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Review Article

Abdominal Aortic Aneurysm and Radiation Therapy

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ABSTRACT
Abdominal aortic aneurism (AAA) is a frequent disorder in older male adults; male to female ratio is approximately 10:3. AAA often causes significant morbidity and mortality if not resolved on time by early detection and timely performed endovascular or open surgical repair. The incidence of rupture with an AAA <7 cm diameter is < 5% per 1 year. This gives enough time to many patients for improvement of possible pre-existing medical conditions before elective repair. There is no evidence that radiation therapy causes aortic aneurysm. In contrast, there is a possibility that radiation slows the growth of AAA. The mechanism of this action is not known.

Keywords: Abdominal aortic aneurism (AAA), Radiation therapy, Rupture of aneurysm, Endovascular repair (evar), Open surgical repair, Psychological depression.

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INTRODUCTION

Prolonged life expectancy leads in elderly patients to multimorbidity.[1] For example, Abdominal aortic aneurism (AAA) occurs concomitantly with malignancy in 1.0 to 17.0% of patients.[2] Radiation therapy (RT) plays a prominent role in the treatment of many cancers since tumors and healthy tissues show significant differences in sensitivity to radiation. That is the reason why diseased tissue faster responds to radiation than healthy tissue, and clinical manifestations of side effects caused by RT may occur years later.[3,4]

The aim of this article is to present abdominal aortic aneurysm, and to show impact of radiation on this vascular defect.

Abdominal aortic aneurysm

The expansion of artery lumen by 50% in relation to the adjacent part of the vessel presents an aneurysm.[5] When infrarenal dilatation of the aorta is in question, it is an AAA. Such change is in most cases without symptoms, until the aneurysm progresses to rupture. The greatest risk for the occurrence of aneurysm occurs in men at the beginning of geriatric age (65 years); the ratio male to female is approximately 10:3. Thoracic aortic aneurysm exhibits no gender difference and it is more prevalent in younger individuals.[6]

Because there are no effective medical therapies, current clinical intervention for large aneurysm includes two options: Endovascular repair (EVAR) and open surgical repair. EVAR is used for both elective repair and at a ruptured case; a bifurcated or tubular stent-graft over the AAA excludes the aneurysm from arterial circulation. This procedure is superior to open surgical repair. Type II endoleak, with an occurrence rate of 20-30%, is the most common complication after EVAR.[7] Elective EVAR results in lower perioperative mortality than traditional open repair, but after 4 years the EVAR survival advantage is not seen; the results of two European trials have also shown worse long-term outcomes with EVAR than with open repair.[8]

A time for the repair has been recommended when the infrarenal aorta diameter becomes larger than 5.5 cm in men and 5.0 cm in women, due to high incidence of ruptures in non-operated aneurysms.[9] This opinion is based on the data obtained 2002 which show a 9% risk of rupture for aneurysms of 5.5-5.9 cm in diameter within 1 year, compared with 19% for those measuring 6.0-7.0 cm, and 33% for > 7.0 cm in diameter. However, recent studies have questioned this because the incidence of rupture in patients with an AAA <7.0 cm diameter was < 5% per 1 year.[10] This finding gives enough time to many patients for improvement of the pre-existing medical conditions before surgical intervention. With AAA diameter above 7.0 cm, a patient faces much higher risk of rupture. The U.S. Preventive Services Task Force recommends that men with a history of smoking who are 65 to 75 years of age should undergo one-time abdominal aortic aneurysm screening with ultrasonography.

Proper control of hypertension, tobacco smoking, diabetes, and blood lipids may partially slow down AAA growth. However,

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ACE inhibitors should not be used for blood pressure control in such patients. It is better to use one of the ARB (e.g. losartan, irbesartan, valsartan), because ACE also acts as a kininase. In fact, ACE and kininase II (Figure 1) are the same enzyme.[11,12] Therefore, administration of an ACE inhibitor has a dual action, it decreases angiotensin II and increases bradykinin levels. The latter peptide may stimulate aneurysm's expansion.

The loss of vascular smooth muscle cells and degradation of the extracellular matrix leads to formation of AAA. New experimental approaches for medical treatment are promising; mouse aneurysm models are frequently used-such as angiotensin II induced abdominal aortic aneurysm in male apolipoprotein E knockout mice (Apoe-/-).[13,14] Pentamethyl quercetin, which inhibits angiotensin II-induced abdominal aortic aneurysm formation by binding to C/EBPβ at Lys253, and reduces the incidence of AAA rupture in mice.[15] Asiatic acid, a triterpene compound, has also been investigated due to its strong anti-inflammatory property. This compound induces aortic remodeling and is useful against blood vessel dissection in the murine model.[16]

