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# Local Surgical, Ablative, and Radiation Treatment of Metastases

Robert D. Timmerman, MD[1], Costas S. Bizekis, MD[2], Harvey I. Pass, MD[3], Yuman Fong, MD[4], Damian E. Dupuy, MD[5], Laura A. Dawson, MD[6], David Lu, MD[7]

## Abstract

Because local therapies directed toward a specific tumor mass are known to be effective for treating early-stage cancers, it should be no surprise that there has been considerable historical experience using local therapies for metastatic disease. In more recent years, increasing interest in the use of local therapy for metastases likely has arisen from improvements in systemic therapy. In the absence of effective systemic therapies, such local treatments were often considered futile given both the difficulty in eliminating all sites of identifiable metastatic disease as well as realities regarding the rapid natural history of uncontrolled tumor dissemination. However, with a higher likelihood of patients surviving longer after effective systemic therapy, even if not cured, the goal of the eradication of residual metastases via potent local therapies can be rationalized. However, this rationalization should be evidence-based so as to avoid harming patients for no established benefit. Although surgical metastectomy remains the most common and first-line standard among local therapies, nonsurgical alternatives, including thermal ablation and stereotactic body radiotherapy, have become increasingly popular because they are generally less invasive than surgery and have demonstrated considerable promise in eradicating macroscopic tumor. Rather than eliminating the need for local therapies, improvements in systemic therapies appear to be increasing the prudent utilization of modern local therapies in patients presenting with more advanced cancer. CA Cancer J Clin 2009;59:145-170. ©2009 American Cancer Society, Inc.

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## Rationale for Local Therapies for Metastatic Cancer

Clinicians recommending local therapy for macroscopic metastatic tumor for reasons other than palliation should be prepared to defend their rationale. It is not surprising that many oncology specialists are skeptical regarding the use of local therapies in patients with metastatic cancer. Patients with large aggregates of macroscopic tumor detectable by physical examination or conventional imaging (ie, the "targets" for local therapy) are likely to also

[1]Professor of Radiation Oncology, Professor of Neurosurgery, University of Texas Southwestern Medical Center, Dallas, TX; [2]Attending Surgeon, Division of Thoracic Surgery, Department of Cardiothoracic Surgery, New York University School of Medicine, New York, NY; [3]Director and Attending Surgeon, Division of Thoracic Surgery, Department of Cardiothoracic Surgery, New York University School of Medicine, New York, NY; [4]Vice Chair, Technology Development, Chief, Gastric and Mixed Tumor Service, Murray F. Brennan Chair in Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY; [5]Professor, Brown Medical School, Director of Ultrasound, Department of Diagnostic Imaging, Rhode Island Hospital, Providence, RI; [6]Associate Professor, Department of Radiation Oncology, Princess Margaret Hospital, University of Toronto, Toronto, Ontario, Canada; [7]Professor, Department of Radiology, Director, Hepatic Tumor Ablation Program, David Geffen School of Medicine at the University of California at Los Angeles, Los Angeles, CA.

Corresponding author: Robert D. Timmerman, MD, Department of Radiation Oncology, University of Texas Southwestern Medical Center, 5801 Forest Park Road, Dallas, TX 75390-9183; robert.timmerman@utsouthwestern.edu

harbor microscopic tumor cell deposits within a variety of organs. At the completion of local therapy, these microscopic deposits would soon replace those removed by the local therapy, making such local therapy a futile and possibly costly misadventure for the patient.

To justify a local treatment, it would be extremely valuable to be confident in the knowledge that a given patient was free of occult microscopic disease because fairly aggressive efforts toward eradicating macroscopic metastases would be reasonable in such cases. Although there has been progress in the diagnosis of smaller and smaller metastases, including better functional imaging and predictive assays guided by molecular markers, the sensitive and specific detection of micrometastases remains elusive. Alternatively, it would be valuable to know a priori that occult microscopic disease has been (or will likely be) eliminated by an effective systemic therapy. Here gains have been more quantifiable, especially if the patient has already experienced a longer progression-free survival. With more confidence in the nonexistence or control of occult microscopic disease, local therapy for metastatic disease becomes more rational.

Strictly local therapies including surgery, radiofrequency ablation (RFA), and focused stereotactic radiation techniques have demonstrated a consistent ability to eradicate tumor and even cure patients presenting with early-stage disease. The case for using a local therapy in patients with established metastatic disease must be justified by assumptions founded in the known characteristics of tumor growth. This justification may be based on low or high levels of evidence. The decision to subject a patient to a potentially toxic, potent local therapy requires a rationale beyond desperation. Kavanagh et al discussed four categories of possible justification in a recent report: 1) anecdotal experience, 2) as consolidation, 3) for oligometastases, or 4) based on the Norton-Simon hypothesis.[1]

Anecdotal experience is low-level evidence for the justification of a treatment. Nevertheless, even uncontrolled experience forms a dataset that deserves some consideration. For example, it may have been observed that healthy patients with certain rare tumors have experienced long-term disease remission after resection of even multiple metastases. In addition, it may have been observed that systemic therapies have little effect on such tumors (eg, metastatic

teratoma). In this circumstance, with a properly consented patient who is aware of limitations in experience and potential costs (both toxicity and monetary), it may be reasonable to attempt to reproduce favorable anecdotal experience in the next similar patient. The timing of the local therapy based on anecdotal experience would be done irrespective of the use of any systemic therapy. At any rate, given its low level of evidence for justification, anecdotal experience should be used only rarely in justifying a local therapy for metastatic disease.

Realistically, few patients with bulky metastatic disease will experience a prolonged disease remission with current systemic therapies for common nonhematologic cancers such as those of the lung, colon, breast, and prostate. Nevertheless, a treated patient occasionally will demonstrate no development of new metastatic cancer and remain free of disease progression for weeks, months, or even years. It might be assumed then that the systemic therapy has prevented micrometastases from progressing or perhaps even eradicated them. One could rationalize that if the original or remaining sites of bulky tumor were eradicated, the patient might be rendered disease free. Therefore, local therapies might be used for this special case of consolidation after a better-than-expected response to systemic therapy. The timing of the local therapy based on the rationale of consolidation would be done after most or all of the planned systemic therapy was delivered. Of note, this same idea of local consolidation after effective systemic therapy has been confirmed to be beneficial for certain types of non-Hodgkin lymphoma based on prospective trials.[2-4]

It is probable that some patients truly have a limited number of tumor deposits within their body, or so-called oligometastases. These patients might be cured if their oligometastases were eradicated. As articulated by Hellman and Weichselbaum, the theory of oligometastases considers that there could be a subgroup of patients with metastatic disease that is intermediate between completely absent and widely metastatic.[5] The trick, therefore, is to find a way to identify these patients among those with similar presentations of metastatic disease. Currently, patients are identified for curative local therapies based on risk factors such as the number of metastases, the interval between disease presentation and the occurrence of metastatic disease, or the histology of the treated tumor. The timing of the local therapy based on the

rationale of presumed oligometastases would be done irrespective of the use of any systemic therapy.

The Norton-Simon hypothesis has been the basis for trials testing the selection of patients, timing, and dose intensity of chemotherapy.[6,7] This hypothesis states that the effectiveness of typical chemotherapy agents (as measured by response) is proportional to the growth rate of the tumor. Gompertzian kinetics demonstrates that the fastest tumor growth rates, and hence the highest degree of chemosensitivity, occur when tumors are not bulky. As such, a "debulking" procedure as might be attained with a potent local therapy would result in a remaining tumor burden that is more chemosensitive. The timing of local therapy based on the Norton-Simon hypothesis would be prior to most or all of the planned systemic therapy. In addition, although more contentious, it would not be essential that all sites of macroscopic metastatic disease be encompassed because the major goal is debulking rather than eradication. Some researchers have speculated that the rapid growth noted in tumors that are not crowded can be attributed to the rapid proliferation of differentiated tumor cells arising from a more resistant population of tumor stem cells.[8,9] Indeed, supporters of this concept believe these stem cells are responsible for metastases. Again, if a potent local therapy could eradicate these tumor stem cells, a patient might experience longer disease remission and fewer subsequent metastases.

It is important to consider how to evaluate the evidence for or against using a local therapy to treat metastatic cancer. Disease-free survival might be improved. However, ideally, improved long-term disease-free survival (ie, cure) or actuarial overall survival would be more convincing evidence. Palliation is important, but it is likely that many patients will have no bothersome symptoms prior to therapy. The treatment-related toxicity may be difficult to measure given that disease progression or comorbid conditions may produce similar problems as noted with the therapy. Finally, the economic costs of treatment, including charges for the treatment, lost work time during recovery, and the treatment of complications, would need to be considered to view the entire treatment on balance.

## Modern Local Therapies

In the remainder of this article, we will review the use of modern local treatments of pulmonary and hepatic metastases. These two organ sites of metastases have been the most commonly investigated, including some prospective trials. They might serve as a model for prudently evaluating any use of local therapy in the treatment of metastatic disease. The article will include general descriptions of surgical, thermal ablative, and stereotactic radiotherapy techniques; discuss patient selection issues for each; and highlight some peer-reviewed published data regarding patient outcomes.

## Principles of Surgical Resection of Metastases (Metastectomy)

More information is available regarding the surgical removal of metastases than for any other therapy. To the best of our knowledge, series describing the surgical removal of metastases, or metastectomy, have the largest patient numbers and longest follow-up periods of any modality of treatment. Although this fact lends credibility to the evidence for surgery, to our knowledge, very little of this research has been conducted in a prospective fashion. As such, there are undoubtedly differences with regard to patient selection, as well as variabilities in treatment technique and extent of follow-up that confound decisive interpretation. Nonetheless, this experience has taught clinicians much about typical outcomes, selection of patients, improved techniques, and follow-up strategies in addition to confirming that patients can be helped or even cured with surgical therapy.

### Surgical Resection: Liver Metastases

Surgery has played an important role in the treatment of liver metastases. Although most of the experience with the surgical management of liver metastases relates specifically to metastases from colorectal carcinoma, some research also exists for other primary histologies. In the case of liver metastases from colorectal cancer, a large body of literature has accumulated over the last 30 years documenting that liver resection can be performed safely and result in 10-year survival rates of 20% to 26% and potential cure, as shown in Table 1.

