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Von willebrand factor plasma level and bleeding scale score before and after radiation therapy for cancer-related bleeding

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Abstract. Radiation therapy has long been used to treat the cessation of cancer-related bleeding. The von Willebrand factor (vWF) plasma level has a major role in initiating platelet adhesion in hemostasis. This study investigated the changes in bleeding response before and after irradiation, the difference in the vWF plasma levels before and after irradiation, and the correlation between the vWF plasma level and bleeding response. Subjects were 23 patients with cancer-related bleeding who received hemostatic irradiation and met other inclusion criteria. Blood samples were taken before and after hemostatic irradiation to examine the vWF plasma levels and the World Health Organization (WHO) bleeding scale score. Two patients died during the study because of the bleeding. The success rate of hemostatic irradiation in stopping bleeding was 91.3%. Hemostatic irradiation significantly decreased the WHO bleeding scale score and significantly increased the vWF plasma level. The increased vWF plasma level was significantly correlated with the decreased WHO bleeding scale score before and after irradiation. Hemostatic irradiation is effective in stopping cancer-related bleeding and has become the preferred modality for the treatment of cancer-related bleeding.

1. Introduction
Malignancy-related bleeding is very disturbing for the patient and their family and is one of the main reasons for visiting a health service center. The incidence of bleeding in patients with advanced cancer is 6%–10% [1,2]. This bleeding can result in death; therefore, treatment must be quick and precise. Radiation has long been used to stop such bleeding, but few published studies have focused on hemostatic irradiation [2].

Von Willebrand factor (vWF) is one of the proteins that initiate platelet adhesion because of injury in endothelial cells. The vWF molecule is synthesized and expressed exclusively in the Weibel–Palade body of endothelial cells and α granules of megakaryocytes, and vWF forms through constitutional
and regulatory pathways [3]. vWF levels in healthy people range widely (50–200 IU/dL). Under normal circumstances, vWF is always formed through a constitutional pathway in which vWF molecules are synthesized as soon as possible after synthesis was completed [3-5].

Under normal circumstances, vWF molecules function as carriers of coagulation factor VIII and as recruiters of platelets in states of high shear stress. These molecules also express mitogenic activity in smooth muscle cells, inducing apoptosis in platelets and tumor cells, and are negative modulators of angiogenesis [6]. vWF plasma levels can be used as an index of endothelial damage in vascular disorders [7,8]. Matured vWF molecules have a half-life of 12–18 hours [8].

In 1994, Verheij et al. conducted an in vitro study using endothelial cells isolated from human umbilical vein and found an increased release of vWF in the culture medium, as well as a significant increase in platelet adhesion within 48 hours, after 20 Gy irradiation [5]. In a 1998 in vivo study, van Kleef et al. subjected female mice to renal irradiation; then, the kidneys were removed, and the glomerulus was assessed immunohistochemically [9]. They found an increase in vWF expression in the kidneys, which caused the formation of thrombus and thereby increased the risk of vascular occlusion [9]. After several weeks to hours of irradiation, the capillary wall permeability was increased in association with the appearance of mild edema [10]. Localized edema might be seen after a single radiation dose of 5 Gy or more, with vascular changes peaking in the first 2 weeks after exposure to single-dose radiation [11]. In addition, it is also known that radiation produces a sealing effect by causing fibrosis in the vascular source of the bleeding [12].

Several studies have shown that the vWF level is higher in patients with malignancies than in healthy people; thus, an increased vWF level could be used as a predictor of tumor progression. In a 2002 comparative study, Damin et al. found that vWF plasma levels were higher in patients with colorectal cancer than in healthy people and that elevated vWF levels tended to be associated with tumor progression [13]. In 2001, Rohsig et al. demonstrated that elevated vWF plasma levels were correlated with breast cancer progression [14]. In 1996, Zietek et al. showed that vWF plasma levels can be used as a predictor of progression of invasive forms of bladder cancer and as a predictor for non-invasive transformation to invasive form [15]. In none of these studies, however, was vWF plasma level in patients with cancer-related bleeding investigated in relation to hemostatic irradiation.

