delivery. Despite this, long-term survival in the general population is very high. Further studies are required to understand the extent to which dose delivery might influence outcomes. 

*Keywords:* Testicular cancer; Germ cell tumor; Chemotherapy; Health services; Population-based study

## 1. Introduction

Metastatic testicular germ cell tumors (GCTs) have a high cure rate with cisplatin-based chemotherapy. The standard treatment for stage II and good risk stage III disease is 3 cycles of bleomycin, etoposide, and cisplatin (BEP) [1−3]; among patients who have a contraindication to bleomycin, 4 cycles of etoposide and cisplatin (EP) is an alternative [4]. Standard therapy for patients with intermediate or poor risk disease is 4 cycles of BEP. Efforts to reduce toxicity by replacing cisplatin with carboplatin have shown inferior survival [5,6]. Reduced doses of etoposide and bleomycin may also be associated with inferior survival [7] although

**Funding:** Dr. Booth is supported as a Canada Research Chair in Population Cancer Care. This work was also supported by the Southeastern Ontario Academic Medical Organization.

*Corresponding author. Tel.: (613)-533-6895; fax: (613)-533-6794.
*E-mail address:* booth@queensu.ca (C.M. Booth).

https://doi.org/10.1016/j.urolonc.2018.10.025
1078-1439/

other studies suggest this may not be the case [8–10]. Despite this limited evidence, practice guidelines strongly recommend avoiding dose reduction and delays in GCTs [2,11].

There is limited literature describing chemotherapy delivery for testicular GCTs in routine practice. To address this gap, we performed a population-based study of all patients in Ontario, Canada treated with orchiectomy and chemotherapy for seminoma and nonseminoma germ cell tumors (NSGCT). The primary objective of this study is to describe delivery of chemotherapy in routine practice including rates of dose reduction/delay and to quantify survival in routine practice.

## 2. Methods

### 2.1. Study design and population

This is a population-based, retrospective cohort study to describe chemotherapy delivery for testicular cancer in the Canadian province of Ontario. Ontario has a population of approximately 13.5 million people and a single-payer universal health insurance program. All incident cases (16+ years of age) of seminoma and NSGCT who underwent orchiectomy from 2005 to 2010 were included in this population-level cohort. Twenty-three cases with chemotherapy, radiation, or retroperitoneal lymph node dissection before orchiectomy were excluded. A primary report describing long-term survival and the adoption of surveillance strategies among all GCT cases 2000to 2010 has recently been published [12]. The study was approved by the Research Ethics Board of Queen's University, Kingston, Canada. This study was designed, analyzed, and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement [13].

### 2.2. Data sources

The Ontario Cancer Registry (OCR) is a passive, population-based cancer registry that captures diagnostic and demographic information on at least 98% of all incident cases of cancer in the province of Ontario [14]. The OCR does not compile information about extent of disease. For this reason, we obtained surgical pathology reports for all orchiectomy procedures. A variety of electronic administrative health databases were linked to the OCR. Records of hospitalization from the Canadian Institute for Health Information (CIHI) provided information about orchiectomy. Provincial physician billing records and treatment records from regional cancer centers were used to identify chemotherapy utilization; these records are created in the act of prescribing treatment. Detailed chemotherapy records were not available prior to 2005, therefore the study population was limited to patients treated from 2005 to 2010.

### 2.3. Measures and outcomes

Comorbidity was calculated classified using the Charlson Index modified for administrative data [15]. Chemotherapy treatment records were available up to December 31, 2013. Electronic treatment records were reviewed to identify the first chemotherapy regimen delivered after orchiectomy. Dose intensity analyses via manual review of all treatment records were performed for patients treated with BEP and EP. *Dose omission* was defined as any case with a chemotherapy drug dose of zero subsequent to the first cycle. *Dose reduction* was defined as the delivery of any dose of chemotherapy that was less than 80% of the initial dose. *Dose delay* was defined as any chemotherapy cycle that was delivered more than 6 days later than the standard 3-week dosing interval. Hospitalization records were used to identify hospital admissions for toxicity. Vital status was available up to December 31, 2015.

