REVIEW ARTICLE

Techniques of Interventional Tumor Therapy

Andreas H. Mahnken, Philipp Bruners, Rolf W. Günther

SUMMARY

Introduction: The last few years have seen the rapid development of new image-guided interventions for the local treatment of malignant tumors. The goal of this article is to provide an overview of the techniques that are most commonly used today in interventional oncology.

Methods: Selective literature review on the current state of image-guided interventional techniques for local tumor therapy.

Results: While surgery, radiation oncology, and systemic chemotherapy are still the three main pillars of tumor therapy, a broad range of minimally invasive, image-guided techniques for local tumor treatment is now available. These may be categorized as percutaneous injection of a toxic substance, transarterial embolization, thermal ablation, and internal radiotherapy. The choice of treatment depends on the type, location, and size of tumor. The greatest amount of clinical experience to date has been gathered in the treatment of primary and secondary hepatic malignancy, but there are interventional treatment options for virtually all regions of the body. At present, the utility of this form of treatment is limited for very large or multiple tumors; novel therapeutic options for these situations are now being studied.

Discussion: The outcome of treatment depends on a judicious determination of the indication for it. The indication should be established by interdisciplinary consensus after all treatment options have been considered.

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Malignant neoplasms are the second most common cause of death in Germany; every fourth German dies of a malignant tumor (e1). Surgery, radiotherapy, and systemic chemotherapy are the established cornerstones of tumor treatment. Minimally invasive, image-guided procedures have also come into widespread use in recent years. These techniques, previously largely focused on the devascularization of tumor vessels, have now been extended to include a large number of direct ablative methods as well as methods to reduce pain and stabilize bone. The term "interventional oncology" has come into use in the English-speaking world for these types of procedures (e2). However, except for the treatment of hepatocellular carcinoma (HCC), there are no uniform guidelines to date regarding the appropriate indications for these procedures. The goal of this article, based on a selective review of the literature, is to provide a summary of the local ablative techniques that are most widely used at present, and of their results.

Techniques and Indications

The local interventional treatments can be classified into four groups according to their mechanisms of action (table):

- Percutaneous direct injection of toxic substances
- Transarterial embolization
- Percutaneous delivery of thermal energy
- Internal radiotherapy.

A further mode of treatment is image-guided stereotactic radiotherapy with modern methods of respiratory synchronization (respiratory gating and tracking). This is not, strictly speaking, an interventional treatment and therefore will not be discussed further in this article (e3).

Percutaneous direct injection

Direct percutaneous ethanol injection (PEI) is the oldest percutaneous method of treating tumors that remains in use (e4). A fine needle is positioned in the tumor under image guidance and pure ethanol is injected through it (figure 1). This results in dehydration and necrosis of the tumor cells. For complete tumor ablation, all parts of the tumor must be reached. This can be achieved either by multiple repositioning of a single needle or by the use of multiple needles. A high dose of alcohol can be given in one treatment session, or else

TABLE

Overview of currently available image-guided interventional techniques for local tumor therapy and their possible indications (source: the authors)

Technique		Organ	Indications*
Percutaneous direct injection	PEI/PAI	Liver	HCC $\leq$ 3 cm (4)
		Other	Decision in individual cases (obsolete)
Transarterial embolization	TACE/TAE	Liver	Inoperable HCC (4), cholangiocellular carcinoma, neuroendocrine tumors, uveal melanoma (colorectal carcinoma, carcinoma of the breast)
		Bones	(Preoperative)
		Kidney	Tumor hemorrhage, before thermoablation, (preoperative)
		Other	Decision in individual cases
Thermoablation	RFA	Liver	Inoperable HCC with $\leq$ 3 foci (4), multifocal metastases $\leq$ 3.5 cm, unifocal metastasis $\leq$ 5 cm (e85)
		Lung	$\leq$ 3 metastases per lung, all of which are $\leq$ 3 cm (inoperable non-small-cell lung cancer)
		Kidney	Tumor $\leq$ 5 cm in a single kidney, von Hippel-Lindau disease, multiple tumors
		Bones	Osteoid osteoma, symptomatic bony metastases
		Other	Decision in individual cases/experimental
	LITT	Liver	See RFA
		Other	Decision in individual cases/experimental
	Microwave ablation	All	Experimental
	Cryotherapy	All	Experimental
	Focused ultrasound	All	Experimental
Internal radiotherapy	SIRT	Liver	After failure or exclusion of all other treatment options (salvage)
	Interstitial brachytherapy	All	Experimental

