original article

Factors associated with development of an acute ischemic event during hospitalization for COVID19- in cancer and non-cancer patients

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BACKGROUND: COVID-19 and solid cancer are both associated with an increased risk of thromboembolism.

OBJECTIVES: Assess whether solid cancer is a risk factor for acute ischemic event development among patients with COVID-19.

DESIGN: Retrospective cohort

SETTING: A tertiary training and research hospital

PATIENTS AND METHODS: Patients who were hospitalized for COVID-19 for ≥3 days between 15 March 2020 and 30 March 2021 at Antalya Training and Research Hospital, Antalya, Turkiye. were included in the study. Independent predictors of the development of acute ischemic events during hospitalization were determined using multivariable logistic regression analysis.

MAIN OUTCOME MEASURES: Risk factors for acute ischemic event development.

SAMPLE SIZE: 538 patients.

RESULTS: Patients diagnosed with solid cancer comprised 11.3% of the cohort (n=61). Forty-one (7.6%) developed an acute ischemic event at a median of 3 (range, 1-15) days after hospitalization. The presence of a solid cancer (OR 3.80, 95% CI 1.20-12.03, *P*=.023) along with length of hospital stay (OR 1.05 per day, 95% CI 1.01-1.09, *P*=.025) were independent predictors of acute ischemic event development during the course of COVID-19. Mortality was reported in 200 (37%) patients at a median of 5 (range, 3-10) days after hospitalization. The presence of solid tumor increased mortality 5.83 times (95% CI 3.19-10.63, *P*<.001) while this ratio was 4.59 (95% CI 2.29-9.23, *P*<.001) for patients who experienced an acute ischemic event.

CONCLUSION: Patients with active cancer carry a significant risk for acute ischemic event development during the course of COVID-19 and such patients may require particular attention in terms of anticoagulation therapy.

LIMITATIONS: Retrospective design and small sample size.

CONFLICT OF INTEREST: None.

Hypercoagulopathy is one of the characteristics of COVID-19, and may be responsible for a considerable number of deaths during the course of the disease.[1] The mechanism is complex and may include platelet activation, inflammation, immunologic events, endothelial dysfunction, and stasis, leading to arterial and venous thrombosis.[2,3] Patients have experienced pulmonary embolism, deep vein thrombosis, ischemic stroke, myocardial infarction, and peripheral arterial embolism during COVID-19 disease.[4-6] In a recent meta-analysis,[7] the frequency of venous thromboembolism and arterial embolism rates among 8271 COVID-19 sufferers were 21% and 2%, respectively. It has been proposed that COVID-19 patients with moderate-to-severe illness benefit from anticoagulation.[8]

Patients with cancer, particularly those of older age or with comorbidities or immunosuppression, may be at a higher risk of developing severe COVID-19.[9] Arterial and venous thromboembolism may occur in cancer patients due to the cancer itself, or as a side effect of therapies.[10] Cancer cells are capable of activating the coagulation cascade and other prothrombotic properties of host cells, and many anti-cancer treatments are known to promote thromboembolism.[11] The risk of thromboembolism in patients with hematological and solid cancer is four times higher than the normal population and particular chemotherapeutics bring additional risk.[12,13] Thromboembolism is the second leading cause of death in patients with cancer, after the cancer itself.[14] Furthermore, among cancer patients receiving chemotherapy, thromboembolism is the leading cause of death (9.2%).[15]

Both COVID-19 and cancer increase the risk of thromboembolism. The risk of developing an acute ischemic event may increase substantially in patients with cancer during the course of COVID-19. This is of considerable importance, since it has been shown that thromboembolism is associated with reduced overall survival in patients with cancer during COVID-19.[16] We hypothesized that among patients hospitalized for COVID-19, the presence of a recent history of cancer increases the risk of all types of acute ischemic events. This study aimed to test this hypothesis.

