Transcatheter and Ablative Therapeutic Approaches for Solid Malignancies

Eleni Liapi and Jean-Francois H. Geschwind

ABSTRACT

The purpose of this article is to present in a concise manner an overview of the most widely used locoregional transcatheter and ablative therapies for solid malignancies. An extensive MEDLINE search was performed for this review. Therapies used for liver cancer were emphasized because these therapies are used most commonly in the liver. Applications in pulmonary, renal, and bone tumors were also discussed. These approaches were divided into catheter-based therapies (such as transcatheter arterial chemoembolization, bland embolization, and the most recent transcatheter arterial approach with drug-eluting microspheres), ablative therapies (such as chemical [ethanol or acetic acid injection]), and thermal ablative therapies (such as radiofrequency ablation, laser induced thermotherapy, microwave ablation, cryoablation, and extracorporeal high-intensity focused ultrasound ablation). A brief description of each technique and analysis of available data was reported for all therapies. Locoregional transcatheter and ablative therapies continue to be used mostly for palliation, but have also been used with curative intent. A growing body of evidence suggests clear survival benefit, excellent results regarding local tumor control, and improved quality of life. Clinical trials are underway to validate these results. Image-guided transcatheter and ablative approaches currently play an important role in the management of patients with various types of cancer—a role that is likely to grow even more given the technological advances in imaging, image-guidance systems, catheters, ablative tools, and drug delivery systems. As a result, the outcomes of patients with cancer undoubtedly will improve.


INTRODUCTION

The role of image-guided locoregional therapies in the management of patients with cancer has grown tremendously in the last decade. Such therapies, which rely on imaging guidance for tumor targeting and response assessment, include various catheter-based and percutaneous ablative techniques. These minimally invasive therapies have been used mainly for palliation but have also increasingly been used with curative intent.

Catheter-based therapies, such as transcatheter arterial chemoembolization used mostly in the treatment of hepatic malignancies, exploit alterations in hemodynamic arterial flow to deliver high concentrations of drugs to a targeted tumor via a percutaneous placed intra-arterial catheter. Such an approach has also been used for palliative treatment of bone, pulmonary, renal, oral cavity, and anterior oropharynx tumors. Percutaneous ablative therapies achieve substantial tumor kill by directly applying chemicals or temperature changes to solid tumors. Most widely accepted for their application in the treatment of liver tumors, these techniques also have rapidly expanded to include treatment of a variety of other solid tumors (renal, bone, prostate, lung, breast, and adrenal tumors). In comparison to traditional cancer treatments, these image-guided locoregional therapies offer the advantage of reduced morbidity and mortality, as well as lower procedural costs when compared with traditional surgical methods. They can also be performed on an outpatient basis, repeated over time, and used in conjunction with other cancer treatments.

This review outlines the current status of the most commonly used image-guided therapeutic approaches for various cancers, with a special emphasis on their roles in the management of patients with liver cancer, and highlights recent research and emerging developments in this field. Because of space limitations, percutaneous chemical and some less commonly used thermal ablative techniques will not be discussed.

LIVER-DIRECTED THERAPIES

During the last two decades, image-guided catheter-based and percutaneous locoregional
ablative interventional therapies (Table 1) have revolutionized the nonsurgical management of patients with primary and metastatic liver cancer. Various forms of catheter-based therapies currently are used, including transcatheter arterial chemoembolization (TACE), transcatheter arterial embolization (TAE), and TAE with drug-eluting beads (DEB). Radiofrequency ablation (RFA) and percutaneous ethanol injection are the most commonly used percutaneous ablative therapies.

**CATHETER-BASED THERAPIES**

**TACE**

First introduced in 1980, TACE exploits the preferential hepatic arterial supply of liver tumors for targeted delivery of chemotherapeutic agents followed by embolization or reduction in arterial flow using various types of particles, while sparing the surrounding liver parenchyma.12,13 This reduction in arterial inflow is conceptually appealing because it directly causes some degree of ischemia within the tumor, which may increase tumor kill and significantly extends tumor drug concentrations (measurable drug levels as long as 1 month after the procedure). As a result, systemic toxicity is reduced because most of the chemotherapy will remain within the tumor bed rather than reach the systemic circulation. A better understanding of liver tumor biology, specifically the relationship between hypoxia, angiogenesis, tumor metabolism, and tumor growth, as well as recent advances in catheter and imaging technology, have resulted in significant modifications of the TACE technique.