Regarding the clinical parameters of bleeding, there has been no universal agreement on the quantification of bleeding yet. Researchers throughout the world report bleeding in various ways. The scale most commonly used as a bleeding assessment standard is the World Health Organization (WHO) bleeding scale, which is used to report toxicity in cancer treatment. To assess the degree of bleeding with malignancies, Miller et al. used clinical parameters with the WHO bleeding scale [16]. In 2012, Bercovitz and O’Brien revealed that there was still difficulty in determining the reliability of the WHO bleeding scale because no comparative studies had been conducted, which, in turn, was because of the complexity and accuracy in assessing bleeding clinically [16].

Comparative and controlled trial studies of hemostatic irradiation have been limited. This study was expected to account for the effectiveness of radiation as one of the modalities in stopping bleeding due to malignancy. The study was also conducted to explore information on vWF plasma levels and WHO bleeding scale scores before and after hemostatic irradiation, as well as the correlations between them.

2. Methods
This study was conducted at the Department of Radiotherapy, Dr. Cipto Mangunkusumo Hospital, Jakarta, and this study lasted for approximately seven months. The certificate of passing the ethical test was obtained from the Health Research Ethics Committe of the Faculty of Medicine, Universitas Indonesia-Dr Cipto Mangunkusumo Hospital.

This investigation was a pre–post study design without comparison to assess the association of vWF plasma level with hemostatic response after hemostatic irradiation in cases of tumor bleeding. The vWF plasma levels were measured before and after irradiation. Clinical evaluation before and after irradiation was assessed with the WHO bleeding scale. Then, the correlation between the difference in vWF levels and change in the WHO bleeding scale score was tested.
The subjects were all adults with cancer-related bleeding who were treated with hemostatic irradiation delivered by the Dr. Cipto Mangunkusumo Hospital between the time of the ethics certification and when the minimum number of samples (18 samples) was obtained. This number was based on hypothesis testing with a single population. The sampling technique was done consecutively.

The inclusion criteria were a diagnosis of cancer, the presence of cancer-related bleeding, and treatment in the form of hemostatic irradiation therapy; patients also gave informed consent to be included in this study. The exclusion criteria were bleeding whose cause was due to treatment within a period of <3 months after the treatment was performed; unresolved signs of shock; poor general condition because of other comorbid conditions, such as sepsis, disseminated intravascular coagulation, or systemic inflammatory response syndrome; a history of diabetes mellitus; consumption of aspirin (Aspilets) in the past 3 months; anticoagulant therapy; and chemotherapy with hemostatic irradiation until the bleeding was stopped.

The independent variables in this study were age, tumor stage, tumor size, histopathologic type, and received radiation dose. The dependent variables were vWF levels before and after irradiation and the clinical response of bleeding according to the WHO bleeding scale score, including the degrees of bleeding before and after irradiation and the bleeding response time (day of bleeding cessation) after irradiation.

The vWF levels were measured at the Clinical Pathology Laboratory, Faculty of Medicine, University of Indonesia- Dr. Cipto Mangunkusumo Hospital. The Technozym vWF:Ag ELISA kit was used with a 450-nm enzyme-linked immunosorbent assay microplate reader. The paired-sample t-test was used to analyze the difference in vWF plasma levels before and after irradiation, and the Wilcoxon test was used to analyze the difference in WHO bleeding scale scores before and after irradiation. The Spearman correlation test was then performed to determine correlation direction and strength between vWF level and WHO bleeding scale score before and after irradiation. SPSS 20.0 software was used to analyze the results.

3. Results
Of the 23 subjects, two patients died because of the bleeding. Thus, the success rate of hemostatic irradiation was 91.3%. Table 1 shows the characteristics of all the 23 subjects.

| Characteristic                  | n  | %  |
|--------------------------------|----|----|
| Gender                         |    |    |
| Male                           | 4  | 17.4|
| Female                         | 19 | 82.6|
| Age Group                      |    |    |
| <35 years old                  | 2  | 8.7 |
| 35–45 years old                | 11 | 47.8|
| 45–55 years old                | 4  | 17.4|
| >55 years old                  | 6  | 26.1|
| Type of Disease                |    |    |
| Cervical cancer                | 14 | 60.8|
| Sinonasal cancer               | 3  | 13.3|
| Breast cancer                  | 2  | 8.7 |
| Skin cancer                    | 1  | 4.3 |
| Extremities cancer             | 1  | 4.3 |
| Oral cancer                    | 1  | 4.3 |
| Malignant trophoblastic disease| 1  | 4.3 |
Table 1. Continue

