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Risk for Arterial Thromboembolic Events (ATEs) in Patients with Advanced Urinary Tract Cancer (aUTC) Treated with First-Line Chemotherapy: Single-Center, Observational Study

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Abstract: Arterial thromboembolism has been associated with cancer or its treatment. Unlike venous thromboembolism, the incidence and risk factors have not been extensively studied. Here, we investigated the incidence of arterial thromboembolic events (ATEs) in an institutional series of advanced urinary tract cancer (aUTC) treated with cytotoxic chemotherapy. The ATE definition included peripheral arterial embolism/thrombosis, ischemic stroke and coronary events. A total of 354 aUTC patients were analyzed. Most patients (95.2%) received platinum-based chemotherapy. A total of 12 patients (3.4%) suffered an ATE within a median time of 3.6 months from the start of chemotherapy. The most frequent ATE was ischemic stroke (n = 7). Two ATEs were fatal. The 6-month and 24-month incidence were 2.1% (95% confidence interval [CI]: 0.9–4.1) and 3.6% (95% CI: 1.9–6.2), respectively. Perioperative chemotherapy increased the risk for ATE by 5.55-fold. Tumors other than UTC and pure non-transitional cell carcinoma histology were also independent risk factors. No association with the type of chemotherapy was found. Overall, ATEs occur in 4.6% of aUTC patients treated with chemotherapy and represent a clinically relevant manifestation. Perioperative chemotherapy significantly increases the risk for ATE. The role of prophylaxis in high-risk groups should be prospectively studied.

Keywords: arterial; thromboembolism; urinary tract; cancer; chemotherapy; observational

1. Introduction

The association between cancer and clinical hypercoagulability is well-known. Cancer itself, through effects on hemostatic and fibrinolytic pathways, represents a major driver of thromboembolic risk, as evidenced by the wide variability in this risk by cancer type and stage [1–4]. Cancer-associated prothrombotic effects include the hematogenous release of cancer-derived microparticles that trigger the coagulation cascade, production of procoagulant factors such as factor X, release of mucins that activate platelets and endothelial cells through the binding of P-selectin, and stimulation of neutrophils to release decondensed chromatin that forms prothrombotic neutrophil extracellular traps [5–7]. This hypercoagulability state is associated with the development of both venous (VTEs) and arterial (ATEs) thromboembolic events. The former are more frequent and have been more extensively studied regarding both treatment as well as prevention [8–14]. In addition, Risk Assessment Models (RAMs) have been developed in order to identify cancer patients in high risk to develop VTE and thus could be candidates for prevention strategies [15,16]. On the contrary, data on ATEs are very limited. Furthermore, the development of these events in patients with cancer may be more complex than that of VTEs, where the most relevant predisposing factors are the malignancy itself or its treatment. Regarding ATEs, multiple other factors may also be relevant. Established risk factors for ATEs, such as smoking and hypertension, are more prevalent in specific cancer types, either as risk factors for the development of cancer, manifestations of the disease itself or as toxicity due to specific anti-cancer therapies. Effects of stress and frequent interruption of antithrombotics may also result in an increased risk for ATEs. Finally, taking into consideration that major ATEs, such as ischemic heart disease and stroke, are leading causes of death, it is plausible that the development of such events may impact on the prognosis of cancer patients [17].

Clinical series have suggested that ATEs may be common in patients with cancer [18–21]. A recent study, which used the Surveillance Epidemiology and End Results (SEER)-Medicare linked database, suggested that the risk of developing ischaemic heart disease and/or stroke differed among different types of cancer [1]. This has already been acknowledged in relation to the development of VTE incidence, which considerably differs among tumors of different origin [21]. Differences in the biology of the tumor, the agents used for systemic therapy and risk factors, which are common for the specific tumor type and for the development of arterial events, may result in distinctly different incidence of ATEs and implications for management and prevention. It is, therefore, useful to collect information on ATEs occurring in specific types of cancers rather than including multiple types of neoplastic diseases.

Advanced urinary tract cancer (aUTC) has been associated with frequent development of ATEs [22]. This is not surprising, taking into consideration the strong association of smoking with both aUTC and ATEs. Furthermore, platinum-based chemotherapy, which represents the standard systemic therapy in aUTC, is also thrombogenic [20]. The incidence and the risk factors associated with the development of ATEs in aUTC have been reported in three retrospective studies [1,10,23]. In two of them, all patients received platinum-based chemotherapy for locally advanced or metastatic disease and the incidence was 4% in both cases [10,23]. In the largest series of approximately 17,000 patients from the SEER database, a 7.1% cumulative incidence in 1 year from cancer diagnosis was reported. This series was considerably different than the previous two, since it predominantly included patients with non-metastatic disease; peripheral arterial disease (PAD) was not evaluated and information about the applied anti-cancer therapies was lacking. Currently, the accurate prediction of the probability of developing ATEs in patients with aUTC receiving cytotoxic chemotherapy and the identification of widely accepted risk factors represents an unmet medical need. For these reasons, we studied the incidence of ATEs in patients who received cytotoxic chemotherapy in our institution.

2. Methods

2.1. Study Design and Patient Population

This is an observational, cohort study. Patients with histologically confirmed UTC (bladder, urethra, renal pelvis or ureter) were selected from our institutional database according to the following criteria: advanced disease (clinical stages T4b [for bladder cancer] and/or N \geq 2 and/or M1); transitional-cell, squamous or adenocarcinoma (pure or mixed) histology; treatment with at least one line of systemic chemotherapy for advanced disease. Clinical data were extracted from patient charts. The variables collected for this analysis are shown in Table 1. All patients gave their Institutional Review Board-approved written consent for the use of their medical data.

Table 1. Baseline characteristics of 354 patients with advanced urothelial cancer who were included in the analyses.

Characteristic	Median		Range		
Age	67		32–88		
Weight	73.5		43–125		
BMI	26		15–51.1		
BSA	1.8		1.3–2.4		
Months after major surgery	6		1–180		
Cycles of chemotherapy	6		1–20		
Characteristic	Total		ATE		p Value
	n	%	Yes (%)	No (%)	
Sex					
Female	59	16.7	0 (0)	59 (17.3)	0.230
Male	295	83.3	12(100)	283 (82.7)	
Diabetes					
Yes	46	13	2 (16.7)	44 (12.9)	0.660
No	308	87	10 (83.3)	298 (87.1)	
BMI >35					
Yes	18	5.1	0 (0)	18 (5.3)	0.084
No	334	94.4	11 (91.7)	323 (94.4)	
Missing	2	0.5	1 (8.3)	1 (0.3)	
BMI > 25					
Yes	208	58.8	7 (58.3)	201 (58.8)	0.097
No	144	40.7	4 (33.3)	140 (40.9)	
Missing	2	0.5	1 (8.3)	1 (0.3)	
Anti-platelet therapy					
Yes	51	14.4	2 (16.7)	49 (14.3)	0.686
No	303	85.6	10 (83.3)	293 (85.7)	
Anticoagulants					
Yes	18	5.1	0 (0)	18 (5.3)	>0.999
No	336	94.9	12 (100)	324 (94.7)	
Antihypertensives					
Yes	137	38.7	4 (33.3)	133 (38.9)	0.773
No	217	61.3	8 (66.7)	209 (61.1)	
Atrial fibrillation					
Yes	12	3.4	0 (0)	12 (3.5)	>0.999
No	342	96.6	12 (100)	330 (96.5)	

Table 1. Cont.

