Review of: "Radiation therapy-associated toxicity: Etiology, management, and prevention"

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Review of: Radiation Therapy-Associated Toxicity: Etiology, Management, and Prevention

The reviewer rated it 5/5

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The recent article by Wang and Tepper is a valuable summary for clinicians about the radiation therapy associated toxicity and its management. Although it is a comprehensive review there is some missing information about the topic.

Firstly, even though the radiation tolerance doses and dose volume constraints for the organs and tissues were previously summarized in Emami, and in the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) reports (1,2), it would be very useful to update and mention this information in detail in this review as well.

Secondly, radiation therapy related toxicity in certain organs like stomach, pancreas and bone has not been sufficiently described.

Pancreas: Information on the radiation related pancreatic toxicity is sparse. Pancreas is a secretory organ which has similarities to salivary glands namely having acinar and Langerhans cells with important exocrine and endocrine functions. Acinar cells both in the salivary glands and the pancreas secrete fluid and enzymes which are important for gastrointestinal system and digestion. Exocrine pancreatic insufficiency results in malabsorption, and endocrine pancreatic insufficiency results in diabetes mellitus. We have demonstrated previously that pancreatic tissue undergoes significant functional and structural changes after abdominal irradiation which results in endocrine pancreatic insufficiency (3). Furthermore, another recent study demonstrated loss of exocrine function of the organ after abdominal irradiation (4). These studies confirm that pancreas loses its structural but also functional capacities after radiation exposure.

Vascular damage is the most common cause of radiation toxicity (3,5). The irradiated pancreatic tissue shrinks in size and becomes extremely fibrotic. While there is atrophy and loss of acinar cells after pancreatic irradiation, the islets of Langerhans are well preserved histologically but their functional capacity decreases. Clinical signs and radiologic findings of chronic pancreatitis were reported years later

after abdominal irradiation at doses ranging from 36–45 Gy (3-5). Radiation doses above 40 Gy with classical fractionation or above 25 Gy single fraction intraoperative radiotherapy administration which can be considered as single fraction stereotactic radiotherapy, 9–15 Gy single or hyperfractionated total body irradiations are clearly toxic to the pancreatic tissue. While exocrine pancreatic insufficiency is observed early, several weeks to months after radiotherapy, endocrine insufficiency occurs relatively lately, several months to years later (3-5). Exocrine part of the pancreas is more sensitive to irradiation in comparison to the endocrine part of the organ.

Although pancreas is a radiation sensitive organ losing its volume and function after radiation exposure, it is not yet considered as an organ at risk for radiotherapy planning. Pancreas should be contoured as an organ at risk, dose-volume histogram for the organ should be created, and special care should be taken to reduce the radiation dose to the organ during treatment planning. Whole organ dose should be tried to be kept under 40 Gy with classical fractionated irradiation or below 20 Gy with stereotactic irradiations. We should advise diet and lifestyle changes for prevention of diabetes mellitus and refer these patients to gastroenterologist for problems associated with malabsorption.

Bone: Decrease in bone mineral density, osteoporosis development and bone toxicity related to radiation has not been studied extensively and it is not well known. Bone toxicity as a late effect of radiotherapy is multifactorial. It results from direct and indirect effects of irradiation on bone resulting either from pelvic irradiation induced ovarian or testicular failure, malabsorption of calcium and vitamin D and other micronutrients related with bone metabolism due to abdominal irradiation induced toxicity on stomach, small intestine and pancreatic tissue or metabolic syndromes which develop after cranial irradiation of hypopyhseal pituitary stalk in survivors of childhood tumors (6,7). Bone fractures are the worst adverse effects of radiation on bone tissue and these fractures are generally called as insufficiency or stress fractures (IFs), which are generally the fractures that result from normal or physiologic stress applied to weakened bone. The major mechanism of radiation induced bone toxicity is due to damage and occlusion of bone microvasculature. Besides vascular damage, radiation causes stasis of osteoclasts and osteoblasts, reduces osteoblast number, arrests osteoblast cell cycle progression, and results in their apoptosis. Radiation damages also bone matrix, increases marrow adiposity, and decreases vascular supply to the bone. All these radiation effects on bone ultimately lead to reduced bone formation (6,7).

Although very frequently observed, radiation induced decrease in bone mineral density (BMD), osteoporosis and IFs have been rarely reported prospectively and are mostly observed in patients who were treated with pelvic irradiations (6,7). The incidence of IFs reported in the literature after abdominal or pelvic irradiations vary between 7 and 45% (6,7).

Although very frequent, bone toxicity related to radiotherapy is a neglected and unknown toxicity. Most oncologists are not aware of these fractures, and sometimes they may be considered as bone metastases resulting in unnecessary interventions and even medicolegal problems.

Bone fractures are increasing nowadays with the implementation of stereotactic irradiations but the mechanism in this setting is probably due to direct bone toxicity of high dose irradiation rather than a

decrease in BMD and osteoporosis development (8). Dose volume constraints for fracture risk in stereotactic irradiations are being explored.

Osteoporosis is observed in patients after abdominal irradiations and IF risk is a significant late effect of radiotherapy. We have recently demonstrated a vertebral fracture risk of 9.6 % in patients who were treated with abdominal irradiation (6). We think that bone should be considered as an organ at risk for radiotherapy planning.

While dose constraints are well-defined for organs at risk and determinant for final plan approval, this is not the case for bone. Although grade III/IV late toxicity rates for organs at risk are not above certain percentages with modern radiotherapy techniques, abdominal, or pelvic radiotherapy related bone toxicity and resulting fractures are indeed higher than the well-known radiation induced grade III/IV late toxicities. As clinicians, we must be aware of this possible complication and take two issues into consideration. Firstly, we should not think of vertebral fractures as the metastases of primary tumor especially if the involved bone is already in the irradiated area. Secondly, we should follow BMDs in this group of patients and take preventive measures against development or progression of osteoporosis and consult these patients with endocrinologists.

We should try to decrease mean radiation doses for the vertebral and pelvic bones within the radiation field especially in the elderly and already osteoporotic patients. We should try to keep radiation doses in bony areas with fracture risk below 25-30 Gy.

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