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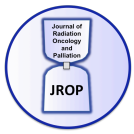

ORIGINAL ARTICLE **Open Access**

Prognostic importance of d-dimer value in cancer patients undergoing radiotherapy

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ABSTRACT

BACKGROUND: *When D-dimer value increasing, first of all suggests the possibility of clotting disorders and venous tromboembolism, cardio vascular diseases. Cancer and other disorders must be considered ıf there is no thromboembolic diseases.*

METHODS: *Histopathologically diagnosed stage III-IV cancer patients have d-dimer values who undergone radiotherapy were included in this study.*

Key woeds: *d-dimer, cancer, radiotherapy*

Ethical approve: *Ethical approve was taken from ethical board of Başakşehir Çam and Sakura City Hospital*

Conflict of Interst: *There is no any conflict of interest between persons or companies.*

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INTRODUCTION

D-dimer is a fibrin degradation product formed by fibrinolytic activity. Therefore, when it increases and clinical findings support this, venous thromboembolism is the first disease that comes to mind (1). If there is no thromboembolism, infectious diseases, especially cancer, trauma, severe atherosclerotic diseases and pregnancy in young women should be considered. D-dimer may also increase after surgeries and trauma (2,3-5). Studies have shown that there is an important relationship between cancer and hemostasis. Unlike usual in cancer, thromboembolism occurs independently of venous thromboembolism and with a systemic activation (6,7).

Fibrin, which is necessary for the formation of tumor stroma, begins to increase even when the tumor is still very small. This occurs with local stimulation of the tumor. As the tumor grows, the increase in fibrin has a procoagulant effect. As a result of the formation of complex aggregates by the interaction of

fibrin, platelets and tumor cells with a systemic effect, tumor thrombi may form by increasing the adhesiveness of the vascular endothelium (8-10.4-6). As fibrin degradation products stimulate angiogenesis, the tumor grows and the metastatic potential increases. Sometimes, even when the tumor is still small, widespread metastases can be seen with excessive activity (11). Therefore, high d-dimer level may be important in showing the stage and prognosis of the disease (12-15).

MATERIAL AND METHODS

We conducted this retrospective study in order to detect widespread metastases that cannot be detected even with PET CT at the time of initial diagnosis of cancer or during follow-up of patients, to determine the true stage of the disease and to facilitate diagnosis.

Study design and study population

In this study, the prognostic importance of d-dimer level was investigated retrospectively in patients who received radiotherapy whose d-dimer level was measured.

Histopathologically diagnosed stage III-IV cancer patients were included in the study. Patients with severe bacterial or viral infection, a history of thromboembolism within the last month, and patients using anticoagulants were excluded from the study. In addition to d-dimer values, the patient was also evaluated according to fibrinogen, prothrombin time, CRP, ferritin, IL-6, lymphocyte percentage, RT daily and total dose and number of fractions, and whether or not he received CT. Patient characteristics are shown in Table 1.

Table 1. Demographic characters of patients

Characters	Patient numbers	%
Age		
34-85	52	100
Stages		
III	30	57.69
IV	22	42.31
Performances		
ECOG		
II	24	46.15
III	17	32.69
IV	11	21.16

Statistical analyses

Çok değişkenli Cox regresyon analizi ile, yaş, tümör yeri, evresi, ECOG performansı, RT dozu ve fraksiyon sayısı gibi hastaya ve tedavisine ait diğer özellikler analiz edildi. Man Witney U, Kruskal Wallis testleri ile de alt grup analizleri yapıldı. P <0.05 istatistiksel olarak anlamlı kabul edildi.

Kaplan-Meier yöntemi, D-dimer seviyeleri ve genel sağ kalım arasındaki ilişkiyi göstermek için kullanıldı. Tüm istatistiksel hesaplamalar SPSS version 23.0 (SPSS, Chicago, IL, USA) ile gerçekleştirildi.

Ethical approvel

Ethical approve was taken from ethical board of Başakşehir Çam and Sakura City Hospital .