Despite some attempts at standardizing the technical aspects of TACE, multiple variations of TACE protocols remain in use throughout the world. Such variations revolve around the number and type of chemotherapeutic agents used, type of embolic material, reliance on lipiodol, and selectivity of catheter positioning. As a result, it has been difficult to compare and interpret results from different centers in a systematic fashion. However, a few trends are evident. The most widely used single chemotherapeutic agent worldwide is doxorubicin, whereas the combination of cisplatin, doxorubicin, and mitomycin is the preferred drug combination in the United States.14 Lipiodol, an iodinated ester derived from poppy-seed oil which was found to be selectively retained by liver tumors, is nearly always added to the chemotherapeutic mixture (to allow emulsification of the drugs) because of its properties as a drug carrier and tumor-seeking agent (Figs 1A and 1B).

Some degree of embolization of the tumor-feeding arteries is also typically performed at the end of the procedure with a variety of embolic agents (polyvinyl alcohol particles, Embospheres; BioSphere Medical Inc, Rockland, MA; or Gelfoam; Pharmacia & Upjohn Company, Kalamazoo, MI) to reduce arterial inflow into the tumor, thereby allowing greater retention of the chemotherapy by the tumor. It is also necessary to ensure that flow in the hepatic arteries is preserved to allow TACE treatments to be repeated,15,16 especially because TACE was shown to be most effective when it can be repeated multiple times (Figs 2A to 2E).

Finally, preservation of some arterial flow to the tumor also may be important to prevent hypoxia-induced upregulation of several molecular factors, including the vascular endothelial growth factor (VEGF) and hypoxia-inducible factor-1, which clearly are associated with stimulation of tumor metabolism, growth, and invasion.17,18 These molecular changes have highlighted the need for additional research in this area and opened the door to new clinical trials combining TACE with newer biologics that are designed specifically to block some of these pathways.

TACE is generally well tolerated and serious complications (liver abscess, tumor rupture, acute liver failure, and pulmonary lipiodol embolism) are extremely rare. The most common adverse effect (3.8% to 10% of all procedures) is the well-described postembolization syndrome, which consists of varying degrees of pain in the right upper quadrant, nausea, vomiting, and persistent fever as well as elevation of liver enzymes. However, this syndrome typically is transient and recovery occurs within 7 to 10 days. Other adverse effects can include alopecia, renal dysfunction, and cardiac toxicity secondary to doxorubicin. Most patients can be discharged from the hospital the day after TACE.

TACE currently is considered the mainstay of therapy for unresectable hepatocellular carcinoma (HCC). In 2002, through the publication of two prospectively randomized controlled trials, TACE was shown to prolong patient survival significantly in selected HCC patients with preserved liver function and adequate performance status.19,20 A subsequent meta-analysis (seven randomized trials of arterial embolization for unresectable HCC) confirmed these findings.21 Indeed, TACE was found to be significantly better at improving

<table>
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<th>Table 1. Liver-Directed Percutaneous Locoregional Oncology Therapies and Their Main Applications in Treating Solid Malignancies</th>
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<td>TACE + intravenous bevacizumab HCC (on-going phase II clinical trials)</td>
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Abbreviations: TACE, transcatheter arterial chemoembolization; HCC, hepatocellular carcinoma; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; LITT, laser-induced thermotherapy; HIFU, high intensity focused ultrasound.

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favorable response to treatment.25,26 However, because most tumors
Criteria in Solid Tumors rely on tumor size reduction to indicate
usually every 4 to 12 weeks. The WHO and the Response Evaluation

tumor response by imaging, hepatic reserve, and a planned interval
patient survival. The decision to retreat is based on assessment of
deposition in the tumor in segment 5.