### Preoperative Evaluation: Liver Metastases

The extent of liver involvement by metastatic cancer is typically evaluated using ultrasound (US) and com-

**TABLE 1. Results of Hepatic Resection for Metastatic Colorectal Cancer**

| STUDY | N | OPERATIVE MORTALITY | 1 YEAR SURVIVAL % | 3 YEAR SURVIVAL % | 5 YEAR SURVIVAL % | 10 YEAR SURVIVAL % | MEDIAN MONTHS |
|---|---|---|---|---|---|---|---|
| Hughes 1986[18] | 607 | — | — | — | 33 | — | — |
| Rosen 1992[22] | 280 | 4 | 84 | 47 | 25 | — | — |
| Scheele 1995[23] | 434 | 4 | 85 | 45 | 33 | 20 | 40 |
| Jamison 1997[19] | 280 | 4 | 84 | — | 27 | 20 | 33 |
| Fong 1999[17] | 1001 | 2.8 | 89 | 57 | 36 | 22 | 42 |
| Minagawa 2000[21] | 235 | 0.85 | — | 51 | 38 | 26 | |
| Choti 2002[16] | 226 | 1 | 93 | 57 | 40 | 26 | 46 |
| Kato 2003[20] | 585 | — | — | — | 33 | — | — |
| Wei 2006[183] | 423 | 1.6 | 93 | 64 | 47 | 28 | 53 |
| Shah 2007[176] | 841 | 3 | 88 | 59 | 43 | — | — |
| Rees 2008[177] | 929 | 1.5 | — | — | 36 | 23 | — |

puted tomography (CT) scanning. CT scanning is enhanced by the use of intravenous and oral contrast agents. More recently, magnetic resonance imaging (MRI) has been increasingly used for determining the number, size, and extent of metastases. Laboratory values of liver and bone marrow function are obtained preoperatively. Baseline liver function may be assessed with serum albumin and prothrombin time, whereas the status of liver drainage or inflammation may be determined based on total bilirubin, alkaline phosphatase, and several liver enzyme levels. Tumor markers, including carcinoembryonic antigen (CEA) and others (depending on the site of the primary tumor), should be drawn prior to resection because these baseline values may be very helpful for subsequent follow-up.

Given the rigors of surgery and the postoperative period, patients being considered for hepatectomy should be in reasonably good health. In particular, cancer-related weight loss should be stabilized or reversed. Although the majority of prognostic indices refer to the status of disease at the time of surgical resection (eg, tumor size, number of metastases, etc.), it is also very important to insure that the patient will have adequate hepatic reserve for normal function after surgery. To this end, it is generally recommended that, after the clearance of all visible macroscopic tumor with negative surgical margins (defined as an R0 resection), there should remain at least two adjacent liver segments with vascular inflow and outflow as well as biliary drainage.[10] This residual liver must include enough functioning tissue (approximately 25%-30% of normal liver volume)

to provide hepatic function postoperatively, adjusted based on consideration of existing liver disease such as cirrhosis or hepatitis.

Evaluation to complete staging, including lung, abdominal, and pelvis CT scans and/or whole-body positron emission tomography (PET) scanning, are performed to evaluate patients for extrahepatic disease, which would generally preclude the rationale for hepatic resection.

### Surgical Technical Issues: Liver Metastases

The goal of surgery should be to achieve an R0 resection (as defined previously) while maintaining the vitality and quality of life of the patient. To constitute resectability for cure, it is required that complete resection of all liver metastases, regardless of size, number, distribution, or width of resection margin, be performed while preserving a sufficient volume of functioning liver parenchyma. According to the Terminology Committee of the International Hepato-Pancreatico-Biliary Association, a major liver resection is defined as the resection of three or more hepatic segments (hemihepatectomy and extended hemihepatectomy).[11] A minor resection is defined as the resection of fewer than three segments, including wedge resections.

### Surgical Complications: Liver Metastases

Complication rates ranging from 20% to 50% have been reported for the resection of liver metastases, depending on the diligence of reporting. The most common complications are symptomatic pleural ef-

fusions (5%-10%),[12,13] pneumonia (5%-10%),[14] liver failure (3%-8%),[14] bile leak/biliary fistula (3%-5%),[14,15] and perihepatic abscess (2%-10%).[13-15] However, most complications are easily treated and do not usually prolong hospital stay. For even the most major liver resections, the reported median hospital stay is now routinely fewer than 2 weeks. The complications that often result in prolonging hospitalization, such as myocardial infarction (1%), pulmonary embolism (1%),[15] or significant hemorrhage, are rare (range, 1%-3%), but remain major causes of perioperative mortality.

The mortality associated with elective liver resection for colorectal metastases is uniformly reported to be less than 5% in recent published series.[16-23] In fact, the safety of such hepatectomies has improved despite the performance of increasingly aggressive and extensive resections.

## Surgical Resection: Lung Metastases

Metastases to the lungs are one of the most common oncologic problems, and ultimately affect a large percentage of cancer patients with a variety of primary tumor histologies. Although pulmonary metastatic disease tends to be an indicator of widespread disease, in certain instances, pulmonary metastatic disease may exist in isolation. The main factors that impact survival after the resection of lung metastases include complete resection of all disease, the number of metastases present, the disease-free interval (DFI), the presence of extrathoracic disease, and the primary tumor type, as shown in Figure 1.[24,25]

### Preoperative Evaluation: Lung Metastases

All candidates for potential resection of lung metastases must be able to tolerate the surgery and postoperative recovery. A thorough workup, including pulmonary function testing and, as appropriate, cardiac evaluation, must be performed. In addition, it is critical that there is control of the primary site of disease and, in most cases, no evidence of extrathoracic disease.[24-26] CT has now largely replaced chest x-ray for the preoperative evaluation.[25,27,28] Nevertheless, conventional CT scans are reported to miss up to 50% of metastatic lung nodules noted at the time of surgery.[29] In a prospective randomized trial by Collie et al, the resolution of spiral CT scans was found to be superior to conventional CT, with up to
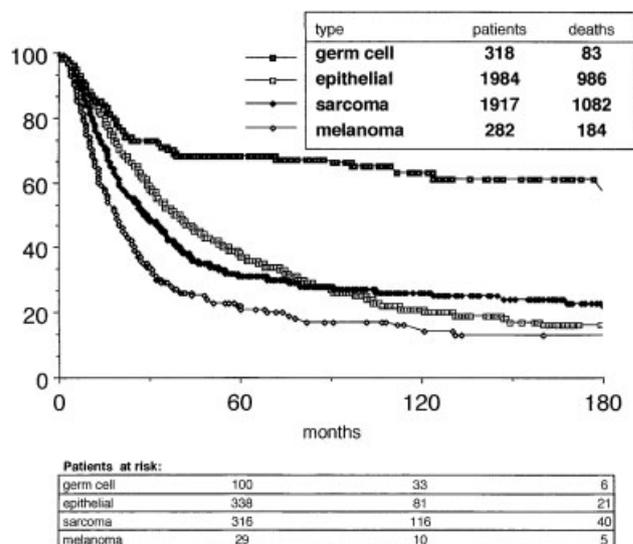


**FIGURE 1.** Survival of Patients Undergoing Complete Resections According to Four Major Primary Tumor Types: Epithelial, Sarcoma, Germ Cell, and Melanoma. Reprinted with permission from Pastorino U, Buyse M, Freidel G, et al. Long-term results of lung metastectomy: prognostic analyses based on 5206 cases. The International Registry of Lung Metastases. *J Thorac Cardiovasc Surg.* 1997;113:37-49.

25% more nodules discovered and confirmed at the time of surgical resection.[29]

More recently, oncologists have turned to PET to improve on the diagnostic capability of CT scans in evaluating pulmonary metastases. PET scans use a radio-labeled glucose molecule (18F-fluoro-2-deoxy-D-glucose [FDG]) which is preferentially absorbed in high concentrations by neoplastic tissue. In a retrospective review by Reinhardt, et al, the sensitivity of PET for lesions measuring 11 mm to 29 mm in greatest dimension approached 94%, and was approximately 78% for lesions measuring 8 mm to 10 mm in size. However, for lesions measuring 5 mm to 7 mm in greatest dimension, the sensitivity was only 41%, demonstrating the limitations of this modality.[30] Simultaneously acquired PET/CT images may provide an even more increased sensitivity of close to 99% for larger nodules.[30]

### Surgical Technical Issues: Lung Metastases

Resection of pulmonary metastases has traditionally been approached through unilateral or simultaneous bilateral posterolateral thoracotomy. Such approaches have been proven to be safe and are associated with generally acceptable morbidity and mortality rates.[31] Advanced techniques for dealing with bilateral disease include both sternotomy and clamshell incisions (bilateral anterolateral thoracoto-

mies).[32] These techniques also provide a safe and efficient method of dealing with bilateral disease with one procedure.

Recently, video-assisted thoracoscopic surgery (VATS) has been used for the resection of lung metastases. VATS provides a minimally invasive approach, minimizes postoperative pain, shortens hospital stay, and hastens a patient's return to normal activity.[31,33-35] On the downside, VATS does not allow for manual palpation of the entire lung, making its use for pulmonary metastectomy controversial. In a prospective evaluation, McCormack et al found that 56% of patients had additional malignant lesions at thoracotomy after an initial VATS exploration, thus concluding that thoracotomy with manual palpation was the gold standard for metastectomy.[31] In a retrospective review by Parsons et al, 22% more malignant nodules were found at thoracotomy than were detected by helical CT scan, thus emphasizing the importance of intraoperative palpation.[36] Still other researchers have found no difference when comparing VATS and thoracotomy. In a retrospective review by Nakajima et al comparing the use of VATS and thoracotomy for the resection of isolated pulmonary metastasis, no significant differences in rates of disease recurrence or survival were noted.[35] In addition, in two reviews published by Mutsaerts et al, no difference in survival was noted when comparing the two techniques.[33,34] However, larger prospectively randomized studies would need to be performed before a definitive conclusion could be drawn comparing VATS with thoracotomy.

The role of lymph node dissection and the prognostic significance of lymph node involvement are topics that must be evaluated carefully when discussing pulmonary metastectomy.[37-40] This will be discussed more later in this article.

### Surgical Complications: Lung Metastases

In general, surgical complications after either open thoracotomy or VATS are less than 10% to 20%.[41-43] The most common sources of morbidity are related to the chest tube placed during surgery, including persistent air leak, pneumothorax, or persistent pleural effusion.[41-44] Such complications rarely prolong the length of hospital stay. The incidence of long-term post-thoracotomy pain syndromes is comparable to that observed when treating primary lung cancer and often requires prolonged analgesic use. However, because patients undergoing pulmonary metastectomy are not as likely to have significant emphysema compared with patients with primary lung cancer, fewer patients will develop a debilitating decline in pulmonary reserve.