### 2.4. Statistical analysis

Comparisons of proportions between study groups were made using the chi-squared test. Factors associated with a dose omission/reduction or delay were evaluated using modified Poisson regression. Overall survival (OS) was determined from start date of chemotherapy using the Kaplan-Meier method and comparisons between groups were made using the log-rank test. Results were considered statistically significant at $P$ value $<0.05$. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

## 3. Results

### 3.1. Study population

From 2005 to 2010, 475 patients were treated with orchiectomy and chemotherapy (Supplemental eFig 1). Thirty-two percent had seminoma (151/475) and 68% had nonseminoma (324/475) GCTs (Table 1). The median age of patients with seminoma and nonseminoma was 37 and 28 years, respectively.

### 3.2. Delivery of chemotherapy

#### 3.2.1. Chemotherapy regimen and number of cycles

The vast majority of patients received BEP (83%, 394/475) with a minority of patients treated with EP (6%, 30/475) and single-agent carboplatin (8%, 36/475) chemotherapy (Table 2). Three percent of patients (15/475) received other regimens. In patients who received BEP or EP, the majority received 3 (61%, 258/424) or 4 cycles (29%, 121/424) of therapy.

Table 1
Characteristics of the patients with seminoma and nonseminoma testicular cancer treated with orchiectomy and chemotherapy in Ontario from 2005 to 2010 ($N = 475$)

| Characteristic | All patients $N = 475$ | Nonseminoma $N = 324$ | Seminoma $N = 151$ |
|---|---|---|---|
| *Patient-related* | | | |
| Age (y)[b] | | | |
| Mean/median | 33/31 | 30/28 | 38/37 |
| 16–20 | 45 (9%) | 43 (13%) | <=5 (1%) |
| 20–29 | 162 (34%) | 134 (41%) | 28 (19%) |
| 30–39 | 157 (33%) | 97 (30%) | 60 (40%) |
| 40–49 | 81 (17%) | 39 (12%) | 42 (28%) |
| 50+ | 30 (6%) | 11 (3%) | 19 (13%) |
| Charlson comorbidity score[b] | | | |
| 0 | 465 (98%) | 317 (98%) | >145 (>95%) |
| 1+ | 10 (2%) | 7 (2%) | <=5 (<5%) |
| *Disease-related* | | | |
| Primary histology[b,a] | | | |
| Seminoma | 190 (40%) | 39 (12%) | 151 (100%) |
| Embryonal carcinoma | 221 (47%) | 221 (68%) | 0 (0%) |
| Teratoma | 37 (8%) | 37 (11%) | 0 (0%) |
| Other[c] | 27 (6%) | 27 (8%) | 0 (0%) |
| Tumor size (cm)[b] | | | |
| Mean/median (interquartile range) | 4.6/4 (3–6) | 4.3/4 (3–6) | 5.3/5 (3–7) |
| ≤4 cm | 255 (54%) | 193 (60%) | 60-65 (40%–43%) |
| >4 cm | 210 (44%) | 125 (39%) | 85 (56%) |
| Unstated | 10 (2%) | 6 (2%) | <=5 (<5%) |
| Rete testis invasion | | | |
| Yes | 174 (37%) | 123 (38%) | 51 (34%) |
| No | 121 (25%) | 86 (27%) | 35 (23%) |
| Not reported | 180 (38%) | 115 (35%) | 65 (43%) |
| Lymphovascular invasion | | | |
| Yes | 220 (46%) | 182 (56%) | 38 (25%) |
| No | 201 (42%) | 114 (35%) | 87 (58%) |
| Not reported | 54 (11%) | 28 (9%) | 26 (17%) |

[a] Nonseminoma cases were defined as having any nonseminoma histologies listed on the pathology reports. One hundred and forty-eight nonseminoma classified cases had a primary histology of seminoma.
[b] As per Institute of Clinical Evaluative Sciences policy, cells were suppressed to ensure that precise small cell values cannot be determined.
[c] Other = yolk sac tumour and choriocarcinoma.