Fig 1. (A) A 50-year-old male with a significant history of ethanol abuse and
hepatitis C diagnosed with primary hepatocellular carcinoma. Selective digital
subtraction angiography image of the right hepatic artery, showing the catheter
placed in the right hepatic artery and tumor blush of a hypervascular tumor at the
periphery of the right hepatic lobe. (B) Postchemoembolization (transcatheter
arterial chemoembolization) nonenhanced computed tomography of the same
patient, performed 24 hours after treatment, demonstrating excellent lipiodol
deposition in the tumor in segment 5.

patient survival than either conservative management or systemic
chemotherapy with fluorouracil.21 TACE achieved a median survival
of more than 2 years and converted some patients into candidates for
resection. Recently published data also support the effectiveness of
TACE in the United States population.22-24

Most centers repeat TACE procedures to maximize its impact on
patient survival. The decision to retreat is based on assessment of
tumor response by imaging, hepatic reserve, and a planned interval
usually every 4 to 12 weeks. The WHO and the Response Evaluation
Criteria in Solid Tumors rely on tumor size reduction to indicate
favorable response to treatment.25,26 However, because most tumors
do not decrease in size even after successful treatment, surrogate
measures of response such as lack of contrast enhancement on com-
puted tomography (CT) or magnetic resonance imaging (MRI) have
been used to determine tumor necrosis.27-29 Lipiodol deposition in
targeted tumors has also been employed as a means of measuring
tumor necrosis after TACE.30 Recent studies have shown that mul-
tiparametric MR imaging (perfusion and functional MRI) may be the
most promising method to successfully determine early tumor
changes after TACE (Fig 3).24,30,31

TACE also has been used as a bridge to orthotopic liver trans-
plantation (OLT).32-34 A recent study, which was undertaken to assess
the role of TACE in selecting patients with HCC suitable for liver
transplantation, showed that sustained response to TACE is a better
selection criterion for OLT than the initial assessment of tumor size or
number, suggesting that TACE may play a role as a determinant of
tumor biology and therefore predict successful response to OLT.35

There is less experience with TACE in the treatment of hepatic
metastases.36 Several studies have an excellent symptomatic and bio-
logic complete response rate of 70% to 73% of patients with metastatic
carcinoid treated with chemoembolization.27 There also is growing
evidence that TACE significantly prolongs the life of patients with
ocular melanoma metastases,38-40 peripheral cholangiocarcinoma,41
and breast cancer metastases.42 The efficacy of TACE in other groups,
such as patients with colorectal metastasis, is less established.43 How-
ever, a recent study showed that TACE can prolong survival of patients
with colorectal metastases significantly, especially because most of
these patients had already been treated with systemic chemotherapy.44

Transcatheter Arterial Bland Embolization

Transcatheter arterial bland embolization, which simulates arte-
rial ligation, induces tumor ischemia by disrupting the blood supply to
the tumor. Advocates of this catheter-based therapy claim that bland
embolization may be equally effective as TACE for palliative treatment
of primary liver cancer.45 Despite a trend toward improved survival
with TACE, no study to date has demonstrated a difference in survival
between the two techniques.46 A randomized trial comparing embo-
lization (without chemotherapy) versus symptomatic treatment in
patients with hepatitis C virus–related liver disease and Child-Pugh
class A liver function failed to demonstrate a 2-year survival advan-
tage.47 Bland embolization has also been used for pain and symptom-
atric control for neuroendocrine and sarcoma metastases to the liver.48

TAE With DEBs

The issue of drug delivery to tumors is a critical one in oncology.
Ideally, drug-loaded carriers should be able to deliver drugs in a
precise, controlled, and sustained manner to achieve high intra-
tumoral concentration without damaging the healthy surrounding
liver parenchyma. To that end, new concepts in drug delivery have
recently emerged.49 Polyvinyl alcohol–based microspheres can be
loaded with various types of chemotherapeutic agents and deliv-
ered intra-arterially in a manner similar to that of conventional
TACE. Such a system loaded with doxorubicin has entered phase I
and II clinical trials in Europe, United States, and Hong Kong.50
The results in patients with unresectable HCC have been promis-
ings, with an advantageous pharmacokinetic profile, reduced adverse
effects, and improved tumor response by imaging when compared with conventional TACE.50,51 Because of their small size
(100 to 300 μm), these beads seem to lodge distally in the tumor
vasculature, possibly at the level of pathologic arterioportal micro-
shunts, thereby allowing slow elution of the doxorubicin out of the
beads, in turn leading to a more pronounced initial tumor
response. DEBs loaded with irinotecan are also currently being investigated in the treatment of patients with colorectal cancer metastases to the liver.\textsuperscript{52}

