Local Interventional Therapy Options in Unimodal and Multimodal Treatment Concepts for Neuroendocrine Tumors (NET)

Petrovitch A, Gotthardt T, Grau P

Zentrum für diagnostische und interventionelle Radiologie, Institut für Interventionelle Radiologie, Zentralklinik Bad Berka GmbH, Zentrum für Neuroendokrine Tumoren Bad Berka Zentralklinik Bad Berka GmbH

Introduction

In the case of active hormone production, endocrine or neuroendocrine tumors are associated with a "hyperfunctional" syndrome or manifest themselves through local expansive growth and / or progressive spreading during the course of the disease. With hormonally active NETs, the hormonal effect is the main symptom, at least until the appearance of local problems comes to the fore.

Along with the rare genuine liver tumors, many NETs metastasize in the liver during their often longer course of disease. The reason for this is the liver's position as filter in the portal and caval circulation. Depending on the kind of primary tumor, hepatic metastasis is to be expected in up to 80% of cases. This involvement of the liver is often also the most significant survival factor.

Even if surgery under the aspect of curative treatment is still the gold standard, it must be determined that at the time of diagnosis less than one-third of patients are curatively operable. Through introduction of new therapeutic approaches, such as radioreceptor therapy, improved systemic chemotherapy protocols, and new interventional techniques, not only could an improvement be seen recently regarding potential tumor curability, but also in terms of long-term survival and quality of life concerning the in part very long course of disease.

Presently used local therapeutic Procedures

Particularly during the phase of isolated involvement of the liver, locoregional therapy poses a meaningful concept for improving prognosis and quality of life. Alongside thermal procedures like cryotherapy (CRYO), radiofrequency thermal ablation (RFTA), laser-induced interstitial thermal ablation (LITT), and chemical procedures, such as ethanol injection (PEI) or acetic acid injection (PAI), transarterial chemoembolization (TACE) has taken a dominant position among local ablative procedures. Recently, it has been supplemented through a further embolization procedure, the selective internal radiation therapy (SIRT). Moreover, there is the possibility of conditioning patients for an expanded liver resection (trisectorectomy) through portal vein embolization (PVE) and achieving a curative resection.

Figure 1. CT-guided placement of 4 RFA-electrodes into a metastasis in the sacrum.

Thermal Treatments (CRYO, LITT, RFTA)

Among the thermal procedures, cryotherapy (CRYO) and laser-induced interstitial thermal ablation (LITT), despite good results, have only comparatively low prevalence due to the substantial effort involved and the costs connected with them. Thermal therapy is currently dominated by radiofrequency-based systems that are presently used primarily by interventional radiologists, but increasingly by surgeons and in part by gastroenterologists and pulmonologists, also. Here, the organ regions have also increasingly broadened: the main region of use is still the liver, but tumors/metastases in the kidneys, lungs, spine, sacrum, and at other bone localizations are also being successfully treated in growing numbers.

Basically, RFTA is differentiated between mono-polar and bipolar systems, whereby the bipolar systems are increasingly establishing themselves in practice. On the one hand, this is a result of their simpler handling (no neutral electrodes required), and on the other the option to also treat larger tumors (up to 5 cm in diameter, in single cases up to 6 cm maximal tumor growth in diameter) and to achieve a safe A0 ablation with a sufficiently wide, tumor-free margin analogous to surgical R0 resection. This option is balanced by the necessity of placing and simultaneously controlling up to six probes with assistance of MRT or CT, which is sometimes difficult to do in practice. In comparison, mono-polar systems offer simple and safe placement, for instance, with use of the LeVeen needle in the case of small foci; however, they only allow for assured tumor destruction up to a limit of 2 cm. (Figure 1 RFTA of the sacral bone, bipolar)

In both procedures, destruction of tissue is caused by warming up to temperatures between 60 – 100°C. In the case of the bipolar Celon® system, this is achieved with the use of a high-frequency alternating current which leads to tissue warming through induction of frictional heat as a result of ion movement. Large vessels closely adjacent to the target region can be problematic. Here, a cooling effect caused by blood flow is to be expected which increases the risk that a vital tumor residue remains at the end of the intervention.