Table 2
Chemotherapy regimen and number of cycles delivered to patients with nonseminoma and seminoma testicular cancer in Ontario from 2005 to 2013 ($N = 475$)

| | Nonseminoma $N = 324$ | Seminoma $N = 151$ |
|---|---|---|
| *Chemotherapy regimen* | | |
| BEP | 298 (92%) | 96 (64%) |
| EP | 17 (5%) | 13 (9%) |
| Carboplatin | 0 (0%) | 36 (24%) |
| Other[a] | 9 (3%) | 6 (4%) |
| *Number of cycles among BEP/EP cases (n = 424)* | | |
| 1–2 | 45 (11%) | |
| 3 | 258 (61%) | |
| 4 | 121 (29%) | |

BEP = bleomycin, etoposide, and cisplatin; EP = etoposide and cisplatin.
[a] Other regimen includes VIP (etoposide, ifosfomide, cisplatin), TIP (paclitaxel, ifosfomide, cisplatin), cisplatin, etoposide-carboplatin, gemcitabine-carboplatin, paclitaxel-carboplatin, topotecan-cyclophosphamide.

### 3.2.2. Dose delivery

Of the 394 patients who received BEP chemotherapy, 32% (125/394) had at least 1 dose omission of bleomycin (Table 3). As the number of cycles of chemotherapy increased, there was a higher probability of bleomycin omission (32% with 2 cycles to 51% with 4 cycles, $P < 0.001$).

Detailed chemotherapy records were reviewed for all patients treated with BEP and EP to identify dose reduction/omission of cisplatin and dose delays. Eight percent of patients (33/397) had at least 1 dose reduction or omission of cisplatin during the course of treatment. Dose reduction/omission increased with number of cycles received (3% with 2 cycles to 14% with 4 cycles, $P = 0.040$). Twenty-one percent of patients (82/397) who received BEP or EP experienced dose delay of more than 6 days. In patients who received 4 cycles, 28% percent (31/111) had a dose delay.

Among all patients treated with BEP or EP, 44% (174/397) had at least 1 form of reduced chemotherapy

Table 3
Dose reduction/omission among 397 patients with testicular cancer treated with orchiectomy and BEP or EP chemotherapy in Ontario from 2005 to 2010

| | Cycle number | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | Total |
| Bleomycin omission[a] | 27% | 32% | 24% | 51% | 32%[a] |
| Cisplatin dose reduction/omission | 0% | 3% | 7% | 14% | 8% |
| Dose delay > 6 d | 8% | 10% | 19% | 28% | 21% |
| Any reduced chemotherapy delivery (omission, delay, or dose reduction) | 31% | 34% | 39% | 59% | 44% |

BEP = bleomycin, etoposide, and cisplatin; EP = etoposide and cisplatin.
[a] For the BEP cases only.
Twenty-seven patients (27/424, 6%) treated with a combination of 3-day and 5-day BEP/EP regimen were not included in this analysis.

delivery (i.e., omission of bleomycin or cisplatin, dose reduction or cisplatin, or dose delay >6 days). Reduced delivery was significantly higher in patients who received 4 cycles compared to those who received 1 to 3 cycles (59% vs. 38%, $P = 0.003$). Number of cycles of chemotherapy was significantly associated with reduced dose delivery in univariate and multivariate analyses ($P < 0.001$; Table 4). There was also a trend toward reduced dose delivery in older patients [age 40+, relative risk (RR) = 1.20 (95% CI 0.90-1.60), $P = 0.224$] and those with higher comorbidity scores [Charlson 1+, RR = 1.58 (95% CI, 0.96-2.60) $P = 0.183$].

### 3.3. Outcomes

We evaluated hospital admission as a proxy for treatment related toxicity. Nineteen percent of patients (91/475) were hospitalized within 30 days from any dose of chemotherapy. Hospital admission rates within 60 and 90 days from chemotherapy were 12% (59/475) and 19% (90/475), respectively. Less than 6 deaths (<1.5%) occurred during chemotherapy.

Median follow-up time was 7.3 years**.** OS at 3 and 5 years for all patients was 95% (Fig. 1A). Five-year OS was lower for patients who received 4 cycles of BEP (i.e., with intermediate/poor-risk disease) compared to those who received 3 cycles of BEP (i.e., good risk disease) (87% vs. 98%, $P < 0.01$; Fig. 1B). There was a trend toward inferior survival in patients who had dose delay/reduction in patients treated with BEP × 3 and BEP × 4 (Fig. 1C and D).