Characteristic	Total		ATE		p Value
	n	%	Yes (%)	No (%)	
Cholesterol-lowering medication					
Yes	54	15.3	2 (16.7)	52 (15.2)	>0.999
No	300	84.8	10 (83.3)	290 (84.8)	
Coronary artery disease					
Yes	48	13.6	1 (8.3)	47 (13.7)	>0.999
No	306	86.4	11(91.7)	295 (86.3)	
Previous peripheral arterial embolism/thrombosis					
Yes	13	3.7	1 (8.3)	12 (3.5)	0.336
No	341	96.3	11 (91.7)	330 (96.5)	
Smoking history					
Yes	174	49.2	6 (50)	168 (49.1)	0.952
No	180	50.9	6 (50)	174 (50.9)	
Solid tumour other than UTC					
Yes	35 ¹	9.9	4 (33.3)	31 (9.1)	0.022
No	319	90.1	8 (66.7)	311 (90.9)	
Previous VTE					
Yes	29	8.2	1 (8.3)	28 (8.2)	>0.999
No	325	91.8	11 (91.7)	314 (91.8)	
Haematologic malignancy					
Yes	3	0.9	0 (0)	3 (0.9)	>0.999
No	351	99.1	12 (100)	339 (99.1)	
Coagulation disorder					
Yes	2	0.6	0 (0)	2 (0.6)	>0.999
No	352	99.4	12 (100)	340 (99.4)	
Major Surgery					
Other major surgery (no cystectomy)	46	13	1 (8.3)	45 (13.2)	>0.999
Cystectomy	186	52.5	7 (58.4)	179 (52.3)	
No major surgery	122	34.5	4 (33.3)	118 (34.5)	
Time since UTC diagnosis					
≤6 months	12	3.4	0 (0)	12 (3.5)	>0.999
>6 months	342	96.6	12 (100)	330 (96.5)	
Histology					
TCC	308	87	10 (83.3)	298 (87.1)	0.084
Mixed	34	9.6	0 (0)	34 (10)	
non-TCC	11	3.1	2 (16.7)	9 (2.6)	
Missing	1	0.3	0 (0)	1 (0.3)	
Primary site					
Bladder	298	84.2	12 (100)	286 (83.6)	0.373
Bladder/Renal pelvis	2	0.5	0 (0)	2 (0.6)	
Renal pelvis	50	14.1	0 (0)	50 (14.6)	
Ureter	3	0.9	0 (0)	3 (0.9)	
Urethra	1	0.3	0 (0)	1 (0.3)	
Performance status					
0	124	35	4 (33.3)	120 (35.1)	0.127
1	132	37.3	8 (66.7)	124 (36.3)	
2	73	20.6	0 (0)	73 (21.4)	
3	25	7.1	0 (0)	25 (7.3)	

Table 1. Cont.

Characteristic	Total		ATE		p Value
	n	%	Yes (%)	No (%)	
Number of disease sites					
1	206	58.2	9 (75)	197 (57.6)	0.754
2	107	30.2	3 (25)	104 (30.4)	
3	33	9.3	0 (0)	33 (9.7)	
4	8	2.3	0 (0)	8 (2.3)	
Location of disease					
Pelvis	237	67	10 (83.3)	227 (66.4)	0.350
Non-pelvis	117	33	2 (16.7)	115 (33.6)	
Type of Chemotherapy					
Cisplatin	188	53.1	5 (41.7)	183 (53.5)	0.139
Carboplatin	150	42.4	5 (41.7)	145 (42.4)	
Other	16	4.5	2 (616.7)	14 (4.1)	
Conventional	199	56.2	7 (58.3)	192 (56.2)	0.880
Dose-dense	155	43.8	5 (41.7)	150 (43.8)	
Gemcitabine	222	62.7	8 (66.7)	214 (62.6)	>0.999
Other	132	37.3	4 (33.3)	128 (37.4)	
Anthracycline	96	27.1	2 (16.7)	94 (27.5)	0.525
Non-anthracycline	258	72.9	10 (83.3)	248 (72.5)	
History of neoadjuvant/adjuvant chemotherapy					
Yes	73	20.6	7 (58.3)	66 (19.3)	0.001
No	281	79.4	5 (41.9)	276 (80.7)	
History of chemotherapy not for UTC					
Yes	6	1.7	1(8.3)	5 (1.5)	0.188
No	348	98.3	11 (91.7)	337 (98.5)	
History of radiation					
Yes	83	23.5	3 (25)	80 (23.4)	>0.999
No	271	76.5	9 (75)	262 (76.6)	
Radiation field					
Pelvis	58	16.4	3 (25)	55 (16.1)	0.424
Other + no radiation	296	83.6	9 (75)	287 (83.9)	
History of hormone therapy					
Yes	9	2.5	0 (0)	9 (2.6)	>0.999
No	345	97.5	12 (100)	333 (97.4)	
Hormone/anthracycline therapy					
Yes	97	27.4	2 (16.7)	95 (27.8)	0.524
No	257	72.6	10 (83.3)	247 (72.2)	
Pre-chemo PLTs > 350,000/ μ L					
Yes	113	31.9	4 (33.3)	109 (31.9)	>0.999
No	241	68.1	8 (66.7)	233 (68.1)	
Hgb < 10 g/dL or ESA					
Yes	34	9.6	1 (8.3)	33 (9.6)	>0.999
No	320	90.4	11 (91.7)	309 (90.4)	
Pre-chemo WBCs > 11,000/ μ L					
Yes	66	18.6	1 (8.3)	65 (19)	0.704
No	288	81.4	11 (91.7)	277 (81)	
ATE					
Yes	12	3.4			
No	342	96.6			

Table 1. *Cont.*

Characteristic	Total		ATE		p Value
	n	%	Yes (%)	No (%)	
Type of ATE					
Peripheral arterial thrombosis/embolism	2				
Ischaemic stroke	7				
Unstable angina	1				
MI	2				
Subsequent lines of therapy					
0	220	62.2	7 (58.3)	213 (62.3)	0.588
1	82	23.1	2 (16.7)	80 (23.4)	
2–5	51	14.4	3 (25)	48 (14)	
missing	1	0.3	0 (0)	1 (0.3)	

BMI: body mass index; BSA: body surface area; ATE: arterial thromboembolic event; Fisher's exact test; ¹: prostate: 17; lung: 4, breast: 3, head and neck: 3, colorectal: 2, parotid gland: 2, basal cell: 1, uterus: 1, thyroid: 1, seminoma: 1; UTC: urinary tract cancer; VTE: venous thromboembolic event; TCC: transitional-cell carcinoma; PLT: platelets; ESA: erythropoiesis stimulating agents; WBC: white blood cells; MI: myocardial infarction.