### PERCUTANEOUS THERMAL ABLATION THERAPIES

The main goal of thermal tumor ablation is to destroy an entire tumor by using a source that produces changes in temperature (either heat or cold) with minimal damage to adjacent vital structures. Because the potential for recurrence exists, it is imperative to treat an additional 0.5- to 1-cm margin of apparently healthy tissue adjacent to the lesion to eliminate microscopic foci of disease and the uncertainty that often exists regarding the precise location of actual tumor margins. There are many different strategies for applying cytotoxic thermal energies to tumors, including but not limited to single straight electrodes, multiple expandable electrodes, pulsed energy delivery systems, or internally cooled systems. Radiofrequency ablation is the most commonly applied thermal ablative therapy.

#### RFA

The use of RFA, first suggested in 1990 for the treatment of hepatic tumors, has virtually replaced percutaneous ethanol injection and is now used throughout the world as the most favored ablative technique.\textsuperscript{53-57} RFA produces coagulative necrosis via an alternating high-frequency electric current in the radiofrequency range (460 to 500 kHz), which is delivered through an electrode placed in the center of a lesion. The movement of ions within the tissue then creates frictional heat as they try to follow this alternating current, with local tissue temperatures ultimately approaching or exceeding 100°C. Several modifications of the generators and needle electrodes have been developed during the past 16 years to enhance the coagulative effect on treated lesions.\textsuperscript{58} RFA initially was considered for patients with unresectable primary liver cancer, but its indications have been expanded to include liver metastases, bridge to liver transplantation, and even as a substitute for patients eligible for surgical resection.\textsuperscript{59-61}

The main advantage of RFA is that it achieves improved objective responses with a few sessions and that it can be used against both primary and metastatic liver tumors. The disadvantages include the high cost of the equipment, and the higher rate and severity of adverse effects (typically consisting of pain in nearly all patients, and fever and cutaneous burns in 8% of patients), with a reported mortality and complication rates of 0.5% and 8% to 35%, respectively.\textsuperscript{62,63} In addition, the key limitation to RFA has been to create adequate volumes of tissue destruction, hence the push for newer, more powerful generators. The ability to effectively treat lesions in all locations in the liver also can be difficult, especially for those tumors located in the perihilar area.
region or near large vascular structures, because of the added risk of injury to the biliary tree (biliary fistulae or strictures) and the heat-sink effect, which dissipates the heat and reduces the potency of the thermal effect. Finally, recurrence rates can be high and complete destruction of the tumor is therefore essential to minimize any possibility of recurrence. The issue of needle track seeding remains somewhat controversial but recent reports have established the risk to be approximately 3%.64

RFA is most effective against small tumors (< 3 cm) and has limited application against tumors measuring more than 4 cm in diameter. An intention-to-treat study of 206 patients, excluded as candidates for transplantation or resection, who underwent RFA as primary treatment of HCC reported 1-, 3-, and 5-year probabilities of survival of 97%, 67%, and 41%, respectively, with a mean follow-up of 24 months.60 This study justified a role for RFA as a first-line therapy for patients with early-stage HCC and for those who were not candidates for surgical therapies. Another study showed that RFA was also effective as a bridge to liver transplantation over a prolonged waiting period.68 It seems that percutaneous ablation may achieve high survival rates in the correct patient population (small tumors and preserved liver function). An important recent study in 282 unresectable patients with early HCC treated with percutaneous ablative techniques revealed excellent 1-, 3-, and 5-year survival rates (87%, 51%, and 27%, respectively).65 Initial complete response after ablation was the best predictor of prolonged survival, with a 42% 5-year survival irrespective of tumor size and hepatic function.65 When compared with other ablative techniques, RFA emerged as the best option because of its better overall survival rate.60 The success of RFA has fueled the debate about whether surgical resection should be preferred to ablation in patients with tumors less than 3 cm. Unfortunately, no randomized trials comparing RFA to resection have yet been conducted, but such a trial clearly is warranted.

**Laser-Induced Thermotherapy**

Laser-induced thermotherapy uses optical fibers to deliver high-energy laser radiation to the target lesion. Because of light absorption, temperatures of up to 150°C are reached within the tumor, leading to substantial coagulative necrosis. The most commonly used device for laser ablation is the Nd:YAG laser. The optical fibers are inserted directly into the lesion under MRI guidance through a percutaneously placed needle, which is removed after localization. A multineedle approach is essential to treat large lesions successfully (> 5 cm). In such tumors, treatment time can approach 1 hour. Thermocoagulation is monitored in real time under MRI, allowing accurate estimation of the actual extent of thermal damage. The indications and contraindications for laser ablation are the same as those for RFA and microwave ablation.