*Indications in parentheses are currently debated.
PAI, percutaneous acetic acid injection; TAE, transarterial embolization; PEI, percutaneous ethanol injection; HCC, hepatocellular carcinoma; TACE, transarterial chomoembolization; RFA, radiofrequency ablation; LITT, laser-induced thermotherapy; SIRT, selective internal radiotherapy

the tumor can be treated in multiple sessions spaced several days apart with a lower dose of alcohol per session. Acetic acid can also be used instead of alcohol. Because the distribution of injected fluid in the hepatic parenchyma is unpredictable, this technique is only applicable to (pseudo-)encapsulated tumors. It has not been found to be useful in the treatment of tumors that grow by infiltration, such as metastases.

Studies on the treatment of histologically verified hepatocellular carcinoma (HCC) with PEI have shown good local tumor control. Total tumor necrosis is regularly achieved in tumors measuring 2 cm in diameter or less (e5) and in two-thirds of tumors measuring 3 cm (e6, e7). The median survival rates after 3 and 5 years are 50% to 80% and 28% to 48%, respectively (1, 2). The use of acetic acid seems to be advantageous for local effectiveness (e8, 3). PEI is not as good as thermoablation with respect to local tumor control and survival (e9) but has a lower complication rate (e10). Current guidelines support the use of PEI to treat up to 3 foci of HCC measuring up to 3 cm and when comorbidity contraindicates surgical treatment (4). PEI is currently undergoing a renaissance, as it is being used in combination with transarterial chemoembolization (TACE) or radiofrequency ablation (RFA) with a resulting prolongation of survival (5, 6).

Typical adverse effects include local pain, postinterventional fever, and transient alcohol intoxication. The more common complications are hemorrhage and tumor cell seeding, with overall complication rates ranging from 1.7% to 3.2% (1, e11).

Transarterial Embolization

In transarterial chemoembolization (TACE), the administration of chemotherapeutic drugs is combined with embolization. In comparison to arterial chemoperfusion, TACE results in a higher concentration of active drug in the tumor, in addition to tumor ischemia. Residual levels of the active drug can be detected in the tumor up to one month after treatment (e12, e13).

Guidelines support the routine use of TACE in the treatment of advanced HCC *(figure 2)* (4). Another accepted indication is for tumor control during the waiting period before liver transplantation (e14). In a randomized controlled study, the 1- and 2-year survival rates after TACE for HCC were 82% and 63%, significantly better than the results obtained with conservative treatment (63% and 27%, respectively) (7). These positive findings have been confirmed in meta-analyses (8, 9). Nodular tumors have a more favorable prognosis than diffusely infiltrative ones when treated with TACE (e15). Repetition of the procedure improves survival (e16). Transarterial embolization (TAE) without any chemotherapeutic agent is also occasionally performed (e17). Although randomized controlled trials have not yet shown any statistically significant difference between TACE and TAE with respect to survival, a trend toward prolonged overall survival has been found after TACE (9).
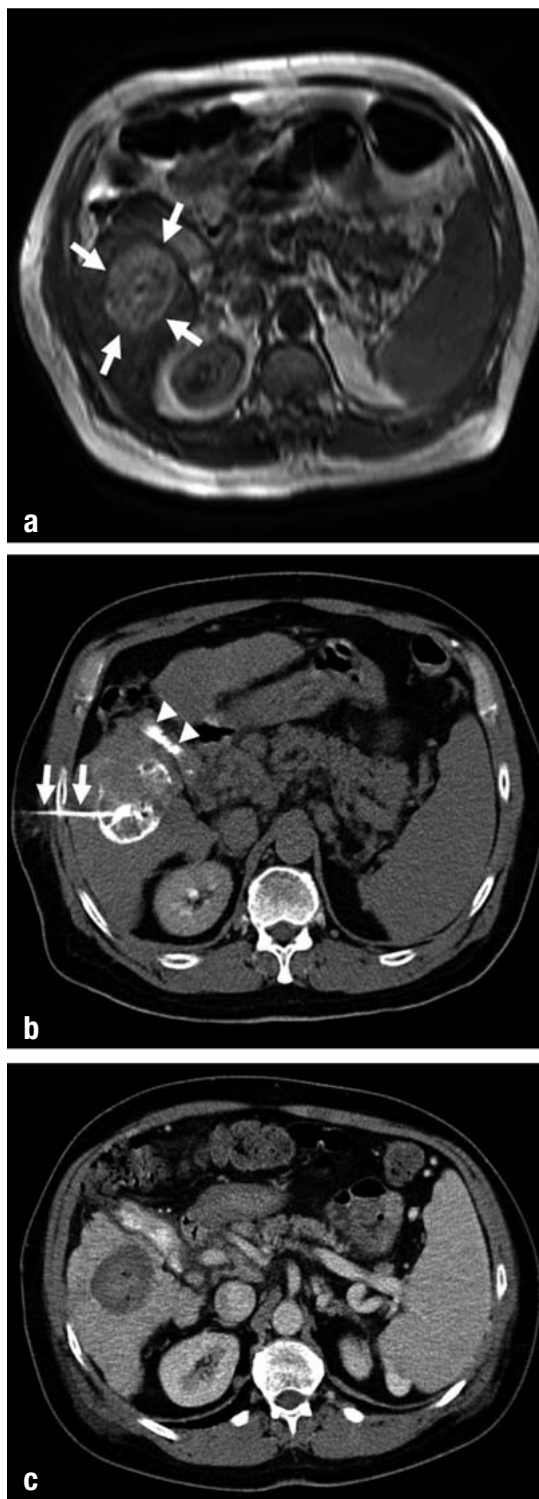

