Case report

Thromboembolic events following brachytherapy: case reports

Jean-Baptiste Guy, MD[1], Alexander Tuan Falk, MD[2], Cyrus Chargari, MD, PhD[3], Laurent Bertoletti, MD, PhD[4,5], Nicolas Magné, MD, PhD[1]

[1]Département de Radiothérapie, Institut de Cancérologie de la Loire – Lucien Neuwirth, Saint-Priest en Jarez, [2]Département of Radiation Oncology, Centre Antoine Lacassagne, Nice, [3]Radiation Oncology, Hôpital d'Instruction des Armées du Val-de-Grâce, Paris, [4]Université Jean-Monnet, Groupe de Recherche surla Thrombose, St-Etienne, [5]Centre Hospitalier Universitaire, Service de Médecine Vasculaire et Thérapeutique, St-Etienne, France

Abstract

Pulsed-dose-rate (PDR) brachytherapy is a recent brachytherapy modality combining the radiobiological advantages of low-dose-rate (LDR) brachytherapy with increased possibilities of dose optimization and radiation safety. However, treatment duration remains protracted, as the prescribed dose is typically delivered through pulses that do not exceed 0.5 Gy/h for critical organs. It is frequently used for the treatment of gynaecological malignancies. Although, the relationship between thrombosis and cancer is well known, specific data on thromboembolic events during brachytherapy are scarce. We report two cases of major thromboembolic events during brachytherapy treatment for gynaecological malignancies. We discuss the possible causal relationship between brachytherapy procedures and the occurrence of thromboembolic events, drawing a preventive practical attitude.

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Purpose

Pulsed-dose-rate (PDR) brachytherapy is a recent brachytherapy modality using short pulses of radiation, one pulse per hour. It improves dose distribution and dose escalation to the tumour while sparing organs at risk. Pulsed-dose-rate brachytherapy has the potential of dose optimization while delivering treatment with relative radiation safety. However, treatment duration remains protracted.

High-dose-rate (HDR) brachytherapy has proven its benefit [1,2] but it was shown that PDR brachytherapy was also effective in the treatment of gynecological malignancies. Most treatment-associated toxicities were mild to moderate [3,4] for this type of brachytherapy delivery. Usually, the dose rate to critical organs is maintained below 0.5 Gy per hour, based on past experiences with low-dose-rate (LDR) brachytherapy. As a consequence, treatment duration is not shortened, as compared with conventional LDR brachytherapy, and patients can be hospitalized for days, depending on total prescribed dose.

Venous thromboembolic events (VTE) are frequent in cancer patients, and more particularly in patients with pelvic malignancies. Pulmonary embolism (PE) is a major thromboembolic complication, associated with malignancy [5], leading to death in many cases. This risk increases when patients receive anticancer therapies, such as surgery, radiation therapy, or chemotherapy [6]. To date, there is limited data regarding VTE in patients treated with brachytherapy.

Although clinical impact is uncertain, it was suggested that exposure to ionizing radiation could activate a platelet cascade [7]. Moreover, patients are immobilized in bed during treatment duration. In pelvic locations, brachytherapy is often administered with anti-coagulation prophylaxis but practices vary widely between centres, and there is no consensus. Here, we report the cases of two major thromboembolic events that occurred during brachytherapy.

Case reports

Case 1

A 79-year-old patient presented with endometrioid adenocarcinoma stage FIGO Ib, grade II, with 20% clear cell component. Initial treatment had consisted of a total hysterectomy with ovariectomy without lymph node dissection, followed by external beam radiotherapy (45 Gy,

Address for correspondence: Alexander T. Falk, MD, Centre Antoine Lacassagne, 33 avenue valombrose 06000 Nice, France, phone: +33 492031000, e-mail: alexander.falk.fr@gmail.com

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1.8 Gy per fraction). The patient was then referred for brachytherapy of the vaginal cavity. The brachytherapy procedure was delivered via a PDR technique with an objective to deliver 15 Gy to the vaginal cavity. No preventive anticoagulation was prescribed for brachytherapy. Ten hours after starting treatment, the patient had an episode of malaise with acute dyspnea and hypotension. The chest CT showed bilateral proximal extended PE with right ventricular dilatation. Transthoracic echocardiography found a right atrial thrombus associated with indirect signs of pulmonary hypertension. Venous Doppler ultrasound of the lower limbs showed a distal bilateral thrombosis. The patient was placed in the intensive care unit (ICU) for eight days and received appropriate anticoagulation. Although indicated, fibrinolysis was not performed because of the high bleeding risk after the local therapy.

The patient remained in the intensive care unit for 8 days and then was transferred to the medical ward for an additional 2 weeks. Three months later, she had stable dyspnea with persistent pulmonary hypertension. Eighteen months later, she is in complete cancer remission.

Case 2

A 59-year-old Caucasian patient presented with a moderately differentiated endometrioid adenocarcinoma FIGO Ib grade II pN0, initially treated by total hysterectomy with ovariectomy and lymphadenectomy followed with 3D conformal external beam radiotherapy (45 Gy, 2.25 Gy/fraction). Brachytherapy was delivered via PDR with the objective to deliver 15 Gy to the vaginal vault. No preventive anticoagulation was prescribed. Shortly before the end of the treatment, the patient had a sudden episode of chest pain, syncope with hypotension, and faintness. An emergency chest CT showed bilateral PEs. Transthoracic echocardiography showed indirect signs of pulmonary hypertension. No deep venous thrombosis were found during the lower limb echo. The patient was transferred to the intensive care unit, received pressor amines and a prescription of low molecular weight heparin.

