Effect of prophylactic anticoagulation on the incidence of venous thromboembolism in patients with testicular germ cell tumor.

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Abstract

Background Testicular germ cell tumors (GCTs) are among the most common solid tumors in young males. With the availability of highly effective treatment, improving patients' quality of life has gained more focus in recent years. Venous thromboembolism (VTE), commonly occurring in patients with GCT, is associated with increased morbidity and mortality. Prophylactic anticoagulation has been shown to decrease the risk of VTE in patients with malignancy. The aim of this retrospective study was to evaluate the effect of low-molecular-weight heparin (LMWH) prophylaxis on the incidence of VTE and outcome in patients with GCT treated with first-line chemotherapy. **Methods** Our study population included chemotherapy-naïve patients with GCT treated with first-line chemotherapy at the National Cancer Institute, Bratislava, Slovakia, from January 2000 to December 2017. VTE was defined as any venous thrombosis or pulmonary embolism, confirmed by imaging, occurring during first-line chemotherapy. Patients diagnosed with VTE on initial staging exam were excluded from the study. No visceral thromboses were observed. **Results** Our cohort included 353 patients with GCT. LMWH prophylaxis was administered to 104 patients (29.5%), and 249 patients (70.5%) did not receive prophylaxis. We observed 14 (4.0%) VTE events. The difference in VTE incidence between patients with and without prophylaxis was not statistically significant (5.8% vs. 3.2% $P = 0.37$). We observed a trend toward longer overall survival in patients without prophylaxis (hazard ratio = 0.61, 95% confidence interval = 0.32-1.13, $p = 0.08$). Patients with extragonadal GCT receiving VTE prophylaxis had significantly shorter survival (hazard ratio = 0.29, 95% confidence interval = 0.08-1.12, $P = 0.04$). This effect was most likely driven by a higher incidence of treatment-related deaths in patients with extragonadal GCT receiving LMWH ($P = 0.06$). **Conclusions** LMWH prophylaxis was not associated with decreased VTE incidence. Moreover, there was a higher incidence of treatment-related deaths in patients with extragonadal tumor location. LMWH prophylaxis during hospitalization should not be used routinely in patients with GCT receiving chemotherapy.

Background

Testicular germ cell tumors (GCTs) represent one of the most common solid neoplasms in young males between the ages of 15 and 35 and the incidence has been steadily rising in the past decades.[1, 2] Cisplatin-based chemotherapy with or without resection of the residual mass are highly effective in the treatment of GCTs with five-year survival rate of more than 95%.[3] As a result, the number of GCT survivors with long life expectancy is rising. Therefore, maintaining patients' quality of life and minimizing treatment-related morbidity and mortality has gained more significant interest in recent years. Venous thromboembolism (VTE) commonly occurs in cancer patients.[4] It affects about 10% of patients with malignancy. The pathophysiology is thought to be multifactorial and is related to the type of tumor, anatomic location, patient's comorbidities, type of treatment, etc.[5] When compared to patients with different type of malignancy, GCT patients have higher incidence of VTE events.[6]

VTE is associated with increased morbidity and mortality in cancer patients. Levitan et al found more than a threefold higher risk of recurrent VTE and death in cancer patients compared to patients with VTE without cancer diagnosis.[7]

Incidence of VTE in GCT patients has been assessed in a few studies and the results vary widely. Honecker et al observed 9% VTE incidence in patients before starting chemotherapy, while there was only a 2% incidence of VTE during first-line chemotherapy.[8] In a different study, Piketty et al found a 14% incidence of VTE during first-line chemotherapy and 5% incidence of VTE after chemotherapy.[6]

Several groups focused on identification of risk factors of VTE events in GCT patients.[6, 9-12] Weijl et al observed an increased risk of VTE in patients with liver metastases (odds ratio = 4.9).[10] Piketty et al identified body surface area > 1.9m² (relative risk (RR) = 5, 95% confidence interval (CI) 1.8-13.9) and elevated serum lactate dehydrogenase (RR = 6.4, 95% CI 2.3-18.2) as independent risk factors. In their study, patients without any risk factors had 4% probability of having VTE, while patients with at least 1 risk factor had 26% probability of having VTE.[6]

Prophylactic anticoagulation has been shown to decrease the risk of symptomatic VTE in cancer patients. (RR = 0.56, 95% CI 0.47-0.68) [13] Gizzi et al studied the incidence of thromboembolic events in GCT patients treated with first-line chemotherapy and observed lower incidence of thromboembolic events in patients receiving thromboprophylaxis when compared to patients without prophylaxis.[12] However, small number of patients in each subgroup of this study makes the interpretation of the results difficult and larger study is needed to elucidate the relationship between thromboprophylaxis and incidence of VTE in GCT patients undergoing cisplatin-based chemotherapy.