Figure 1:

The MRI scan of this 56-year-old man with longstanding hepatic cirrhosis due to hepatitis B and histologically confirmed hepatocellular carcinoma (HCC) reveals, in segments V/VI, a 4.6 cm sized tumor with nodular growth (a; arrows). The CT after tumor puncture with a dedicated 20 gauge needle with side holes (b; arrows) and injection of a mixture of ethanol and contrast medium shows a good distribution of contrast throughout the tumor. Gallstones are also seen (b; arrowheads). A CT obtained three months later shows the fully necrotic tumor as a parenchymal defect that does not take up contrast medium (c).
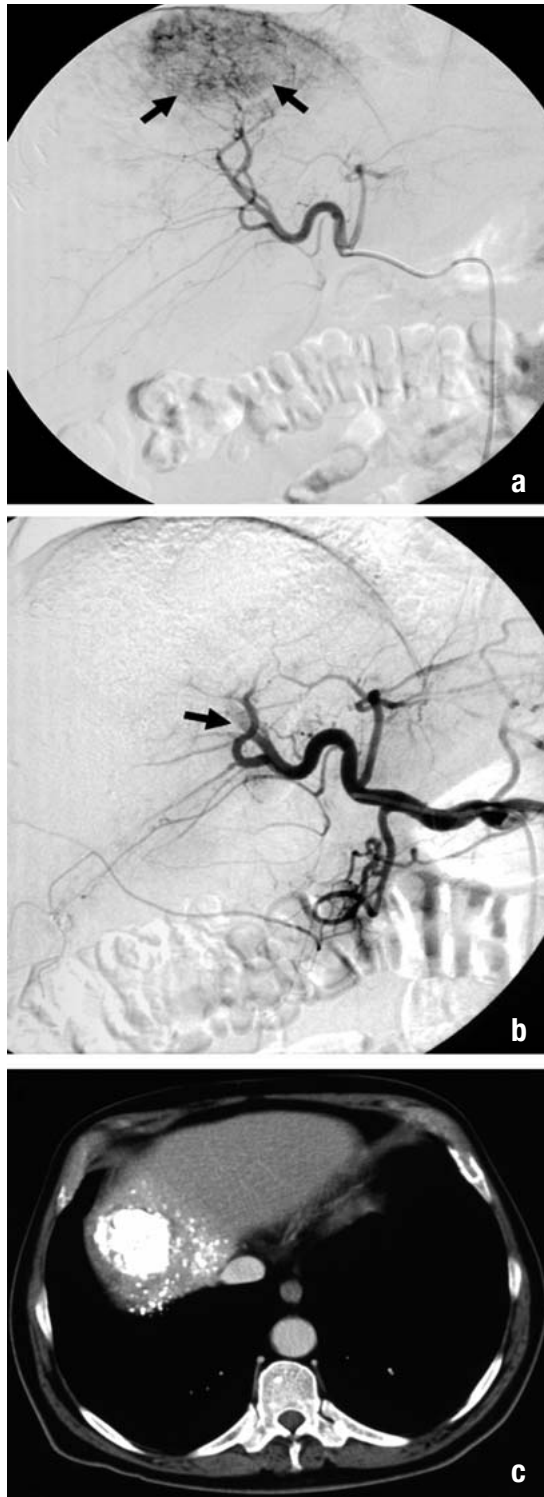
Figure 2:
The angiogram of this 63-year-old man with histologically confirmed hepatocellular carcinoma shows a 5.6 cm sized, markedly hyper-vascularized tumor in the right hepatic lobe (a; arrows). The tumor is no longer seen in a second angiogram performed immediately after selective transarterial chemoembolization (TACE) of the tumor-bearing hepatic segment with a mixture of doxorubicin and an oil-based contrast medium. The feeding vessel of the tumor is occluded (b; arrow). A noncontrast CT obtained the following day confirms successful embolization with good coverage of the tumor by radio-opaque embolization material (c).