## Nonsurgical Treatment of Metastases

As mentioned previously, nonsurgical treatments of metastases discussed in this review include RFA and stereotactic body radiotherapy (SBRT). The obvious benefits of nonsurgical treatments are limited morbidity and speedier recovery. However, the breadth of experience, length of follow-up, and quantity of patient outcome data described for either of these nonsurgical therapies are meager in comparison with the data available regarding surgery for metastatic disease. Nevertheless, a higher percentage of reports describing nonsurgical treatments include prospective reports. Prospective reports describe research in which patient selection is specified, endpoints and evaluations are determined in advance, patients are treated uniformly, follow-up conduct is strict, and ongoing, peer-reviewed scrutiny is required. In addition, results from prospective trials are more likely to be published, regardless of whether the experience is positive or negative. As such, the understanding gained from a prospectively designed study allows considerable application even when patient numbers are modest.

Nonetheless, the limited data describing outcomes after nonsurgical therapies are a significant shortcoming. Given the larger experience with surgery, it is reasonable to use surgical guidelines for patient evaluation and selection for nonsurgical therapy, with the exception that nonsurgical therapies are likely to be more tolerable in frail patients. In addition, the benefits and harms of nonsurgical therapies would be appropriately compared with the larger surgical experience. Hopefully, with promising results being reported after adequate follow-up of the pilot experiences using nonsurgical therapy for metastatic disease, the oncology community will conduct properly designed Phase III trials comparing surgical and nonsurgical therapies to find the best fit for all of the respective therapies.
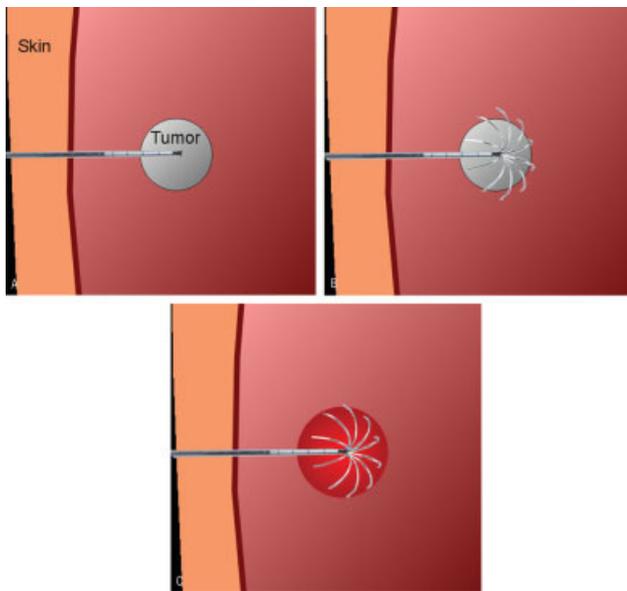
**FIGURE 2.** Process for Radiofrequency Ablation (RFA). (A) Transcutaneous insertion of the RFA needle electrode (usually via image guidance) into the tumor. (B) The 10 retractable tines are deployed into the vicinity of the tumor. (C) Radiofrequency excitation generates a zone of heat that ablates the tumor.

## Principles of RFA

Both extremes of heat and cold can lead to cellular destruction with necrosis, known as thermal ablation. This section, however, will focus on the use of high temperatures delivered via the minimally invasive technique known as RFA given its more widespread use and larger treatment experience in comparison with other thermal ablation methods. A conductive probe (electrode) is inserted into the tumor by image-guided or manual techniques.[45] High-frequency alternating current is transmitted from the tip or tips of the probe into the immediate tissue. This causes excitation of molecules and heating of tissue to a degree capable of causing coagulative necrosis. Tissues, including tumor and surrounding microvasculature, in the vicinity of temperatures greater than 60°C become significantly damaged. This process is depicted in Figure 2. The amount of destruction is correlated with the impedance of the tissue and distance from the electrode. This effect may be modulated by cooling from an immediate heat sink such as a large blood vessel adjacent to the tumor.

### RFA: Liver Metastases

One of the larger reported RFA experiences is in the treatment of liver metastases. The RFA probe has been directed toward metastatic liver lesions by both image guidance in the radiology suite as well as by direct palpation or visualization in the operating room by surgeons. Collectively, this experience has shown RFA to constitute a potent anticancer treatment with broad applicability.

### Pre-RFA Evaluation: Liver Metastases

Patient selection as determined by a thorough pretreatment evaluation is essential for RFA to be successful. Patients should be generally healthy with adequate liver function as ascertained by performance status and serum albumin and prothrombin time; however, patients may be frailer than those selected for major liver resections. For liver tumors, most studies have demonstrated improved outcomes in patients with a limited disease burden. Generally, the best outcomes are noted in patients with 4 or fewer tumors measuring less than 2.5 cm in maximum dimension each.[46] When treating multiple tumors, the sum of the dimensions of all tumors should be less than 10 cm.[47] A multidisciplinary team approach in patient selection is encouraged.

Certain tumors are poorly visible with current imaging techniques. This is a fundamental limitation for image-guided RFA treatment. Tumors close to the hepatic hilum and especially those adjacent to the common hepatic duct or the ductal confluence are absolute contraindications to RFA so as to avoid major injury to the bile duct. RFA of subcapsular tumors abutting the bowel is contraindicated, and largely exophytic tumors are best avoided. Other subcapsular tumors can be safely ablated if they are accessible through normal liver tissue.[48] The presence of biliary-enteric communications is a relative contraindication due to the high risk for abscess formation at the ablation site.[49] Lu et al initially reported higher local recurrence rates in tumors abutting hepatic vessels measuring greater than 3 mm, but this was a lesson to point out the necessity of technical refinement in treating such lesions, and not a contraindication.[50]

### RFA Technical Issues: Liver Metastases

Generally, patients are premedicated with intravenous antianxiety and pain medications titrated to patient comfort during the procedure.[45] Grounding pads are placed horizontally on the anterior or posterior chest wall and connected to the reference electrode port on the radiofrequency (RF) generator. Under direct or image guidance, the RF electrode is

inserted into the mass. The RF electrode is connected to an RF generator and treated with the maximum allowable current for between 2 and 12 minutes. In some systems, a pump is used to direct chilled water (15°C-20°) through the perfusion port of the electrode to both prevent tissue charring and to improve the radius of RF energy deposition. The electrode tip temperature is maintained at typical temperatures of approximately 90°C for 2 minutes. Temperature feedback is required to insure adequate heating is achieved. US may be used to detect the appearance of microbubbles, or temperature probes associated with the RF electrode can measure the achievement of a cytotoxic temperature of 50°C within the mass.

RFA for liver tumors can be performed percutaneously, laparoscopically, and via laparotomy. From a practical standpoint, tumors measuring larger than 5 cm or multiple tumors (greater than 5) become technically challenging for the percutaneous approach, but are more easily addressed by an open approach. Laparoscopy is well suited for subcapsular tumors that may be technically difficult to access percutaneously. Both surgical modalities can also protect adjacent stomach and bowel tissue from thermal injury. If no technical restrictions exist, the percutaneous approach is the least invasive, has a well-established safety profile, is repeatable, and can be performed on an outpatient basis. However, the open approach has the advantage of permitting access to large and multiple tumors, superb delineation of tumor extent by intraoperative sonography, and the ability to protect adjacent sensitive organs. Temporary hepatic inflow occlusion (Pringle maneuver) can also be performed to decrease perfusion-mediated heat loss and shorten ablation time. It also offers the possibility of concurrent resection. As an example, Yu et al reported a 5-year survival rate of 32% for RFA of a large-burden, unresectable colorectal metastases (mean of 3.2 tumors, and 4.2-cm dominant mass size), combining interventional radiology and surgical expertise in a joint intraoperative approach.[51]

RFA induces focal coagulative necrosis to eradicate small areas of tissue in a controlled fashion. The typical imaging changes noted before and after thermal ablation are demonstrated in Figure 3. If the cytotoxic threshold of temperature for microbubble formation is not reached, an additional RF treatment can be performed. Immediate loss of the color-Doppler signal
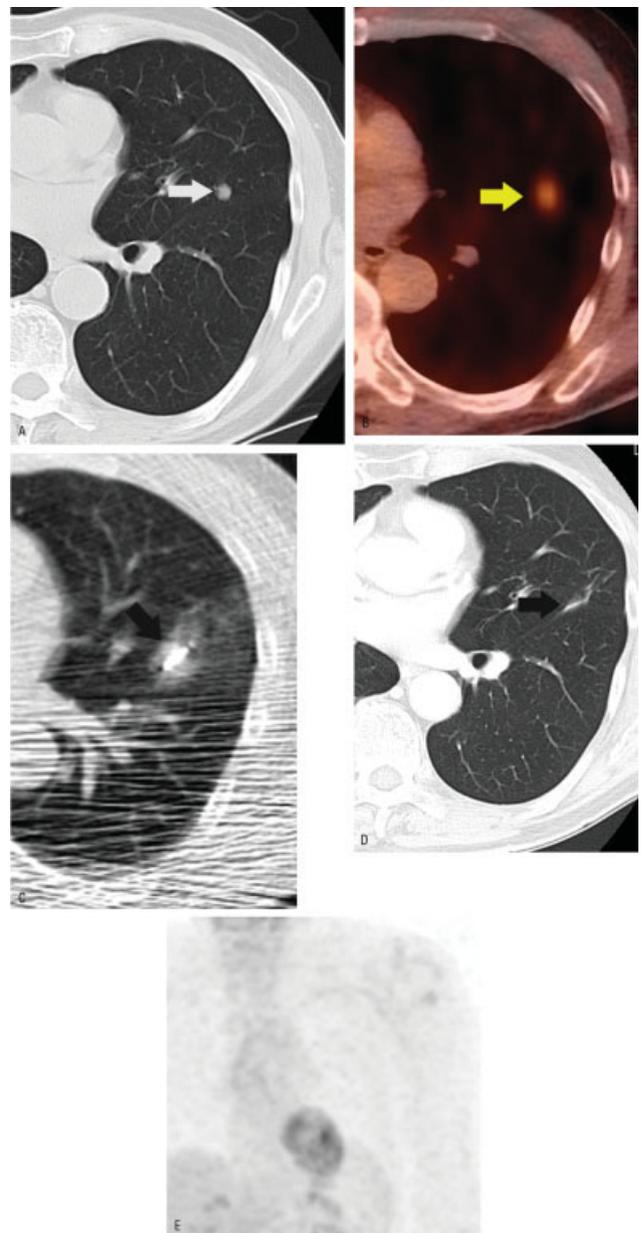


**FIGURE 3.** Case Example of Radiofrequency Ablation (RFA) for Lung Metastasis in a 67-Year-Old Man With Metastatic Melanoma to the Lung and Abdominal Wall. The abdominal wall metastasis was resected surgically and the patient was referred for lung RFA to treat the solitary pulmonary metastasis. (A) Axial computed tomography (CT) image showing a solitary lung metastasis in the left upper lobe (indicated by arrow). (B) Positron emission tomography (PET)/CT image showing the increased metabolic activity corresponding to the nodule (arrow). (C) Axial CT-fluoroscopy-guided image showing the microwave antenna within the nodule and the hazy ground glass treatment changes from the tumor heating (arrow). (D) Follow-up CT image 7 months after RFA showing a linear scar within the treatment site (arrow). (E) PET projection image showing a lack of uptake in the corresponding lung.

within a treated lesion that was previously hypervascular can also be taken as adequate evidence of appropriate thermocoagulation in cases in which microbubble formation is not observed. Continuous impedance, current delivery, power output, and temperature of the RF electrode tip can be monitored with the RF generator.