## 4. Discussion

In this population-based study, we describe delivery of chemotherapy in routine clinical practice among all patients with testicular GCTs diagnosed in Ontario from 2005 to 2010. There are several important findings. First, 44% of all patients in routine practice have chemotherapy dose omissions,

Table 4
Factors associated with reduced chemotherapy dose intensity[a] among patients with testicular cancer treated with orchiectomy and BEP chemotherapy in Ontario from 2005 to 2010 ($n = 394$).

| | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| Characteristic | Proportion with reduced dose intensity | *P* value | RR (95% CI) | *P* value |
| Age | | 0.280 | | 0.224 |
| <30 | 43% | | Ref. | |
| 30–39 | 50% | | 1.21 (0.96–1.52) | |
| 40+ | 51% | | 1.20 (0.90–1.60) | |
| Charlson | | 0.191 | | 0.183 |
| 0 | 47% | | Ref. | |
| 1+ | 71% | | 1.58 (0.96–2.60) | |
| Histology | | 0.356 | | 0.289 |
| NSGCT | 46% | | Ref. | |
| Seminoma | 51% | | 1.14 (0.90–1.44) | |
| Cycles | | <0.001 | | <0.001 |
| 1 | 36% | | 0.49 (0.22–1.07) | |
| 2 | 39% | | 0.56 (0.35–0.90) | |
| 3 | 40% | | 0.55 (0.45–0.67) | |
| 4 | 69% | | Ref. | |

95% CI = 95% confidence interval; NSGCT = nonseminoma germ cell tumors.
[a] Reduced dose intensity is defined as any dose omission of bleomycin or cisplatin, dose reduction cisplatin or dose delay >6 days.