Positive results are available for the treatment of hepatic metastases of neuroendocrine tumors (e18), uveal melanoma (e19), carcinoma of the breast (e20), and cholangiocellular carcinoma (e21). On the other hand, TACE appears to be indicated for the treatment of metastases of colorectal carcinoma only in patients who have already been maximally treated with chemotherapy (e22, e23).

Drug-releasing particles for use in TACE are currently being clinically tested (e24). Initial data regarding the use of doxorubicin-releasing particles to treat HCC show a radiological treatment response in 75% of patients (e25). Initial trials with irinotecan-releasing particles are now being performed for the treatment of hepatic metastases of colorectal carcinoma (e26).

In principle, embolization can be performed in any other area of the body as well. Particularly in the kidneys and bones, this technique can be performed preoperatively or as a palliative measure (e27–e29). There is some debate about the results at present, however (e30), so the use of embolization in these ways remains restricted to selected, individual cases.

Thermoablation

Hyperthermic ablation techniques have come to be used much more widely in recent years. These techniques involve the deposition of thermal energy (ie, heat) in tumor tissue under image guidance. Local heating of tissue to 60°C to 100°C causes protein denaturation and coagulation necrosis.

Radiofrequency ablation

In radiofrequency ablation (RFA), a high-frequency alternating current is applied to the tumor tissue through probes placed under image guidance. The current causes movement of ions, resulting in frictional heat that spreads through the tissue in a pattern determined by the design of the applicator (e31). Thus, the shape and size of the heat-induced necrosis can be controlled (e31, e32). As in all thermal techniques, local cooling effects occur, particularly at the periphery of the heated zone (e33). Therefore, tumor tissue bordering on large vessels may be inadequately heated, so that there is a locally elevated risk of recurrence. The latter risk can be reduced by the performance of embolization before RFA. Since the use of RFA for tumor ablation in animal experiments was first described in 1992, the technique has developed into the currently most commonly used thermal ablation technique (e34).

RFA was initially established as a useful method of treating inoperable primary malignancies of the liver. The indications for the procedure were rapidly extended. It is now also used to bridge the waiting period before liver transplantation, and even, in some cases, as a competing alternative to surgery. Guidelines recommend the use of RFA (just as they recommend the use of PEI) to treat up to 3 HCC foci measuring up to 3 cm in diameter when comorbid problems contraindicate surgical treatment (4). The 1-, 3-, and 5-year survival times are 87%

to 97%, 51% to 67%, and 27% to 54% (10, 11, e35). Long-term survival depends on an initially complete ablation with an adequate safety margin around it (e36). The former improves 5-year survival from 27% to 42% (e35). In randomized controlled studies, the results of RFA did not differ significantly from those of surgery for small (≤5 cm) HCC tumors: the 1-year survival rates were 94% to 96% vs 91% to 93%, and the 3-year survival rates were 71% to 87% vs 73% to 86% (e37, e38).