Strategies for solving this are temporary blocking of blood inflow through placement of a balloon catheter or prior embolization of the target region. Alternatively, a laparoscopic procedure or open surgery with temporary interruption to the flow of blood through the vessels (Pringle manoeuvre) is possible. If proximity to other vital structures is too close, for instance, to hollow organs, the latter variations also offer the possibility of safely performing RFTA.

Chemolytic Procedures (PEI, PAI

In the case of very small tumor foci (up to 2 cm max.), tumor destruction can also be realized through coagulation of the tissue as a result of applying 95% ethanol (PEI) or concentrated acetic acid (PAI). Both, already older therapeutic procedures have been increasingly pushed aside by the thermal ablation procedures; however, they do find use in single cases if thermal ablation or embolization is not possible. With tumors >2 cm they do not pose a meaningful therapeutic option. Performance is technically simple: after localization of the focus in an imaging procedure, lysate marked with a contrast medium is slowly perfused into the tumor using a centrally inserted needle under local anesthesia until the tumor parenchyma including the tumor margin is filled, whereby the application of the procedure on tumors with a detected tumor capsule is limited.

Embolization Procedures (TACE, SIRT, PFE)

Embolization procedures presently dominate local ablative treatment strategies for NET since thermal procedures often cannot be used because of tumor size or the number of foci. Due to their dominance of the local ablative treatment regimens and their significance for multi-modal therapeutic approaches, embolization

procedures should be covered more thoroughly here and critically examined.
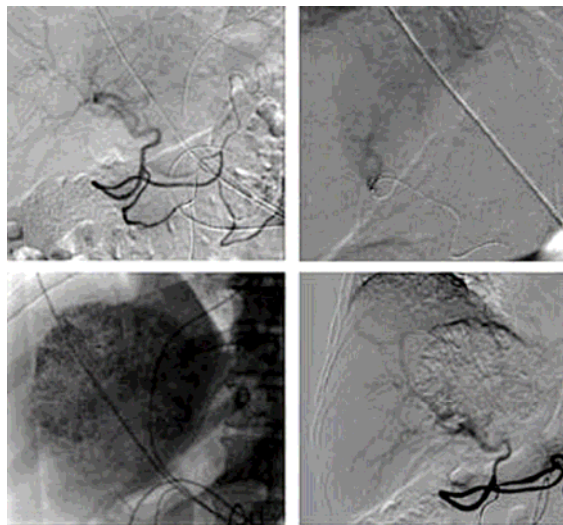
Figure 2. Complete TACE using DC-Beads with Doxorubicin and additional Lipoidol in a patient with functionally active NET and paraneoplatic hypercalcemia.
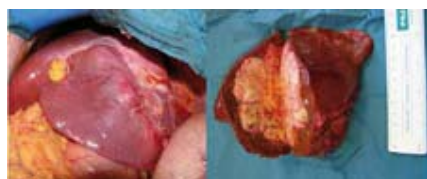
Figure 3. Surgical situs of the patient illustrated above. The tumor is completely embolized with a tumor-free resection margin.

Transarterial Chemoembolization (TACE)

Alongside purely palliative approaches, TACE is currently also used more and more in terms of new multi-modal treatment concepts for tumor mass reduction with the goal of "downsizing" and achieving secondary resectability, as well as for local tumor control in "bridging" until scheduled transplantation. Also in the case of a "hyperfunctional syndrome" caused by hormone-producing tumors, TACE is a good therapeutic approach because not only is the tumor itself attacked, but perfusion eliminates the tumor vascular bed thus quickly interrupting the hormonal flow. (Figure 2 Complete pre-operative TACE of a hormonally active NET of the liver; Figure 3 Intraoperative site for Figure 2)