### RFA Complications: Liver Metastases

Few major complications are generally reported with RFA for liver metastases. First, a small incidence of needle track seeding by tumor has been observed. More rarely, serious complications such as perforations, infections, and liver inflammation (hepatitis) may occur. Certain patients, including the frail and those with significant pretreatment liver damage (eg, cirrhosis) are more likely to experience side effects from RFA. As with all local therapies for liver neoplasms, the risk of complications increases with proximity of the treatment to the porta hepatis. Injury to larger bile ducts and nearby bowel tissue may have serious effects. Exposure to toxicity increases with increasing tumor dimensions. Nevertheless, in a multicenter survey of 2,320 patients treated with percutaneous RFA, the major complication rate was only 3%.[52] In a separate, open RFA series of 382 patients, the major complication rate was also acceptable at 11.2%.[53]

## RFA: Lung Metastases

Because of natural history, patients with metastatic deposits from renal cell carcinoma, sarcoma, and colorectal carcinoma appear to benefit from thermal ablation strategies for lung metastases.[54] For patient populations at high risk of morbidity secondary to a potential thoracotomy or for those who refuse surgery, RFA is an attractive nonsurgical alternative. RFA can be administered in tandem with many systemic therapies. RFA may be used both in these patients and in certain patients in whom a small number of slowly growing metastases are identified.[55-58]

### Pre-RFA Evaluation: Lung Metastases

Similar to RFA for liver metastases, evaluations aimed at selecting appropriate patients are critical for treatment success. Evaluating the target tumor(s) position relative to emphysematous blebs or other avoidance structures is helpful for avoiding complications including pneumothorax and bleeding. To our knowledge, the exact size and number of pulmonary lesions appropriate for thermal ablation therapies has yet to be defined, but it is reasonable to use parameters similar to those that have been applied for RFA of liver tumors (ie, four or fewer metastases). While the maximum size for effective treatment has not been established with consensus, Kang et al[59] found a lack of dissipation in tumors outside of a 3.5-cm dimension. As such, lesions measuring 3 cm or less in size are more optimal candidates given the treatment regions achievable with current thermal ablation technology.

### RFA Technical Issues: Lung Metastases

Techniques for RFA in the lung are relatively similar to those described for liver metastases, with CT being the primary imaging modality. In the case of the lung, the air spaces within the pulmonary tissues act as an insulator, protecting tissue beyond the tumor target. Heating is deemed adequate when both the feedback thermistors within the probe indicate adequate temperature and the alveolar tissue immediately surrounding the tumor becomes more hyperintense on CT pulmonary windows. This CT "blush" provides some indication that adequate heat for coagulation was transmitted to the margin of the tumor target.

### RFA Complications: Lung Metastases

The most likely significant complication that occurs after RFA for lung metastases is a pneumothorax.[45,57] A visible pneumothorax occurs in approximately half of patients as a result of the percutaneous placement of the RF probe. The risk of pneumothorax is less with bronchoscopic guidance. However, only approximately half of the patients who develop a pneumothorax will require chest tube placement whereas the remainder of cases will resolve spontaneously without medical intervention. Treated sites will frequently cavitate after RFA, but this rarely causes serious complications such as fistula, hemorrhage, or infection. Instead, the treated site generally collapses over time, with the formation of distinct scar bands.

Yan et al[58] and Yasui et al[60] reported that there is a real learning curve for the RFA procedure, because experience significantly reduces the incidence of overall morbidity, pneumothorax, and requirements for chest drainage. Furthermore, the distribution of lung metastases (unilateral versus bilateral) is an independent risk factor for overall morbidity and pneumothorax.[61]

On Septemeber 24, 2008, the US Food and Drug Administration (FDA) made an official public health notification clarifying the regulatory status of lung RFA. The notification indicated that FDA approval for the devices used to conduct RFA was for the ablation of soft tissues, not pulmonary tissue, such

that manufacturers should not market them for intrapulmonary indications. Although deaths and injuries have been reported with the use of lung RFA, to our knowledge the actual adverse event rate of lung RFA compared with other treatments could not be determined. Factors related to adverse events could be patient selection and management, technical use of the RF device, postprocedural treatments, and management of complications.

## Principles of SBRT

SBRT is a noninvasive, nonsurgical approach that constitutes the translation of intracranial stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT) toward applications in the body. Unlike conventionally fractionated radiotherapy (CFRT), which is typically delivered over many weeks, the stereotactic treatments use a limited number of ablative radiation treatments such that the entire course is completed in a few outpatient sessions. SBRT was developed later than SRS and SRT because it is technically more challenging. For example, tumors in the body are subject to motion related to natural physiologic process such as breathing and digestion. Adding large safety margins as compensation for motion, which is commonly done with CFRT, would result in severe normal tissue injury during SBRT due to the ablative fractionation. Instead, SBRT delivery requires appropriate motion management such that normal tissue is excluded without compromising tumor control. Furthermore, because the treatments are highly focused, it is required that there is confidence in the target extent both for diagnostics and treatment planning. By the early 1990s, technologic advances in both tumor motion quantification and image guidance allowed the concepts of SRS and SRT to be extrapolated to extracranial sites as SBRT, in which the new therapy could be tested in controlled clinical trials.

As noted earlier, the most significant characteristic of SBRT is the use of ablative fractionation that is facilitated by technologic innovation. The field of radiotherapy has witnessed other innovations in recent years, including intensity-modulated radiotherapy and charged particle delivery (eg, proton therapy). However, these innovations have been used mostly to perform variations of CFRT. CFRT has been used extensively in metastatic disease, but mostly for palliation. Palliation does not generally require that a tumor be eradicated or durably controlled; rather, it requires that a tumor will simply shrink or at least not progress during the typically short remaining life of the patient. With longer survival being reported in patients treated with CFRT (unless given to very high cumulative dose levels), the treatment frequently fails, with the development of local disease progression. Some CFRT trials have been conducted with the objective of improving survival in patients with metastases. For example, researchers at the University of Michigan have conducted a series of trials in patients with hepatic metastases with the aim of controlling metastases and characterizing toxicity after administering radiation therapy twice daily with concurrent chemotherapy.[62] Although they demonstrated the ability to safely deliver high cumulative dose levels of greater than 70 Gy with improved survival and control, control rates are still lower than what has been demonstrated with SBRT. As such, most researchers have moved their emphasis to SBRT rather than CFRT when high rates of long-term tumor control are the objective.

### SBRT: Liver Metastases

The majority of clinical experience with SBRT for liver metastases has been for tumors measuring less than 5 cm in size,[63-69] although tumors as large as 8 cm have been irradiated with 3-fraction SBRT,[70] and tumors as large as 10 cm have been irradiated with lower dose, 6-fraction SBRT.[71] Generally, no more than three metastases can be irradiated with SBRT simultaneously. The safest application of SBRT for liver metastases is for small, noncaudate tumors within the liver that are at least several cm from the stomach or duodenum. The majority of series include SBRT for the treatment of liver metastases from colorectal cancer, but patients with metastases from other gastrointestinal cancers, renal cell carcinoma, breast cancer, bladder cancer, and ovarian cancer have also been included in many series. Local control appears to be reduced in patients with colorectal carcinoma, which is perhaps related to the fact that they are generally highly pretreated and surgically unresectable.[72]

### Pre-SBRT Evaluation: Liver Metastases

Patients treated with SBRT should have a limited number of demarcated tumors that, if eradicated,

would likely improve the patient's overall outcome. In general, SBRT for consolidation or oligometastases should follow the same general treatment philosophy relating to indications for surgical metastectomy. If improvement in survival is the goal, the treatment would likely be most beneficial in patients with controlled primary tumors, limited metastatic disease, metachronous appearance of primary and metastatic disease, younger age, and higher performance status. In general, all macroscopically viable metastatic disease should be treated if survival improvements are to be realized. For palliative intent, treatment is performed to improve quality of life. Therefore, it must first be clear that the targeted tumor is indeed the culprit in degrading the patient's quality of life, and that shrinking and controlling this tumor will likely improve the quality of life. Furthermore, the side effects of the treatment should not be severe so as to avoid a further decrease in quality of life. Extremely frail patients or patients with widespread metastatic disease rarely benefit from SBRT.

