Case Report

Uptake of Prostate-Specific Membrane Antigen (PSMA) in adenoid cystic carcinoma – Is PSMA-PET-CT a helpful tool in radiation oncology?

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Abstract

This case report shows the high PSMA-uptake in a patient with an adenoid cystic carcinoma of the maxillary sinus. Due to the intense ligand-uptake additional information for target volume delineation was obtained and the Treatment plan for bimodal radiotherapy with carbon ions was adapted accordingly.

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Background

Adenoid cystic carcinoma (ACC) is a rare tumor entity with a yearly incidence of 3–5 cases per million [1]. Nevertheless, ACCs account for 1% of all head and neck malignancies and 10% of all salivary gland tumors [2,3]. Histopathologically, ACC displays a cribriform arrangement of tumor cells and invasion of surrounding tissue. One of the main characteristics is an invasive growth pattern with spread along nerves in this relentlessly growing tumor [4], which is an unfavorable prognostic factor, associated with distant metastases and an adverse outcome. The clinical course is characterized by slow tumor growth and often results in local recurrences, even after long intervals from previous radical treatment [5].

Due to this rather indolent behavior, with frequent local relapses, treatment of choice is radical surgical resection followed by postoperative radiotherapy [6]. Chemotherapy only plays an inferior role in treatment of ACC and is recommended as a palliative treatment option in patients with progressive, symptomatic disease, mainly in more aggressive subtypes [7].

Furthermore, ACC belongs to a group of rather radioresistant tumors. Due to the infiltrative growth along the neural tracts in the skull base, applying high doses of radiotherapy remains challenging in view of close proximity to critical structures (e.g. optical nerve, brainstem). Therefore, in the last two decades, bimodal radiotherapy with particle therapy and photon irradiation has been used in our institution in patients with ACC. Carbon ions in particular offer several favorable features: due to the Bragg peak, they show a sharp increase of dose in depth followed by a rapid dose fall-off beyond this maximum, which allows to apply high doses in close proximity of organs at risk [8,9].

With the addition of a carbon ion boost, bimodal radiotherapy resulted in superior local control, progression free survival and overall survival compared to photon radiotherapy alone [10,11]. Furthermore, there was no difference between patients who had been subtotally resected or treated with definitive radiotherapy due to inoperability [10].

PSMA (Prostate-specific membrane antigen) is a cell surface protein with transmembrane location and a large extracellular domain. Owing to the enzymatic activity, PSMA allows for development of specific inhibitors and their internalization after ligand binding [12]. As described recently, 68Ga-labelled PSMA-ligands have been developed to detect relapses and metastases of prostate carcinoma [13,14]. PSMA is highly expressed in prostate carcinoma cells, but
also non-malignant tissues like kidney tubules or salivary glands [15], resulting in an additional intense tracer uptake in these organs in PET (positron emission tomography)-imaging [13]. Additionally, recent observations revealed that PSMA-expression is found in the neo-vasculature of non-prostatic solid tumors like squamous cell carcinoma, glioma, lung or breast cancer [16–18]. Physiologic tracer uptake into the salivary glands – even exceeding the uptake of healthy prostate tissue – was one of the most pronounced observations during evaluation of PSMA-ligands normal biodistribution. The knowledge of organ specific uptake (either driven by PSMA-expression or small molecule transporters) provides a strong rationale to ameliorate soft tissue delineation of tumors with origin in the salivary glands by PSMA-PET/CT.

Case presentation

In 2013, a 58-years old male patient presented with nasal airway obstruction, a visual deficit on the left eye and mild hypoesthesia of the left maxillary nerve. In a rhinoscopic examination a mass in the left nasal cavity with origin in the left maxillary sinus was detected. A biopsy was taken and histologically confirmed the diagnosis of an adenoid cystic carcinoma. Magnetic resonance imaging showed a large tumor mass with infiltration of the left maxillary sinus, pterygoid muscle, oral cavity and maxillary bone as well as a penetration to the cavernous sinus and left orbit. Additionally, growth into the anterior cranial fossa with resulting compression of the left temporal lobe was seen (Fig. 2a, dashed arrows). MRI and histological examinations both showed perineural growth and invasion, typical for ACCs. Chest CT-scan, abdominal sonography and bone scintigraphy did not show any signs of metastatic disease. Initial staging consequently was: c2T4b c2N0 c2M0.

An operation was refused by the patient due to the mutilating extent and he was referred to our institution for a definitive bimodal radiotherapy.

Due to the observation of physiologic PSMA tracer-uptake in salivary glands we decided to additionally perform a 68Ga-PSMA-PET-CT in this patient to see, if malign tumors of the salivary glands show these characteristics.