RESULTS

The median D-dimer level was 1 µg/mL. The median D-dimer level was 1.1-2 µg/mL in patients with lung cancer and 1 µg/mL in breast cancer. The median d-dimer level was found to be 0.4-1 µg/mL in gastrointestinal system (GIS) cancers and 0.1-0.3 µg/mL in head and neck cancers. The median d-dimer level was determined as 0.4-1 µg / mL in patients with adenocarcinoma pathology and 1-2.1 µg / mL in squamous cell cancer. The median D-dimer level was found to be 1.1-2 µg/mL in patients with distant metastases. The median D-dimer level was found to be 1.1-2 µg/mL in patients with additional comorbid cardiovascular disease. In cancer patients with elevated D-dimer and anticoagulation with low molecular weight heparin, median survival increased by 2 months. It has been determined that d-dimer elevations due to cardiovascular problems are concentrated at the level of 1.1-2 µg/mL values.

Survival rates according to the RT doses and fractions applied to the patients are shown in Table 2.

Table 2. Survival rates according to RT doses and fractions applied to patients

RT	Patient number	Median d-dimer (µg / mL)	Median survival (months)
Number of fract. and dose (cGy)			
15-37x160-200	32	0.3	22
8-18x250	10	1.6	15
8-10x300	5	1.6	4
8-13x350	3	2.1	2.5
5-6x400	2	3.7	2

Fract: Fraction

Survival rates according to d-dimer values in all patients are shown in Table 3.

Table 3. Survival rates according to d-dimer values in all patients

D-dimer (µg / mL)	Patient number	%	Median survival (months)
0.1-0.3	19	36.53	23
0.4-1	7	13.46	16
1.1-2	11	21.15	8
2.1-3	6	11.53	10
3.1-24	9	17.30	5

Table 4 shows d-dimer values and median survival rates in metastatic patients.

Table 4. D-dimer values and median survival in metastatic patients

D-dimer (µg / mL)	Patient number	%	Median survival (months)
0.1-0.3	3	13.6	22
0.4-1	2	9.09	15
1.1-2	7	31.81	7
2.1-3	2	9.09	15
3.1-4	3	13.6	2
4.1-5	2	9.09	2
5.1-10	1	4.54	3
10.1-24	2	9.09	1
0.1-24	22	100	7

Survival rate of patients according with d-dimer levels shown (Figure 1).

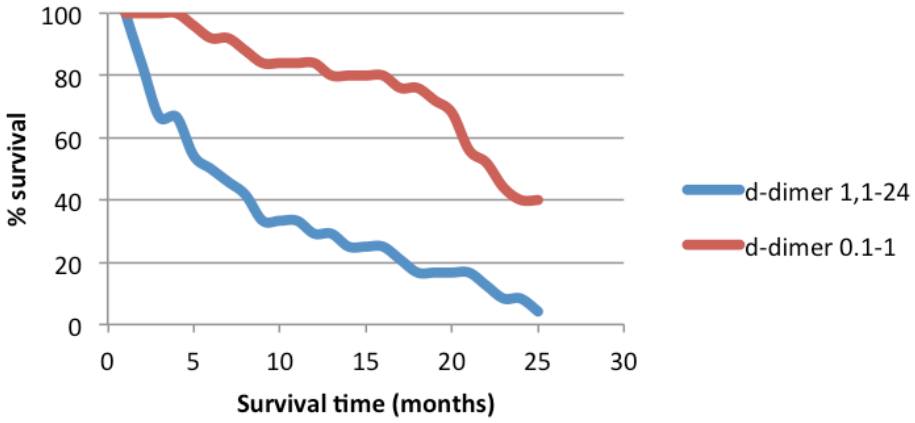

Figure 1. Survival rate of patients according to d-dimer rates

Venous thrombo embolization (VTE) developed in 11 (21.25%) of the study population during follow-up. Disseminated intravascular coagulation (DIC) developed in 22 of the 28 patients (78.57%) who died in the last month. Anticoagulation was performed with low molecular weight heparin in 25 (48.07%) of the patients with a D-dimer level of 1 or above.