Laser ablation has been shown to be effective in inducing complete necrosis in HCC. As with the other ablative techniques, long-term success rates are related to tumor size, and 82% complete response rate has been reported for lesions measuring 3.2 cm in diameter. In a series of 74 patients with small HCCs, survival rates at 1, 3, and 5 years were 99%, 48% and 15%, respectively.65 Similar success was also reported in a series of 109 patients with 6.5 cm tumors, of whom 85% had tumors measuring 3 cm or less.66

**Microwave Coagulation Therapy**

Microwave ablation is the most recent development in the field of tumor ablation. Under imaging guidance (ultrasound, CT, or MRI), the tumor is localized and a thin (14.5 gauge) microwave antenna is placed directly into the tumor. A microwave generator emits an electromagnetic wave through the exposed, noninsulated portion of the antenna, which in turn agitates water molecules in the surrounding tissue, producing friction and heat, thereby inducing cell death via coagulation necrosis. As with RFA, the heat-sink effect is also a concern, making complete necrosis for lesions located near blood vessels difficult. In 1994, Seki et al.69 first reported on the use of percutaneous microwave therapy as an effective method for the treatment of small (< 2 cm) HCC. Other investigators have confirmed such findings since.70,71 The microwave ablative technique has been used principally in Japan and China.

Although microwave coagulation therapy produces a thermally coagulated area that is smaller than that produced by RFA, its main advantages are quite impressive and include consistently higher intratumoral temperatures, faster ablation times, and an improved convective profile versus those obtained with RFA. In a study on patients with small HCCs randomly assigned to microwave ablation or RFA, the same rates of complete ablation and complications were observed. The shorter time of microwave therapy was counterbalanced by a greater number of sessions (2.4 with microwave therapy vs 1.1 with RFA) to achieve complete necrosis.72 A large series including 288 patients with HCCs treated by microwave ablation reported encouraging results, with a 1-, 3-, and 5-year survival of 92%, 72%, and 51%, respectively.73 Although still in its infancy, technical developments as well as new clinical indications (treatment of secondary liver disease, primary and secondary lung malignancies, renal and adrenal tumors, and bone metastases) undoubtedly will help establish this technology.

**COMBINATION THERAPIES**

The concept of combining various therapies is appealing because it relies on therapeutic approaches that are synergistic, thus maximizing therapeutic potency. For example, the combination of TACE and RFA exploits the properties of hepatic neovascularization to diffuse energy and distribute chemotherapeutic agents to increase the size of the ablation zone and the effectiveness of treatment for intermediate and large lesions. The combination of RFA and TACE is the most commonly used and has already been found to be quite potent against HCC.74 TACE has also been combined with interstitial laser photocoagulation, microwave coagulation, ethanol injection, or high-intensity focused ultrasound.75-78

Other combination therapies are under investigation, such as that using TACE and bevacizumab, one of the new biologics used against various types of cancer. Bevacizumab, the first humanized monoclonal antibody that binds the VEGF commercially available in the United States, prevents the interaction of VEGF with its receptors on the surface of endothelial cells.79 When unblocked, this interaction may lead to endothelial cell proliferation and new blood vessel formation.80 This antibody has shown both cytostatic and cytotoxic effects in clinical trials.81,82 Objective responses, such as reduction in tumor growth and increase in time to tumor progression, have been documented for various types of solid tumors.81-86 Because TACE has been shown to increase VEGF levels, it became conceptually appealing to...
use a specific VEGF blocker in combination with TACE. A recent pilot study conducted in selected HCC patients treated with the combination of TACE and intravenous bevacizumab showed encouraging results, with good drug tolerance and prolonged disease control.57 As a result, several phase II trials currently are evaluating the safety and efficacy of such combination therapy in patients with liver cancer.88,89

**OTHER SOLID TUMOR ABLATIVE APPROACHES**

Catheter-based and percutaneous tumor ablative therapies also have been used for a variety of other solid tumors, especially renal, lung, and painful bone tumors.