The aim of this retrospective study was to evaluate the effect of low molecular weight heparin (LMWH) prophylaxis on incidence of VTE events and outcome in germ cell tumor patients treated with first-line chemotherapy.

Methods

Study patients

This retrospective study was conducted using the National Cancer Institute medical records database. The study was approved by the Institutional Review Board, and a waiver of consent form was granted. Patients diagnosed with germ cell tumors treated with first-line/adjuvant chemotherapy at the National Cancer Institute, Bratislava, Slovakia, from January 2000 to December 2017 were eligible. Patients with any concurrent malignancy other than nonmelanoma skin cancer in the previous 5 years were excluded from the study. Patients with previous chemotherapy, venous thromboembolism diagnosed on the initial staging exam and anticoagulation therapy (therapeutic or prophylactic) started before the initiation of first-line chemotherapy were excluded.

Definition of VTE event

VTE events were defined as any venous thrombosis or pulmonary embolism occurring between Day 1 of the first cycle of first-line chemotherapy and Day 21 of the last cycle of first-line chemotherapy. Cases of superficial phlebitis were not classified as events. Every VTE event had to be confirmed by imaging studies, either Doppler ultrasonography or a CT scan. Depending on the patients' presenting symptoms, the events were divided into symptomatic and incidental if discovered on imaging performed for a different purpose. The Khorana score was calculated as described previously.[14]

Baseline data

During the initial staging, patients had a CT scan of the chest, abdomen and pelvis. Baseline data regarding age, primary tumor location, tumor histology, TNM stage, International Germ Cell Cancer Collaborative Group (IGCCCG) risk class and first-line chemotherapy regimen were recorded. Blood coagulation tests were not routinely performed during the initial screening.

VTE prophylaxis

LMWH prophylaxis was not routinely prescribed before January 2010 during hospitalization. At our institution, all patients with GCT are hospitalized during chemotherapy. In December 2007, the American Society of Clinical Oncology released clinical practice guidelines recommending prophylactic anticoagulation for hospitalized patients receiving chemotherapy.[15] Therefore, starting in January 2010, we progressively implemented prophylactic anticoagulation with low-molecular-weight heparin (nadroparin 0.4 ml or equivalent). However, not all physicians integrated this guideline into their practice, and LMWH prophylaxis was prescribed at the individual physician's discretion.

STATISTICAL ANALYSIS

We performed a retrospective review of patients' medical records. All thromboses or pulmonary embolisms, confirmed by imaging modality, were classified as events. Patient characteristics were tabulated and summarized as the median (range) value for continuous variables and frequency (percentage) for categorical variables. Fisher's exact test was used for statistical analysis to compare VTE events between groups with and without prophylaxis.

The primary outcome was the overall incidence of VTE events occurring between Day 1 of the first cycle of first-line chemotherapy and Day 21 of the last cycle of first-line chemotherapy. Secondary outcomes were incidences of VTE events in various subgroups and overall survival.

Time to VTE was calculated from the start date of chemotherapy to the date of VTE diagnosis. The log-rank test was used to compare the differences between time to VTE between patients with and without prophylaxis.

Median follow-up was calculated as the median time of observation of the study patients. Overall survival was calculated from the start date of chemotherapy to the date of the last follow-up or death of the patient. The Kaplan-Meier method was used to estimate overall survival. The log-rank test was used to compare differences in survival between patients with and without prophylaxis. All calculations were performed using NCSS 2019 statistical software.[16]

Results

Patient characteristics

Our cohort included 353 chemotherapy-naïve patients with GCTs treated with first-line chemotherapy (**flow diagram**). The patient characteristics are summarized in **Table 1**. The median age of patients at the time of enrollment was 32 years (ranging from 17 to 63 years). The majority of patients (75.9%) had nonseminomatous germ cell tumors. All patients received platinum-based chemotherapy.