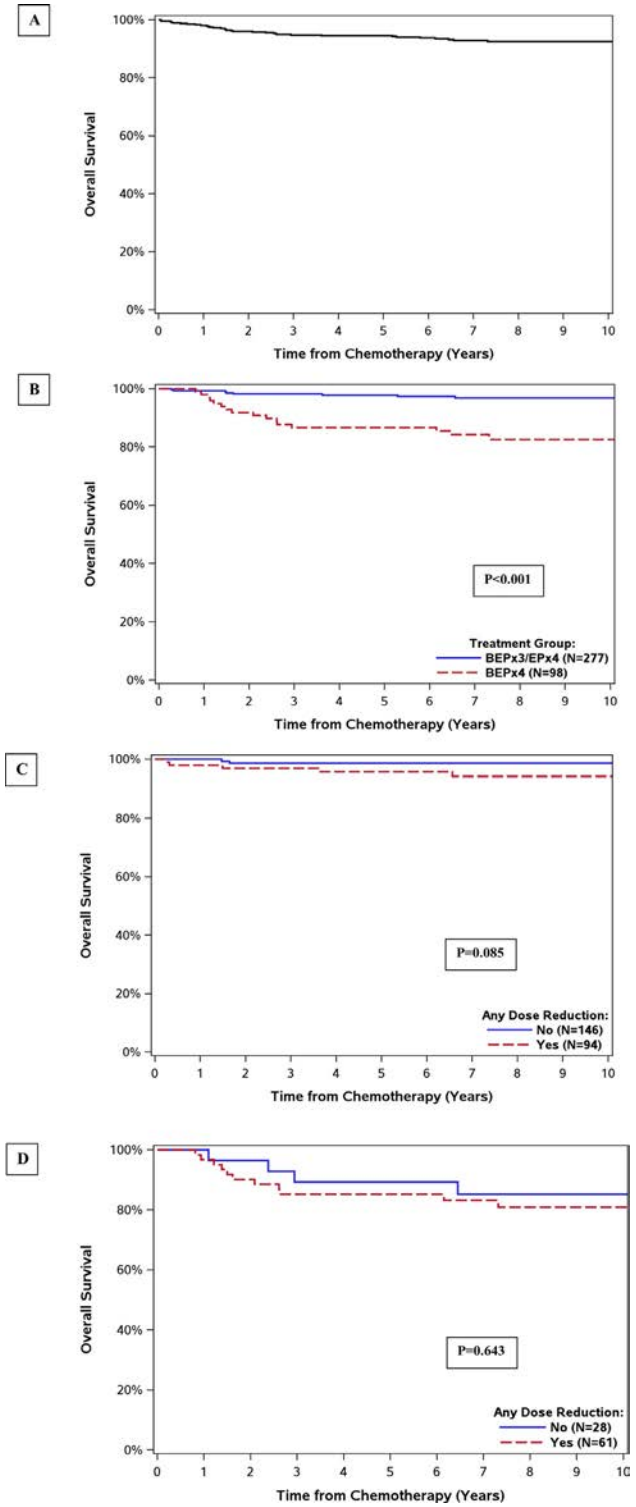


Fig. 1. Overall survival (OS) of patients with testicular cancer in Ontario treated with orchiectomy (2005–2010) and chemotherapy. (A) All patients N = 475; (B) Patients treated with BEP × 3/ EP × 4 vs. BEP × 4 ($N = 375$); (C) Patients treated with BEP × 3 by dose intensity ($n = 240$); (D) Patients treated with BEP × 4 by dose intensity ($N = 89$). BEP = bleomycin, etoposide, and cisplatin; EP = etoposide and cisplatin.

reductions, and/or delay; this rate increases to 59% among patients treated with 4 cycles of chemotherapy. Second, despite frequent dose reductions/delay, survival in routine practice is excellent (5-year OS 95%). Third, while 19% of patients are admitted to hospital within 30 days of chemotherapy, deaths during chemotherapy are infrequent (<1.5%).

In our study, we found that the majority of cases who receive chemotherapy are treated with either 3 or 4 cycles of BEP. This is similar to findings in other population-based studies of testicular cancer [16,17]. For example, Osswald et al. analyzed the National Cancer Institute's SEER database on 702 men diagnosed with testicular cancer in 1999. They found that more than 75% of men who received chemotherapy for seminoma, regardless of stage, were given BEP while another 11% received EP. Similarly, in patients with nonseminoma, 88% received cisplatin and etoposide with or without bleomycin [17].

Bleomycin dose omissions occurred in almost one third of patients who received BEP in our study. This rate increased with the number of cycles, with more than half of patients who received 4 cycles having a dose omission. Although we were unable to determine the number of patients who switched over to a regimen of 4 cycles of EP to compensate for an omission in bleomycin, rates of bleomycin omission of 30% to 50% are potentially concerning. In a meta-analysis of first-line randomized clinical trials, the rates of all-grade pulmonary toxicity from bleomycin were approximately 12% [18]. Similarly, analysis of a single institution in Denmark reported that only 9% of patients discontinued bleomycin because of a ≥25% decline in the hemoglobin-corrected diffusing capacity of the lungs for carbon monoxide [19]. The rate of Bleomycin omission in our study is much higher than what would be anticipated based on these data. This may reflect higher rates of toxicity in routine practice and/or omission of Bleomycin in some centers due to low blood counts. Up to 10% of patients in our study also had a dose omission/reduction in cisplatin. This rate is similar to that found in a Japan single center series of 41 patients [20].

The proportion of patients who had a dose delay of more than 6 days in our study (21%) is noteworthy. The European Cancer Consensus group recommends that postponing treatment, at a maximum of 3 days for each decision, should only be considered in cases of existing fever or significant cytopenia [11]. Similarly, the Canadian consensus guidelines note that only in exceptional circumstances should chemotherapy be delayed [2]. In the study by Kawai et al., only 17% (7/41) of patients had a delay of more than 3 days and this was primarily due to patient incompliance or bone marrow suppression [20]. Further work is required to determine the reasons for these delays in our study population and the extent to which is might be associated with outcomes. Data from other studies have suggested that GCT case volumes are associated with patient outcomes [21]. While it has been hypothesized that the volume effect may be mediated by chemotherapy dose intensity, data from our study do not suggest a strong association between dose delivery and survival. Information available in our study data-set does not provide insight into the institution

where chemotherapy was delivered. However, surgical records demonstrate that among all 2,650 orchiectomy procedure performed in Ontario from 2000 to 2010, surgery was performed at a teaching hospital in 28% of cases (754 of 2650) and at a community hospital in 72% of cases (1,896 of 2,650).