| Characteristic                                      | n  | %   |
|-----------------------------------------------------|----|-----|
| History of Herbal Medicine                         |    |     |
| Yes                                                 | 7  | 30.4|
| No/denied                                          | 16 | 69.6|
| Histopathology                                      |    |     |
| Adenocarcinoma/adenosquamous carcinoma              | 5  | 21.7|
| Kaposi sarcoma                                      | 11 | 47.8|
| Lymphoma                                            | 1  | 4.3 |
| Melanoma                                            | 1  | 4.3 |
| Neuroendocrine tumor                                | 2  | 8.7 |
| Neurofibroma                                         | 1  | 4.3 |
| Trophoblast, malignant                              | 1  | 4.3 |
| Sarcoma                                             | 1  | 4.3 |
| Stage                                               |    |     |
| I                                                    | 0  | 0   |
| II                                                   | 1  | 4.3 |
| III                                                  | 16 | 69.6|
| IV                                                   | 6  | 26.1|
| Tumor Size                                           |    |     |
| ≤4 cm                                                | 6  | 26.1|
| 5-6 cm                                               | 10 | 43.5|
| >6 cm                                                | 7  | 30.4|
| Type of Verification                                |    |     |
| Gammagraphy                                         | 5  | 21.7|
| Electronic portal imaging device                    | 14 | 60.8|
| None                                                | 4  | 17.5|
| Type of Radiation Equipment                         |    |     |
| Cobalt-60                                           | 3  | 13.0|
| Linac Varian                                        | 14 | 60.8|
| Platform                                            | 6  | 26.1|
| External Radiation Dose                              |    |     |
| 5 × 4 Gy                                            | 4  | 17.5|
| 5 × 3 Gy                                            | 5  | 21.7|
| 6 × 2.5 Gy                                          | 1  | 4.3 |
| 10 × 3 Gy                                           | 3  | 13.0|
| 25 × 2 Gy                                           | 10 | 43.5|

All the 21 samples showed a significant decrease in WHO bleeding scale score after hemostatic irradiation treatment (p < 0.001; Table 2).

Table 2. World Health Organization bleeding scale score medians before and after hemostatic irradiation.*

|                          | n  | Score median (min–max) | p   |
|--------------------------|----|------------------------|-----|
| Before treatment         | 21 | 3 (2–4)                | <0.001|
| After treatment          | 21 | 1 (0–1)                |     |

*Wilcoxon test.
Figure 1 shows a comparison of the vWF plasma levels before and after irradiation in 19 patients.

![Graph showing vWF plasma levels before and after hemostatic irradiation (RE).]

**Figure 1.** The von Willebrand factor (vWF) plasma levels before and after hemostatic irradiation (RE).

Table 3 shows that the vWF plasma levels before and after irradiation were significantly different ($p = 0.001$; 95% confidence interval, 6.23–18.53 IU/dL).

| n(sample) | Mean ± SD | Mean Difference ± SD | $p$  |
|-----------|-----------|----------------------|------|
| vWF level before irradiation | 19 | 129.98 IU/dL ± 14.13 | 12.38 ± 12.75 | 0.001 |
| vWF level after irradiation | 19 | 142.36 IU/dL ± 15.34 |

* $t$-test.

Table 4 shows the correlation between the difference in WHO bleeding scale scores before and after irradiation and the difference in vWF plasma levels before and after irradiation. The Spearman test was used to determine the correlation, and the result was significant ($p = 0.019$), with a correlation coefficient of $-0.533$.

| WHO Bleeding Scale Score Difference | $R$ | $p$ | $n$ |
|--------------------------------------|-----|-----|-----|
| Increased vWF Plasma Level Before and After Radiation | $-0.533$ | 0.019 | 19 |

* Spearman test.
Table 4 shows that in hemostatic irradiation, increases in vWF plasma level were usually accompanied by decreased WHO bleeding scale scores. A linear regression test of the result was performed, and the result of the regression equation \( y = -2.154 - 0.022 \times x \), where \( x \) is the difference in vWF plasma levels.