Principle of TACE

TACE is based on the various vasculatures of liver tumors and healthy liver parenchyma. Depending on tumor type, masses in the liver are supplied up to 95% arterially, while only approximately 25% of normal liver parenchyma is nourished from the arterial vascular bed. For this reason, normal liver parenchyma nourished by the portal venous system is mostly protected during embolization of the arterial system, while ischemic necroses are caused in the tumorous tissue. Embolization of the vessels nourishing the tumor is combined with local superselective application of cytostatics and through this a superadditive effect is achieved in comparison to both individual procedures. On the one hand, this is caused by slow liver passage and on the other by a possible heightened effect with hypoxia. Due to liver clearance and the long length of time spent in the tumor, the systemic effects of the cytostatics are minimized and chemoembolization is better tolerated than systemic chemotherapies.

Indication/Contraindication for TACE

While the TACE for HCC introduced in 1978 by Yamada is to be viewed as standard procedure for the therapy options for downstaging or tumor control, it has been used in the treatment of liver metastases, particularly of NET also, colorectal carcinomas, and mamma carcinomas since the 1990's, though discussed controversially. However, what all approaches have in common is that TACE is only meaningful for those tumors/MTS which allow for detection of hypervascularization. However, contrary to this common opinion, it has been shown many times that with superselective probing of tumor capillary beds, even in cases of poorly vascularized tumors, a positive therapeutic effect is to be achieved.

Contraindications for TACE are tumor involvement of >75% of the liver, poor general condition (Karnowsky Index <50%), and severely limited liver function

(Quick <40%, PTT >45s, albumin <2g/dl), along with obstruction of bile ducts (bilirubin >3 mg/dl) or pronounced ascites. Florid infection or myelosuppression (leukocytes <2000/ml and thrombocytes <70,000/μl) are also contraindications for TACE. Occlusion of the portal vein is in principle a contraindication for TACE, but with good collateralization, superselective chemoembolization can be performed in exceptional cases. Another relative contraindication is biliodigestive anastomosis, especially if bacterial colonization of the bile ducts is to be assumed.

Presently there are basically two approaches for TACE available:

a) *Classic TACE* with suspensions of cytostatics and embolization media. Occlusion of the tumor capillary bed can be done principally with microspheres, Lipiodol, polyvinyl alcohol (PVA), or gelfoam. As cytostatics, adriamycin, mitomycin, cisplatin, doxorubicin, 5-fluorodeoxyuridin, 5-fluorouracil, dacarbazin, and streptozotocin are used in various combinations and mixed with different embolization media. A uniform concept for therapy has not yet been able to establish itself. At our institution, the combination of cisplatin/epirubicin with Lipiodol has proven itself effective. The procedure is subject to the new approach described under (b); however, it allows for semiselective embolization in wedge position under difficult vessel conditions since the accidentally embolized healthy liver vasculature recanalizes through RES following Lipiodol removal. As a result, this form of the procedure still finds use when superselective probing of the tumor capillary bed is not possible. Long retention of Lipiodol in the tumor is typical which hinders differentiation in relation to contrast media during CT and makes further monitoring of disease progression difficult. Here also, necroses are observable in the tumor; however, complete tumor destruction is hardly achieved.

b) *DC Bead TACE*. This form of superselective TACE was introduced in 2005. Here, microspheres, on whose surface highly-soluble doxorubicin is absorbed, function as the embolization medium. In the tumor, cytostatics are exchanged for water over a period of 14 days and released in a protracted manner. The procedure is by far more effective than classic TACE (a) since the microspheres absorb water in exchange for cytostatics, continue to expand, and occlude the vessels definitively. Since recanalization or removal via RES is not possible, the procedure requires an explicit superselective probing of the tumor capillary bed. The formation of air bubbles in the tumor in the days following is typical. This is caused by rapid tumor lysis and not to be assessed as a sign of abscess. During the continued course of events, colliquative necrosis of the embolized area and cystic conversion occur during the following weeks. With complete embolization, this area shrinks in the subsequent months due to reabsorption of the decomposed material.

