7. SUMMARY

EFFECTS OF INTRA-OPERATIVE PHOTODYNAMIC THERAPY WITH THE POTOSENSITIZER MTHPC ON RABBIT LARGE BLOOD VESSELS, NERVES, MICROCIRCULATION AND MUSCLE-TISSUES

Photodynamic therapy (PDT) represents a new encouraging treatment concept in tumour treatment. This treatment modality is based on the intravenous application of a photosensitizing drug that is supposed to accumulate in tumour cells and is activated by light of specific wavelengths (laser light).

Under oxygen influence singlet oxygen and free radicals develop which damage different cell components and lead to cell death. This treatment is already used successfully in different fields of oncology. For example, squamous cell carcinomas of the skin or oral cavity, adenocarcinomas of the chest and tumours of the bladder can be destroyed. Intraoperative photodynamic therapy in addition to surgical tumour resection has been proposed to clean the former tumour bed by destroying any remaining tumour cells in order to minimize the danger of local recurrences.

Especially in the head and neck area with its complex anatomical situation there is a risk of damaging blood vessels and nerves that are exposed during the treatment which causes functional disorder of these vital structures. Meso(tetrahydroxyphenyl)chlorin (mTHPC) is the mainly used photosensitizer for head and neck cancer but so far there are no detailed investigations to the effect of intraoperative PDT on these vital structures.

In this study large blood vessels and nerves at the neck and groin area as well as the surrounding striated muscletissue and the microcirculation of clinically healthy rabbits were treated by intraoperative PDT using the photosensitizer mTHPC. In order to find the treatment parameters, which cause maximum tissue destruction the light intensity (10 J/cm^2, 20 J/cm^2) and drug-light-interval (3 minutes, 6, 24, 48, 72 and 96 hours) were varied. The mTHPC dose stayed a constant 0,3 mg/kg which was assessed very well in other investigations. After surgical exposion of the large blood vessels (A. carotis, V. jugularis, A. femoralis as well as V. femoralis) and nerves (N. vagus and N. femoralis) the PDT took place directly in the open operation site. The effects of the photodynamic therapy on large blood vessels, nerves, microcirculation as well as the surrounding tissue were histologically examined and evaluated.

Supplemantary fluorescence microscopic investigations were carried out to achieve additional information about the localization of the photosensitizer at different time intervals after injection.

Our results haven shown that mTHPC mediated intra-operative PDT led to partly significant histological impact onto the vital structures in the irridation area. As described in literature, the stronger tissue reactions were caused by a light dose of 20 J/cm^2 as well as by using shorter treatment intervals (24 hours in relation to 96 hours). The consequence of the very short treatment interval (3 minutes) on the other hand was only minimal damage.

The mainly observed photodynamic effects on the blood vessels were hyperplasia of the vessel wall cells up to obliteration, formation of cobblestone endothelium, separation of the endothelium of venous vessels as well as thrombosis, but this did not result in any clinical symptoms. In seven of altogether 148 cases the vessels showed thrombosis or obliteration. The photodynamic therapy further led to a decrease of the myelin sheaths of the nerves however without any paresis. The striated musculature as well as the other surrounding tissues is subject to a pronounced necrosis.

There were no systemic side effects only due to PDT observed. Four of the however altogether 48 animals suffer from incurable respiratory symptoms. Three rabbits died of this, one had to be sacrificed. These four animals were subject to the strongest treatment conditions, 24 hours and 20 J/cm². Probably it was a matter of a subclinical disease which exists already before PDT, and the death of the animals is not due to the PDT. Some complications in woundhealing like developing of abscesses are common in rabbits and are not to see as consequence of the PDT.

The results from the histological investigations stood contrary to the fluorescence localization of the photosensitizer in the tissue. The strongest fluorescence was present in the lumen of the blood vessels partially at level of the endothelial cells, furthermore perivascular and perimysial.

Briefly after the injection (6 minutes) absolute fluorescence was largest. 24 hours after the injection it was clearly smaller and after 72 hours fluorescence was hardly noticeable.

Summarizing from these findings it can be concluded that intraoperative PDT with mTHPC leads to substantial histological changes of the large blood vessels as well as the nerves and the surrounding tissues. The extent of damage the depended on treatment parameters, however clinical or vital complications were not observed. mTHPC mediated intraoperative PDT seems to be a promising and safe treatment option which could complement existing treatment modalities in order to improve total survival rate in tumour patients.