The correlation between the hemostatic irradiation dose and the time to bleeding response (day of bleeding cessation) was significant \( (p = .030; \text{Table 5}) \); therefore, so it can be concluded that there was a significant association between the time of bleeding cessation and the given radiation dose. The relative risk (RR) value was 3.63, which means that the effect of dosing on bleeding cessation time was a precursor effect with RR > 1. These results illustrate that hemostatic irradiation with hypofractionated doses is capable of accelerating bleeding cessation as much as threefold to sixfold faster than conventional doses.

### Table 5. Association between hemostatic irradiation dose and time to bleeding cessation.

| Radiation Dose     | Time to Bleeding Cessation | p     |
|--------------------|-----------------------------|-------|
|                    | ≤5 days | >5 days |       |
| Hypofractionated   | 8 | 73 | 3 | 27 | 0.030 |
| Conventional       | 2 | 20 | 8 | 80 |      |
| Total              | 10 | 47.6 | 11 | 52.4 |      |

### 4. Discussion

The incidence of bleeding among patients with advanced cancer is only 6%–10% [1,2]. Cancer-related bleeding can cause death. According to the GLOBOCAN 2012 project, 8.2 million people throughout the world died of cancer-related causes; in comparison, there were 7.6 million such deaths in 2008 [17]. In the hemostatic treatment of cancer-related bleeding, irradiation is very effective. However, comparative and controlled trial studies of the effectiveness of hemostatic irradiation are still limited [3].

The hypothesis of this study was that after hemostatic irradiation, the WHO bleeding scale scores would decrease, the vWF plasma levels would increase, and the difference in WHO bleeding scale scores would be correlated with the difference in vWF plasma levels. The general objective of this study was to obtain information on the effectiveness of irradiation on cancer-related bleeding at the Department of Radiotherapy, RSUPN Dr. Cipto Mangunkusumo Hospital. Of the 23 patients, only two died because of unresolved bleeding. In other words, the success rate of irradiation as the hemostatic treatment was quite high (91.3%). This finding was consistent with the results of other studies: In 1995, Biswal et al. showed that irradiation controlled bleeding in cervical cancer in 100% of patients within 12–48 hours [12] in 1997, Rees et al. [18] suggested that palliative radiotherapy for lung cancer, administered for 8 weeks, improves hemoptysis symptoms in >50% of patients; and in 2008, Hashimoto et al. stated that palliative irradiation for bleeding in nonoperable gastric cancer was successful in 68% of cases [19].

As shown in Table 2, hemostatic irradiation significantly decreased the WHO bleeding scale scores, with \( p < 0.001 \), from a median of 3 to a median of 1, which indicates that the post-treatment bleeding response was successfully achieved.

To understand the role of radiation in the hemostatic treatment of cancer-related bleeding, vWF plasma levels were measured before and after irradiation. According to the literature, vWF plays a role in more than just hemostasis. One function of vWF is as a carrier of clotting factor VIII and other proteins in the circulation and another is as a platelet recruiter in the condition of high shear stress in blood vessels, which contributes to the occurrence of venous thromboembolism and atherothrombotic complications. In addition, the vWF level is an expression of proinflammatory activity in stroke, atherosclerosis, and other circumstances during inflammation. Furthermore, it is known that vWF
expresses mitogenic activity in smooth muscle cells, induces apoptosis in platelets and tumor cells, and is a negative modulator of angiogenesis [6].

As a coagulation protein, vWF plays a role in adhesion between thrombocytes and endothelial cells. Some literature suggests that vWF also plays a role in metastasis [20,21] and that increased levels of vWF antigen in plasma are correlated with poor prognosis and metastasis [20]. Irradiation has been shown to cause injury to the vascular endothelium and stimulate the release of vWF as the initiator of platelet adhesion and primary hemostasis. As stated previously, platelet adhesion increased significantly within 48 hours after 20-Gy doses of radiation were administered [5], and vWF expression in the kidneys increased after in vivo radiation, which increased the risk of vascular occlusion due to thrombus formation [9]. In addition, in 1996, Jahroudi et al. demonstrated that 20-Gy doses of radiation induced the release of vWF by increasing vWF mRNA levels in the endothelial cells of humans and cows [22]. As shown in Table 3, the present study shows that irradiation increases the vWF plasma level significantly (p = 0.001), which answered the specific objective of this study. As depicted in Figure 1, vWF plasma levels were higher after irradiation than before.