Although practice guidelines emphasize the importance of chemotherapy dose intensity in GCTs [2,11], the literature to support this assertion is not strong. The highest level of evidence comes from a randomized controlled trial of 2 different chemotherapy regimens [7]. The 2 regimens differed in several respects including number of cycles (3 vs. 4), total dose of Etoposide/Cisplatin/Bleomycin, and delivery schedule. Survival was improved among those patients treated with 3 cycles of chemotherapy. It is not clear whether this was due to inadequate dosing of bleomycin in the 4 cycle arm, different delivery schedule of etoposide/cisplatin, or different doses of etoposide/cisplatin (etoposide dose higher in 3 cycle arm, cisplatin dose higher in 4 cycle arm). The regimen used in the 3-cycle arm has become the standard dosing schedule for BEP. It is therefore not known whether dose intensity for this specific regimen is associated with outcome. Several other small studies report mixed results on this issue. Single center series from Japan ($n = 25$ evaluable patients treated with bleomycin, vinblastine, and cisplatin) and UK ($n = 53$ patients treated with cisplatin, vincristine, methotrexate, bleomycin, actinomycin D, cyclophosphamide, and etoposide) suggest that survival may be inferior with reduced dose intensity [22,23]. A larger study from Australia ($n = 253$ patients treated with vinblastine, bleomycin, and cisplatin) did not find an association between dose delivery and survival [10]. The evidence in support of the relationship between dose intensity and outcome of men with GCTs is therefore limited. Our study contributes to the knowledge base but given important methodologic limitations we believe the extent to which dose intensity is associated with survival remains unclear.

Rates of hospitalization in our cohort were very high. To our knowledge, there has been no other study that has quantified hospital admission rates in patients with testicular GCTs. Despite the frequency of hospitalization, treatment-related mortality in our study (<1.5%) is comparable the relevant clinical trials (1%–3%) [24,25]. Long-term survival in Ontario also appears to be excellent. The 5-year OS of patients in our cohort treated with 3 cycles of BEP or 4 cycles of EP was 98%. This compares favorably to the reported IGCCC's 5-year OS of 91% (95% CI 86%–90%) for patients with good risk disease [26,27]. Patients who received BEP × 4 had a 5-year OS of 87% in our study. These patients likely had intermediate risk seminoma, intermediate risk NSGCT, or poor risk NSGCT; 5-year OS for these groups has historically been reported as 72%, 79%, and 48% respectively [26].

Our study should be interpreted in the context of certain methodological limitations. Existing data records do not include stage data or serum tumor markers; this limits our ability to comment on the appropriateness of the number of cycles or timing of chemotherapy delivery. This also limits detailed analysis of management and outcomes per stage and by dose reduction status. Dose reduction was defined as the delivery of any subsequent dose that was <80% of the starting dose; our data therefore underestimate the frequency of smaller dose reductions. We were not able to determine the rate of bleomycin-induced lung toxicity in this cohort, and therefore the extent to which bleomycin was appropriately omitted. However, our rates of bleomycin omission far exceed those that have previously been shown to be caused by bleomycin lung toxicity. Chemotherapy drug records come from electronic order entry which might not include all inpatient chemotherapy which could be written using paper order sheets. For this reason it is possible that our cohort underestimates utilization of etoposide, ifosfamide, cisplatin (VIP) or paclitaxel, ifosfamide, cisplatin (TIP) inpatient regimens. However, because this report focuses on first-line regimen it is unlikely that there are a substantial number of missing VIP/TIP cases in this setting as these are usually used in the salvage setting after BEP/EP. Our cohort does not include 23 patients treated with chemotherapy/radiation before orchiectomy who may have been at high risk of toxicity. This may also include patients with primary mediastinal germ cell tumors. The treatment records also do not allow us to identify the intended number of cycles; therefore, any patients that were planned to receive 4 cycles of chemotherapy but only completed 3 cycles may have been incorrectly classified as not having any dose reduction. In addition, hospital admissions may have been due to various reasons including toxicity or resection of residual disease. Therefore these rates may be difficult to interpret. Finally, the available administrative data-sets do not allow us to understand reasons for dose delay/reduction/omission. Given the limitations of our observational data and the risks of confounding in evaluating treatment delivery and outcomes [28], our findings should not be used to support the application of liberal dose reduction policies for chemotherapy delivery in testicular cancer.