Because the liver is often the first and only site of metastasis of colorectal tumors, local therapy has the potential to prolong life. In one study, RFA treatment of inoperable patients with fewer than 5 hepatic metastases measuring less than 5 cm in diameter and without any extrahepatic metastases resulted in a 5-year survival rate of 30% (12, 13, e39). Important parameters influencing the success of treatment include the pre-interventional level of carcinoembryonic antigen (CEA) and the number and size of metastases (e40). Positive results have also been reported for the treatment of neuroendocrine tumors with RFA. The rate of local tumor control has been reported to be 75% to 90% after 21 to 38 months of follow-up (e41, e42).

The complication rate of hepatic RFA is 2% to 10%, with a mortality of 0.09% to 1.4% (e43, e44). The more common complications are hemorrhage, pleural effusion, and hepatic abscess. The major drawback of RFA at present is the lack of prospective, randomized clinical trials with clearly defined patient groups and study protocols.

After the liver, the lung is the second most common site for metastases (e45). Pulmonary RFA has been in increasing use for local tumor therapy since its initial publication in 2000 (e46). When RFA, as opposed to surgical resection, is used to treat primary lung tumors, mediastinal lymphadenectomy cannot be performed. It follows that curative RFA is only possible if there is no lymphogenous metastatic disease (N0) and if the tumor spread is no more than local (stage Ia/Ib). Thus, RFA should be used to treat a primary lung tumor only if the patient's impaired pulmonary function or comorbid conditions contraindicate surgery. The reported survival rates after RFA in this patient group with an a priori worse prognosis are 78% at 1 year, 36% at 3 years, and 27% at 5 years (14). Another study yielded comparable results, with an overall survival of 71% and a tumor-free survival of 34% at 18 months (e47).

The most common indication for pulmonary RFA is the treatment of pulmonary metastases (figure 3). Reported survival rates of RFA for pulmonary metastases of colorectal carcinoma are 85% to 87% at 1 year and 46% to 57% at 3 years, with a median survival time of 27.5 to 33 months (14, e48, e49). Repeated procedures after incomplete ablation are thought to carry a worse prognosis (e49).

The most common complications are fever and pneumothorax (e50). The major drawback of pulmonary RFA is the lack of clear indications, so that the decision to perform this procedure must be made on an
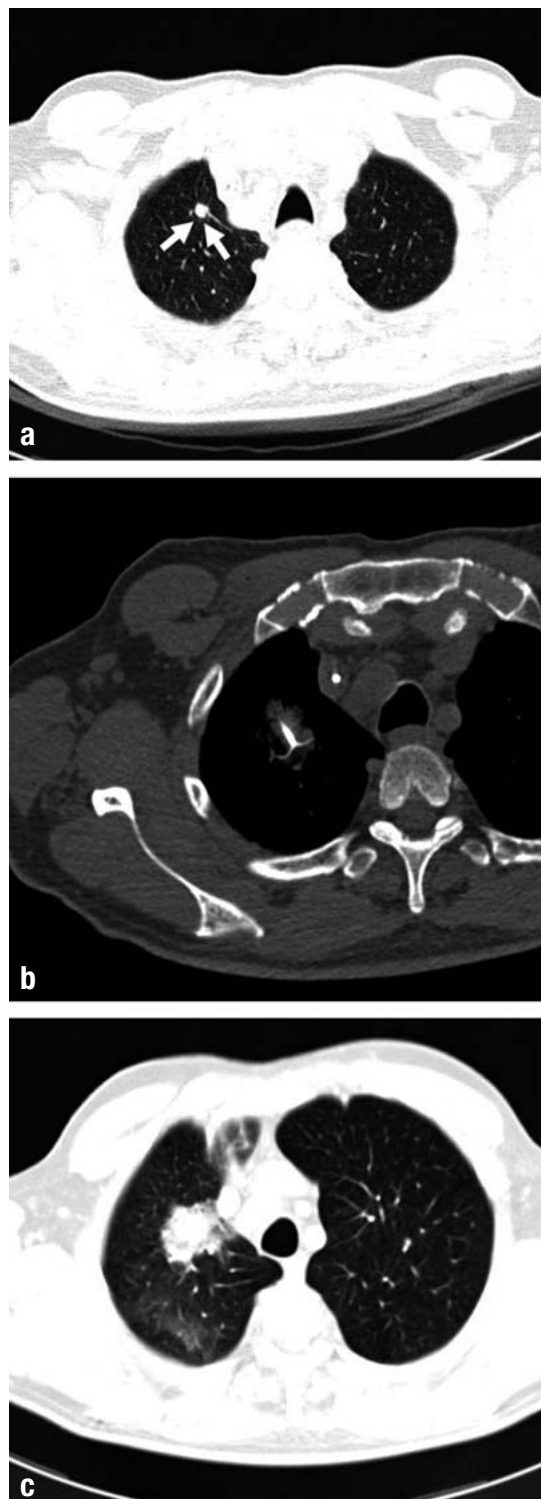