The patient had an improvement in symptoms at 3 months with the disappearance of pulmonary hypertension on echocardiography. She then received vitamin K antagonist. She remains in complete remission at eighteen months follow-up.

Brachytherapy technique

The intra vaginal device was positioned after gynaecological clinical examination to ensure complete healing. For the two patients, CT was acquired with 2.5 mm slice thickness extending from L1 to the proximal third of the femur's diaphysis. Patients were positioned supine with their arms above the head. No oral or *i.v.* contrast was administrated. The considered organs at risk (OAR's) were rectum, bladder, small bowel, bone marrow, and femoral heads. A single radiation oncologist completed contouring of the bladder, rectum, and small bowel prior to commencement of the project. The PDR dosimetry plan was designed on the Varian Eclipse 8.9.08 treatment planning system (TPS) (Varian Medical Systems, Palo Alto, CA, USA). Brachytherapy treatment occurred in a sealed room for duration of 25 hours (0.5 Gy/pulses for a total of 15 Gy for each patient, using a radioactive source of Iridium 192). Given the short duration of time, the patients were not prophylactically treated with anti-coagulation.

Discussion

Herein, we reported two cases of high-risk pulmonary embolisms occurring during brachytherapy treatment for pelvic cancer. Currently brachytherapy is considered as a treatment technique without serious adverse effects [1,3,4,8,9]. In the above cases, brachytherapy demonstrates an association with the occurrence of VTEs, and therefore, demonstrating a potential life-threatening complication of brachytherapy.

Cancer is an independent risk factor for venous thromboembolic disease, increasing the risk 4-6 times depending on studies [6,10]. This risk, although related to the inflammation of cancerous pathology, is particularly linked with the cancer therapy used. Association with chemotherapy is demonstrated [11], and is very probable for external radiation therapy, especially in lung cancer [12]. Dusenbery *et al*. [13] reported the existence of thromboembolic complications during brachytherapy, including one case of pulmonary embolism. To date, this is the only published data on VTE and brachytherapy, showing that these events are probably underestimated. Nevertheless, patients treated by brachytherapy are likely exposed to an accumulation of risk factors. Pelvic location, cancer surgery, chemotherapy, comorbidities related to the patient, bed rest, and ionizing radiation are all risk factors. Indeed, pelvic tumours are known to be at risk [14] because of pelvic vessels compression risk. Furthermore, brachytherapy tends to be increasingly used, particularly with new planning and dose modulation techniques.

However, it is worth noting how early thromboembolic events appear in this series. In the first case, symptoms occurred after 10 hours of treatment, and in the second case, at the end of the treatment, only after 25 hours of immobilization. In both cases, brachytherapy was performed three months after pelvic surgery. As a consequence, this short immobilization is probably insufficient to explain alone the occurrence of massive PE. In parallel, it is also necessary to highlight the importance of anticoagulation prophylaxis during 4 weeks after surgery, which is now a grade A recommendation [15]. Nevertheless, in some cases, brachytherapy can be used as a primary radical treatment for endometrial cancer [2]; VTE risk should be different in these cases.

It is thus important to report such events involving the vital prognosis of patients, for a treatment technique that remains very well tolerated. To focus solely on brachytherapy's role is challenging: immobilization added to the cell destruction and inflammation are accessible factors for prevention. Major brachytherapy centres already use low molecular weight heparin prevention for any pelvic brachytherapy (as the Gustave Roussy Institute in Villejuif, France). The risk-benefit of such care remains to be

discussed, as well as the treatment duration. Bleeding risk is negligible for vaginal vault brachytherapy but it may be considered in interstitial brachytherapy, especially in anal canal or prostate locations. So far, international recommendations do not mention brachytherapy treatment as an indication for DVT prophylaxis [15-17].

A final factor that must be considered is the radiobiological consequence of ionizing radiation on vessels. Indeed, the biological rational calls for coagulation cascade activation by ionizing radiation [1]. This radiobiological parameter is accepted for external radiotherapy but is probably negligible in brachytherapy. The delivered dose far from the remote device is minimal, as for pelvic vessels. Based on these two cases and after dosimetric analysis, the delivered iliac vessels dose was insignificant (< 0.01 Gy). However, the impact on the micro vascularization of the pelvis and the long-term risk should be discussed further.

Further research is needed to accurately assess the prevalence of symptomatic and asymptomatic VTE to determine the true risk in brachytherapy treatment, and therefore the need for prevention.

Conclusions

We have described two major clinical thromboembolic events during a PDR brachytherapy treatment. There is scant data in the literature for a specific association between brachytherapy and thrombosis. However, it appears important to highlight this type of event: to draw practical recommendations on the strategy of preventive treatment, including low molecular weight heparin prophylaxis and compression stockings as minimum but also to serve as a starting point for further research on the association of ionizing radiation and thrombosis in pelvic cancers.

Disclosure

Authors report no conflict of interests.

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