PATIENTS AND METHODS

Adult patients with a positive polymerase chain reaction (PCR) test for SARS-CoV-2, and were hospitalized for at least 3 days between 15 March 2020 and 30 March 2021 were included in the study. The study was conducted at Antalya Training and Research Hospital, a tertiary care hospital in Antalya, Turkey. Data were retrieved from electronic medical files. The presence of ''recent solid cancer'' was defined as the presence of an active solid cancer within the previous year.[16]

Severity of COVID-19 disease was determined according to the following: mild-to-moderate pneumonia with respiratory rate ≥24 and SpO_2 ≤93%; or mild-to-moderate pneumonia and blood lymphocyte count <800/μL or serum CRP >10 mg/L × upper limit of normal or ferritin >500 ng/mL or D-dimer >1000 ng/mL; or severe pneumonia (change of consciousness, respiratory distress, respiratory rate ≥ 30, SpO_2 ≤ 90% in room air, bilateral diffuse (>50%) involvement in lung imaging); or hypotension (<90/60 mmHg, mean blood pressure <65 mmHg) and tachycardia (>100); or sepsis, septic shock, myocarditis, acute coronary syndrome, arrhythmia, or acute kidney injury.[17] Exclusion criteria were a negative PCR test (even imaging findings were compatible with COVID-19 pneumonia); hematological cancer- metastatic cancer; active pregnancy; age <18 years old; 5) previous thrombolysis; platelet counts <50,000/mm^3; hemodialysis within 14 days; infection within 14 days; brain tumor; or unwilling to participate.

The term ''acute ischemic event'' was based on multiple mechanisms, including increased activation of both platelets and the coagulation system, and a mismatch between demand and supply of circulation. A number of radiological imaging techniques (arterial and/or venous Doppler ultrasound, CT angiography, and MRI) when particular symptoms suggested a diagnosis of an acute ischemic event.

A comparison for demographic and clinical characteristics was made between patient groups who had or had not experienced acute ischemic events. Subsequently, determinants of acute ischemic event development were assessed. Finally, the cohort was divided into four groups according to the presence of a recent history of solid cancer and acute ischemic event development during the course of COVID-19 as follows: 1) no cancer, no ischemic event; 2) ischemic event, no cancer, 3) cancer, no ischemic event; 4) cancer and ischemic event. This classification was made to capture any possible factor that may explain differences between cancer and non-cancer groups for acute ischemic event development. This study was approved by the local ethics committee. Informed consent was waived due to the retrospective design.

Variable distributions were assessed by the Kolmogorov–Smirnov test. Quantitative variables are expressed as mean standard deviation (SD) if normally distributed, or as median with the interquartile range (IQR 25-75%) for non-normal distributions. Qualitative variables are expressed as proportions. Means of con-

tinuous variables of patient groups who developed acute ischemic events, and those who did not were compared using t test or Mann–Whitney U test, depending on the normality of distribution. Means of continuous variables of the two groups were compared using the Kruskall-Wallis test. Bonferroni and Tamhane tests were used for post-hoc analysis. For comparisons between proportions chi-squared tests or the Fisher exact test were used, as appropriate. Multivariable logistic regression analysis was performed to determine independent predictors of acute ischemic event development. Variables that had a significant association with acute ischemic event development in the univariate analysis were included in the final multivariate model. A stepwise method was applied using backward elimination. Results were expressed as odds ratios and 95% confidence intervals. A *P* value of .05 was considered to be statistically significant. Statistical analysis was performed using IBM SPSS 22.0 version (IBM SPSS, Chicago, IL).

RESULTS

Five hundred and thirty-eight patients were included in the study. The median age of the entire cohort was 57 years, ranging from 19 to 94 years; 320 (60%) were males (**Table 1**). Patients with solid cancer comprised 61 (11%) of patients. The most common cancer types were lung (16 patients, 26%), breast (10 patients, 16%), and colorectal (7 patients, 11%) cancers. Types of cancers and treatment type of patients are provided in the **Supplemental Table**. Treatment of patients with COVID-19 (not only severe COVID-19, but all patients with COVID-19) included a mixture of glucocorticoids (184 patients, 34%), hydroxychloroquine (83 patients, 15%), favipiravir (424 patients, 79%), and remdesivir (4 patients, 0.7%). Within the entire cohort of 538, most of the patients (286 patients, 53%) had severe COVID-19. In cancer patients, the rate of severe COVID-19 was 83.6%. Of the 185 (34.3%) transferred to the intensive care unit, 40 (65.5%) had cancer .

During the median follow up of 5 (3-10) days, 41 (7.6%) developed an acute ischemic event at a median of 3 (range, 1-15) days after hospitalization. These included acute coronary syndrome (n=9), acute ischemic stroke (n=16), acute limb ischemia (n=5), and pulmonary embolism (n=11). Patients with acute ischemic events were more likely to be older, have a higher Charlson comorbidity index, solid tumor, lower hemoglobin, lower lymphocyte count, higher serum CRP, to require glucocorticoid therapy, have severe COVID-19 pneumonia, require intensive care support, and have a longer hospital stay. Thirty-four of 286 (12%) patients with severe COVID-19 developed an acute ischemic event, while this rate was 3% (7 of 252 patients) among patients who did not have severe COVID-19 (*P*<.001). Of the 185 patients who required ICU admission, 27 (15%) experienced acute ischemic event. In comparison, 14 of 353 (4%) who did not need ICU support had an acute ischemic event (*P*<.001).