VTE prophylaxis

LMWH prophylaxis was administered to 104 patients (29.5%) for the duration of hospitalization for chemotherapy, and 249 patients (70.5%) did not receive LMWH prophylaxis. Before January 2010, 7 out of 174 (4.0%) patients received LMWH prophylaxis, and 97 out of 179 (54.2%) patients treated after January 2010 received prophylaxis (**flow diagram**). The majority of patients (74.3%) receiving LMWH prophylaxis after January 2010 were stage II.B or higher. Heparin assays were not routinely performed to confirm the levels.

VTE events

In our study population, most VTE events occurred even before starting chemotherapy. We identified 41 out of 394 (10.4%) patients who developed VTE before starting treatment. These patients were excluded from the study (**flow diagram**).

During the study period, we observed 14 (4.0%) VTE events. Deep vein thrombosis was observed in 13 patients (3.7%), and one patient (0.3%) had pulmonary embolism. No visceral thromboses were observed (**Supplementary Table S1**). One event (7.1%) was fatal. In patients without prophylaxis, we documented eight events (3.2%), while six events (5.8%) were documented in patients receiving LMWH prophylaxis.

The difference was not statistically significant ($P = 0.37$). The data are summarized in **Table 2**. The median age of patients with and without VTE was 34 years vs. 31 years, $P = 0.24$.

Out of the fourteen VTE events, 8 events were symptomatic and 6 events were incidental. There were two symptomatic VTE events in patients receiving LMWH prophylaxis, and six symptomatic events occurred in patients without prophylaxis (75% vs. 33.3%, $P = 0.28$). In patients who experienced VTE, the median time to VTE was 28.5 days (15-83 days) in patients without prophylaxis and 53.5 days (1-92 days) in patients with prophylaxis (hazard ratio (HR) = 0.53, 95% CI 0.17 - 1.7, $P = 0.24$).

The incidence of VTE in patients without prophylaxis before 2010 was similar to the incidence of VTE in the subgroup of patients with prophylaxis after 2010, as well as in the subgroup analysis based on the IGCCCG risk group (**Supplementary Table S2**).

Association between VTE prophylaxis and patient/tumor characteristics

There were 12 VTE events in patients with nonseminomatous germ cell tumors (NSGCTs), and 2 events occurred in patients with seminoma. There were no statistically significant differences in VTE incidence between patients with and without prophylaxis based on tumor histology.

Twelve VTE events (3.8%) occurred in patients with gonadal tumors. Four events (4.4%) occurred in patients with prophylaxis, and eight events (3.5%) occurred in patients without prophylaxis. The difference was not statistically significant ($P = 0.75$). Two VTE events occurred in patients with extragonadal tumors. Both patients received LMWH prophylaxis. The difference was not statistically significant (0.0% vs. 14.3%, $P = 0.15$).

Out of the fourteen VTE events, five events occurred in patients with good risk according to the IGCCCG classification, three events occurred in patients with intermediate risk, and 6 events occurred in patients with poor risk. Patients with intermediate or poor risk were more likely to suffer VTE events than patients with good risk according to the IGCCCG classification (7.3% vs. 2.2%, $P = 0.02$). However, VTE incidence did not differ significantly in patients with and without prophylaxis for any of the risk groups. Similarly, the Khorana score and/or size of retroperitoneal lymph nodes had no impact on the effect of prophylactic anticoagulation (**Table 2**).

Out of the fourteen patients suffering VTE events, 8 patients received bleomycin, etoposide and cisplatin (BEP); 3 patients had a dose-dense regimen[17]; two patients received paclitaxel, bleomycin, etoposide and cisplatin; and one patient was treated with etoposide and cisplatin.

In patients receiving the BEP regimen, there were 2 VTE events (3.0%) in patients receiving LMWH prophylaxis and 6 events (3.3%) in patients without LMWH prophylaxis. In patients receiving chemotherapy regimens other than BEP, there were 4 events (10.8%) in patients with LMWH prophylaxis

and 2 events (3.0%) in patients without prophylaxis. The difference was not statistically significant ($p=0.1844$).