In summary, a significant proportion of patients treated with chemotherapy for GCTs in routine practice have dose reductions/delays. Despite this reduced dose intensity, survival of patients treated in the general population is excellent. However, we do not suggest these data support the indiscriminate reduction of dose intensity in men with GCTs. Further work is required to understand the reasons for reduced chemotherapy delivery, high rates of postchemotherapy hospitalization and the extent to which reduced chemotherapy delivery may impact survival.

## Conflict of interest

The authors report no conflicts of interest.

## Acknowledgments

Parts of this material are based on data and information provided by Cancer Care Ontario and CIHI. However, the analysis, conclusions, opinions, and statements expressed herein are those of the authors and not necessarily those of Cancer Care Ontario or CIHI.

This study was supported by the Institute for Clinical Evaluative Sciences (ICES), which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). Parts of this material are based on data and information compiled and provided by CIHI. The opinions, results, and conclusions reported in this paper are those of the authors and are independent from the funding sources and CIHI. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred.

Dr. Booth 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.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.urolonc.2018.10.025.

## References

[1] Mead GM. International germ cell consensus classification: a prognostic factor- based staging system for metastatic germ cell cancers. J Clin Oncol 1997;15(2):594–603.

[2] Wood L, Kollmannsberger C, Jewett M, Chung P, Hotte S, O'Malley M, et al. Canadian consensus guidelines for the management of testicular germ cell cancer. Can Urol Assoc J 2010;4(2):e19–38. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2845668/%5Cnhttp://www.ncbi.nlm.nih.gov/pmc/articles/PMC2845668/pdf/cuaj-2-e19.pdf.

[3] Albers P, Albrecht W, Algaba F, Bokemeyer C, Cohn-Cedermark G, Fizazi K, et al. Guidelines on testicular cancer: 2015 update. Eur Urol 2015;68(6):1054–68.

[4] Culine S, Kerbrat P, Kramar A, Théodore C, Chevreau C, Geoffrois L, et al. Refining the optimal chemotherapy regimen for good-risk metastatic nonseminomatous germ-cell tumors: a randomized trial of the Genito-Urinary Group of the French Federation of Cancer Centers (GETUG T93BP). Ann Oncol 2007;18(5):917–24.

[5] Bajorin DF, Sarosdy MF, Pfister DG, Mazumdar M, Motzer RJ, Scher HI, et al. Randomized trial of etoposide and cisplatin versus etoposide and carboplatin in patients with good-risk germ cell tumors: a multiinstitutional study. J Clin Oncol 1993;11(4):598–606.

[6] Horwich A, Sleijfer DT, Foss SD, Kaye SB, Oliver RTD, Cullen MH, et al. Carboplatin in good-prognosis metastatic nonseminomatous germ cell cancer : a Multiinstitutional Medical Research Council/ European Organization for Research and Treatment of Cancer Trial. J Clin Oncol 1997;15(5):1844–1852.

[7] Grimison PS, Stockler MR, Thomson DB, Olver IN, Harvey VJ, Gebski VJ, et al. Comparison of two standard chemotherapy regimens for good-prognosis germ cell tumors: updated analysis of a randomized trial. J Natl Cancer Inst 2010;102(16):1253–62.

[8] Husband D, Green J. POMB/ACE chemotherapy in non-seminomatous germ cell tumours: outcome and importance of dose intensity. Eur J Cancer 1992;28(1):86–91.

[9] Miyanaga N, Akaza H, Hattori K, Takeshima H, Koiso K. The importance of dose intensity in chemotherapy of advanced testicular cancer. Urol Int 1995;54(4):220–5.

[10] Levi J, Thompson D, Bishop J, Raghavan D, Tattersall M, Byrne M, et al. Dose intensity and outcome with combination chemotherapy for germ cell carcinoma. Australasian Germ Cell Trial Group. Eur J Cancer Clin Oncol 1989;25:1073–7.

[11] Schmoll HJ, Souchon R, Krege S, Albers P, Beyer J, Kollmannsberger C, et al. European consensus on diagnosis and treatment of germ cell cancer: a report of the European Germ Cell Cancer Consensus Group (EGCCCG). Ann Oncol 2004;15(9):1377–99.

