Evaluation of the effects of irradiation on bone and osteoradionecrosis of the mandible in a large animal model

Valorisation addendum

INTRODUCTION

In the western world, head and neck cancer constitutes approximately 5% of all cancers. In the Netherlands, head and neck cancers account for 2500 new cancer cases annually. For head and neck malignancies, current treatment regimens can include radiotherapy (RT). RT has known beneficial effects both as a primary and as a secondary treatment, i.e., postoperative RT after surgical resection. However, despite improving and refining radio-therapeutic techniques, such as intensity-modulated radiation therapy (IMRT), irradiation effects on the surrounding healthy tissue continue to cause complications.

One of the known complications of RT is osteoradionecrosis (ORN), which can affect all bony structures in the field of irradiation, but is most commonly seen in the mandible at a frequency of 2-22%. The diagnosis is generally based on a clinical presentation. ORN is defined as "irradiated bone, which becomes devitalised and is exposed through the overlying skin or mucosa and does not heal within a period of three months, without tumour recurrence". Several factors have been identified that increase the risk of developing ORN including treatment-related factors, such as the radiation dose and the volume of irradiation. ORN can be triggered by surgical intervention or pressure sores from dentures and can occur spontaneously. It can arise at any point after irradiation therapy even several years later.

Treatment of ORN ranges from conservative management with or without surgical debridement to wide resections in severe cases. Due to the compromised local tissue condition, reconstruction with micro-surgical free-flap transfer is the standard treatment. This is a major surgical intervention in patients with severe comorbidities. Functional and aesthetic limitations are inevitable and dramatically reduce the quality of life of the affected patients.

Between 2007 and 2013, our head and neck team at the MUMC+ treated approximately 1200 new oncologic cases of which an estimated 300 cases received partial irradiation of the mandible. We recorded 15 cases of ORN, which gives an estimated frequency of 5%. This figure is comparable to the incidences mentioned in the literature.

Due to the variability in onset and presentation as well as the variable progression of mandibular ORN, clinical studies are difficult to perform. The exact pathophysiological mechanisms leading to the development of ORN are not yet fully understood, and therefore, a targeted treatment strategy is lacking.

To study the pathophysiological conditions leading to ORN, we developed a large animal model. With regard to bone physiology, the Göttingen minipig has anatomical and biological characteristics highly comparable to human beings. This enabled us to study the pathophysiological processes that are similar to the human situation under controlled conditions. Increasing irradiation doses were applied with and without surgical interventions. Moreover, imaging to assess mandibular ORN has received little attention in the literature. The added value of the visualisation of the pathophysiological processes, however, is evident.

RESULTS

The animal model and experiments described in this thesis are realistic, because three of the twelve irradiated animals developed ORN using a radiation pattern with two fractions. Another research group irradiated minipigs with only one fraction, and all animals developed ORN. However, in our study, only one in four animals developed ORN. Therefore, the radiation pattern based on only two fractions resulted in clinically comparable outcomes with respect to ORN.
Using laser Doppler flowmetry, we found a non-significant progressive decrease in the local blood flow. This was confirmed histologically, where a decreased vascular diameter due to intima fibrosis could be demonstrated. Using conventional CT imaging, we found a non-progressive decrease in bone mineral density after irradiation, which was likely caused by prolonged and insufficient remodelling after irradiation.
All animals underwent both MR- and CT-imaging. In the ORN animals, cortical destruction and marrow involvement were present. With an increase in the irradiation dose, MR-imaging revealed progressive bone marrow oedema due to the irradiation on both the surgical and non-surgical side. Furthermore, there was a considerable variance between the animals from the same irradiation groups. One animal had no clinical signs of ORN, but had radiological ORN and histological changes; these variable results emphasise the need for imaging.
Additional imaging was performed using dual energy CT (DE-CT). With this technique the evaluation of the bone marrow is made possible using CT. We compared the density of the bone marrow on virtual non-calcium images to the signal intensity of the bone marrow from the STIR images. We found that the DE-CT images were comparable to the MR-imaging for the detection of the marrow oedema pattern. This is potentially a new application for the detection of ORN in patients after clinical validation.
Histological evaluation revealed progressive fibrosis in general and especially in the vascular wall of the inferior alveolar artery. Necrosis and bone destruction were clearly visible in the ORN cases. The bone remodelling was markedly decreased with an increase in the irradiation dose.
Based on the findings of our animal model, we can conclude that the pathophysiological process leading to ORN is a variable process; therefore not all animals developed ORN.
ORN appears to be caused by vascular compromise combined with reduced and insufficient bone regeneration.

CLINICAL IMPLICATIONS

The specific groups that will benefit from this study are head and neck cancer patients receiving RT and the multidisciplinary team involved in the treatment of head and neck cancer. With renewed attention to the problematic complication of ORN and the need

for careful planning of the RT, early diagnosis and treatment and intensified follow-up after RT are necessary. We expect that such an approach can improve the patient quality of life after radiotherapy for head and neck cancer. Hopefully early detection of preclinical ORN using CT- and MR-imaging can prevent the progression of the disease using medical treatment, such as treatment with pentoxyphilin, tocopherol and clodronate.

SHARING KNOWLEDGE

The knowledge gained by this study will be shared both by means of scientific publications in peer-reviewed journals and in presentations at national and international congresses. Furthermore, the intensified collaboration with the departments of radiology and radiotherapy will increase the multidisciplinary awareness of ORN. The results will be shared to the entire multidisciplinary head and neck oncology team; therefore, patients will benefit from these findings.

FUTURE PERSPECTIVES

To prevent the development of ORN, investigations should focus on further improvements and refinements in radiotherapy for head and neck cancer. Second, to detect preclinical ORN and to initiate immediate medical treatment, regular and intensified follow-up of irradiated patients is necessary. This preclinical detection would prevent the worsening of ORN and the deterioration of the patient's quality of life after radiotherapy.

In addition to improvements in clinical detection, future studies should aim for clinical validation and implementation of the dual energy CT technique for detecting ORN in human subjects. The use of this technology would make the diagnostic work-up for the early detection of ORN easier and faster.

Dual energy CT might also be a promising tool for assessing bone quality after irradiation prior to surgical procedures in the mandible or during follow-up.