Association between overall survival and prophylactic anticoagulation

The median follow-up of all patients was 71 months (0-224 months). The median follow-up of living patients was 122 months (1-224 months). There were 51 deaths (14.45%) in our study population. The 2- and 5-year overall survival rates of the study group were 87.99% (95% CI 84.49% – 91.49%) and 84.27% (95% CI 80.22% – 88.31%), respectively. There was no difference in overall survival in patients with or without prophylaxis (HR = 0.61, 95% CI 0.32-1.13; $P = 0.0784$) (**Figure 1**). The results are summarized in **Table 3**. Patients with extragonadal GCT and patients with NSGCT histology receiving VTE prophylaxis had significantly shorter survival than patients without prophylaxis (HR = 0.29, 95% CI 0.08-1.12; $P = 0.0373$, HR = 0.50, 95% CI 0.25-0.99; $P = 0.0179$, respectively) (**Figure 2A and 2B**). We also observed a trend toward shorter overall survival in patients receiving prophylaxis with chemotherapy regimens other than BEP (HR = 0.50, 95% CI 0.22-1.12; $P = 0.0614$).

We analyzed the incidence of treatment-related deaths (TRDs) in patients with primary extragonadal tumors and NSGCT histology based on LMWH prophylaxis (**Supplementary Table S3**). Treatment-related death was defined as death during first-line chemotherapy. Patients with extragonadal tumors receiving LMWH prophylaxis had a higher incidence of TRD than patients without prophylaxis (21.4% vs. 0.0%, $P = 0.0556$). Patients with NSGCT histology on LMWH prophylaxis also had a higher incidence of TRD than patients without prophylaxis (10.9% vs. 3.9%, $P = 0.0552$). In the subgroup analysis of patients with NSGCT histology, we found that this trend was driven by TRD in patients with primary extragonadal tumors.

Incidence of major bleeding during VTE prophylaxis

In our cohort, there were 13 patients who suffered major bleeding (grade 3-5). There were 7 patients (2.8%) who received no prophylaxis, and 6 patients (5.8%) received LMWH prophylaxis. The difference was not statistically significant ($P = 0.22$).

Discussion

In the present study, we examined the relationship between prophylactic anticoagulation during chemotherapy and the incidence of VTE events as well as the association between prophylactic anticoagulation and the overall survival of patients with GCT treated with first-line chemotherapy. To assess the effect of prophylactic anticoagulation on the incidence of VTE events, we included only events occurring during first-line chemotherapy when patients were also receiving LMWH prophylaxis.

We have observed that most VTE events occur even before the initiation of chemotherapy. There was a 4% incidence of VTE events occurring during chemotherapy. The observed incidence of VTE events is in line with the incidences reported in the literature.[6, 8, 10, 18-20] However, there is a wide variation in the reported incidences.[21] While the lowest reported incidence is 2%, in a different study, there was an incidence of thromboembolic events of 23.7%.[8, 20] A significant part of this variation is probably caused by different inclusion criteria, such as including arterial events, including patients with VTE events before the start of chemotherapy, and events occurring several months after chemotherapy. The small number of patients in some studies may also contribute to this variability.

We observed no significant differences in VTE incidence between patients with and without LMWH prophylaxis. While there have been several studies assessing VTE incidence and identifying VTE risk factors in patients with GCT, most of them included only a small number of the study patients with LMWH prophylaxis. We did not observe a beneficial effect of prophylactic anticoagulation even in patients with recognized risk factors for VTE, including a high Khorana score and/or increased retroperitoneal lymph node size.[14, 22]

Solari et al. compared the incidence of thromboembolic events in patients receiving limited and extended LMWH prophylaxis. Limited prophylaxis was administered only during hospitalization. Extended prophylaxis was administered daily from Day 1 of the first cycle to Day 21 of the last cycle of chemotherapy. They did not observe significant differences between these two groups. However, their study did not include a control group with no prophylaxis; therefore, the effect of LMWH prophylaxis cannot be assessed. Paradoxically, the incidence of thromboembolic events reported in their study (23.7%) was much higher than in other studies.[20] However, arterial events were also included in their analysis. Gizzi et al. also compared the VTE incidence in patients with GCT with and without LMWH prophylaxis. In their study, prophylaxis was administered to a subgroup of patients with risk factors for VTE (elevated lactate dehydrogenase or high body surface area). They observed no statistically significant difference in VTE incidence between the two groups. However, neither the type of LMWH used nor the dosing of prophylaxis were mentioned.[12]

Unexpectedly, there was a trend toward shorter overall survival in our patients who received LMWH prophylaxis. On further analysis, we found a significantly shorter overall survival in patients receiving LMWH prophylaxis with NSGCT histology or extragonadal tumor location.