Older age, a higher Charlson comorbidity index, presence of solid tumor, longer hospital stays, admission to ICU, treatment with corticosteroids, lower hemoglobin and lymphocyte levels, a higher serum CRP, and severe COVID-19 pneumonia were associated with acute ischemic event development in the univariate analysis (**Table 2**). Presence of a solid tumor (OR 3.80, 95% CI 1.20-12.03, *P*=.023) along with total days in hospital (OR 1.05 per day, 95% CI 1.01-1.09, *P*=.025) were independent predictors of acute ischemic event development during the course of COVID-19 in the multivariate regression analysis. There was no significant association between a particular type of cancer and development of an acute ischemic event. There was no statistical association between a particular type of cancer and a particular type of ischemic event. **Table 3** shows differences for clinical characteristics of patients between groups with no cancer and no acute ischemic event, acute ischemic event without cancer, cancer without acute ischemic event, and cancer plus acute ischemic event. In general, demographic and clinical findings such as age, severity of COVID-19, serum CRP levels, and ferritin levels were more unfavorable in groups with cancer and/or an acute ischemic event.

Mortality occurred in 200 (37%) patients at a median 5 (3-10) days of hospitalization. Patients with solid tumor (73.7% versus 32.4%), *P*<.001) or with an acute ischemic event during the hospital stay (71% versus 34%, *P*<.001) were more likely to die. The odds ratio of solid tumor for mortality was 5.83 (95% CI 3.19-10.63, *P*<.001) while it was 4.59 (95% CI 2.29-9.23, *P*<.001) for those who experienced an acute ischemic event. Twenty-nine of 200 (15%) of patients who had mortality experienced an acute ischemic event, while this rate was 4% (12 of 337) in patients who lived (*P*<.001).

DISCUSSION

While both cancer and COVID-19 are disease states that are usually characterized by increased tendency to thrombosis, it is not known to what extent the risk increases with their coexistence. In our study, the rate of thrombosis among patients with cancer was considerably higher than in those without cancer (36.5% vs 9.2%). Moreover, a recent history of solid cancer was

Table 1. Demographic and clinical characteristics of patients.

Variables	All cohort (n=538)	Acute Ischemia (n=41)	No Ischemia (n=497)	*P* value
Age (years)	57 (28.8, 19-94)	65 (17, 34-87)	56 (30, 19-94)	**.004**
Male sex	320 (59.4)	28 (68.2)	292 (58.7)	.232
History of smoking	208 (38.6)	21 (51.2)	187 (37.6)	.086
Charlson comorbidity index	1 (1-3)	3 (1-3)	1 (1-2)	**<.001**
Comorbidities				
Diabetes mellitus	96 (17.8)	7 (17)	89 (17.9)	.893
Hypertension	135 (25)	12 (29.2)	123 (24.7)	.521
Hyperlipidemia	219 (40.7)	22 (53.6)	197 (39.6)	.079
Obesity	175 (32.5)	8 (19.5)	167 (33.6)	.064
Solid tumor	61 (11.3)	15 (36.5)	46 (9.2)	<.001
History of acute ischemia	37 (6.8)	3 (7.3)	34 (6.8)	.908
Severe COVID-19	286 (53.1)	34 (82.9)	252 (50.7)	**<.001**
Treatments during COVID-19				
Anti-platelet	25 (4.6)	2 (4.8)	23 (4.6)	.942
Low-molecular weight heparin	42 (78.3)	35 (85.3)	386 (77.8)	.259
Glucocorticoids	184 (34.2)	27 (65.8)	157 (31.5)	**<.001**
Hydroxychloroquine	83 (15.7)	5 (12.1)	78 (15.6)	.551
Favipiravir	424 (78.8)	34 (82.9)	390 (78.4)	.502
Remdesivir	4 (0.7)	0	4 (0.8)	-
Immune plasma	19 (3.5)	1 (2.4)	18 (2.6)	.693
Anti-IL-6	7 (1.3)	0	7 (1.4)	-
Laboratory parameters				
White blood cell count ($10^3/mm^3$)	6.7 (4.9-10.2)	8.8 (5.9-16.3)	6.5 (4.9-10.0)	**.006**
Hemoglobin (g/dL)	12.9 (7.1)	11.6 (2.7)	13.0 (7.4)	**.009**
Platelet ($10^3/mm^3$)	219 (97)	193 (102)	221 (97)	.091
Lymphocyte (%)	16.8 (8.6-26.8)	10.9 (6.6-20.1)	17.1 (8.8-27.6)	**.008**
C-reactive protein (mg/L)	46 (10-121)	112 (32-222)	53 (11-126)	**.009**
D-Dimer (µg/L)	245 (140-560)	463 (272-1725)	232 (135-527)	**<.001**
Ferritin (µg/L)	153 (56-367)	544 (109-1079)	145 (50-330)	**<.001**
Serum creatinine (mg/dL)	1.00 (0.8-1.2)	1.09 (0.90-1.49)	0.99 (0.80-1.22)	**.019**
Serum albumin (g/dL)	3.6 (0.8)	2.9 (0.7)	3.6 (0.8)	**<.001**
Admission to intensive care unit	185 (34.3)	27 (65.8)	158 (31.7)	**<.001**
Hospitalization (days)	5 (3-10)	11 (6-18)	5 (3-10)	**<.001**