### SBRT Technical Issues: Liver Metastases

The term "stereotactic" simply relates to the correlation of the tumor target position with reliable fiducials with a readily known position. Fiducials define a coordinate system that can be used to target the tumor, orient the treatment planning process, and ultimately guide the therapy toward the intended location in the body. With sophisticated real-time image guidance, such as might be obtained from megavoltage or kilovoltage CT on the treatment couch, the tumor itself can serve as the fiducial, thereby negating the need for the external markers that have classically characterized stereotactic treatments.[73-75] SBRT combines potent dose fractionation, careful target definition, motion control (four-dimensional therapy), image guidance, conformal and compact dose distributions, and high levels of quality assurance in treatment. A typical arrangement of beams for SBRT is shown in Figure 4. The American College of Radiology and the American Society of Therapeutic Radiology and Oncology have published guidelines that define SBRT and its proper conduct.[76]

### SBRT Complications: Liver Metastases

One of the most serious complications after liver irradiation is radiation-induced liver disease (RILD),
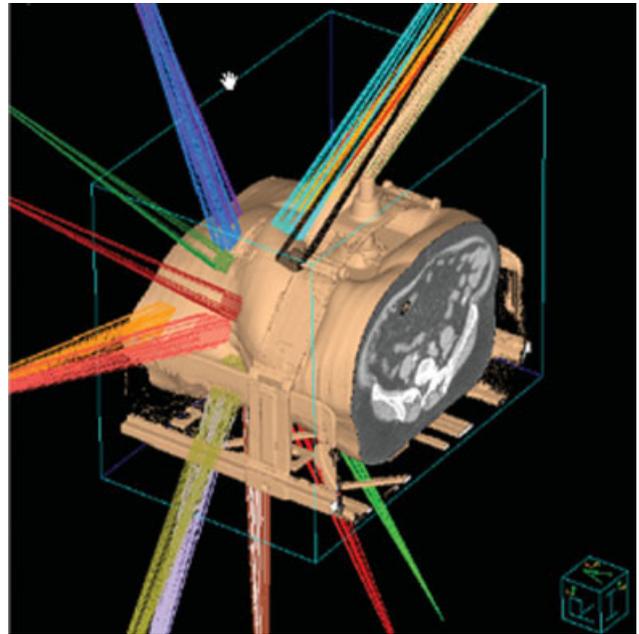


**FIGURE 4.** Beam Arrangements for Stereotactic Body Radiotherapy. Three-dimensional reconstruction of a patient with liver metastases showing numerous noncoplanar beams aimed toward the abdomen. This treatment simulation uses abdominal compression to dampen inherent respiratory motion.

a clinical syndrome of anicteric hepatomegaly, ascites, and elevated liver enzymes occurring within 3 months after the completion of therapy. RILD has been observed after whole-liver irradiation with CFRT to 32 Gy in 16 fractions or more and after focal conformal liver irradiation.[62] RILD is very rare after SBRT for liver metastases, but has been reported occasionally.[70,77] To keep the risk of liver toxicity low, a substantial volume of liver must be spared from irradiation, and reirradiation is not recommended. This can be done by keeping the dose to 700 cc of uninvolved liver to less than 15 Gy delivered in 3 fractions[13] or ensuring that no more than 50% of the liver receives 15 Gy in 3 fractions (or 7 Gy in 1 fraction), and no more than 30% of the liver receives 21 Gy in 3 fractions (or 12 Gy in 1 fraction).[70,77] Other potential hepatic toxicities, including a transient increase in liver enzymes, reactivation of hepatitis B, and a general decline in liver function, have been reported after SBRT for hepatocellular carcinoma but are believed to be uncommon after SBRT for liver metastases unless there is underlying liver disease or prior liver irradiation has been delivered.[67,70] Portal venous enhancement on CT scans can be observed transiently in volumes of the liver irradiated to high SBRT doses, approximately 1 to 4 months after therapy.[64] Such changes should not be

confused with tumor progression. Ultimately, fibrosis of the portions of the liver included within the high-dose volume is common, as is compensatory hypertrophy of the portions of the liver spared from radiation. Biliary sclerosis and hepatic subcapsular injury are other potential toxicities. Although to our knowledge biliary sclerosis has not been reported after SBRT for liver metastases to date, it has been reported after hypofractionated proton therapy for hepatocellular carcinoma. Gastrointestinal bleeding, small bowel obstruction, gastric outlet obstruction, and fistula formation are other possible late sequelae if the esophagus, stomach, duodenum, or large bowel are irradiated to high doses. Hemorrhagic gastritis was reported to develop after a dose of 14 Gy delivered in 2 fractions to the gastric wall of a patient with a liver metastases,[64] and ulcers and perforations were noted when greater than 30 Gy in 3 fractions was delivered to the intestines.[77] Subcutaneous fibrosis and tissue breakdown are also possible if care is not taken to avoid overlapping of the radiation beams.[66]

## SBRT: Lung Metastases

The majority of published experience with SBRT for lung treatment relates to treating early-stage, primary lung cancer,[70,78-83] not metastases. The majority of these reports convey experiences with medically inoperable patients who often have severe underlying pulmonary disease. Typically, such patients would have poor tolerance of therapy, and require less extensive surgery, smaller volumes and lower doses of conventional radiotherapy, and fewer cycles or a lower intensity of chemotherapy. However, toxicity studies using SBRT in these frail patients have demonstrated that very potent doses may be delivered, resulting in high rates of local control. This experience can, and has been, prudently translated to the treatment of patients with limited metastases in the lung. Although patients with metastatic disease often have undergone extensive pretreatment with chemotherapy, thereby affecting functional pulmonary reserve, they typically have been reported to have better pulmonary function than patients with medically inoperable, early-stage primary lung cancer who have tolerated potent SBRT in several published reports. However, the confounding effects of multiple lesions observed with metastatic presentations compared with solitary targets may significantly increase toxic-

ity in patients with oligometastases, therefore requiring the careful selection of patients for SBRT.

### Pre-SBRT Evaluation: Lung Metastases

Prior to undergoing SBRT, patients should have a baseline pulmonary function assessment with spirometry, diffusing capacity, and arterial oxygen tension. In addition, baseline imaging with contrast-enhanced spiral CT as well as combined PET/CT is routine. SBRT does not appreciably affect blood counts, liver enzymes, or kidney function, and therefore routine baseline laboratory testing is not generally necessary. Patients under consideration for SBRT for lung metastases actually have few medical contraindications because even patients with severe emphysema and chronic obstructive pulmonary disease have tolerated the procedure with acceptable side effects reported.[81] However, patients with tumors near the central mediastinal and hilar areas should either not be treated out of concern for toxicity[84] or should be treated on a clinical trial because to our knowledge no safe dose of SBRT has been determined to date for tumors in such locations. Patient selection for SBRT based on disease characteristics should be similar to what was discussed earlier in the sections regarding surgical metastectomy.

### SBRT Technical Issues: Lung Metastases

The administration of SBRT for lung metastases is very similar to that described earlier for liver metastases. However, careful consideration must be made for the proper accounting of lung tissue density correction for lung SBRT. Large errors in dose prescriptions of up to 20% to 40%, particularly from using older generation algorithms such as the pencil beam and Clarkson method, have been observed in phantom measurements and when using sophisticated Monte Carlo methods.[85]

There is a clear need to deliver high doses of SBRT to control lung metastases. At Kyoto University in Japan, Nagata et al use a higher dose for lung metastases than for primary lung cancer due to higher observed rates of local failure in the former group of patients.[78] Ideally, dose escalation studies would be performed for patients with lung metastases, as has been done for patients with primary lung cancer using SBRT.[81] One such important Phase I study was performed by Schefter et al using SBRT for lung

metastases.[86] Although that prospective study is still maturing, the preliminary results indicate that high doses can be delivered using SBRT techniques. Using a 3-fraction regimen, Schefter et al reported that up to 20 Gy per fraction (60 Gy total) can be safely delivered to selected patients with lung metastases from a variety of tumor tissue types.[86] Other Phase I dose escalation toxicity studies are needed in patients with lung metastases, particularly using different SBRT fractionation schedules.

### SBRT Complications: Lung Metastases

The hilar and central mediastinal structures in the chest appear to be very sensitive to the negative effects of SBRT.[84] To our knowledge, the majority of toxicity reports regarding SBRT in the lung describe patients with medically inoperable, early-stage primary lung cancer. Primary lung cancer patients tend to present with considerably poorer baseline pulmonary function (due to chronic tobacco abuse) compared with patients with lung metastases from other primary tumor sites. The risk of hypoxia, atelectasis, pneumonitis, decline in pulmonary function, and hemoptysis is greatest for tumors located in the central chest, in which most primary lung cancers occur. As metastases are more typically peripheral in location, treatment is generally better tolerated. Radiation pneumonitis, a common problem encountered with conventional pulmonary radiotherapy, is less likely to occur with SBRT because the volume of lung receiving high and intermediate doses is limited by the multiple-field techniques. Instead, there is a risk of decreasing pulmonary reserve, which may not manifest as a toxicity until many years later, particularly if the patient continues smoking. Chest wall complications including pleural effusions, chest wall pain, and rib fracture may occur with pleural-based lesions. In a recent toxicity report from a multicenter trial of SBRT in frail patients with lung cancer, the protocol-defined major toxicity rate was approximately 10%.[87]

## Clinical Evidence and Recommendations

### Approach to Evaluating the Evidence

Because patients with metastases are at significant risk of dying within a short period due to disease progression, treatment toxicity, and other comorbidities, they may die prior to experiencing a local recurrence of their treated metastases. When treating diseases with a high likelihood of immediate fatality, the practice of reporting gross rates of benefit (eg, the number of patients without local disease progression divided by the total number of patients treated) may erroneously convey benefit. This is because such analysis is devoid of the statistical censorship of patients who were removed from the pool of total patients as a function of time from treatment. Instead, the nontreatment-related death or loss to follow-up of a patient prior to experiencing a negative outcome (eg, local disease recurrence after local therapy) makes the overall "benefit" rate appear to improve even though such events are unrelated to any merit of the therapy. This issue is mostly resolved by prospective testing, careful and prudent imaging evaluation after therapy, and reporting outcome by actuarial statistical methodology rather than gross rates. Although pertinent to measurement after local therapy, local control is not always a surrogate for establishing longer survival. Furthermore, to define better survival after local therapy with confidence would require a randomized trial. Unfortunately, practitioners must currently interpret the benefit of local therapies based on a limited number of prospective trials (mostly Phase II) and a larger volume of retrospective reports. Retrospective chart analysis, even if large in patient numbers by combining institutional results, is no substitute for prospective testing. The feasibility of trials is complicated by the fact that a metastases to the liver or lung may result from a large variety of primary tumor sites, each with unique characteristics that may affect survival.

The surgical experience is considerably larger than that reported with RFA or SBRT. With larger surgical series, separate subset analyses can often be performed for a variety of metastases from a variety of primary tumors. Such analysis is less often available with RFA and not available for SBRT, in which to our knowledge no results for specific histologies (eg, liver metastases from colorectal cancer) have been published to date. In the following section, the results of therapy for specific tumor presentations will be presented, followed by the more general reports typical of RFA and SBRT.