The primary endpoint was objectively confirmed ATEs after the initiation of chemotherapy for advanced disease. The ATE definition included: peripheral arterial thrombosis/embolism, ischaemic stroke and coronary events (unstable angina or myocardial infarction [MI]). ATE had to be documented by at least one of the following methods: computerised tomography; magnetic resonance imaging, angiography. Major surgery was defined as any open or laparoscopic abdominal and/or pelvic surgery, including cystectomy. Disease was categorised as lymph-node/local (LNL) only (including only bladder or local relapse and/or lymph node metastases) and other (presence of non-lymph node metastases \pm LNL disease).

2.2. Statistical Analysis

Cumulative incidence function (CIF) for ATE was calculated from the time of initiation of first-line chemotherapy and gives the proportion of patients at a specific time period who have an ATE, accounting for the fact that they may die before this. Thus, the CIF for ATE not only depends on the hazard of ATE but also on the hazard for death. CIF curves and competing events of death were presented in graphical form (Figure S1). The association of baseline and treatment-related factors with the development of ATE was assessed using competing-risk regressions [24]. Cause-specific hazard ratios from Cox models were estimated to be compared with Sub-distribution hazard ratios (SHRs) of Fine and Gray [24]. The latter was chosen as a better approach to acknowledge that patients may die before having an ATE.

Any covariates in the univariate analysis with a p -value ≤ 0.200 were evaluated in a multivariate, competing risk regression model. SHRs were calculated for each factor. The subgroup analyses were carried out using the same multivariate competing risks model. Schoenfeld residuals were calculated and plotted as a diagnostic measure of the model. Interactions and time-varying effects were also tested. Survival was computed by Kaplan–Meier curves and the impact of ATE on outcome was tested with the log-rank test. Subgroup analyses according to the type of ATE were also performed.

3. Results

Three hundred fifty-four patients who started first-line chemotherapy for aUTC from April 1995 to September 2015 at our institution were included in the analysis (Figure S2). Their pre-chemotherapy characteristics are shown in Table 1. Most patients received cisplatin-based (187, 53.1%) or carboplatin-based (150, 42.4%) first-line chemotherapy. The chemotherapy administered is depicted in detail in Table S1 [25–37]. The median follow up, following initiation of chemotherapy was 9.3 months (95% CI: 7.8–11). At the time

of initiation of the first-line chemotherapy, 5.1% of patients were receiving anticoagulant therapy and 14.4% received antiplatelet agents. No patient had had a central venous catheter (CVC). Seventy-three patients (20.6%) received perioperative chemotherapy. Most patients (62%) did not receive any chemotherapy beyond the first-line.

3.1. Incidence of ATEs and Association with Clinical Characteristics

ATE occurrence according to patient demographics and clinical characteristics are shown in Table 1. Twelve patients (3.4%) suffered an ATE: peripheral arterial thrombosis/embolism: 2, ischemic stroke: 7, unstable angina: 1, non-ST elevation myocardial infarction (nSTEMI): 1, STEMI: 1. The median time from start of chemotherapy to the occurrence of the first ATE was 3.6 months (25th–75th percentile: 2.2–9). Four events (33.3%) occurred within the first 3 months, seven (58.3%) within the first 6 months and ten (83.3%) within the first year. The remaining two events (16.7%) occurred between 12 to 60 months after the initiation of first-line chemotherapy. Ten of the 12 patients received platinum-based first-line chemotherapy (cisplatin:5, carboplatin:5). One patient received vinflunine and the other gemcitabine/ifosfamide. The time of occurrence, management and outcomes of ATEs are depicted in Table S2. Two events (both ischaemic strokes) were fatal.

The cumulative 6-month and 24-month incidence of ATE were 2.1% (95% CI: 0.9–4.1) and 3.6% (95% CI: 1.9–6.2), respectively (Table 2). The absolute cumulative incidence over time from the initiation of first-line chemotherapy, with death as competing risk, is shown in Figure 1a. The CIF of ATEs at discrete time periods from the initiation of chemotherapy are shown in Table 2. Risk increased over time, up to 2 years after the initiation of chemotherapy.

Table 2. Arterial thromboembolic (ATE) risk in 354 patients with advanced urinary tract cancer receiving first-line chemotherapy. Incidence function was calculated with death as a competing risk. The 95% confidence intervals are shown in parentheses.

		n (%)	Incidence Function (%)			
			3-Month	6-Month	12-Month	24-Month
Total ATE cases		12 (100)	1.2 (0.4–2.8)	2.1 (0.9–4.1)	3.2 (1.6–5.6)	3.6 (1.9–6.2)
Ischaemic stroke		7 (58.3)	0.3 (0.3–1.6)	1 (0.3–2.6)	2 (0.8–4.2)	2 (0.8–4.2)
Cisplatin						
	Yes	188 (53.1)	1.1 (0.2–3.6)	2.3 (0.8–5.4)	2.9 (0.8–5.4)	2.9 (1.1–6.3)
	No	166 (46.9)	1.3 (0.3–4.1)	1.9 (0.5–5.1)	3.5 (1.3–7.4)	4.4 (1.8–8.8)
Dose dense chemotherapy						
	Yes	155 (43.8)	1.3 (0.3–4.3)	2.8 (0.9–6.6)	3.6 (1.3–7.7)	3.6 (1.3–7.7)
	No	199 (56.2)	1 (0.2–3.4)	1.6 (0.4–4.2)	2.8 (1.1–6.1)	3.6 (1.5–7.2)
Gemcitabine						
	Yes	222 (62.7)	1.4 (0.4–3.8)	2.5 (0.9–5.3)	3.1 (1.3–6.3)	3.9 (1.7–7.5)
	No	132 (37.3)	0.8 (0.1–3.8)	1.6 (0.3–5.1)	3.2 (1.1–7.5)	3.2 (1.1–7.5)
Histology						
	TCC + mixed	342 (96.9)	0.6 (0.1–2.1)	1.6 (0.6–3.5)	2.7 (1.3–5)	3.1 (1.5–5.7)
	Other	11 (3.1)	18.2 (2.9–44.2)	18.2 (2.9–44.2)	18.2 (2.9–44.2)	18.2 (2.9–44.2)
Solid tumour other than UTC						
	No	319 (90.1)	1.3 (0.4–3.1)	1.7 (0.6–3.6)	2.4 (1.1–4.7)	2.9 (1.3–5.4)
	Yes	35 (9.9)	-	6.5 (1.2–18.7)	11 (2.7–25.9)	11 (2.7–25.9)
History of adjuvant/neoadjuvant						
	None	281 (79.4)	0.8 (0.2–2.5)	1.2 (0.3–3.1)	1.6 (0.5–3.8)	2.1 (0.8–4.7)
	One at least	73 (20.6)	2.8 (0.5–8.6)	5.7 (1.8–12.8)	9 (3.7–17.4)	9 (3.7–17.4)