[12] Leveridge M, Siemens D, Brennan K, Izard J, Karim S, An H, et al. Temporal trends in management and outcomes of testicular cancer: a population-based study. Cancer 2018;124(13):2724–32.

[13] Von EE, DG A, Egger M, Pocock SJ, Peter C, Gøtzsche P, et al. Guidelines for reporting observational studies Strengthening the reporting of observational studies in epidemiology (STROBE) statement. Br Med J 2007;335(October):19–22.

[14] Jensen O, Parkin D, MacLennan R, Muir C, Skeet R. Cancer registration in Ontario: a computer based approach. In: IARC, ed. Cancer Registration Principles and Methods. Lyon, France; 1991. p. 246–57.

[15] Deyo RA, Cherkin DC. MAC. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45(6):613–9.

[16] Kier MG, Lauritsen J, Mortensen MS, Bandak M, Andersen KK, Hansen MK, et al. Prognostic factors and treatment results after bleomycin, etoposide, and cisplatin in germ cell cancer: a population-based study. Eur Urol 2017;71(2):290–8. Available from: http://dx.doi.org/10.1016/j.eururo.2016.09.015.

[17] Osswald M, Harlan LC, Penson D, Stevens JL, Clegg LX. Treatment of a population based sample of men diagnosed with testicular cancer in the United States. Urol Oncol 2009;27(6):604–10. Available from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=-med5&NEWS=N&AN=18799329.

[18] Necchi A, Miceli R, Oualla K, Sonpavde G, Giannatempo P, Raggi D, et al. Effect of bleomycin administration on the development of pulmonary toxicity in patients with metastatic germ cell tumors receiving first-line chemotherapy: a meta-analysis of randomized studies. Clin Genitourin Cancer 2017;15(2):213–20.

[19] Lauritsen J, Kier M, Bandak M, Mortensen M, Thomsen F, Mortensen J, et al. Pulmonary function in patients with germ cell cancer treated with bleomycin, etoposide and cisplatin. J Clin Oncol 2016;34(13):1492–9.

[20] Kawai K, Ando S, Hinotsu S, Oikawa T, Sekido N, Miyanaga N, et al. Completion and toxicity of induction chemotherapy for metastatic testicular cancer: an updated evaluation of Japanese patients. Jpn J Clin Oncol 2006;36(7):425–31.

[21] Tandstad T, Kollmannsberger CK, Roth BJ, Jeldres C, Gillessen S, Fizazi K, et al. Practice makes perfect: the rest of the story in testicular cancer as a model curable neoplasm. J Clin Oncol 2017;35(31):3525–8.

[22] Miyanaga N, Akaza H, Hattori K, Takeshima H, K K. The importance of dose intensity in chemotherapy of advanced testicular cancer. Urol Int 1995;54:220–5.

[23] Husband DJ, Green JA. POMB/ACE chemotherapy in non-seminomatous germ cell tumours: outcome and importance of dose intensity. Eur J Cancer 1992;28(1):86–91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1373636.

[24] Loehrer Sr PJ, Johnson D, Elson P, Einhorn LH, Trump D, Loehrer PJ, et al. Importance of bleomycin in favorable-prognosis disseminated germ cell tumors: an Eastern Cooperative Oncology Group

trial. J Clin Oncol 1995;13(2):470–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7531223.

[25] Toner G, Stockler M, Boyer M, Jones M, Thompson D, Harvey V, et al. Comparison of two standard chemotherapy regimens for good- prognosis germ-cell tumours : a randomised trial. Lancet 2001;357:739–45.

[26] International Germ Cell Collaborative Group. International germ cell consensus classification: a prognostic factor-based staging system for metastatic germ cell cancers. J Clin Oncol 1997;15(2):594–603.

[27] Canadian Cancer Society. Testicular cancer. [cited 2018 Mar 29]. Available from. http://www.cancer.ca/en/cancer-information/cancer-type/testicular/prognosis-and-survival/survival-statistics/?region=on.

[28] Booth CM, Karim S, Peng Y, Robert Siemens D, Brennan K, MacKillop WJ. Radical treatment of the primary tumor in metastatic bladder cancer: potentially dangerous findings from observational data. J Clin Oncol 2018;36(6):533–5.