Psychic changes in AAA patients

Cases of sudden death due to aneurysm rupture were rarely described in the distant past. An example was described in 1887; Alexander Borodin, a professor of pathology and famous Russian composer died at age of 55 due to the rupture of coronary artery aneurysm.[17] Coronary ar.tery aneurysm can cause death due to thrombosis or rupture. It is usually associated with destruction of the tunica media, due to atherosclerosis and inflammation.[18] RT my cause atherosclerosis, including coronary artery disease, valvular disease, constrictive pericarditis and heart failure.[19] Today, abdominal and thoracal scanning examinations have revealed the presence of the AAA in many persons and this expanded public knowledge of what danger the aneurysm presents. When an aneurysm is discovered in a patient, especially the AAA, this may cause psychological disorders, including depression that occurs more often in older subjects. That is why it is necessary to monitor the psychiatric status of a patient with aneurysm and perform emergency intervention when necessary.[20] Additional problem presents significantly increased (33%) incidence of delirium following abdominal aortic repair.[21]

Radiation therapy and AAA

In addition to cancerous cells, ionizing radiation also affects rapidly proliferating cells; e.g. endothelial and bone marrow cells. DNA damage causes the cell cycle arrest and apoptosis of healthy tissue. High doses result in depletion of vascular endothelial cells and both macro- and microvascular effects are induced.[22] The radiation therapy is associated with an increased risk for cardiovascular damage; for example, neck and cranial RT have been associated with significant long-term toxicities including accelerated occlusive carotid artery disease, autonomic dysfunction due to baroreceptor harm, and development of metabolic syndrome caused by damage to the hypothalamic-pituitary axis.[23] In addition, intracranial aneurysms often appear after radiation therapy.[24,25] Modern radiotherapy techniques reduce the damage of heart and major coronary vessels exposed to high doses, yet some exposure is frequently unavoidable and some radiation damage occurs. For example, inflammatory changes in the microvasculature cause myocardial damage, local ischemia, progressive myocardial cell death and fibrosis. Irradiation of large vessels causes endothelial cell lining damage and this leads to adhesion of circulating monocytes who transform into activated macrophages and the process of atherosclerosis is initiated, microthrombi are formed and vessels occluded.[26] Clinical studies also demonstrate regional perfusion defects in non-symptomatic breast cancer patients after radiotherapy.

Therefore, it is unexpected finding that radiation therapy for pelvic cancers, including prostate carcinoma, reduces abdominal aneurysm growth.[27,28] This finding would be worth examining in more detail and determine the effect of the RT at the cellular and molecular level.

ACE activity in rat aorta was increased 1-24 hr after whole body irradiation in a dose of 2.5 Gy with a peak in 2 hr after exposure.[29] Male Wistar rats were exposed to whole body or local (chest) X-ray irradiation (200 kV, 1-7.5 Gy). Such radiation dose is equal

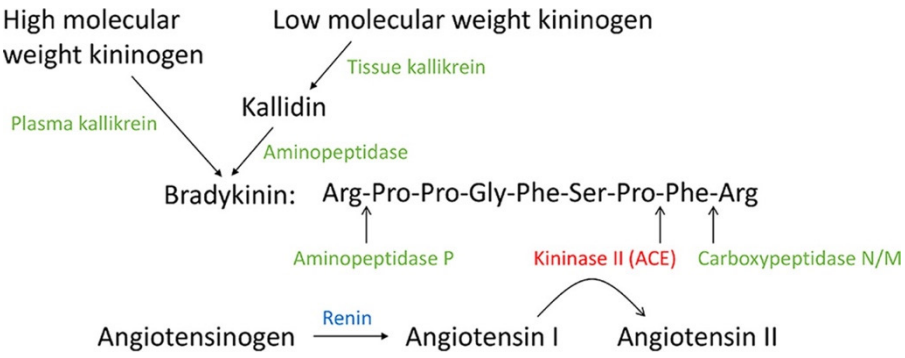

Figure 1: The peptides and peptidases in the Kallikrein-Kinin System (KKS) and Renin Angiotensin System (RAS). The enzymes in the KKS are shown in green, and renin is shown in blue; ACE (kininase II) is shown in red.

to one fraction dose that is used in tumor radiation. The activity of the enzyme in aorta segments was measured in 1-48 hr after irradiation by hydrolysis of hippuryl-histidine-leucine substrate. The early effect of radiation is probably caused by the influence of radiation at the aortic endothelial cells. However, the long-term changes due to increased enzyme activity on the AAA is not determined.

LIMITATION

This paper has not focused on the RT risk at the separate occurrence of the AAA in men and women.

CONCLUSION

It is well known that ionizing radiation affects both cancerous and non-cancerous cells, especially rapidly proliferating cells, e.g. endothelial cells. There is no evidence that radiation therapy causes abdominal aortic aneurysm. On the contrary, there are data that radiotherapy slows the growth of abdominal aorta aneurysm. The mechanism of this action is unknown.

CONFLICT OF INTEREST

The author declare that there is no conflict of interest.

ABBREVIATIONS

AAA: Abdominal aortic aneurysm; **ARB:** Angiotensin II receptor blockers; **ACE:** Angiotensin converting enzyme; **Apoe-/-:** Presents an apolipoprotein (Apoe) knockout (-/-), most widely used murine models for atherosclerosis; **C/EBPβ:** The gene that encodes a transcription factor in regulating gene expression; **Gy:** SI unit "grey". 1 Gy = 1 Joule/kilogram = 100 rad; **KKS:** Kallikrein kinin system; **Lys253:** Lysin253; **RAS:** Renin angiotensin system; **RT:** Radiation therapy; **US:** United States.

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