(Figure 4 Superselective TACE with DC Beads with multilocular involvement, angio and CT finding)

In both cases, embolization occurs after transfemoral access under fluoroscopic control in order to avoid embolisate reflux in the large arteries and to protect the A. gastroduodenalis and A. cystica.

Along with the usual risks involved with angiography: hemorrhaging, aneurysm spurium, arterial embolism, vessel occlusion and reaction to contrast media, the specific risks of TACE must be explained. Besides rapid tumor lysis with post-embolization syndrome and tumor lysis syndrome, partial liver necroses ranging to hepatic failure can

occur. These complications are rare. Even more infrequently do bile duct necroses and cholangitis or abscesses appear. The low rate of incidence for these rare complications is assured only by a superselective approach; with an unselective approach an increase in the rate of complications is to be anticipated.
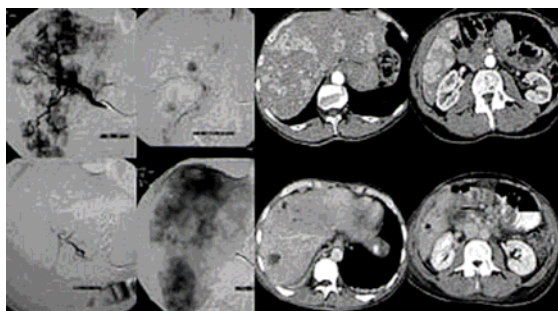

Figure 4. Superselective TACE, multiple interventions due to extensive metastases in the liver due to non-functional NET. In the panels of the left side angiographic images and on the right CT with intravenous contrast. Upper panels depict the situs before TACE and lower panels after the second TACE. Most metastases are completely embolized.

At our institution, pre-medication of patients with 15 mg (Dipidolor®), 2000 mg ampicillin/1000 mg sulbactam, and 4 mg odensatron (Zofran®) as brief infusions has proven itself effective. Post-embolization syndrome (see above) appears only seldom.

A follow-up of the therapy's success and embolic distribution should be done after 4 – 6 weeks in a CT of the abdomen. Since Lipiodol shows itself to be natively hyperdense during CT, saturation of the mass and possible diversion of the embolisate can be evaluated easily. Following classic TACE, to check for the presence of remaining vital residual tumorous tissue, Doppler sonography, if applicable contrast-enhanced liver sonography or contrast-enhanced MRT, should primarily be used since due to the inhomogeneous embolic distribution assessment of tumor vitality is made difficult during contrast-enhanced CT. In cases of not yet complete embolization or newly detectable vital tumor in the margin zone, re-embolization can take place after 4 -6 weeks. With DC Bead TACE, a four-phase CT with contrast medium is recommended since with the same method an easier comparison can be made for pre-interventional imaging and due to higher local resolution, the local vessel situation can also be evaluated at the same time before a possible re-intervention.
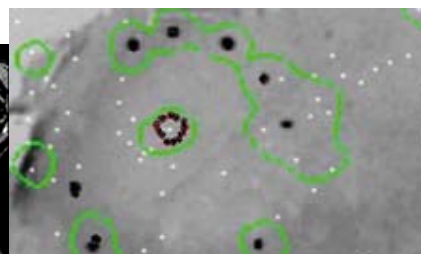
Figure 5. Isodose distribution after SIRT.
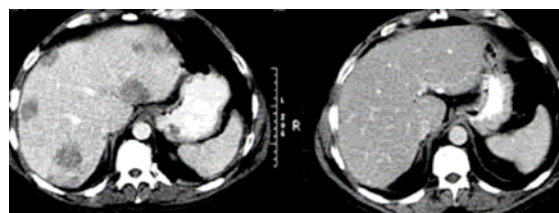
Figure 6. Complete remission of liver metastasis after SIRT 15 months after the procedure.