### Colorectal Carcinoma: Liver Metastases

The liver is the most common site for blood-borne metastasis from colorectal cancer. Approximately

25% of patients with colorectal cancer will have synchronous hepatic metastases, and an additional 50% of patients will develop metachronous hepatic metastases.[88] Survival for untreated metastases is measured in months.[89,90] The length of survival is related to the extent of liver replacement by tumor. The 1-year survival rate is approximately 5% for patients with bilobar liver disease, 27% for those with unilobar disease, and 60% for patients with solitary metastasis.[90] However, even patients with solitary metastases, when untreated, have 3-year survival rate of only 20%,[89] and a 5-year survival rate of less than 3%.

### Clinical Evidence in Colorectal Liver Metastases

A large number of published series have confirmed that hepatectomy, the surgical removal of portions of the liver (in this case portions involved with tumor), may result in long-term survival and potential cure for patients with colorectal cancer metastatic to the liver. Table 1 includes most series published to date with greater than 200 patients. In a multiinstitutional collected series of 859 patients, Hughes et al[18] reported the actuarial 5-year patient survival rate to be 33%. A more recent multiinstitutional series[91] with more than 1,500 patients has verified these findings. The literature clearly indicates that 5-year survival rates of 25% to 51% and a median survival of 28 to 59 months after surgical resection can be expected. In series with long enough follow-up, the 10-year survival rate is reported to be approximately 20%.[16,17,19,21,23,91] There is no doubt that patients can actually be cured by surgical resection.

Published data have demonstrated convincingly that the number of tumors and tumor bulk are both important determinants of improved outcome for patients undergoing surgical resection for liver metastases.[15,22,46,47,92-94] When considering local therapy, therefore, it is important to have as a basis of comparison the results of patients who had only a few, small tumors who underwent resection. Figure 5 demonstrates the survival of 372 patients with 3 or fewer tumors, each measuring less than 5 cm, who were treated at the Memorial Sloan-Kettering Cancer Center by hepatectomy between 1990 and 1996. During this period, the majority of patients did not receive adjuvant chemotherapy and therefore these results convey the independent effect of hepatectomy. This is of historical significance because most patients currently undergo chemotherapy as part of
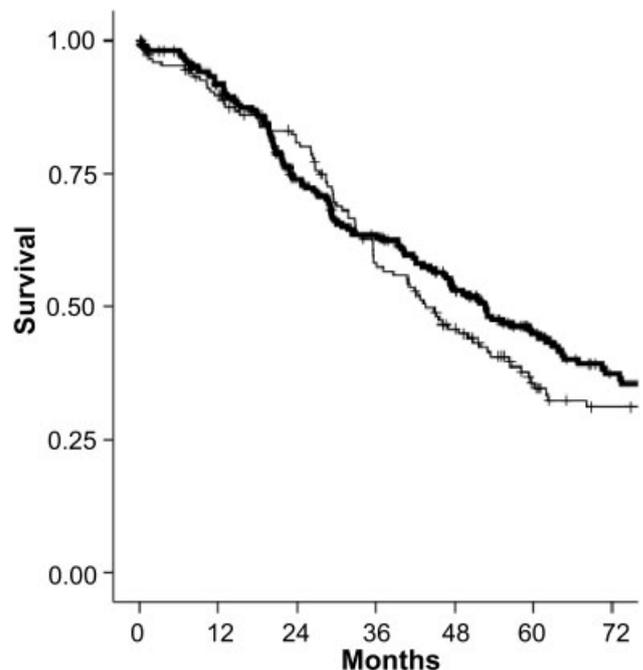


**FIGURE 5.** Survival of Patients After Resection of Limited-Volume Hepatic Colorectal Metastases. Data from 372 patients with 3 or fewer tumors, each measuring less than 5 cm, who were treated with hepatectomy at the Memorial Sloan-Kettering Cancer Center between 1990 and 1996 are shown. The survival of the 218 patients with solitary lesions is indicated by the thick curve and the survival of the 154 patients with 2 or 3 tumors is indicated by the thin line.

their treatment for colorectal metastases. The survival of 218 patients with solitary lesions is indicated by the thick curve and demonstrates a 1-year survival rate of 92%, a 2-year survival rate of 74%, a 3-year survival rate of 64%, and a 5-year survival rate of 45%. The survival for 154 patients with 2 or 3 tumors is indicated by the thin line. The survival rate was 90% at 1 year, 81% at 2 years, 58% at 3 years, and 36% at 5 years. Thus, it appears that surgical therapy can achieve a favorable long-term outcome with low treatment-related mortality, although at the cost of significant morbidity.

Many patient and tumor factors have been found to be predictive of poor outcome in individuals with hepatic metastases from colorectal cancer. These include male gender,[95] lymphatic metastases from the primary tumor,[18,93] symptomatic disease,[18,93] extremely elevated CEA levels,[7] a short DFI between the time of diagnosis of the primary tumor and hepatic metastases,[22] large tumors,[93, 94] multiple tumors,[93] bilateral tumors,[92] and the presence of satellite lesions.[15,22] Many investigators have attempted to collate some of these factors into scoring systems for the overall assessment of patient prognosis. Two such often-quoted syntheses of data are those of Nord-

linger et al, who analyzed a multicenter series of greater than 1,500 patients,[91] and Fong et al, who analyzed a series of 1,001 patients treated at a single institution.[17] The results from both series were found to be very similar. The most significant preoperative factors that were found to predict outcome were 1) lymph node metastases from the primary tumor, 2) short DFI, 3) largest tumor measuring greater than 5 cm, 4) more than 1 liver metastasis, and 5) a CEA level over 200 ng/mL. From these factors, a clinical risk score (CRS) system was created (Table 2) counting each criteria as one point.[17] The CRS is a simple, easily remembered staging system for classifying patients with hepatic colorectal metastases.

The most common site for disease recurrence after the surgical resection of colorectal liver metastases is the residual liver, and the liver is the sole site of first recurrence for approximately 15% to 40% of patients. Of these patients, only approximately one-third will be suitable for further resection.[96] As liver surgeons have become increasingly comfortable with performing primary liver resection, an increasing number of reports have examined the utility of re-resection as treatment for recurrent disease. The majority of the data until the last decade concerning re-resection can be characterized as anecdotal or small series that serve mainly to indicate the feasibility of performing re-resections. Two larger series have recently demonstrated not only the safety of these procedures, but also the resulting favorable long-term outcome. Yamamoto et al[97] reported on re-resection performed in 75 patients, and demonstrated a 5-year survival rate of 23%. Petrowsky et al[96] reported on 126 patients who underwent re-resection and found a 5-year survival rate of 34%. The reports published to date also indicate that patients chosen for re-resec-

tion are likely to be even more highly selected than those selected for first-time resection because surgical death is rare. The complications and complication rates (approximately 24%-50%) reported are similar to those reported for patients undergoing their first hepatectomies.[96,97] The median hospital stay for patients undergoing repeat liver resections was reported to be 10 days.[96] A comparison of re-resection results with historic data regarding untreated colorectal metastases strongly suggests that survival is prolonged by surgical therapy. The median survival of untreated cases of disease recurrence after liver resection is reported to be approximately 4 months.[98]

RFA has played an increasingly important role in the treatment of liver metastases from colorectal carcinoma. The technique may be performed percutaneously using an image-guided approach or by direct visualization intraoperatively. In the latter case, it is not unusual to perform surgical resection for some lesions and RFA for others. After a previous liver resection, the abdomen and particularly the right upper quadrant can be difficult to navigate surgically because of adhesions and distortion of the anatomy. Repeat liver resections can be lengthy and difficult. Ablative therapy may allow more patients to be effectively treated. It is likely that ablative therapy will in some cases replace the current use of repeat surgical resection.

Table 3 summarizes the major studies published to date that have reported long-term outcomes data for RFA of nonresectable colorectal hepatic metastases.[46,47,51,99-107] The reported overall 5-year survival rate was found to range from 17% to 55%. Because RFA is a relatively new treatment modality and a learning curve is expected, it is not surprising that better outcomes can be expected from the more recent reports. Hildebrand et al studied outcomes of liver RFA at their institution based on experience and reported that 2-year survival rates in their latter 42 patients were significantly better than that of their first 42 patients (89% versus 46%, respectively).[108]

Whether due to patient selection or technique, some studies have reported better local recurrence rates after open RFA compared with percutaneous RFA. Table 4 shows local recurrence rates reported from major studies. There was a trend toward decreasing local recurrence noted with the more recently reported percutaneous RFA trials compared with earlier studies. Advances in image guidance

TABLE 2. Clinical Risk Score (CRS) for the Determination of Prognosis in Patients With Hepatic Colorectal Metastases*

| |
|---|
| Lymph node-positive primary tumor |
| Disease-free interval of <12 mo between colon resection and appearance of metastases |
| Size of largest lesion >5 cm |
| More than 1 tumor |
| Carcinoembryonic antigen level >200 ng/dL |

*One point is assigned for each positive criterion. The sum of points is the CRS.

TABLE 3. Major Outcome Studies of Colorectal Metastases to the Liver Treated With Radiofrequency Ablation*

| STUDY | NO. OF PATIENTS | ACCESS | SIZE, CM | NO. OF TUMORS | MEDIAN SURVIVAL, MONTHS | OVERALL SURVIVAL RATE AT 3 YEARS AND 5 YEARS |
|---|---|---|---|---|---|---|
| Solbiati 2001[107] | 117 | Percutaneous (P) | 2.8 | | 36 | |
| Gillams 2004[101] | 167 | P | 3.9 | 4.1 | 32 | 3-y: 40%<br>5-y: 17% |
| Lencioni 2004[46] | 423 | P | 2.7 | 1.4 | 25 | 3-y: 47%<br>5-y: 24% |
| De Baere 2003[100] | 155 | P | 2.5 | 1.3 | 27 | 3-y: 31% |
| Solbiati 2006[106] | 121 | P | 2.1 | 2.1 | 47 | 3-y: 60%<br>5-y: 35% |
| Pereira 2006[104] | 177 | P | 2.2 | 2.2 | | 3-y: 71%<br>5-y: 55% |
| Siperstein 2007[105] | 235 | Laparoscopic (L) | 3.9 | 2.8 | 24 | 3-y: 20%<br>5-y: 18% |
| Machi 2006[47] | 100 | P, L, open (O) | 3.0 | 3.5 | 28 | 3-y: 42%<br>5-y: 31% |
| Iannitti 2002[103] | 52 | P, L, O | 5.2 | | | 3-y: 50% |
| Hildebrand 2006[102] | 56 | P, L, O | 3.5 | 3.5 | 28 | 3-y: 42% |
| Abdalla 2004[99] | 57 | O | 2.5 | 1.7 | | 3-y: 37%<br>4-y: 22% |
| Yu 2006[51] | 50 | O | 4.2 | 3.3 | 37 | 3-y: 52%<br>5-y: 32% |

*Minimum of 50 patients in studies with 3-year survival data.

technology, including ultraprecise navigation systems, can potentially offset many of the shortcomings of present-day US, CT, and MRI compared with intraoperative US.[109] In addition, new interventional techniques are already being introduced that enable thermal protection of adjacent organs without laparoscopy or laparotomy, including percutaneous hydrodisplacement of bowel.[110] Nevertheless, the decision regarding which surgical approach to use

ultimately depends on the availability of local expertise, which, as previously mentioned, requires advanced skills and experience, regardless of whether an open, laparoscopic, or percutaneous approach is used. A multidisciplinary team approach is necessary to optimize treatment strategy in these patients.

