9 General discussion

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This thesis is based on the results of a number of studies focussing on the role of radiation therapy in pituitary adenomas. An important finding of our series of non-functioning pituitary adenomas (NFA) is that immediate postoperative radiation therapy in case of residual disease strongly reduces the likelihood of re-growth. Health-related quality of life in treated NFA patients was found to be similar to that of the normal population, and the results of our study suggest that radiation therapy does not adversely affect health status. Life expectancy in both irradiated and non-irradiated NFA-patients with well-substituted hypopituitarism is comparable with the general population. Just in a very small proportion of patients with residual non-functioning pituitary adenoma, immediate postoperative radiation therapy may be regarded as over-treatment. There are, however, currently no predictive factors available, which could reliably select patients for either immediate postoperative radiation therapy or an active surveillance policy.

The possible induction of radiation-induced side effects is often used to delay or reject radiation therapy in NFA. However, in our series, this policy can not be confirmed as the incidence of possible treatment-related side effects after immediate postoperative radiation therapy were similar to that observed in case of an active surveillance policy in residual NFA. These results indicate that the possible treatment-related side effects, such as pituitary insufficiency induced by radiation therapy, are counterbalanced by hypopituitarism resulting from tumour re-growth and/or repeated surgical procedures. The consequences of an active surveillance policy, including frequent MRI-imaging, the risk of a second or even multiple operations and finally radiation therapy, should therefore not be underestimated. The possible (psychological) consequences of the uncertainties for the patient and his or her family in case of such a policy should also be taken into consideration.

It should be emphasised that patients included in this thesis were treated between 1970 and 2000 with relatively conventional radiation delivery techniques such as 3D-conformal radiation therapy. Since then, technological developments in radiation oncology have rapidly evolved. Currently, more advanced radiation techniques such as intensity modulated radiation therapy and stereotactic radiation therapy are clinically available and enable radiation oncologists to achieve a steeper dose gradient from the target volume to normal tissues, and thus, theoretically, to a further increase in the therapeutic ratio.

It is important that patients are well informed about the arguments in favour of and against radiation therapy and other possible treatment modalities. Therefore, an informative visit to a radiation oncologist, with expertise in the field of pituitary adenoma, should be part of the standard procedure.

As presented in this thesis, radiation optic neuropathy (RON) after conventionally fractionated radiation therapy in patients with acromegaly and non-functioning pituitary adenoma is a rarely occurring side-effect. It still remains unclear whether RON is more frequently occurring among patients with acromegaly than among those with non-functioning pituitary adenoma. Acromegaly with its endocrine syndrome is accompanied by damage to the blood vessels, and as a consequence, these patients are assumed to be more susceptible for radiation damage. Another explanation can be that the reported doses, received by the optic nerves and optic chiasm, are an underestimation of the really applied dose to the optic system due to limitations of the different radiation therapy calculation methods used over time. The pituitary in the sella turcica is surrounded by air cavities. In acromegaly generally these cavities are enlarged. Depending on the radiation treatment technique used, the different radiation beams pass more or less air cavity-length to reach the pituitary fossa. In air the radiation beam is less attenuated in comparison with normal tissue. The calculation methods in the past were not accurate enough to implement the attenuation factor for air. As a consequence the dose in the optic system will then be higher than assumed and reported. This might result in a small rise in occurrence of RON in acromegaly in comparison with non-functioning pituitary adenoma patients. On the other hand, in acromegaly the osseous structures are also more prominent in comparison with patients with NFA, which may also have an impact on dose distribution. The reported dose-response curves for radiation optic neuropathy are worthwhile, but should be interpreted with keeping these remarks in mind.

The basal pathophysiological mechanism of RON remains to be clarified. In addition, it still remains unclear why the optic chiasm/optic nerves are more susceptible for radiation damage in comparison with the other cranial nerves. Basic research is needed to understand the responsible mechanism, enabling the clinician to prevent and treat this very rare but serious side effect after radiation therapy. Fortunately, it is to be expected that the use of currently available advanced radiation therapy techniques will further diminish this very rare side effect.

Nowadays, position verification is considered standard in case of radiation therapy for all curative indications, including pituitary adenoma. With the introduction of three-dimensional-conformal and intensity modulated radiation therapy, non-coplanar radiation beam techniques are easier to apply in comparison with the past. The verification procedures for these techniques are discussed in one of the chapters and although complicated, resulted in adequate reproducibility.

The first step in radiation therapy for these patients is the production of a perfect immobilisation device system. Second, the use of high quality CT-scans in treatment position and co-registration with high quality MRI- and PET scans are essential in order to define the target volume as accurate as possible. Improved set up accuracy and advanced verification procedures during treatment will enable smaller margins from clinical target volume to planning target volume to account for the different uncertainties. Improving target volume definition methods will result in smaller radiation volumes and, theoretically less side effects. The availability of radiation dose calculation systems, that take into account the tissue inhomogeneities and provide information closer to the actual radiation dose distribution in both the target volume and the surrounding normal tissues, are essential.

Radiosurgery is a radiation technique that is increasingly used for small pituitary adenomas, which are located more than 3 mm from the optical system. Some assume that the fall-off effect on hypersecretion is more rapid in comparison with conventionally fractionated radiotherapy and that sparing the normal pituitary function with radiosurgery is superior to conventional techniques. Until now these assumptions have not been confirmed by adequate data[1,2]. The assumed benefit of radiosurgery is mainly based on selection bias, because only smaller adenomas are suitable and selected for radiosurgery. In case radiosurgery can be safely applied, however, it should be considered, as the number of visits to the radiation therapy department can be reduced considerably, which is more convenient for the patient. Fractionated stereotactic radiation therapy is a suitable technique for larger tumours.

Further improvement of the therapeutic ratio can be expected from particle therapy[3]. The beam properties of proton or heavy ions radiosurgery or stereotactic radiation therapy will result in lower doses to the non-target tissues in and outside the brain, which is superior to the currently used photons. The better dose conformity that can be obtained with particles will also allow for hypofractionation, particularly in the case of larger tumours, which might also be interesting in terms of cost-effectiveness.

Radiation therapy is a so-called tertiary medical specialty. This means practically, that the decision to refer patients with pituitary adenomas to the radiation oncologist is generally taken by endocrinologists and neurosurgeons. Thus far, this decision has been dependent to a large extent on their personal opinion about the role of radiation therapy. This thesis contributes to an evidence-based approach of radiation therapy of patients with pituitary adenomas. In our centre, the pro's and con's of neurosurgery, radiation therapy and medical treatments are discussed in a multidisciplinary team in which all relevant medical disciplines involved do participate. Such a multidisciplinary approach, using clear guidelines for every patient with a pituitary adenoma should become standard in order to improve the quality of outcome for the patients. Given the relative low incidence of this disease, the wide range of possible treatment modalities and the required expertise, this approach will also enable to initiate translational and clinical research projects.

References

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