SIRT

Principle of SIRT

The goal of selective internal radiation therapy (SIRT) is to apply a high radiation dose to the tumor tissue and to only minimally expose the surrounding tissue. To do this, emitters with a short range, e.g. ^{90}Y (ß emitter), are bound to a suitable carrier medium (glass or resin microspheres). As in the procedure involving TACE, the microspheres are slowly infused into the arterial blood flow following catheterization of the vascular areas affected by tumor. In contrast to TACE, in general no multiple superselective probing of the tumor capillary bed is possible because of potentially high radiation exposure to the examiner. The guide catheter is placed in the main capillary bed of the side of liver affected by tumor (right or left half of the liver) and the embolisate infused slowly and fractionally. Similar to semiselective embolization in wedge

position, the very small microspheres with SIRT (30 – 100 μm) follow the blood flow and accumulate heavily primarily in the hypervascularized tumor capillary bed. At the end of the procedure, an intense radiation dose in the target volume is achieved alongside devascularization of the tumor capillary bed.

Our own experiences are based on the use of resin-bound microspheres (SIR-Spheres from Sirtex) containing ^{90}Y, a pure, high-energy ß emitter with a half-life of 54.2 hours. Each sphere contains 50 Bq, the maximum energy emitted is 2.27 MeV with a mean of 0.93 MeV; the range of emissions in tissue is 11 mm with a mean of 2.5 mm. After a period of 11 days, 94% of the radiation on average is delivered in the target volume making the action time of SIRT comparable to the cytostatic release from the conjugates with DC microspheres (complete delivery after approximately 14 days). Prior to actual SIRT, a coiling of the A. gastroduodenalis and, if relevant the A.cystica also, must take place in order to exclude incorrect embolic distribution with the consequent severe ulceration/tissue necroses. Likewise, an advance technetium scan for determining shunt volume is a necessary pre-requisite since a shunt volume of >20% precludes SIRT.

Indication/Contraindication/Risks of SIRT

SIRT is well-suited for treatment of multilocular liver involvement because, in comparison with TACE, a "comprehensive" application of the therapy is possible. Unlike with TACE, the embolic effect is less pronounced and therefore there is less risk of perfusion damage in normal liver parenchyma. Hypervascularization of the tumors is pre-requisite. If tumor vascularization is minimal in comparison with surrounding liver parenchyma, then SIRT is contraindicated since in this case only a minimal therapeutic effect in the target volumes, but an increased radiation exposure to the liver parenchyma, is to be expected. The main risk involved with SIRT is radiation-induced liver disease, followed by consecutive liver failure under certain circumstances. In particular, the risk is heightened with increased levels of bilirubin/disruption of bile flow so that an overall bilirubin level of 2 mg/dl is to be considered an absolute contraindication. Likewise, the indication in patients with limited hepatic function is to be viewed critically. A serum albumin of < 3 mg/dl and an increase of ASAT/ALAT by more than five times the norm, for instance, can be considered as a reference value for excluding SIRT. Such patients to be classified as high-risk do not profit from SIRT; their survival is clearly shortened with 108 days following therapy when compared with the survival of low-risk patients who have 466 days. SIRT in high-risk patients (see above) is therefore not advisable. Analogous to TACE, the indication in the case of previously existing biliodigestive anastomoses should be strictly limited because with bacterial colonization of the bile ducts an increased risk of post-interventional abscess is to be assumed.

Figure 7. Embolization of the portal vein: Central coiling and additional embolization with Histoacryl/Lipiodol.

Portal Vein Embolization (PVE)

Portal vein embolization (PVE) is an alternative method in the curative therapy of isolated, unilateral (usually right side) involvement of the liver if a curative surgical approach is planned. Expanded liver resection (trisectorectomy) as R0 resection is the basis of the concept. This can usually only be performed with a sufficient volume of remaining prospective remnant liver. In case of too low a prospective remnant liver volume (<0.5% body weight), hypertrophy of the remnant liver can be induced.

Figure 8. CT before and after 4 weeks portal vein embolization and trisectorectomie. The hypertrophy of segments 2/3 are clearly visible.