With increasing experience and technologic advances in image guidance and ablative technology, the outcome data for RFA has steadily improved. In

TABLE 4. Major Studies Reporting Local Recurrence Rates in Radiofrequency Ablation of the Liver

| STUDY | NO. OF PATIENTS | NO. OF TUMORS | TUMOR TYPE | ACCESS | AVERAGE SIZE, CM | MACROSCOPIC LOCAL RECURRENCE RATE |
|---|---|---|---|---|---|---|
| Solbiati 2001[107] | 117 | 179 | Colon | Percutaneous (P) | 2.8 | 39% |
| Lencioni 2004[46] | 423 | 615 | Colon | P | 2.7 | 25% |
| De Baere 2003[100] | 155 | 251 | Colon | P | 2.5 | 10% |
| Solbiati 2006[106] | 121 | 320 | Colon | P | 2.1 | 14% |
| Siperstein 2007[105] | 235 | 658 | Colon | Laparoscopic (L) | 3.9 | 18% |
| Bleicher 2003[177] | 153 | 447 | Mixed | P, L, open (O) | 2.5 | 12% |
| Elias 2004[178] | 88 | 227 | Colon | O | 1.5 | 6% |
| Abdalla 2004[99] | 57 | 110 | Colon | O | 2.5 | 9% |
| Yu 2006[51] | 50 | 181 | Colon | O | 4.2 | 6% |

a series of 47 patients with solitary colorectal metastases to the liver, Oshowo et al recently reported survival rates for RFA that the authors claim rival that of surgical resection.[111] This has caused some to call for randomized trials between RFA and hepatic resection for selected patients with colorectal metastases to the liver.[112] Until then, however, hepatic resection should continue to be considered the gold standard for these patients. Some surgeons have proposed the "test of time" management approach before hepatectomy, such that a watchful waiting interval with systemic therapy alone may select patients who will best benefit from surgical resection due to favorable biology, and those who will ultimately develop previously undetected nonresectable metastases would then have been spared an unnecessary major surgery.[113] Livraghi et al described the use of RFA in 88 patients in the interval before potential resection, and reported that 67 patients were spared an unnecessary surgery (either because their lesions were controlled by RFA or they developed new, nonsurgical lesions), and the procedure did not preclude eventual surgical resection in the remaining 21 patients.[114] Many of these questions will eventually be answered with more data and well-designed trials, but it is already clear that RFA may have a significant impact on the management of patients with colorectal hepatic metastases.

For SBRT, the majority of reports include colorectal cancer metastases along with other histologies without making any distinction. However, in 1 recent series, 64 patients with 141 colorectal cancer liver metastases (including 44 liver metastases deemed not suitable for RFA or surgery) who were treated with SBRT had a 5-year survival rate of 13%, indicating the possibility of long-term survival after SBRT for oligometastases.[77]

### Recommendations for Colorectal Liver Metastases

In approaching a patient with colorectal liver metastases for consideration of local therapy such as surgical metastectomy, the first goal should be to remove all macroscopic tumor (R0 resection) without leaving the patient with severely impaired residual hepatic function. Although patients with solitary tumors have better prognosis, multiple lesions do not inherently preclude local therapy unless the distribution of tumors limits the likelihood of the first goal. To our knowledge, there is no established role for debulking.

Furthermore, there should be no uncontrolled extrahepatic disease, and the primary tumor should be under control.

The hepatic metastases prognostic scoring system used under the circumstances described in the preceding paragraph and shown in Table 2 has been verified by independent investigators from Norway.[115] This scoring system has also proven important for selecting the appropriate staging test for patients with hepatic metastases, including yield of PET scanning[116] and laparoscopy.[117] The CRS also has been shown to predict the outcome of ablative therapy.[118] This scoring system has been updated with a computer nomogram that includes most of the known prognostic factors and can be easily used on a personal digital assistant (PDA).[119] At the bedside, however, the original CRS remains a simple and validated staging system that should be used in predicting patient outcome and comparing treatments for patients with hepatic metastatic disease from colorectal primary tumors.

Given the considerably longer and larger experience with regard to patient outcome, appropriately selected patients should first be considered for surgical resection rather than RFA or SBRT. This discussion should ideally be held between the patient and an oncology surgeon familiar with the surgical procedures and outcomes. However, in patients who refuse surgery or those considered too frail for surgery, both RFA and SBRT have become valid second-line standard therapies.

## Colorectal Cancer: Lung Metastases

Approximately 10% of colorectal cancer patients will develop pulmonary metastases, and treatment with chemotherapy alone rarely results in a cure.[120-122] As such, there is a large and growing experience using local therapies aimed at improving survival in this group of patients.

### Clinical Evidence in Colorectal Lung Metastases

Published 5-year survival rates of 38% to 63% have been reported after pulmonary metastectomy in patients with metastatic colorectal cancer.[121-124] In addition, there is a significant incidence of patients who present with concurrent hepatic and pulmonary metastases. Many would consider this a contraindication to surgery, but several centers have included surgery and nonsurgical local therapies as

part of their treatment algorithm. Using this approach, 5-year survival rates of 30% to 43% have been published.[122]

Although the majority of studies of RFA for metastatic colorectal pulmonary disease have inadequate sample sizes for subset analyses of specific tumor types, some treatment centers have begun to examine data. In 2004, a group from the University of New South Wales reported their follow-up on RFA in a group of 23 patients with 53 colorectal metastases.[125] After 1 year, CT findings demonstrated that 40 lesions were classified as having disappeared (17 lesions), decreased (5 lesions), remained the same size (4 lesions), or increased (14 lesions). More recently, this same group[61] reported more follow-up results and predictors for survival in their cohort of 55 patients with colorectal pulmonary metastases. After a univariate analysis found that largest size of the lung metastasis, location of the lung metastasis (hilar or nonhilar), and need for repeat RFA were predictive of survival, only size (less than 3 cm) of the lung metastasis was found to remain predictive in the multivariate model (hazards ratio = 4.456; $P$ = .003). The overall median survival was 33 months, with 1-year, 2-year, and 3-year actuarial survival rates of 85%, 64%, and 46%, respectively. Interestingly, this survival was achieved even though 55% of the patients had undergone a prior liver resection for liver metastases. Furthermore, patients with bilateral resectable pulmonary metastases had a survival that was similar to those patients with unilateral pulmonary metastases. The data from Rhode Island Hospital demonstrated a survival rate of 57% at 5 years in a cohort of 18 patients with colorectal cancer metastases to the lungs.[56]

While investigation is ongoing, to our knowledge there are no published reports specifically describing the outcome of colorectal lung metastases using SBRT with which to draw valid conclusions. Series with mixed primary histologies, including some patients with colorectal cancer, will be discussed below.

### Recommendations for Colorectal Cancer Lung Metastases

The majority of studies published to date report improved survival in patients undergoing surgery for pulmonary metastases from colorectal cancer when they have a solitary lesion, a longer DFI prior to detection of the metastases, lower CEA levels, smaller tumors, absent hilar or mediastinal metastatic lymphadenopathy, and limited extrapulmonary disease. Ideally, then, the patient should have fewer than 2 to 3 pulmonary lesions, a disease-free survival of 12 months or more, a CEA level of less than 10 ng/mL, tumors measuring less than 5 cm, no metastatic lymphadenopathy, and absent extrapulmonary disease.

As with colorectal liver metastases, it would be most prudent to offer legitimate consideration of surgical metastectomy as first-line therapy prior to RFA or SBRT. However, again, in those patients who refuse surgery or are too frail, these nonsurgical therapies are legitimate ablative therapies in properly selected individuals.

## Osteosarcoma Lung Metastases

Prior to the routine use of effective chemotherapy, pulmonary metastases from osteosarcoma would develop in up to 85% of patients treated with local therapy alone to the primary bone tumor. Even with effective systemic therapy substantially reducing the incidence of lung metastases, lung metastases will ultimately be the primary cause of death in most patients with treatment-resistant cancer.[25,126]

### Evidence and Recommendations for Osteosarcoma Lung Metastases

Analyses of prognostic factors for survival after resection of osteosarcoma lung metastases have been performed in published reports. Consistently, the DFI, number of lesions (seven or fewer), control of primary disease, and effectiveness of chemotherapy have been found to predict better ultimate survival in a strategy that includes metastectomy along with modern systemic therapy. In one retrospective report, similarly matched patients who all received systemic therapy were treated with or without surgical removal of their pulmonary metastases. The median survival of the group treated with metastectomy was 51 months compared with 30 months among those receiving systemic therapy alone.[43] Although further prospective testing will be needed to determine the limits of patients who benefit, surgery remains a very crucial part of the treatment of pulmonary metastases secondary to osteogenic sarcoma.

## Soft Tissue Sarcoma Lung and Liver Metastases

Metastases to the lung from soft tissue sarcomas occur in approximately 20% of all patients during the course of their disease, but are much more likely to occur in those with large and/or high-grade tumors.[127] Metastases from soft tissue sarcoma are most likely to be found in the lung, but isolated liver metastases are less frequently reported.

### Soft Tissue Sarcoma: Evidence and Recommendations for Lung and Liver Metastases

Unlike osteosarcoma, to our knowledge no effective systemic therapies for use as adjuvant therapy in high-risk patients or primary therapy for patients with metastatic disease have been identified to date. Nonetheless, 5-year survival rates published in the literature are as high as 20% to 40% in series including pulmonary metastectomy for patients who develop metastatic disease.[128, 129] Indeed, one recent review published a 5-year survival of up to 57% in patients who were underwent complete resection.[130] Several published series have included histology, histologic grade, DFI, number of metastates, and bilaterality as factors influencing survival, whereas other series have presented conflicting results.[130-132] Similarly, there are early reports of RFA in the treatment of sarcoma metastases to the liver.[133-135] Berber et al reported a median survival of 25 months in 18 patients using a laparoscopic approach,[133] and Lee et al reported a mean survival of 57 months in 8 patients with 30 liver metastases who were treated with open RFA.[134] Despite the use of multiple different chemotherapy regimens, survival remains poor, and local therapy remains an integral part of the treatment of pulmonary metastases from soft tissue sarcomas.