Data are n (%), mean (standard deviation) or median (interquartile range, minimum-maximum).

Table 2. Univariate and multivariable logistic regression analysis of acute ischemic events among hospitalized patients diagnosed with COVID-19.

Variable	Univariate			Multivariable		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age	1.03	1.01-1.05	**.005**	1.01	0.99-1.03	.710
Charlson comorbidity index (per 1 point increase)	1.44	1.15-1.80	**.001**	1.08	0.93-1.33	.550
Solid tumor	5.66	2.80-11.44	**<.001**	3.80	1.20-12.03	**.023**
ICU admission	4.14	2.11-8.11	**<.001**	1.45	0.55-3.83	.459
Total days in hospital	1.06	1.03-1.10	**<.001**	1.05	1.01-1.09	**.025**
Hemoglobin (per 1 g/dL increase)	0.83	0.73-0.94	**.004**	0.91	0.77-1.07	.910
Lymphocyte (per 100/mm^3 increase)	0.96	0.93-0.99	**.010**	1.01	0.97-1.05	.686
C-reactive protein (per 10 mg/L increase)	1.00	1.00-1.01	**.021**	1.00	1.00-1.01	.968
Corticosteroid therapy	4.18	2.13-8.18	**<.001**	1.49	0.61-3.64	.378
COVID-19 severity	4.72	2.06-10.85	**<.001**	1.77	0.59-5.23	.310

Multivariable model fit statistics: Omnibus test of model coefficients (P=.004), deviance= 281.564 , Cox & Snell R Square = .015 , Nagelkerke R Square =.037.

an independent predictor of thromboembolism development along with a longer hospital stay. Interestingly, in another study that included 45 patients with cancer who were hospitalized for COVID-19, findings were different; the rate was even higher in those who did not have cancer (14% versus 18%).[18] Different patient and cancer characteristics may explain discrepancies between studies.

In a study from China,19 205 patients with cancer who suffered COVID-19, the most common types of solid cancers were breast (20%), colorectal (14%), and lung (12%). Lung cancer was the most common type in our study, comprising 33% of our patients. One would expect to see a higher incidence of thromboembolism among particular types of cancers, but we found no association, which might be related to the few patients with each type of cancer.

The frequency of the type of ischemic event differs between studies. Pulmonary embolism, acute ischemic stroke, acute coronary syndrome, and acute limb ischemia occurred in 2%, 2.9%, 1.6%, and 0.9% of our cases, respectively. A similar study reported a higher incidence of stroke with 2.5% and a lower incidence of acute coronary syndrome with 1.1%.[20] A study by Poissy and colleagues reported a much higher incidence of pulmonary embolism, over 20%.[21] Frequent use of angiographic methods for a diagnosis of pulmonary embolism in their study probably helped to detect all cases. Thus, in addition to patient characteristics, usage of different diagnostic methods may also explain such differences between studies.

