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Radionuclide therapy by direct intratumoural / intracystic approach

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When radiotherapy and chemotherapy - either alone or combined - have minimal impact on the local growth and control of solid tumours, when tumours are nonresectable and predominantly affect one organ or just parts of it, and when the local situation determines outcome and survival of the patients radionuclide therapy by the direct intratumoural/intracystic approach may be a promising alternative to other therapeutic strategies.

Among the clinical applications targeting tumours by direct administration of radionuclides bound to various biological vehicles, the treatment of malignant glioma, liver malignancies and pancreatic cancer plays a more predominant role while others such as in bulky lymph node metastasis or ovarian cancer and uterine carcinoma warrant further evaluation.

Malignant glioma is one of the most suitable tumor types for direct intratumoral/intracystic radionuclide therapy. Major benefits of a locoregional application of radiolabelled antibodies or peptides into the resection cavity of malignant glioma by use of an indwelling catheter are the low systemic toxicity, the favourable distribution, accretion and residence time of the radioimmunoconjugate / radiopeptide, the delivery of very high radiation doses to the target cells, the circumvention of the blood brain barrier, and the low risk of development of HAMA's (in case of antibody treatment), which could potentially hamper follow-up therapies. Most clinical trials have used tenascin-antibodies (BC-4, 81C6, labelled with ^{131}I or ^{90}Y) for locoregional radioimmunotherapy (RIT). Tenascin (TN) is an extracellular matrix glycoprotein, which is expressed in high-grade glioma but not in normal brain. In general RIT with TN-antibodies has been performed as additive treatment in patients who had previously undergone surgery and conventional radiotherapy. Based on the experience of several hundred treated glioma patients, locoregional RIT has been shown to be well tolerated, adverse events were rare and most often transient. Most importantly, however, it has been concordantly reported that locoregional RIT led to a significant increase in median survival of glioma patients at a high quality of life. Ongoing trials aim to further improve these achievements. Among those the pre-targeting approach (3-step method comprising locoregional administration of biotinylated anti-TN MoAb followed by administration of avidin about 24 hrs and of ^{90}Y-biotin another 14 to 16 hrs later) without or combined with systemic chemotherapy has gone another step forward and has also provided promising results (1). Beyond that approach other new strategies aim to increase therapeutic efficacy by the use of more potent radionuclides such as ^{188}Re or even α-emitters such as ^{211}At (5), the use of antibody fragments or even small diffusible peptides. As an example for the latter, ^{90}Y-DOTATOC has been locally injected in somatostatin receptor-expressing low grade and anaplastic astrocytoma demonstrating clinically meaningful responses (4).

Liver malignancies including hepatoma and (solitary) liver metastases have been either treated by ultrasound or computerized tomographic guided injection of ^{32}P chromic phosphate or ^{90}Y glass microspheres directly into the central part of the tumor (3). The procedure required local anesthesia and was in general performed in several sessions with time intervals of about 4 to 6 weeks in between. By these techniques high doses have been achieved in the tumours without or only with minor toxicity. Even though feasibility of the mentioned approaches has been documented and beneficial outcome has been reported there is some doubt whether these strategies may be able to compete with the various other locoregional treatment modalities such as radiofrequency ablation or e.g. selective internal radiation therapy, which makes use of the same principle, namely injection of ^{90}Y-labeled glass or resin based microspheres, however via intraarterial administration, thus enabling to treat multifocal lesion within one session. Analogous to direct instillation into the liver also in pancreatic carcinoma CT guided instillation of radionuclides directly into the tumour mass has been performed mainly using colloidal ^{32}P. Prior to intratumoural infusion macroaggregated albumin was given to blockade the exiting vasculature. By this technique in malignancies limited to the pancreas local control of disease has been achieved together with improved survival and quality of life of the patients (2). Adjuvant intraperitoneal admi-

nistration of ^{32}P chromic phosphate in patients with early and more advanced stage ovarian carcinoma or uterine carcinoma has shown to be feasible and was well tolerated. However, further large scaled studies are warranted to reliably answer whether by this approach intraperitoneal recurrence may be effectively prevented.

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