Principle of PVE:

Fundamentally, embolization of the arterial and venous capillary systems in the side affected by tumor can find use here. Due to the fact the liver is primarily supplied by portal circulation (approximately 75%), arterial embolization is clearly inferior to portal vein embolization in inducing liver growth. Following transcutaneous ultrasound and x-ray-assisted puncture of the portal venous region affected by tumor, stepwise embolization of the individual segments occurs with Lipiodol®/Histoacryl® or particles. The central portal vein areas of the affected side of the liver are occluded with detachable balloons or metal spirals (coils). Open portal vein ligature and transmesocolic portal vein embolization after exposure of the mesenterial vein are available as surgical alternatives, but find use only in special cases due to their great invasiveness in practice.

Embolization leads to complete occlusion of portal vein perfusion of the affected side and with it to the demise of embolized liver sections. The contralateral side hypertrophizes as a consequence of hyperperfusion and the simultaneous release of growth mediators. (Figures 7 and 8 Performance of PVE and CT before and after PVE/resection)

Indication/Contraindication/Risks:

Unclear is the question concerning parallel inducement of tumor growth in the embolized remnant liver. Aside from the desired hypertrophy of the healthy hepatic lobule, at least some studies also show increased tumor volume by 20 – 50% in the embolized hemisphere. This can in some patients lead to secondary inoperability. Likewise, (rare), previously unknown micrometastases can grow in the assumed healthy liver segments. While these presented an absolute contraindication for trisectorectomy up until a few years ago, today in individual cases involving favorably located single MTS in the prospective remnant liver and sufficient hepatic volume, RFTA of the metatstases can initially be performed and subsequently trisectorectomy is still possible to carry out. This very extensive approach is, however, to be viewed as applicable to single cases and not proven in this form by studies. If tumor foci are present near to the planned resection border, a superselective TACE of the involved tumor areas should be done before PVE in order to prevent tumor spreading to the prospective remnant liver as far as possible. Indication for a combined approach should be very strictly limited since the risk of severe liver damage is increased with simultaneous intervention into the arterial and portal systems. At the same time, however, the effectiveness of growth inducement is also increased.

Despite the possible restrictions mentioned above, pre-operative portal vein embolization has become an important tool now at centers specialized in liver surgery and radiology as an interdisciplinary approach to the curative treatment of advanced liver tumors/MTS.

Tumor entity/ Indication	Type of embolic therapy	Method of approach	Combination	Treatment goal
Large (>20 cm), solitary, inoperable; hyper-/hypovascularized superselective possible	TACE DC Bead + doxorubicin HL	Sequential, multiple sessions	If tumor residue size is <6 cm, RFTA of the residue	Tumor mass reduction and ablation of residue; Tumor control Full remission possible.
Multifocal both hemispheres; hyper-/ hypovascularized superselective possible	TACE DC Bead + doxorubicin HL	Sequential, multiple sessions	-	Palliative tumor control or bridging until transplant
Large, central or multifocal unilateral; hyper- or hypovascularized superselective possible	TACE DC Bead + doxorubicin HL	Single shot – complete embolization in one session	Portal vein embolization after one week to induce growth of the remaining liver; after 4 weeks resection	Curative. Tumor control and suppression of tumor expansion in the contralateral liver during growth phase.
Not more than 5 foci; foci <10 cm hypervascularized Not superselective	TACE Lipiodol+ cisplatin/epirubicin in wedge position	If possible, single shot	-	Palliative. Tumor control; not so effective as DC Bead TACE; more systemic side effects
<5 foci; <5 cm/focus	- Embolization, only if, as a result of a cooling effect on adjacent vessels, complete RFTA cannot be expected.	Embolization without cytostatics, e.g. contour, bead block, etc. superselective	Primarily RFTA for tumor destruction Note: expanded necroses with prior arterial embolization	Curative
Multifocal, many small foci not selective, only hypervascularized	SIRT (selective internal radiotherapy)	Embolization with yttrium-90 glass microspheres	Combine with systemic chemotherapy – SIRT in the pauses between blocks possible; note: Avastin.	Palliative; tumor mass reduction, partial or full remission possible
Multifocal, condition following radioreceptor therapy selection receptor-negative clone	TACE with DC Bead + doxorubicin HL	Sequential, since foci usually numerous		Palliative; tumor mass reduction

Table 1 Combinations of tumor embolization with other local or systemic treatments

TACE/SIRT/RFTA – When to apply which procedure?