Compared to the overall cohort of our study, patients with solid cancer more commonly experienced an ischemic event (7.6% versus 24.5%). Zavras and colleagues reported an ischemic event in 12.2% of their patients with cancer who suffered from COVID-19.[16] They reported a similar incidence of thrombosis for hematologic and solid malignancies. Similarly, the presence of metastasis did not bring an additional risk for thrombosis. Hematological malignancy or the presence of metastatic cancer were some of the exclusion criteria in our paper, due to possible bias. The rate of acute ischemic event among patients who needed intensive care support was 14.5% (versus 7.6% in the overall cohort). While intensive care unit admission was significantly associated with thromboembolism development in the univariate analysis in our cohort, statistical significance was lost after adjustments for other variables. Zavras et al found no statistically significant association between intensive care unit requirement and thromboembolism.[16] According to the study by Lodigiani and colleagues, the rate of thromboembolism was significantly higher among hospitalized COVID-19 patients who needed intensive care (6.4% versus 27.6%).[20]

Table 3. Clinical characteristics of patients between groups with no cancer and no acute ischemic event (Group 1, n=451), acute ischemic event without cancer (Group 2, n=26), cancer without acute ischemic event (Group 3, n=46), and cancer plus acute ischemic event (Group 4, n=15).

Variable	Group 1 (No cancer, no ischemic event, n=451)	Group 2 (Ischemic event, no cancer, n=26)	Group 3 (Cancer, no ischemic event, n=46)	Group 4 (Cancer and ischemic event, n=15)	*P*
Age	54.0 (39.0-68.0)	61.5 (53.3-71.0)	68.0 (58.0-76.0)	67.0 (58.5-72.5)	<.001[a]
Male sex	263 (58.3)	19 (73)	29 (63)	9 (60)	.477
History of smoking	178 (39.4)	15 (57.6)	9 (19.5)	6 (40)	.011
Charlson comorbidity index	1 (1-2)	1 (1-2)	4 (3-5)	4 (3-4)	<.001[b,c,d]
Comorbidities					
Diabetes mellitus	81 (17.9)	4 (15.3)	8 (17.3)	3 (20)	.983
Hypertension	112 (24.8)	7 (26.9)	11 (23.9)	5 (33.3)	.888
Hyperlipidemia	174 (35.5)	12 (46.1)	23 (50)	10 (66.6)	.072
Obesity	154 (34.1)	4 (15.3)	13 (28.2)	4 (26.6)	.200
History of acute ischemia	30 (6.6)	2 (7.6)	4 (8.6)	1 (6.6)	.960
Severe COVID-19	216 (47.8)	19 (73)	36 (78.2)	15 (100)	<.001
Treatments for COVID-19					
Anti-platelet	20 (4.4)	1 (3.8)	3 (6.5)	1 (6.6)	.900
Low molecular weight heparin	347 (77.1)	23 (88.4)	39 (84.7)	12 (80)	.373
Glucocorticoids	127 (28.1)	17 (65.3)	30 (65.2)	10 (66.6)	<.001
Hydroxychloroquine	78 (17.2)	5 (19.2)	0	0	-
Favipiravir	381 (84.4)	24 (92.3)	9 (19.5)	10 (66.6)	<.001
Remdesivir	4 (0.8)	0	0	0	-
Immune plasma	18 (3.9)	1 (3.8)	0	0	-
Anti-IL-6	7 (1.5)	0	0	0	-
White blood cell count (10^3/mm^3)	6.5 (4.9-9.2)	8.0 (5.6-12.9)	11.1 (5.8-19.7)	12.6 (8.6-19.5)	<.001[b]
Hemoglobin (g/dL)	13.2 (7.7)	12.6 (2.5)	10.9 (2.2)	9.8 (2.2)	<.001[b,c]
Platelet (10^3/mm^3)	222 (93)	200 (89)	212 (124)	182 (125)	.154
Lymphocyte (%)	18.2 (9.9-28.4)	16.6 (6.6-22.1)	8.9 (5.0-14.9)	8.3 (4.7-13.5)	<.001[b,c]
C-reactive protein (mg/L)	37 (7.5-111)	54 (14-186)	109 (32-187)	174 (70-230)	<.001[b,c]
D-Dimer (µg/L)	217 (127-426)	391 (192-1113)	1021(635-2159)	733 (418-3275)	<.001[b]
Ferritin (µg/L)	143 (46-311)	132 (84-668)	349 (129-875)	1544(885-2173)	<.001[c,e]
Serum creatinine (mg/dL)	0.98 (0.80-1.19)	1.05 (0.91-1.53)	1.20(0.90-1.60)	1.10(0.90-1.50)	<.001[b]
Serum albumin (g/dL)	3.7 (0.7)	3.2 (0.8)	2.9 (0.6)	2.6 (0.5)	<.001[b,c]
Admission to intensive care unit	131 (29)	14 (53.8)	27 (58.6)	13 (86.6)	<.001
Days in hospital (days)	5 (3-10)	12 (7-19)	7 (4-9)	7 (5-16)	<.001[a,d]