A prospective study assessing the effect of prophylactic anticoagulation in patients with GCT receiving chemotherapy compared to no prophylaxis is lacking. However, the data available suggest that LMWH prophylaxis does not offer the expected benefits in terms of decreased incidence of VTE events in patients with GCT.[12, 20] In contrast, our data suggest that administering LMWH prophylaxis might confer a higher risk for treatment-related deaths in patients with extragonadal tumors. Given the small number of patients with extragonadal tumors included in our study and selection bias, this result is only hypothesis generating. Further research should focus on examining the possible association between LMWH and increased incidence of TRDs. In October 2019, the American Society of Clinical Oncology

published an updated guideline on the use of thromboprophylaxis in patients with cancer. According to this guideline, hospitalized patients with active malignancy without additional risk factors may be offered pharmacologic thromboprophylaxis. However, routine use of thromboprophylaxis in patients with cancer hospitalized solely for administration of chemotherapy is no longer recommended.[23]

To the best of our knowledge, this is the largest study evaluating the effect of LMWH prophylaxis on VTE incidence in patients with GCT receiving chemotherapy. Our study has several limitations. First, LMWH prophylaxis was not random, possibly causing selection bias. It is possible that patients at higher risk for VTE were given thromboprophylaxis more frequently, which could in turn obscure the effect of thromboprophylaxis. However, the incidence of VTE in patients without prophylaxis before 2010 was similar to the incidence of VTE in the subgroup of patients with prophylaxis after 2010, as well as in the subgroup analysis based on the IGCCCG risk group (**Supplementary Table S1**). This supports the conclusion of no beneficial effect of prophylaxis in patients with GCT. Second, the study has a retrospective design. Some VTE events could have been missed as a result of incomplete medical records.

Conclusion

In conclusion, in this large retrospective analysis, we showed that LMWH prophylaxis was not associated with decreased VTE incidence. Moreover, there was a higher incidence of treatment-related deaths in patients with extragonadal tumor location. Taking into account these data, LMWH prophylaxis during hospitalization should not be used in patients with GCT receiving chemotherapy.

Abbreviations

BEP – bleomycin, etoposide, cisplatin

CI – confidence interval

GCT – germ cell tumor

HR – hazard ratio

IGCCCG - International Germ Cell Cancer Collaborative Group

LMWH – low-molecular-weight heparin

NSGCT - nonseminomatous germ cell tumor

RR – relative risk

TRD – treatment-related death

VTE – venous thromboembolism

Declarations

Ethics approval and consent to participate The Institutional Review Board of the National Cancer Institute, Bratislava, Slovakia, approved this study and granted a waiver of consent form for the collection, analysis and publication of the retrospectively obtained and anonymized data for this noninterventional study.

Consent for publication

Not applicable.

Availability of data and materials

The dataset supporting the conclusions of this article is included within the article.

Competing interests

None declared.

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Authors' contributions

NH, MCh, KR, KK, JO, PP, VDE, ZSM, JM and MM participated in the conception and design, acquisition, analysis and interpretation of data. NH drafted the article, and all authors revised it critically for important intellectual content. All the authors read this manuscript and gave final approval of the version to be published.

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Tables

Table 1 Patient characteristics

	N	%
All	353	100
Histology		
Seminoma	79	22.4
NSGCT	268	75.9
Unknown	6	1.7
Primary tumor		
Gonadal	318	90.1
Extragenital	35	9.9
Retroperitoneum	22	6.2
Mediastinum	10	2.8
Brain	2	0.6
Unknown	1	0.3
Stage		
I.A/B	38	10.8
I.S	22	6.2
II.A	30	8.5
II.B	47	13.3
II.C	44	12.5
III.A	43	12.2
III.B	42	11.9
III.C	87	24.6
IGCCCG risk group		
Stage IA/B	38	10.8
Good	192	54.4
Intermediate	46	13.0
Poor	77	21.8
Treatment regimen		
BEP	250	70.8
Other	103	29.2
Follow-up status		
Alive	300	84.99
Exitus	51	14.45
Unknown	2	0.57
Khorana score		
1	231	65.44
2	73	20.68
3	44	12.46
4	5	1.42
N-stage		
N0	84	23.80
N1	47	13.31
N2	75	21.25
N3	136	38.53
Unknown	11	3.12