The strength of the microsphere-based (DC Bead) TACE lies in the possibility to treat not only hypervascularized and weakly vascularized tumors/MTS of the liver through superselective application, but also those of the lung, kidney, and pancreas. If a superselective approach is not possible and despite this TACE is to be attempted, then the "classic procedure" for TACE should be followed with a suspension of cytostatics (e.g. cisplatin/epirubicin) and Lipiodol, an oleic-acid derivate as embolization medium. If multilocular liver involvement with hypervascularized tumors is present, SIRT is a good treatment alternative. If single liver foci are to be treated (5 foci maximum with a maximum diameter of 5 cm, "rule of five"), RFTA is preferable, percutaneous, or if that is not possible, then through open surgery or laparoscopy. Often the combination of embolizing procedures with other local ablative methods or systemic treatments is worthwhile. Examples are presented in Table.... The decision which uni- or multi-modal therapeutic approach to pursue should be met in interdisciplinary tumor consultation.

Quality of life

With all palliative procedures, their influence on quality of life and hospitalization time are important factors. In terms of TACE, the differences in the safety of both procedures are remarkable. In our own study (SF36, VAS, DHI) of a total of 514 cases, 22% of patients showed postembolization syndrome with pain, nausea, fever, and long-lasting fatigue with a comparably superselective approach with classic TACE using Lipiodol, while only 3% of patients following DC Bead TACE complained of postembolization syndrome (see Table 1 for study overview). Hospitalization time following intervention was on average two days shorter for DC Bead TACE with comparable severity of intervention. This superiority of TACE using DC Bead microspheres is most probably due to the stronger binding of the cytostatic and its slower release into the tumor, as well as to only a minimal elutive effect, while with classic TACE, high plasma levels of the cytostatics can be detected in the first two days. In both procedures, abscesses are extremely rare to appear; with DC Bead TACE, there was only one case of liver abscess development in a total of 158 cases; however, it was repeated during the second round, also. Retrospectively, colonization of the bile ducts following biliodigestive anastomosis was established as the cause. This observation moved us to view biliodigestive anastomosis as relative contraindication (q.v.) for future TACE procedures.

Clinical Use

Along with local tumor control with a gain in survival time, an improvement of B symptoms during therapy is also to be noted in some patients. In particular, stabilization of body weight and stamina occurred. In addition, the local ablative therapy offers a good approach for treatment of patients suffering pain caused by capsule expansion in the case of marginal liver metastases which is otherwise difficult to treat.

Conclusions:
With local ablative therapy, highly effective procedures for tumor control and tumor mass reduction are available which are well-suited for the palliative treatment of NET patients on the basis of their comparably minimal invasiveness and negative effects on general condition. In addition, they are a valuable component of multi-modal, curative therapeutic approaches in combination with other systemic and surgical treatments.

Directly because of their inclusion in multi-modal therapy concepts, the decision regarding their use should be made in interdisciplinary tumor consultation between radiologists, surgeons, oncologists, gastroenterologists, and nuclear medicine specialists.

Alexander Petrovitch MD

Thomas Gotthardt MD

Patricia Grau MTRA

Contact:

Zentrum für diagnostische und
interventionelle Radiologie
Institut für Interventionelle Radiologie
Zentralklinik Bad Berka GmbH
Robert-Koch-Allee 9
99437 Bad Berka
zdir-irad@zentralklinik-bad-berka.de