Several studies have shown that the vWF level is higher in patients with malignancies than in healthy people and that increased vWF can be used as a predictor of tumor progression. As mentioned previously, vWF plasma levels were higher in patients with colorectal cancer and breast cancer than in healthy people, and increased vWF levels tended to be associated with progression of both types of cancers; reportedly, the vWF plasma level might be used as a predictor of bladder cancer progression and as a predictor for non-invasive transform to invasive forms [13,14,15].

As used in the treatment of various cancers, radiation causes damage to the vasculature, which results in decreased anticoagulation and increased procoagulant activity of endothelial cells. Radiation stimulates vWF release, which mediates the increase in platelet deposition, which, in turn, can lead to thrombus formation in patients undergoing irradiation [22]. This post-radiation increase in vWF levels is closely related to increased vWF expression at the transcription level [22].

The results of this study supported the theory that vWF plasma levels increased after radiation, followed by clinical bleeding cessation (p = 0.001). The correlation between the difference in vWF plasma levels and the difference in WHO bleeding scale scores before and after radiation was significant (r = −0.533, p = 0.019), which means that increased vWF plasma levels were correlated with decreased WHO bleeding scale scores after radiation. The correlation coefficient was moderately strong, which indicates that the vWF plasma level was possibly not the only major factor in the hemostatic response to cancer-related bleeding; therefore, further study is required. In addition, it is possible that the clinical parameters of the degree of bleeding used were inadequate and less objective in assessing cancer-related bleeding. The WHO bleeding scale has been used frequently to assess cancer-induced toxicity, but it is a broad categorical scale, and subjective interpretation may vary between examiners [16]. There are still no bleeding scales to assess the effects of bleeding on the quality of life of patients and their families [16].

A large difference in the vWF plasma level was expected to be accompanied by large changes in the WHO bleeding scale scores or a slight difference in the vWF plasma level was expected to be accompanied by slight changes in the WHO bleeding scale scores. However, the results of this study indicate that the differences in the vWF plasma levels before and after low-dose radiation were not always indicative of the size of changes in the WHO bleeding scale scores. Thus, other causes of bleeding cessation were thought to exist. A larger sample size is required for analyzing the correlation.

Table 5 shows a significant association between the hemostatic radiation dose and the time of bleeding cessation (p = 0.03), and the calculation of RR showed that the hypofractionated dose produced hemostatic effects 3.6 times faster than the conventional dose. In 1995, Biswal et al. showed that large hypofractionated doses are superior to conventional doses for hemostatic purposes. In this regard, the results of the present study were in accordance with those of previous studies [12]. The acute effect of irradiation and tumor response was related to the dose per fraction received by the tissue. Biswal et al.’s study also included patients with bleeding who received conventional-dose radiation therapy. Chi-square statistical analysis with a 2 × 2 table differentiated patients into two
groups: those receiving the conventional dose (2 Gy per fraction) and those receiving the hypofractionated dose (>2 Gy per fraction).

In Verheij et al.’s [5] study in 1994, vWF release in the culture medium increased significantly within 48 hours after 20-Gy irradiation compared with control conditions. Verheij et al. also stated that increased platelet adhesion was the result of an increased level of vWF in the matrix. Thus, it could be said that platelet adhesion was highly dependent on the vWF level [5]. In another study, hemostatic irradiation with doses >30 Gy was correlated with an increase in overall survival [2]. The results of the present study were in accordance with the statement that for patients who have better generalized conditions, conventional radiation doses are chosen.

5. Conclusion
The success rate of hemostatic irradiation as a treatment for cancer-related bleeding at an advanced stage of malignancy was quite high, reaching 91.3%. Irradiation as hemostatic treatment for cancer-related bleeding provided a good clinical response, with significant differences in the WHO bleeding scale scores. vWF plasma levels increased significantly after irradiation. Increased vWF plasma levels were significantly correlated with decreased WHO bleeding scale scores after irradiation, and the negative correlation was moderately strong. There was a significant association between the time to bleeding cessation and the given dose per fraction of radiation. The hypofractionated dose produced a bleeding response that was 3.6 times faster than that produced by conventional doses.