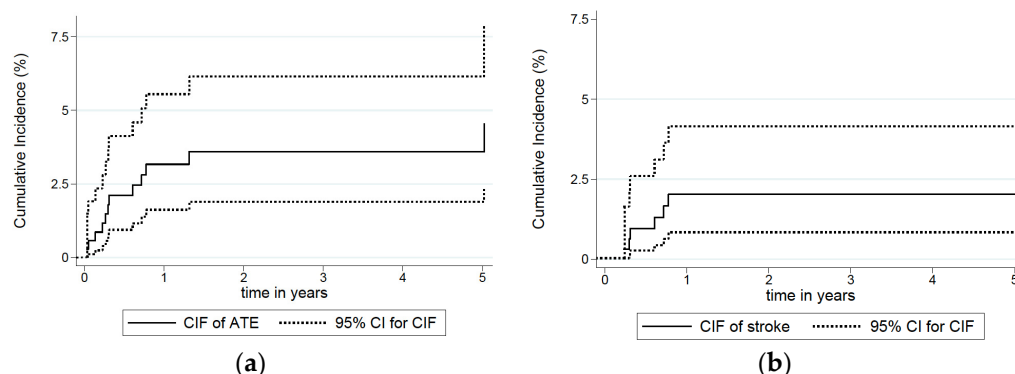


Figure 1. Cumulative incidence function (CIF) of all arterial thromboembolic events (ATEs) (a) and specifically for ischaemic strokes (b) over time from the initiation of first-line chemotherapy, with death as competing risk, for 354 patients treated for advanced urinary tract cancer. CI: confidence interval.

The cumulative 6-month and 24-month incidence of ischaemic strokes was 1% (95% CI: 0.3–2.6) and 2% (95% CI: 0.8–4.2), respectively (Table 2). The absolute cumulative incidence over time from the initiation of first-line chemotherapy is shown in Figure 1b. Further subgroup analyses based on other types of ATEs were not performed due to the limited number of events in the other subgroups.

3.2. Association of ATEs with Type of Chemotherapy

Unadjusted cumulative ATE incidence functions based on the first-line chemotherapy regimen are shown in Table 2. Use of dose-dense regimen vs. conventional schedule chemotherapy, and cisplatin vs. carboplatin were not associated with increased risk of ATEs. Incidence of ATEs among gemcitabine-treated patients was almost 2-fold vs. those treated with non-gemcitabine-containing regimes (5.7% vs. 3.2%) but this difference was not statistically significant.

3.3. Uni- and Multivariate Analysis of ATE Risk

In the univariate analysis, cumulative ATE incidence was significantly increased in patients with history of perioperative therapy, solid tumor other than UTC and those with histology other than transitional cell carcinoma (TCC) or mixed (Table 3). The respective cumulative ATE incidence functions at discrete time periods are shown in Table 2, while the absolute cumulative incidence over time from the initiation of the first-line chemotherapy, with death as competing risk, is depicted in Figure 2. Post first-line therapy was not associated with the development of ATE.

Table 3. Univariate, multivariate, cox and competing risk regression analysis of arterial thromboembolism based on clinical characteristics. Variables with $p < 0.200$ are presented.

Factor	Univariate							Multivariate		
	n	Cox Regression Analysis			Competing Risks Analysis			Competing Risks Analysis		
		HR	95% CI	p	SHR	95% CI	p	SHR	95% CI	p
Solid tumour other than UTC				0.010			0.008			0.028
No	319	Ref			Ref			Ref		
Yes	35	4.88	1.46–16.3		5.01	1.53–16.33		3.71	1.15–11.97	
Histology				0.003			0.020			0.028
TCC + mixed	342	Ref			Ref			Ref		
Other	11	10.15	2.16–47.68		6.77	1.35–33.9		7.79	1.25–48.43	
History of adjuvant/neoadjuvant				0.005			0.004			0.010
None	281	Ref			Ref			Ref		
One at least	73	5.17	1.63–16.41		5.38	1.73–16.76		5.55	1.51–20.48	

UTC: urinary tract cancer; HR: hazard ratio; SHR: sub-distribution hazard ratio; CI: confidence interval.

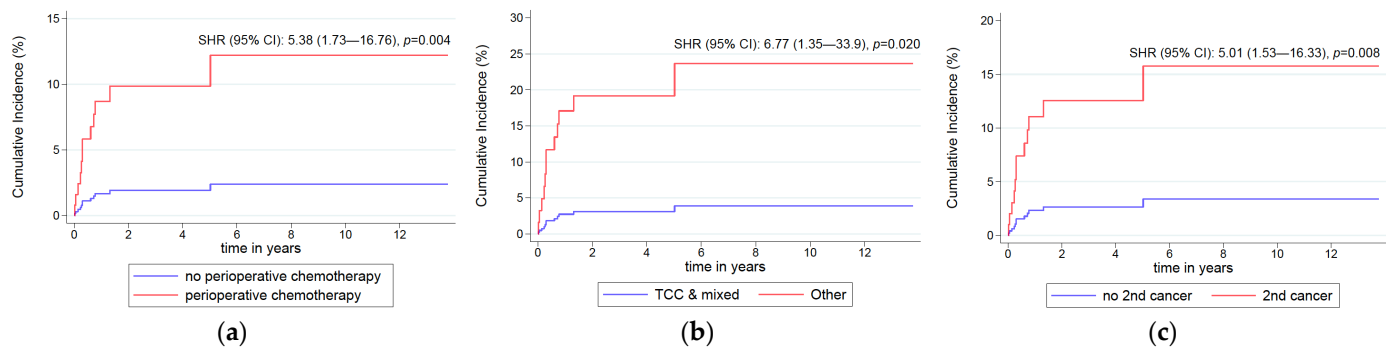


Figure 2. Competing-risks predicted cumulative incidence functions according to the presence of: (a) previous perioperative chemotherapy; (b) non-transitional-cell histology; (c) history of solid tumor other than urinary tract cancer (UTC). SHR: sub-distribution hazard ratio, CI: confidence interval.