Figure 3:
CT images of a 72-year-old man with hepatic and pulmonary metastases of colorectal carcinoma. After repeated radiofrequency ablation (RFA) of the liver with local tumor control, a new pulmonary metastasis is found in the right upper lobe (a; arrow). A shielded electrode is placed in the tumor under CT guidance for RFA (b). The post-interventional CT shows an infiltrate surrounding the tumor, documenting the success of treatment. Because of the intratumoral hemorrhage that is typically produced by the intervention, the tumor appears larger than it was before treatment for the first six months after RFA (c).

interdisciplinary basis and only in selected, individual cases.

Many studies have demonstrated the effectiveness of RFA in the treatment of renal tumors (15, 16, e51). Typical indications are multiple tumors, single kidneys, or von Hippel-Lindau disease. Exophytic tumors and those measuring 3 cm or less can regularly be totally ablated (16). Repetition of the procedure may be necessary for local control of 3-cm tumors. Repeatability without the problem of a more difficult surgical approach is a major advantage of RFA, particularly when multiple interventions can be expected to be needed, as in von Hippel-Lindau disease. The procedure can be made more effective by a TAE performed beforehand; a combination of embolization and RFA is recommended for 3-cm renal tumors (e52). Residual and recurrent tumors were encountered more frequently in earlier clinical series because of technical inadequacies; in recent series, local tumor control was achieved in nearly all cases (15, e53, e54). This is confirmed by initial long-term results after more than 4 years of follow-up without any recurrence of tumor (17).

RFA has also become an important means of treating symptomatic bony tumors and indeed the treatment of choice for benign osteoid osteoma (e55). For bone metastases, RFA is an effective method of relieving pain with palliative intent (e56). In particular, RFA combined with osteoplasty is a minimally invasive way of relieving pain rapidly while simultaneously stabilizing the bone (e57, 58).

RFA has also been reported in a few cases of tumors of the adrenal gland, pancreas, lymph nodes, thyroid gland, and breast (e59–e63). These uses are still considered experimental.

Laser-induced thermotherapy

In laser-induced thermotherapy (LITT), thermal energy is applied to a tumor in the form of laser light delivered through interventionally inserted light guides. Photon absorption generates heat within the tissue that then spreads by conduction. When large tumors are treated, the laser applicator must be repositioned, or else multiple applicators must be used. The intervention can be guided by ultrasonography, computerized tomography (CT), or magnetic resonance imaging (MRI). MRI offers the additional opportunity to monitor the temperature in the treated tissue continuously and noninvasively (e64, e65).

The successful use of LITT has been shown in many different organ systems (e66–e68). The reported survival rates after LITT for hepatic metastases of colorectal tumors are 94% at 1 year, 56% at 3 years, and 37% at 5 years (18). Comparable figures have been published for LITT for hepatic metastases of breast carcinoma: 96%, 63%, and 41% (e69). There are no available studies comparing LITT to surgical treatment. Despite these favorable results, LITT is used in no more than a few centers because of the sophisticated equipment that it requires and its correspondingly high cost.

Other thermal ablation techniques

Microwave ablation and focused ultrasound are two further hyperthermic ablation techniques (19, 20). Microwave ablation is still in an early phase of clinical application; to date, it is used mainly to treat small HCC tumors (e70, e71). Focused ultrasound, although it has yielded encouraging results in the treatment of breast carcinoma, HCC, and osteosarcoma (20, e72), is now used only to treat prostate cancer, and only in rare cases (e73). Percutaneous cryotherapy (a hypothermic technique) is now used almost exclusively to ablate small renal tumors (21).

Internal radiotherapy

Another class of interventional tumor therapies involves radiotherapy delivered from within the body. Selective internal radiotherapy (SIRT) and image-guided interstitial brachytherapy are treatments of this type. Both of these are among the newer treatment methods for which only phase I and phase II trials have been published to date.