Statistical analyses

The overall survival curve according to d-dimer levels using the Kaplan-Meier method is shown in Figure 1. Overall survival time was found to be significantly lower in patients with high d-dimer levels (P <0.0001). D-dimer value has been determined as an independent prognostic factor for survival rates in cancer patients. In palliative patients, survival was found to be significantly lower in patients receiving hypofractionated RT between 300-400 cGy compared to 250 cGy fraction dose (P <0.0001) (Table 2). Survival rates were found to be significantly lower in patients with high ECOG, IL-6 cytokine, CRP and ferritin levels. Survival rates were significantly lower in patients with low lymphocyte percentages than in those with high lymphocyte percentages (P <0.0001). Survival rates were found to be significantly higher in patients with high D-dimer values and those who underwent CT (P <0.001). In metastatic patients, median survival was 7 months in patients with d-dimer levels of 0.1-24 µg/mL and 1.1-2, while it was 15 months in patients with 2.1-3.

DISCUSSION

Argument In this study, it was shown that high plasma d-dimer levels were associated with an increased risk of mortality. D-dimer values were found to be higher, especially in advanced stage and metastatic cancer. At the end of 24 months of follow-up, survival rates were found to be significantly lower than in patients with low d-dimer values. The prognosis was significantly worse, especially in patients with d-dimer values of 3 and above. Survival rates were found to be lower in patients with d-dimer values between 1.1-2 µg/mL compared to 2.1-3, probably due to the contribution of comorbid cardiological problems. Because it was determined that

d-dimer increases due to cardiovascular problems were concentrated at the level of 1.1-2 µg / mL. In this study, the median survival in metastatic patients with d-dimer values between 0.1-0.3 and 0.4-1 µg / mL is 22 and 15 months, respectively, showing that even in palliative patients, a low d-dimer value has a significantly positive effect on life. However, when looked at in general, regardless of d-dimer value, it has been statistically shown that survival rates in metastatic patients are significantly lower. Although the findings in other cancers in this study were found to be compatible with studies in the literature, the lower d-dimer values in breast cancer patients compared to those in the literature may be due to the low number of patients with breast cancer in this study (13,14). It was previously predicted that d-dimer values were only associated with VTE. When anticoagulation with low molecular weight heparins was applied to these patients, it was observed that it did not prolong life significantly. For this reason, it was reported that d-dimer value may be a factor that can indicate cancer-specific progression (3,15). In this study, it was shown that elevated d-dimer may increase progression and metastases, regardless of VTE. Conventional RT doses and fractions were applied in patients with low d-dimer values, but higher dose hypofractionated RT methods such as 250-400 cGy were preferred in palliative patients. In patients with high D-dimer values, worse results were obtained with high-dose hypo-fractionated treatments compared to treatments with 250 cGy or lower fraction doses. It has been reported that anticoagulation with low molecular weight heparins has positive effects on the survival of cancer patients with elevated d-dimer (16). In a small study involving 40 patients with colorectal cancer, d-dimer levels were reported to be associated with postoperative survival time (17). It has also been reported that d-dimer levels increase in breast cancer patients in correlation with lymph node metastasis, stage, lymphovascular invasion and tumor burden (18-20)). D-dimer Levels in ovarian cancer patients with high CA-125 values It has been shown that n also increases in parallel. Similarly, it has been reported that the carcino-embryonic antigen (CEA) level parallels the d-dimer level in colorectal cancer (17). Although studies have shown that the D-dimer value has prognostic properties in cancer patients, it has not yet become widely accepted (18-25). The most important reason for this is that it is claimed that it is difficult to differentiate since it can also increase due to reasons other than cancer. However, studies show that d-dimer value is an independent prognostic factor in cancer. To prevent misconceptions on this subject, more randomized studies should be conducted in separate and homogeneous groups for each cancer.

CONCLUSION

Although this study is small and heterogeneous, statistically determining the d-dimer value as an independent prognostic factor may shed light on the literature.

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