The three above variables were entered into a competing-risk cox regression model for multivariate analysis. Other factors, which could potentially be associated with increased thrombogenic activity, i.e., pre chemotherapy platelet count $\geq 3.50 \times 10^{11}$ /L, hemoglobin level < 10 g/dL or the use of red cell growth factors, pre-chemotherapy leukocyte count $> 1.1 \times 10^{10}$ /L, BMI ≥ 35 kg/m², anthracycline treatment, time since cancer diagnosis > 6 months, cardiovascular risk factors and comorbidities (composed by at least two of the following predictors: history of peripheral arterial embolism/thrombosis, coronary artery disease [CAD], hypertension, use of cholesterol-lowering drugs, diabetes) were also included in the model, although they were not associated with a p value ≤ 0.200 in the univariate analysis. The multivariate analysis (using the backward stepwise selection) confirmed the independent significance of all three factors identified in univariate analysis (Table 3). Interactions and time-varying effects of these variables were tested and none was found statistically significant. Regarding the clinical relevance of these factors, it is important to underline that only eleven patients had pure non-TCC histology, which accounted for only two of the total 12 ATEs. More importantly, both patients with pure non-TCC histology who developed ATE had received perioperative chemotherapy. Similar findings were observed for patients with tumors other than UTC: only one of the four patients suffering an ATE had not received perioperative chemotherapy.

4. Discussion

Cancer is frequently associated with an increase in thrombogenic potential. Although this might affect both venous and arterial circulation [21,38–44], ATEs have been largely disregarded in most studies of cancer-associated thrombosis (CAT). As a result, relative data for UTC are also very limited. Three large studies including mixed populations confirmed the significant increase in ATE risk in UTC compared to cancer-free controls [1,3,4]. In two smaller studies including only patients with aUTC who received platinum-based chemotherapy, the incidence was 4% in both cases [10,23]. In all studies, peripheral arterial thromboembolism was not included in the ATE incidence, while the three first studies included all stages, and the patients may not have received systemic therapy. Our study adds new information to these prior reports by including a homogenous population regarding cancer stage and therapy, while it is the first to include peripheral artery thromboembolism as an event in our calculations. We found a cumulative incidence of 4.6% close to that of the two previous smaller series [10,23]. The incidence reported by all three studies is lower than a 10.4% incidence at 2 years after the diagnosis of cancer, reported in a recent series from the SEER database [1]. This was true both for myocardial infarction as well as ischemic strokes. The reason for this discrepancy is not entirely clear. Several differences in patients' selection exist between the SEER database analysis and the three other studies: patients from all stages and not only advanced disease were included in the first study, while details about the management (i.e., use of any therapy or not, type of therapy) were not available in the former. More importantly, the SEER population may represent a population in

higher risk for cardiovascular disease: approximately 60% of patients had hypertension, atrial fibrillation or both, while the respective conditions in our population were 33% and 3%, respectively. The high risk of the SEER population is also suggested by the 8.7% risk for stroke or CAD of the controls at 2 years of follow up. These findings underline the importance of identifying risk factors for the development of ATEs among patients with specific types of cancer.

Ours is the first study to identify risk factors exclusively for the development of ATEs in aUTC, since previous studies studied composite (VTE and ATE) end points [10,23] or could not evaluate several of the parameters that we were able to [1]. We identified pure non-TCC histology, solid tumor other than UTC and history of perioperative chemotherapy as independent adverse factors for the development of ATE. The first has also been identified as a risk factor for venous thromboembolism but the mechanism underlying this association is obscure [45]. The association of the risk for ATE with the history of another tumor seems intuitive, since cancer is associated with increased risk for ATEs [1–4]. Nevertheless, the clinical relevance of these two factors is limited by the rarity of these conditions. Furthermore, all but one patient with at least one of these factors experiencing ATE also belonged to the group who received perioperative chemotherapy, suggesting that the third factor may be more relevant. A substantial 20% of our patients underwent neoadjuvant or adjuvant chemotherapy or both, and, according to contemporary trends, it is likely that this percentage is higher in current practice [46]. Approximately 10% of these patients suffered an ATE, accounting for seven of the twelve ATEs in the whole series. These findings might support the notion that specific populations who could be candidates for prevention strategies can be identified within the various types of cancer. The reason for the association we found is not clear. Patients who underwent perioperative chemotherapy did not have higher incidence of known factors predisposing for CAD, PAD or ischemic stroke. Thus, exposure to previous chemotherapy remains the most plausible factor to explain the association we found. Perioperative chemotherapy was platinum-based chemotherapy for all our patients. This type of therapy is thrombogenic [23]. It could, therefore, be speculated that double exposure to chemotherapy might increase the likelihood for ATE development.

Identifying risk factors predisposing for the development of ATEs is also important for the implementation of prophylaxis strategies. In contrast to VTEs, such research has not been extensive for ATEs. Incident cancer is not an established independent risk factor for arterial thromboembolism, and patients with cancer do not routinely receive therapies to prevent myocardial infarction and stroke [47–49]. Other factors also make this field more complicated, compared to VTEs: treatment of ATEs is not as homogenous as that of VTEs; equally medical treatment is not the only method of prevention, since surgery holds a significant role. Nevertheless, recent data add to the emerging consensus that arterial and venous thromboembolism are not quite as disparate as previously thought [50]. Common strategies for thromboprophylaxis could be designed, since anticoagulant therapy can also prevent ATEs. This notion is supported by the results of the CASSINI study, which demonstrated that rivaroxaban could reduce the composite incidence of venous and arterial thromboembolism in ambulatory patients with cancer [51]. Prophylaxis is particularly relevant in aUTC patients, since the high prevalence of cardiovascular risk factors, such as advanced age and smoking, expose them to high risk of cardiovascular events.

There are several limitations to our analysis. Despite being the largest institutional series of the specific population studied, the number of patients in our study is fairly small. Our study is limited by the inherent confounders and biases associated with any retrospective analysis. The validity of data regarding comorbidities and pre-existing medication was based on information from the patients and were not confirmed in all cases. Thus, some inaccuracies in reporting cannot be excluded. In this respect, the fact that all patients were treated in our institution represents an advantage, since we were able to review each file and limit inaccuracies to a certain extent. Specifically, we ensured that the diagnosis of ATEs had always been confirmed by standard imaging and was never based solely on patients' information. Additionally, the treatment was fairly homogenous and

the majority of patients had been treated with standard chemotherapy, while experimental targeted agents or immunotherapy were not included. Finally, our study cannot estimate the additive effect of chemotherapy to the risk of developing ATEs in patients with aUTC. This would require a non-chemotherapy cohort, which under the current guidelines, would not exist. In this respect, information provided by our study is in concert with current everyday practice and thus clinically relevant.