Selective internal radiotherapy

In selective internal radiotherapy (SIRT), arterial microembolization is combined with high-dose interstitial radiation therapy. Particles bearing radioactive ^{90}yttrium are applied for this purpose by way of the hepatic artery (22, 23). A meticulous preinterventional diagnostic evaluation is essential for the success of treatment: this includes invasive catheter angiography of the hepatic arteries as well as scintigraphy after the intra-arterial application of ^{99m}technetium-labeled albumin particles for quantitative prediction of the distribution of the ^{90}yttrium spheres and of the hepatopulmonary shunt volume. The applied radiation dose of no more than 3 GBq is individually adapted to the tumor volume and the hepatopulmonary shunt volume (e74). Typical adverse effects and complications of SIRT include nausea, vomiting, pain, and fever. A few cases of hyperbilirubinemia, duodenal and gastric ulcers, and necrosis of the peripheral biliary ducts have been reported (e75, e76).

SIRT is considered to be indicated for the treatment of primary or secondary hepatic tumors for which all other treatment options have failed or cannot be applied. The presence of extrahepatic tumor is considered to be a relative contraindication. Also, SIRT is occasionally used when hepatic involvement is held to be a prognosis-limiting factor (23). Initial data show that this form of treatment can delay local tumor progression for 6 to 19 months (23, e75, e77). Chemotherapy with 5-fluorouracil and leucovorin combined with SIRT has been found both to delay tumor progression significantly (18.6 vs 3.6 months) and to prolong overall survival (29.4 vs 12.8 months) (e78). It should be noted that more effective chemotherapeutic treatments have become available in the meantime. On the basis of the currently available data, therefore, SIRT should be regarded as a so-called salvage option.

Image-guided interstitial brachytherapy

The image-guided insertion of treatment catheters is the underlying principle of image-guided interstitial brachytherapy and the methodological factor that distinguishes it from percutaneous radiotherapy. The radiation source for single-shot radiotherapy is brought into position by way of the treatment catheters. ^{192}Iridium sources have been used in the studies published to date. After insertion of the catheters, a CT scan of the area to be treated is obtained. The image data are then used to plan the radiation treatment based on the position of the catheters. A target dose of 20 Gy is desired at the tumor edge (e79). The radiation exposure to neighboring radiosensitive organs must be kept as low as possible (e80); the applied dose is adjusted locally for this purpose.

Publications regarding image-guided interstitial brachytherapy have focused to date on hepatic and pulmonary tumors (24, 25). Its use at other sites has only been sporadically reported (e81). Interstitial brachytherapy seems to be particularly suitable for the treatment of large tumors. Although no data are yet available on long-term survival, initial case series show that local control, even of large tumors, can be achieved for up to 18 months (e82).

Combined treatment

The additive effect of combinations of these techniques has barely been studied to date. The available initial findings on combinations of different types of local treatment are promising. The combinations of RFA with TACE, PEI with TACE, and RFA with PEI have all been found to be superior to any of these therapies used alone to treat hepatocellular carcinoma (5, 6, e9, e83). Hardly any data are available on combinations of systemic and local treatment options. The CLOCC trial comparing chemotherapy alone to a combination of RFA and chemotherapy is the only EORTC study on this subject and was concluded in June 2007 (www.cancer.gov/clinicaltrials/EORTC-40004). Further studies on combined treatments, eg, chemotherapy with RFA, are currently in the recruiting phase (www.clinicaltrials.gov/ct/gui/show/NCT00183885? order=1). Preliminary data on a combination of TACE with angiogenesis inhibitors show improved local control of HCC (e84). This concept seems plausible because embolization raises the level of vascular-endothelial growth factor (VEGF) and is currently being studied in a number of trials for the treatment of HCC (www.clinicaltrials.gov/ct/gui/show/NCT00055692).

Conclusion

Many image-guided techniques for local tumor therapy in various organs are now available. The choice of treatment depends on the size and location of the tumor. Combinations of multiple techniques are an important prospect for further development. Although this review centers on local therapeutic techniques, the key to the success of interventional tumor therapy lies in the interdisciplinary determination of the treatment plan resulting in the gradated application of systemic, radiotherapeutic, surgical, and interventional treatment options.

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