Treatment planning was based on all available diagnostic procedures, contrast enhanced CT and MR images as well as 68Ga-PSMA-PET-CT.

The patient was treated with a carbon ion boost to the macroscopic tumor disease of 18.0 Gy(RBE) in 6 fractions (single dose 3.0 Gy(RBE)) and a comprehensive photon plan of 54.0 Gy in 27 fractions (2.0 Gy single dose) with helical intensity modulated radiotherapy (IMRT). Carbon ion radiotherapy was applied at Heidelberg Ion Beam Therapy Center (HIT) with 3 beams in active raster scanning technique (Fig. 2e and f), whereas photon IMRT was applied via helical Tomotherapy® (Fig. 2g and h).

Radiotherapy was tolerated with mild toxicity. By the end of the treatment the patient was suffering from mucositis CTCAE grade II, mild dysphagia as well as a radiation dermatitis CTCAE grade I. In the follow up scans, 3, 6 and 9 months after treatment, partial remission (RECIST criteria) was detected (Fig. 2c and d), the previous radiographic side effects were declining with only mild xerostomia, CTCAE grade I persisting.

For treatment planning, MRI and a 68Ga-PSMA-PET-CT-scan (Fig. 1a-c) were performed. Additional 68Ga-PSMA-PET-CT was performed for research purposes and showed an intense tracer uptake inside the tumor in the left maxillary sinus with a SUV_{max} of 23.25 (Figs. 1 and 2). The infiltrative tumor growth along the nerves in the skull base was detected well in the 68Ga-PSMA-PET images and also showed contact to the temporal lobe (Fig. 2a, dashed arrows). Furthermore, 68Ga-PSMA-PET-CT showed a significantly increased uptake in the right maxillary sinus (Fig. 1a-c dashed white arrows), so that it seemed likely that the tumor had already spread to the contralateral side. In the MRI scan, contrast enhancement in the right maxillary sinus was interpreted as mucosal swelling and not as tumor infiltration.

Therefore, this finding changed the concept of target volume delineation, since this area of higher uptake was also included to the gross tumor volume (GTV) and the final clinical target volume (CTV) encompassed the complete right maxillary sinus.

PSMA-positivity in ACC was shown in previous reports and was used for diagnostic visualization of local recurrent but also distant metastatic disease [19,20].

As far as we know, this is the first report describing a potential use of 68Ga-PSMA-PET-CT for radiooncological purposes regarding target volume delineation. Nevertheless, due to the retrospective nature of this report, validation of quantitative segmentation and SUV thresholds for target volume delineation is lacking and should be investigated in future studies.

For secondary confirmation of PSMA-positivity we performed an immunohistochemistry (IHC)-staining for PSMA which showed low cytoplasmatic positivity in approximately 5% of ACC cells, similar to a recently published report [20]. Although, PSMA-expression in IHC was low, 68Ga-PSMA-PET-CT revealed high SUV_{max} values (see Fig.1).

Discussion and conclusion

Especially in ACC of the paranasal sinuses, target volume delineation remains challenging due to the frequent infiltration of the

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Fig. 1. 68Ga-PSMA-ligand PET CT. (a) non-contrast enhanced CT-scan shows a tumor of the left maxillary sinus with ipsilateral infiltration of skull base (black arrows) (b) intense 68Ga-PSMA-ligand uptake in the tumor with a SUV_{max} of 23.25 (c) fused images confirm infiltration of the contralateral maxillary sinus (dashed white arrows).
skull base along the cranial nerves and due to the close proximity of organs at risk in this area. Contrast-enhanced MR-imaging does not always differentiate between inflammatory changes, mucosal swelling or tumor infiltration. Due to the intense PSMA-ligand uptake of ACC cells, additional information from 68Ga-PSMA-PET-CT may be helpful in optimizing target selection and treatment planning. The potential therapeutic implication of a radionuclide-PSMA targeted treatment in a disease with limited treatment options such as ACC should be evaluated in the future.

Furthermore, these results show that 68Ga-PSMA-PET-CT might be useful as a noninvasive staging tool in patients with ACC.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical approval was obtained from the local Ethics Committee of Heidelberg University (S-321).

Availability of data and material

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Funding

This work was supported by the Medical Faculty providing a research grant for LK.

Author’s contributions

LK carried out data collection and analysis, drafted and finalized the manuscript. HH performed radiotherapy planning and assisted with figure and table preparation. FG conceived of the study. CK, JD and UH participated in data interpretation. CF and MH performed the immunohistochemistry-staining. All authors read and approved the manuscript.

Competing interests

All authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ctro.2017.10.003.

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