In conclusion, our study offers important information on the incidence of and risk factors associated with the development of ATEs in aUTC. ATEs are less frequent than VTEs but may be a more complicated condition regarding both management and prevention. Since anti-coagulation may also prevent arterial thromboembolism, the field should consider abandoning the assessment of thromboprophylaxis exclusively in relation to VTEs and evaluate its role in ATE prevention among cancer patients.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/curroncol29090478/s1>, Figure S1: Stacked Cumulative Incidence functions (CIF) of arterial thromboembolic events (ATE) and death over time; Figure S2: Study flow; Table S1: Detailed description of 1st-line chemotherapy administered to the 354 patients included in the analysis; Table S2: Management and outcomes of the 12 arterial thromboembolic events (ATEs), which occurred among 354 patients with advanced urothelial cancer, treated with platinum-based chemotherapy.

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Abbreviations

VTEs	Venous thromboembolic events
ATEs	Arterial thromboembolic events
RAMs	Risk Assessment Models
SEER	Surveillance Epidemiology and End Results
aUTC	Advanced urinary tract cancer
PAD	Peripheral arterial disease
LNL	Lymph-node/local
CIF	Cumulative incidence function
SHR	Sub-distribution hazard ratio
CVC	Central venous catheter
nSTEMI	Non-ST elevation myocardial infarction
STEMI	ST elevation myocardial infarction
TCC	Transitional cell carcinoma
CAD	Coronary artery disease
CAT	Cancer-associated thrombosis

References

1. Navi, B.B.; Reiner, A.S.; Kamel, H.; Iadecola, C.; Okin, P.M.; Elkind, M.S.V.; Panageas, K.S.; DeAngelis, L.M. Risk of Arterial Thromboembolism in Patients With Cancer. *J. Am. Coll. Cardiol.* **2017**, *70*, 926–938. [[CrossRef](#)] [[PubMed](#)]
2. Navi, B.B.; Reiner, A.S.; Kamel, H.; Iadecola, C.; Elkind, M.S.; Panageas, K.S.; DeAngelis, L. Association between incident cancer and subsequent stroke. *Ann. Neurol.* **2015**, *77*, 291–300. [[CrossRef](#)] [[PubMed](#)]
3. Zöller, B.; Ji, J.; Sundquist, J.; Sundquist, K. Risk of coronary heart disease in patients with cancer: A nationwide follow-up study from Sweden. *Eur. J. Cancer* **2012**, *48*, 121–128. [[CrossRef](#)] [[PubMed](#)]
4. Zöller, B.; Ji, J.; Sundquist, J.; Sundquist, K. Risk of haemorrhagic and ischaemic stroke in patients with cancer: A nationwide follow-up study from Sweden. *Eur. J. Cancer* **2012**, *48*, 1875–1883. [[CrossRef](#)]
5. Yeh, E.T.H.; Chang, H.M. Cancer and clot: Between a rock and a hard place. *J. Am. Coll. Cardiol.* **2017**, *70*, 939–941. [[CrossRef](#)]
6. Bang, O.Y.; Chung, J.W.; Lee, M.J.; Kim, S.J.; Cho, Y.H.; Kim, G.M.; Chung, C.-S.; Lee, K.H.; Ahn, M.-J.; Moon, G.J. Cancer cell-derived extracellular vesicles are associated with coagulopathy causing ischemic stroke via tissue factor-independent way: The OASIS-CANCER Study. *PLoS ONE* **2016**, *11*, e0159170. [[CrossRef](#)]
7. Demers, M.; Wagner, D.D. NETosis: A new factor in tumor progression and cancer-associated thrombosis. *Semin. Thromb. Hemost.* **2014**, *40*, 277–283. [[CrossRef](#)]
8. Khorana, A.A. If Trousseau had a stroke. *Blood* **2019**, *133*, 769–770. [[CrossRef](#)]
9. Barceló, R.; Muñoz, A.; López-Vivanco, G. Prospective evaluation of major vascular events in patients with non-small cell lung carcinoma treated with cisplatin and gemcitabine. *Cancer* **2005**, *103*, 994–999.
10. Tully, C.M.; Apolo, A.B.; Zabor, E.C.; Regazzi, A.M.; Ostrovskaya, I.; Furberg, H.F.; Rosenberf, J.E.; Bajorin, D.F. The high incidence of vascular thromboembolic events in advanced urothelial cancer treated with platinum chemotherapy agents. *Cancer* **2016**, *122*, 712–721. [[CrossRef](#)]
11. Lyman, G.H.; Bohlke, K.; Khorana, A.A.; Kuderer, N.M.; Lee, A.Y.; Arcelus, J.I.; Balaban, E.P.; Clarke, J.M.; Flowers, C.R.; Francis, C.W.; et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *J. Clin. Oncol.* **2016**, *33*, 654–656. [[CrossRef](#)]
12. Agnelli, G.; George, D.J.; Kakkar, A.K.; Fisher, W.; Lassen, M.R.; Mismetti, P.; Mouret, P.; Chaudhari, U.; Lawson, F.; Turpie, A.G. Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. *N. Engl. J. Med.* **2012**, *366*, 601–609. [[CrossRef](#)]
13. Agnelli, G.; Gussoni, G.; Bianchini, C.; Verso, M.; Mandalà, M.; Cavanna, L.; Barni, S.; Labianca, R.; Buzzi, F.; Scambia, G.; et al. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: A randomised, placebo-controlled, double-blind study. *Lancet Oncol.* **2009**, *10*, 943–949. [[CrossRef](#)]
14. Carrier, M.; Abou-Nassar, K.; Mallick, R.; Tagalakis, V.; Shivakumar, S.; Schattner, A.; Kuruvilla, P.; Hill, D.; Spadafora, S.; Marquis, K.; et al. Apixaban to prevent venous thromboembolism in patients with cancer. *N. Engl. J. Med.* **2019**, *380*, 711–719. [[CrossRef](#)]
15. Khorana, A.A.; Kuderer, N.M.; Culakova, E.; Lyman, G.H.; Francis, C.W. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood* **2008**, *111*, 4902–4907. [[CrossRef](#)]
16. Gerotziakas, G.T.; Taher, A.; Abdel-Razeq, H.; AboElnazar, E.; Spyropoulos, A.C.; El Shemmari, S.; Larsen, A.K.; Elalamy, I.; COMPASS-CAT Working Group. A predictive score for thrombosis associated with breast, colorectal, lung, or ovarian cancer: The prospective COMPASS-Cancer Associated Thrombosis Study. *Oncologist* **2017**, *22*, 1222–1231. [[CrossRef](#)]
17. Kim, A.S.; Johnston, S.C. Global variation in the relative burden of stroke and ischemic heart disease. *Circulation* **2011**, *124*, 314–323. [[CrossRef](#)]
18. Velders, M.A.; Boden, H.; Hofma, S.H.; Osanto, S.; van der Hoeven, B.L.; Heestermans, A.A.; Cannegieter, S.C.; Jukema, J.W.; Umans, V.A.; Schalij, M.J.; et al. Outcome after ST elevation myocardial infarction in patients with cancer treated with primary percutaneous coronary intervention. *Am. J. Cardiol.* **2013**, *112*, 1867–1872. [[CrossRef](#)]
19. Navi, B.B.; Singer, S.; Merkle, A.E.; Cheng, N.T.; Stone, J.B.; Kamel, H.; Iadecola, C.; Elkind, M.S.; DeAngelis, L.M. Recurrent thromboembolic events after ischemic stroke in patients with cancer. *Neurology* **2014**, *83*, 26–33. [[CrossRef](#)]
20. Moore, R.A.; Adel, N.; Riedel, E.; Bhutani, M.; Feldman, D.R.; Tabbara, N.E.; Soff, G.; Parameswaran, R.; Hassoun, H. High incidence of thromboembolic events in patients treated with cisplatin-based chemotherapy: A large retrospective analysis. *J. Clin. Oncol.* **2011**, *29*, 3466–3473. [[CrossRef](#)]
21. Zareba, P.; Duivenvoorden, W.C.M.; Pinthus, H.J. Thromboembolism in Patients with Bladder Cancer: Incidence, Risk Factors and Prevention. *Bladder Cancer* **2018**, *4*, 139–147. [[CrossRef](#)]
22. Seng, S.; Liu, Z.; Chiu, S.K.; Proverbs-Singh, T.; Sonpavde, G.; Choueiri, T.K.; Tsao, C.-K.; Yu, M.; Hahn, N.M.; Oh, W.; et al. Risk of venous thromboembolism in patients with cancer treated with cisplatin: A systematic review and meta-analysis. *J. Clin. Oncol.* **2012**, *30*, 4416–4426. [[CrossRef](#)]
23. Czaykowski, P.M.; Moore, M.J.; Tannock, I.F. High risk of vascular events in patients with urothelial transitional cell carcinoma treated with cisplatin based chemotherapy. *J. Urol.* **1998**, *160 Pt 1*, 2021–2024. [[CrossRef](#)]
24. Fine, J.; Gray, R. A proportional hazards model for the subdistribution of a competing risk. *J. Am. Stat. Assoc.* **1999**, *94*, 496–509. [[CrossRef](#)]