Data are n (%), mean (standard deviation) or median (25th-75th percentile). Letters denote statistically significant differences for means or medians of continuous variables between groups; [a]Groups 1 and 2; [b]Groups 1 and 3; [c]Groups 1 and 4; [d]Groups 2 and 3; [e]Groups 2 and 4; [f]Groups 3 and 4.

One of our observations was the association between the presence of solid tumor or acute ischemic event development during the hospital stay. In the study of Zavras and co-workers, patients who experienced thrombosis were more likely to die (81% vs 47%).[16] While ischemia was associated with an increased risk of death in the overall cohort, this association did not reach statistical significance in the subgroup of cancer patients. Some characteristics of patients with cancer such as being elderly or having a severe COVID-19 pneumonia may increase the risk of an acute ischemic event irrespective of the cancer itself. Many other findings such as lower hemoglobin, and lymphocyte count, and higher serum ferritin, CRP, and D-dimer levels, and more frequent admission to the ICU were observed in cancer groups. Moreover, our patients with cancer were older and had more severe COVID-19. However, the association between cancer and acute ischemic event development remained significant after adjustment for such important factors. While some traditional risk factors for ischemia development were more commonly observed in patients who experienced acute ischemic events, results were not statistically significant. In addition to the low sample size in subgroups, lack of significance may be explained by different mechanisms of ischemia development during the course of COVID-19. For instance, most arterial thrombosis events are due to a combination of factors, and the majority are related to a mismatch between the demand and supply of circulation (ie, secondary myocardial infarction).[22] For this reason, traditional risk factors for thrombosis may not have the same impact in these events. Also, ischemia groups were composed of combinations of patients with arterial and venous events, which have different pathogeneses and correspondingly unique risk factors.

We recognize the limitations of our study. The subgroup of patients who experienced acute ischemic events was small, and data was obtained from electronic medical records. Despite these limitations, we showed that among numerous important variables, a history of solid tumor was an independent predictor of thromboembolism development during the course of COVID-19. Effects of cancer treatments and vaccines could not be determined due to the lack of data. While ischemic events were associated with an increased risk of mortality in the overall cohort, we could not demonstrate this specifically in the subgroup of patients with cancer, probably due to the small sample size. Study sample size was enough to demonstrate significant results, however, collaboration with other centers would strengthen the reliability of our results. In conclusion, the presence of recently diagnosed patients with solid cancer is associated with development of an acute ischemic event among patients who suffer from COVID-19. Cancer patients with COVID-19 may require a more specific management in terms of anticoagulation.

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Supplementary Table. Types of cancers and treatment if treated.

Cancer type	Number (%)	CT	IT+CT	IO	TT	TT+CT	TT	RT+CT	RT
Lung	16 (27)	9	1	1	-	-	1	3	1
Gastrointestinal	16 (27)								
Colorectal	7(11)	3	-	-	-	3	-	-	-
Pancreas	2 (3)	2	-	-		-	-	-	-
Biliary tract	2 (3)	2	-	-	-	-	-	-	-
Stomach	4 (7)	1	-	-	-	2	-	1	-
Liver	2 (3)	-	-	-	-	-	2	-	-
Genitourinary	10 (16)								
Prostate	3 (5)	1	-	-	2	-	-	-	-
Ovary	3 (5)	2	-	-	-	1	-	-	-
Bladder	2 (3)	2	-	-	-	-	-	1	-
Renal	1 (2)	-	-	-	-	-	1	-	-
Testicular	1 (2)	1	-	-	-	-	-	-	-
Other	18 (30)								
Breast	10 (16)	6	-	-	2	1	1	-	-
ENT	5 (8)	-	-	-	-	2	-	3	-
Skin	2 (2)	-	-	-	-	-	-	1	1
Mesothelioma	1 (2)	1	-	-	-	-	-	-	-

CT: chemotherapy; ENT: Ear-Nose-Throat,IT: Immunotherapy, RT: Radiotherapy, TT: Targeted-therapy