References
[1] Pereira J and Phan T 2004 Management of bleeding in patients with advanced cancer Oncologist 9 561–70 www.TheOncologist.com
[2] Cihoric N, Crowe S, Eyechmüller S, Aebersold D M and Ghadjar P 2012 Clinically significant bleeding in incurable cancer patients: effectiveness of hemostatic radiotherapy Radiat. Oncol. 7 132 http://www.ro-journal.com/content/7/1/132
[3] Ruggeri Z M 2007 The role of von Willebrand Factor in thrombus formation Thromb. Res. 120 S5–9
[4] Lyons S E and Ginsburg D 1994 Molecular and cellular biology of von Willebrand Factor Trends Cardiovasc. Med. 4 34–9
[5] Verheij M, Dewit L G H, Boomgaard M N, Brinkman H J M and Van Mourik J A 1994 Ionizing radiation enhances platelet adhesion to the extracellular matrix of human endothelial cells by an increase in the release of von Willebrand Factor Radiat. Res. 137 202–7
[6] Lenting P J, Casari C, Christophe O D and Denis V 2012 Von Willebrand Factor: the old, the new and the unknown J. Thromb. Haemost. 10 2428–37
[7] Rao SV et al. 2006 A comparison of the clinical impact of bleeding measured by two different classifications among patients with acute coronary syndromes J. Am. Coll. Cardiol. 47 809–16
[8] Denis C V 2001 Molecular and cellular biology of von willebrand factor Int. J. Hematol. 143
[9] Van Kleef E M, te Poel J A, Oussuren Y G, Verheij M, van de Pavert I, Brunhut S J, Dewit L G and Stewart F A 1998 Increased expression of glomerular von willebrand factor after irradiation of the mouse kidney Radiat. Res. 150 528–34
[10] Van Kleef E M, Verheij M, te Poel H, Oussoren Y, Dewit L and Stewart F 2000 In vitro and in vivo expression of endotelial von willebrand factor and leukocyte accumulation after fractionated irradiation Radiat. Res. 154 375–81
[11] Byhardt R W 2010 The Blood Vessels and Heart Radiation Oncology (9th Edition) ed DJ Cox and KK Ang (Philadelphia: Mosby-Elsevier) pp 411–23
[12] Biswal B M, Lal P, Rath G K and Mohanti B K 1995 Hemostatic radiotherapy in carcinoma of the uterine cervix Int. J. Gynecol. Obstet. 50 281–5
[13] Damin D C, Rosito M A, Gus P, Roisemberg I, Bandinelli E and Schwartzmann G 2002 Von willebrand factor in colorectal cancer Int. J. Colorectal Dis. 17 42–5
[14] Rohsig L M, Damin D C, Stefani S D, Castro Jr C G, Roisemberg I and Schwartzmann G 2001
Von Willebrand Factor antigen levels in plasma of patients with malignant breast disease
*Braz. J. Med. Biol. Res.* **34** 1125–9

[15] Zietek Z, Zietek II, Paczulski R, Kotschy M and Wolski Z 1996 Von Willebrand Factor Antigen in blood plasma of patients with urinary bladder carcinoma *Thromb. Res.* **83** 399–402

[16] Bercovitz R S and O’Brien S H 2012 Measuring bleeding as an outcome in clinical trials of prophylactic platelet transfusions. everyday bleeding disorder. *Hematology* **157**–60

[17] The International Agency for Research on Cancer (IARC) World Cancer Statistics GLOBOCAN 2012 Available from: http://www.uicc.org/iarc-release-latest-world-cancer-statistics. [Accessed on 25 March 2014]

[18] Rees G J G, Devrell C E, Barley V L and Newman H F V 1997 Palliative radiotherapy for lung cancer: two versus five fractions *Clin. Oncol.* **9** 90–5

[19] Hashimoto K, Mayahara H, Takashima A, Nakajima T E, Kato K and Hamaguchi T 2009 Palliative radiation therapy for hemorrhage of unresectable gastric cancer: a single institute experience *J. Cancer Res. Clin. Oncol.* **135** 1117–23

[20] Shavit J A and Motto D G 2006 Coagulation and metastasis- an unexpected role for von willebrand factor *J. Thromb. Haemost.* **4** 517–8

[21] Franchini M, Frattini F, Crestani S, Bonfanti C and Lippi G 2013 von Willbrand Factor and Cancer: a renewed interest *Thromb. Res.* **131** 290–2

[22] Jahroudi N, Ardekani A M and Greenberger JS 1996 Ionizing irradiation increases transcription of the von willebrand factor gene in endothelial cells *Blood* **88** 3801–4