25. Bamias, A.; Dafni, U.; Karadimou, A.; Timotheadou, E.; Aravantinos, G.; Psyrris, A.; Xanthakis, I.; Tsiatas, M.; Koutoulidis, V.; Constantinidis, C.; et al. Prospective, open-label, randomized, phase III study of two dose-dense regimens MVAC versus gemcitabine/cisplatin in patients with inoperable, metastatic or relapsed urothelial cancer: A Hellenic Cooperative Oncology Group study (HE16/03). *Ann. Oncol.* **2013**, *24*, 1011–1017. [[CrossRef](#)]
26. Ardavanis, A.; Tryfonopoulos, D.; Alexopoulos, A.; Kandylis, C.; Lainakis, G.; Rigatos, G. Gemcitabine and docetaxel as first-line treatment for advanced urothelial carcinoma: A phase II study. *Br. J. Cancer* **2005**, *92*, 645–650. [[CrossRef](#)]
27. Bamias, A.; Tiliakos, I.; Karali, M.-D.; Dimopoulos, M.A. Systemic chemotherapy in inoperable or metastatic bladder cancer. *Ann. Oncol.* **2006**, *17*, 553–561. [[CrossRef](#)]
28. Bellmunt, J.; Albiol, S. Chemotherapy for metastatic or unresectable bladder cancer. *Semin. Oncol.* **2007**, *34*, 135–144. [[CrossRef](#)]
29. Kaufman, D.S.; Carducci, M.A.; Kuzel, T.M.; Todd, M.B.; Oh, W.K.; Smith, M.R.; Ye, Z.; Nicol, S.J.; Stadler, W.M. A multi-institutional phase II trial of gemcitabine plus paclitaxel in patients with locally advanced or metastatic urothelial cancer. *Urol. Oncol.* **2004**, *22*, 393–397. [[CrossRef](#)]
30. Lin, C.-C.; Hsu, C.-H.; Huang, C.-Y.; Keng, H.-Y.; Tsai, Y.-C.; Huang, K.-H.; Cheng, A.-L.; Pu, Y.-S. Gemcitabine and ifosfamide as a second-line treatment for cisplatin-refractory metastatic urothelial carcinoma: A phase II study. *Anticancer. Drugs* **2007**, *18*, 487–491. [[CrossRef](#)]
31. Bamias, A.; Mouloupoulos, L.A.; Koutras, A.; Aravantinos, G.; Fountzilias, G.; Pectasides, D.; Kastiris, E.; Gika, D.; Skarlos, D.; Linardou, H.; et al. The combination of gemcitabine and carboplatin as first-line treatment in patients with advanced urothelial carcinoma. A Phase II study of the Hellenic Cooperative Oncology Group. *Cancer* **2006**, *106*, 297–303. [[CrossRef](#)] [[PubMed](#)]
32. Bellmunt, J.; Ribas, A.; Eres, N.; Albanell, J.; Almanza, C.; Bermejo, B.; Solé, L.-A.; Baselga, J. Carboplatin-based versus cisplatin-based chemotherapy in the treatment of surgically incurable advanced bladder carcinoma. *Cancer* **1997**, *80*, 1966–1972. [[CrossRef](#)]
33. Kyriakakis, Z.; Dimopoulos, M.A.; Kostakopoulos, A.; Karayiannis, A.; Sofras, F.; Zervas, A.; Giannopoulos, A.; Dimopoulos, C. Cisplatin, ifosfamide, methotrexate and vinblastine combination chemotherapy for metastatic urothelial cancer. *J. Urol.* **1997**, *158*, 408–411. [[CrossRef](#)]
34. Von der Maase, H.; Sengelov, L.; Roberts, J.T.; Ricci, S.; Dogliotti, L.; Oliver, T.; Moore, M.J.; Zimmermann, A.; Arning, M. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. *J. Clin. Oncol.* **2005**, *23*, 4602–4608. [[CrossRef](#)] [[PubMed](#)]
35. Dreicer, R.; Manola, J.; Roth, B.J.; See, W.A.; Kurosu, S.; Edelman, M.J.; Hudes, G.R.; Wilding, G. Phase III trial of methotrexate, vinblastine, doxorubicin, and cisplatin versus carboplatin and paclitaxel in patients with advanced carcinoma of the urothelium. *Cancer* **2004**, *100*, 1639–1645. [[CrossRef](#)] [[PubMed](#)]
36. Pistamaltzian, N.; Tzannis, K.; Pissanidou, V.; Peroukidis, S.; Milaki, G.; Karavasilis, V.; Mitsogiannis, I.; Varkarakis, I.; Papatsoris, A.; Dellis, A.; et al. Treatment of relapsed urothelial bladder cancer with vinflunine: Real-world evidence by the Hellenic Genitourinary Cancer Group. *Anticancer. Drugs* **2016**, *27*, 48–53. [[CrossRef](#)] [[PubMed](#)]
37. Dimopoulos, M.A.; Bakoyannis, C.; Georgoulas, V.; Papadimitriou, C.; Mouloupoulos, L.A.; Deliveliotis, C.; Karayannis, A.; Varkarakis, I.; Aravantinos, G.; Zervas, A.; et al. Docetaxel and cisplatin combination chemotherapy in advanced carcinoma of the urothelium: A multicenter phase II study of the Hellenic Cooperative Oncology Group. *Ann. Oncol.* **1999**, *10*, 1385–1388. [[CrossRef](#)]
38. McGale, P.; Darby, S.C.; Hall, P.; Adolphsson, J.; Bengtsson, N.O.; Bennet, A.M.; Fornander, T.; Gigante, B.; Jensen, M.-B.; Peto, R.; et al. Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden. *Radiother. Oncol.* **2011**, *100*, 167–175. [[CrossRef](#)]
39. Chen, P.C.; Muo, C.H.; Lee, Y.T.; Yu, Y.H.; Sung, F.C. Lung cancer and incidence of stroke: A population-based cohort study. *Stroke* **2011**, *42*, 3034–3039. [[CrossRef](#)]
40. Maduro, J.H.; den Dekker, H.A.; Pras, E.; de Vries, E.G.; van der Zee, A.G.; Klokman, W.J.; Reyners, A.K.; van Leeuwen, F.E.; Langendijk, J.A.; de Bock, G.H.; et al. Cardiovascular morbidity after radiotherapy or chemoradiation in patients with cervical cancer. *Int. J. Radiat. Oncol. Biol. Phys.* **2010**, *78*, 1337–1344. [[CrossRef](#)]
41. Chu, C.N.; Chen, S.W.; Bai, L.Y.; Mou, C.H.; Hsu, C.Y.; Sung, F.C. Increase in stroke risk in patients with head and neck cancer: A retrospective cohort study. *Br. J. Cancer* **2011**, *105*, 1419–1423. [[CrossRef](#)]
42. Moser, E.C.; Noordijk, E.M.; van Leeuwen, F.E.; le Cessie, S.; Baars, J.W.; Thomas, J.; Carde, P.; Meerwaldt, J.H.; Van Glabbeke, M.; Kluin-Nelemans, H.C. Long-term risk of cardiovascular disease after treatment for aggressive non-Hodgkin lymphoma. *Blood* **2006**, *107*, 2912–2919. [[CrossRef](#)]
43. Kuan, A.-S.; Chen, S.-C.; Yeh, C.-M.; Hung, M.-H.; Hung, Y.-P.; Chen, T.-J.; Liu, C.-J. Risk of ischemic stroke in patients with gastric cancer: A nationwide population-based cohort study. *Medicine* **2015**, *94*, e1336. [[CrossRef](#)]
44. Kuan, A.-S.; Teng, C.-J.; Wu, H.-H.; Su, V.-Y.; Chen, Y.-T.; Chien, S.-H.; Yeh, C.-M.; Hu, L.-Y.; Chen, T.-J.; Tzeng, C.-H.; et al. Risk of ischemic stroke in patients with ovarian cancer: A nationwide population-based study. *BMC Med.* **2014**, *12*, 53. [[CrossRef](#)]
45. Ramos, J.D.; Casey, M.F.; Crabb, S.J.; Bamias, A.; Harshman, L.C.; Wong, Y.N.; Bellmunt, J.; De Giorgi, U.; Ladoire, S.; Powles, T.; et al. Venous thromboembolism in metastatic urothelial carcinoma or variant histologies: Incidence, associative factors, and effect on survival. *Cancer Med.* **2017**, *6*, 186–194. [[CrossRef](#)]