**Renal Neoplasms**

The incidence of small renal cell carcinomas is increasing, and 25% to 49% of all renal tumors currently are diagnosed incidentally at cross-sectional imaging.90 Direct tumor ablation is an extension of the expanding area of nephron-sparing surgery, which has developed during the last decade. Given the challenge and recovery time from laparoscopic partial nephrectomy, an aging population with an increased incidence of small tumors, and the demand for minimally invasive procedures, the role of nephron-sparing minimally invasive techniques, especially percutaneous ablative therapies such as RFA and cryoablation, has grown rapidly. Recent studies have shown that RFA is an effective therapy for the treatment of solid renal masses, with minimal morbidity and no mortality associated with the procedure.90,91 In addition to the low complication rate, RFA preserves renal function, is well tolerated by patients, and can eradicate small renal tumors in a high percentage of patients. Similarly, cryotherapy has shown promising results, including a very low rate of residual disease at 3 to 4 years of follow-up.92

**Lung Lesions**

Although the use of electric current to treat lung lesions percutaneously was suggested in 1997, the applicability of this therapy only became apparent much more recently.93 Since 2000, at least 25 peer-reviewed articles have been published on the topic of RFA of lung cancer.94-98 Lung tumors are well suited for RFA because the surrounding air in adjacent normal lung parenchyma provides an insulating effect and concentrates the RF energy within the tumor tissue.99 Hence, less RF energy deposition than is necessary with liver tumors is required to achieve adequate tumor heating. Initial experience shows that lung RF is well tolerated.99 Although common and probably present radiographically to some degree in nearly all patients, pneumothoraces rarely (less than 20%) require treatment with needle aspiration or chest tube placement. Postprocedural small pleural effusions after the treatment of peripheral lesions are self-limited. Productive cough with brown sputum lasting 1 to 2 weeks after ablation has been observed occasionally. Positron emission tomography imaging has been shown to play an important role in assessing tumor response after treatment as ablated lung tumors become metabolically inactive.100,101

RFA is best used in patients who are not amenable to surgery with stage I non–small-cell lung cancer and patients with a limited number of small, slow-growing metastases restricted to the lungs.102 Clearly, the best results in terms of complete tumor ablation are achieved in patients with lesions no larger than 3 cm in diameter. Preliminary survival data are encouraging, but definitive evidence supporting the use of RFA to prolong survival is still lacking.

Because most lung metastases result from embolization of tumor cells from the primary tumor into small-caliber pulmonary arteries, pulmonary metastases primarily are supplied by pulmonary arterial branches. Preliminary reports on the use of transpulmonary chemoembolization for treatment of limited vascular pulmonary metastases have indicated potential effectiveness and safety.9

**Painful Bone Metastases**

Painful bone metastases can be extremely difficult to treat effectively, hence the search for alternative strategies involving the use of percutaneous image-guided ablative approaches such as ethanol,102 laser-induced interstitial thermotherapy,103 RFA,104 and cryoablation.9 Of these methods, RFA was shown in a multicenter trial to substantially reduce pain in patients with bone pain refractory to standard treatments. Despite such success, RFA showed some limitations, including the inability to depict the ablation margin under CT imaging, increased periprocedural and immediate postprocedural pain, and a period of weeks before substantial pain reduction was achieved.

Experience with percutaneous cryoablation of metastatic bone disease has been rather limited; however, a recent prospective study suggested that it was well tolerated and could play a role in the treatment of symptomatic bone metastases.8,105

In conclusion, image-guided transcatheter and ablative approaches currently play an important role in the management of patients with various types of cancer—a role that is likely to grow even more given the rapid pace of evolution of these technologies. In selected patient populations, these approaches already offer survival rates that are comparable to those of surgery, with the added benefits of reduced morbidity and costs, improved quality of life, and shortened recovery time. As the management of cancer patients continues to evolve toward disease containment rather than cure, and locoregional targeted therapy rather than systemic approaches, image-guided techniques, by definition, are perfectly suited for this combat. Results from clinical trials involving such approaches are increasingly promising, and the potential for improvement remains vast. As a result, these therapeutic approaches undoubtedly will positively impact the outcomes of patients with cancer.

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

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Collection and assembly of data: Eleni Liapi, Jean-Francois H. Geschwind

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