Table 2 VTE events

	No prophylaxis		VTE prophylaxis		p value
	N	%	N	%	
All VTE events	8/249	3.2	6/104	5.8	0.3681
Incidental events	2/8	25.0	4/6	66.7	0.2774
Symptomatic events	6/8	75.0	2/6	33.3	
Histology					
Seminoma	1/45	2.2	1/34	2.9	1.0000
NSGCT	7/197	3.4	5/64	7.8	0.1653
Primary tumor location					
Gonadal	8/228	3.5	4/90	4.4	0.7461
Extragenadal	0/21	0.0	2/14	14.3	0.1529
IGCCCG risk group					
Stage IA/B	0/34	0.0	0/4	0.0	1.0000
Good	4/135	3.0	1/57	1.8	1.0000
Intermediate	1/31	3.2	2/15	13.3	0.2444
Poor	3/49	6.1	3/28	10.7	0.6622
Chemotherapy regimen					
BEP	6/183	3.3	2/67	3.0	1.0000
Other	2/66	3.0	4/37	10.8	0.1844
Khorana score					
1	6/171	3.5	1/60	1.7	0.6800
2	2/52	3.8	1/21	6.4	1.0000
3	0/22	0.0	4/22	1.8	0.1078
4	0/4	0.0	0/1	0.0	1.0000
N-stage					
N0	1/70	1.4	1/12	8.3	0.2871
N1	2/38	5.3	1/6	16.7	0.3907
N2	1/43	2.3	0/31	0.0	1.0000
N3	3/85	3.5	4/44	9.1	0.2426

Table 3 Overall survival

	VTE prophylaxis	N	HR	Lower 95% CI	Upper 95% CI	p value
All patients	0/1	249/104	0.61	0.32	1.13	0.0784
IGCCCG risk group						
Stage IA/B	0/1	34/4	0.00	0.00	0.00	0.6532
Good	0/1	135/57	1.09	0.12	9.99	0.9425
Intermediate	0/1	31/15	0.72	0.06	9.36	0.7836
Poor	0/1	49/28	0.69	0.36	1.33	0.2368
Chemotherapy regimen						
BEP	0/1	183/67	0.94	0.37	2.42	0.8975
Other	0/1	66/37	0.5	0.22	1.12	0.0614
Tumor histology						
Seminoma	0/1	45/34	0.58	0.03	10.34	0.6988
NSGCT	0/1	204/64	0.5	0.25	0.99	0.0179
Primary tumor location						
Gonadal	0/1	228/90	0.76	0.38	1.53	0.4178
Extragonadal	0/1	21/14	0.29	0.08	1.12	0.0373
Khorana score						
1	0/1	171/60	0.83	0.25	2.76	0.7555
2	0/1	52/21	0.71	0.23	2.23	0.5272
3	0/1	22/22	0.69	0.26	1.83	0.4461
4	0/1	4/1	0.38	0.02	8.45	0.3508
N-stage						
N0	0/1	71/13	0.67	0.12	3.94	0.6161
N1	0/1	40/7	0.54	0.03	8.24	0.5824
N2	0/1	44/31	0.42	0.07	2.52	0.3179
N3	0/1	88/48	0.88	0.38	2.00	0.7475

Figures

Figure 1

Kaplan–Meier estimates of probabilities of overall survival according to VTE prophylaxis in testicular germ cell tumor patients (n = 353), HR = 0.61, 95% CI 0.32-1.13; P = 0.0784, 0 – no prophylaxis, 1 – prophylaxis

Figure 2A

Figure 2B

Figure 2

2A Kaplan–Meier estimates of probabilities of overall survival according to VTE prophylaxis in non-seminomatous germ cell tumor patients (n = 268), HR = 0.29, 95% CI 0.08 - 1.12; P = 0.0373, 0 – no prophylaxis, 1 - prophylaxis. 2B Kaplan–Meier estimates of probabilities of overall survival according to VTE prophylaxis in extragonadal germ cell tumor patients (n = 35), HR = 0.50, 95% CI 0.25-0.99; P = 0.0179, 0 – no prophylaxis, 1 – prophylaxis.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Flowdiagramandtables.docx](#)
- [VTEwSupplementarytablesrevised182020Clean.docx](#)