46. Reardon, Z.D.; Patel, S.G.; Zaid, H.B.; Stimson, C.J.; Resnick, M.J.; Keegan, K.A.; Barocas, D.A.; Chang, S.S.; Cookson, M.S. Trends in the Use of Perioperative Chemotherapy for Localized and Locally Advanced Muscle-invasive Bladder Cancer: A Sign of Changing Tides. *Eur. Urol.* **2015**, *67*, 165–170. [[CrossRef](#)]
47. Goff, D.C., Jr.; Lloyd-Jones, D.M.; Bennett, G.; Coady, S.; D'Agostino, R.B.; Gibbons, R.; Greenland, P.; Lackland, D.T.; Levy, D.; O'Donnell, C.J.; et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* **2014**, *129*, S49–S73. [[CrossRef](#)]
48. Meschia, J.F.; Bushnell, C.; Boden-Albala, B.; Braun, L.T.; Bravata, D.M.; Chaturvedi, S.; Creager, M.A.; Eckel, R.H.; Elkind, M.S.V.; Fornage, M.; et al. Guidelines for the primary prevention of stroke: A statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* **2014**, *45*, 3754–3832. [[CrossRef](#)]
49. McSweeney, J.C.; Rosenfeld, A.G.; Abel, W.M.; Braun, L.T.; Burke, L.E.; Daugherty, S.L.; Fletcher, G.F.; Gulati, M.; Mehta, L.S.; Pettey, C.; et al. Preventing and experiencing ischemic heart disease as a woman: State of the science: A scientific statement from the American Heart Association. *Circulation* **2016**, *133*, 1302–1331. [[CrossRef](#)]
50. Brenner, B.; Bikdeli, B.; Tzoran, I.; Madridano, O.; López-Reyes, R.; Suriñach, J.M.; Blanco-Molina, Á.; Tufano, A.; Núñez, J.J.L.; Trujillo-Santos, J.; et al. Arterial ischemic events are a major complication in cancer patients with venous thromboembolism. *Am. J. Med.* **2018**, *131*, 1095–1103. [[CrossRef](#)]
51. Khorana, A.A.; Soff, G.A.; Kakkar, A.K.; Vadhan-Raj, S.; Riess, H.; Wun, T.; Streiff, M.B.; Garcia, D.A.; Liebman, H.A.; Belani, C.P.; et al. Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer. *N. Engl. J. Med.* **2019**, *380*, 720–728. [[CrossRef](#)]