## Breast Cancer Liver Metastases

Despite the use of more effective systemic chemotherapy (eg, anthracyclines and taxanes), antihormonal therapy (eg, aromatase inhibitors), and directed biologic agents (trastuzumab), patients with liver metastases from breast cancer are reported to have a poor median survival, ranging from 3 to 15 months.[136-138]

### Breast Cancer Liver Metastases: Clinical Evidence and Recommendations

Selected patients who are treated surgically to remove liver metastases may experience a doubling or tripling of this median survival.[139] Most series have reported the best prognosis in patients with a long DFI, an older age, smaller tumor volume in the liver, fewer metastatic lesions, the absence or control of extrahepatic disease, and a history of complete resection.[140-150] More recent series have also included positive hormone receptor status and other markers associated with better systemic therapy response as predictors of better survival.[138,139,141]

Recent initial reports have been published of liver-dominant metastases treated with RFA in addition to systemic therapy.[149,151,152] Livraghi et al first reported a 92% complete necrosis rate with a local disease progression rate of 8% in 24 patients with liver-dominant breast metastases after a median follow-up of 10 months.[151] Similarly, Sofocleous et al recently reported a median survival from RFA of 60 months and a median survival from the time of diagnosis of 145 months based on a retrospective review of 12 patients.[152] To our knowledge, only a few reports of SBRT used solely for breast metastases have been published to date. Finally, Katz et al reported the outcomes in 69 patients with 174 metastatic liver tumors who were treated with a more protracted fractionation schedule compared with most reports using stereotactic techniques.[65] Sixteen of the patients in their prospective trial had breast cancer. The local control rate was 57% at 20 months, with a median survival of 14.5 months.[65] In a recent report from the same group, patients with oligometastases specifically from breast cancer were found to have significantly better survival and control compared with patients with oligometastases from other primary tumor sites.[153]

## Melanoma Liver and Lung Metastases

The overall population of patients with metastatic melanoma has a very poor prognosis, with a median survival of fewer than 8 months and a 5-year survival rate of less than 5%.[154,155] Up to 40% of these patients will present with isolated lung metastases.[154] Systemic therapy options are limited, prompting several investigations of metastectomy.

### Evidence and Recommendations for Melanoma Liver and Lung Metastases

Several large but retrospective series have evaluated prognostic factors for improved survival in patients with liver and lung metastases from melanoma. For liver metastases, a large database review and a smaller but more modern series demonstrated a median survival of 20 to 22 months and a 5-year overall survival rate of 20% in highly selected patients (those with a long DFI and absent extrahepatic tumor) with liver metastases.[156,157] Similarly, prudently selected patients with lung metastases (eg, 2 or fewer metastases, absent extrathoracic disease, and a longer DFI) were reported to have a 5-year survival rate as high as 39% after surgical resection.[158] Given the poor outcomes of other treatment modalities and the evidence summarized earlier, surgical resection or other local therapies should be considered in a select group of patients with metastatic melanoma. More importantly, given the poor prognosis and incidence within a wide age group, patients with metastatic melanoma should be considered for prospective clinical trials.

## Renal Cell Carcinoma Lung Metastases

Approximately one-third of patients with renal cell carcinoma have pulmonary metastases, 60% have metastasis in general,[159] and one-half of patients who have undergone nephrectomy for renal cell carcinoma will develop pulmonary metastases at a later date.[160]

### Evidence and Recommendations for Renal Cell Carcinoma Lung Metastases

In several series, a 5-year overall survival rate of approximately 35% to 40% was observed after resection of lung metastases in selected patients with limited metastatic disease.[161-163] Although the data are far from conclusive, there is enough of a basis to contemplate surgery, RFA, or SBRT in patients without lymph node involvement and fewer than two to three metastatic tumors.

## Germ Cell Tumor Lung Metastases

Since the addition of cisplatin-based chemotherapy regimens to the treatment of germ cell tumors, the prognosis of all patients, including those with pulmonary, brain, and retroperitoneal metastases, has been outstanding.[164-166]

### Evidence and Recommendations for Germ Cell Tumor Lung Metastases

In situations in which residual disease in the thorax is discovered after the completion of chemotherapy, surgical resection can be potentially curative by removing a residual malignant germ cell tumor or chemotherapy-resistant teratoma.[167-169] Greater than 30% of these lesions will have histology that is different from that of the primary lesion, including the potential for a benign teratoma that progresses despite effective chemotherapy and can be cured by surgical resection. Given the high rates of cure, even with disseminated tumor at the time of presentation, germ cell tumors constitute a special category of oncologic care. Patients should be evaluated and treated by an experienced multidisciplinary team to achieve the most ideal outcome results.

## Results of SBRT for Nonspecific Histologies

Several reports, including prospective Phase I and II trials, have described the outcomes of patients treated with SBRT without making a distinction regarding the primary tumor histology. Although these data allow for the assessment of local control and toxicity, such reports do not permit the determination of outcomes for metastatic presentations of specific tumor primary sites such as colorectal cancer or breast cancer. Nonetheless, the information allows for the assessment of local effects and will be presented below.

A representative collection of patient outcomes after SBRT to the liver is shown in Table 5. To our knowledge, the first report of liver SBRT came from Blomgren et al in 1995, in which 29 liver tumors occurring in 23 patients (14 with metastases) were treated with 20 to 45 Gy in 1 to 4 fractions.[70] Complete responses occurred quickly in patients with small tumors, but the time to maximal response was prolonged for those with larger tumors (eg, up to 16 months). Updates from the same group revealed a median survival of 17.8 months,[170] which compares favorably with the University of Michigan conformal radiotherapy experience (median survival of 15.8 months),[62] in which much longer treatment times were utilized. This same group also demonstrated the feasibility of using SBRT for recurrent liver metastases after hepatic resection.[171] In a Phase I/II study, Herfarth et al from Heidelberg University used single-fraction SBRT to treat 60 liver tumors diagnosed

TABLE 5. Selected Results of Liver Metastases Stereotactic Body Radiotherapy Series

| STUDY | NO. OF PATIENTS | TUMOR TYPE, METASTASES/OTHER | DOSE, GRAYS (NO. OF FRACTIONS) | LOCAL CONTROL RATE, TIME | SURVIVAL RATE, TIME |
|---|---|---|---|---|---|
| Blomgren 1995[70] | 23 | 14/9 | 20-45 (1-4) | Not reported (NR) | NR |
| Wulf 2001[69] | 23 | 23/0 | 30 (3) | 61%, 24 mo | 41%, 24 mo |
| Herfarth 2001[64] | 37 | 60/0 | 15-26 (1) | 67%, 18 mo | NR |
| Schefter 2005[68] | 18 | 25/1 | 36-60 (3) | NR | NR |
| Mendez Romero 2006[67] | 25 | 34/11 | 37.5 (3) | 82%, 24 mo | 50%, 24 mo |
| Katz 2007[65] | 69 | 174/0 | 30-55 (5-15) | 57%, 20 mo | 37%, 20 mo |

in 37 patients (56 metastases; 26 from colorectal carcinoma).[64,72] The median tumor size was 10 cc (range, 1 cc-132 cc). The single dose was safely escalated to 26 Gy, without any dose-limiting toxicity reported.[64,72] The actuarial local control rate was reported to be 67% 18 months after therapy. Since that report, 3-fraction SBRT (range, 36-60 Gy) has been shown to be associated with similar or improved local control in both prospective[66-68] and retrospective studies.[69] A North American Phase I study confirmed the safety of SBRT in 18 patients with 25 tumors with a maximal dimension of 6 cm.[68] Patients with 1 to 3 liver metastases were treated with 36 to 60 Gy in 3 fractions. Patients treated with doses higher than 54 Gy in 3 fractions were found to have improved local control compared with those treated with lower doses.[66] A Canadian Phase I/II study of 6-fraction SBRT used an individualized dose allocation (30-60 Gy in 6 fractions) to allow patients with larger liver metastases to be irradiated.[71] Using this dose allocation scheme, no dose-limiting toxicity was observed in greater than 60 patients with liver metastases. Finally, outcomes after SBRT for 174 liver

metastases from colorectal, pancreatic, breast, and lung cancers diagnosed in 69 patients were recently reported.[65] A total dose of 30 to 55 Gy was delivered at a rate of 2 to 6 Gy per fraction, with 10-month and 20-month local control rates of 76% and 57%, respectively; a median survival of 14.5 months; and no grade 3 toxicity (Common Toxicity Criteria for Adverse Events, Version 3.0, National Institutes of Health, National Cancer Institute, June 10, 2003). Based on this experience, the Radiation Therapy Oncology Group opened a study of 10 fractions of SBRT for liver metastases.

Representative outcome results for a number of reports using SBRT in patients with lung metastases are shown in Table 6, whereas a typical treatment response is shown in Figure 6. To our knowledge to date, local control and toxicity have for the most part been the primary endpoint of SBRT trials in patients with lung metastases. Although toxicity has been low and local control rates high, the assessment of survival has been less well-described given the relative immaturity of trials in this arena.

TABLE 6. Outcome After Stereotactic Body Radiotherapy for Lung Metastases

| STUDY | NO. OF PATIENTS | NO. OF TARGETS | MEDIAN FOLLOW-UP, MONTHS | LOCAL CONTROL RATE | LOCAL CONTROL METHODOLOGY |
|---|---|---|---|---|---|
| Blomgren 1995[70] | 10 | 14 | 8 | 92% | Crude rate |
| Uematsu 1998[82] | 22 | 43 | 9 | 98% | Crude rate |
| Nakagawa 2000[179] | 14 | 21 | 10 | 95% | Crude rate |
| Wulf 2001[69] | Not reported | 11 | 8 | 76% (2 y) | Actuarial |
| Nagata 2002[78] | 9 | 9 | 18 | 67% | Crude rate |
| Hara 2002[180] | 14 | 18 | 12 | 78% (13 mo) | Actuarial |
| Lee 2003[181] | 19 | 25 | 18 | 88% (18 mo) | Actuarial |
| Whyte 2003[182] | 8 | 9 | 18 | Not available | Not available |
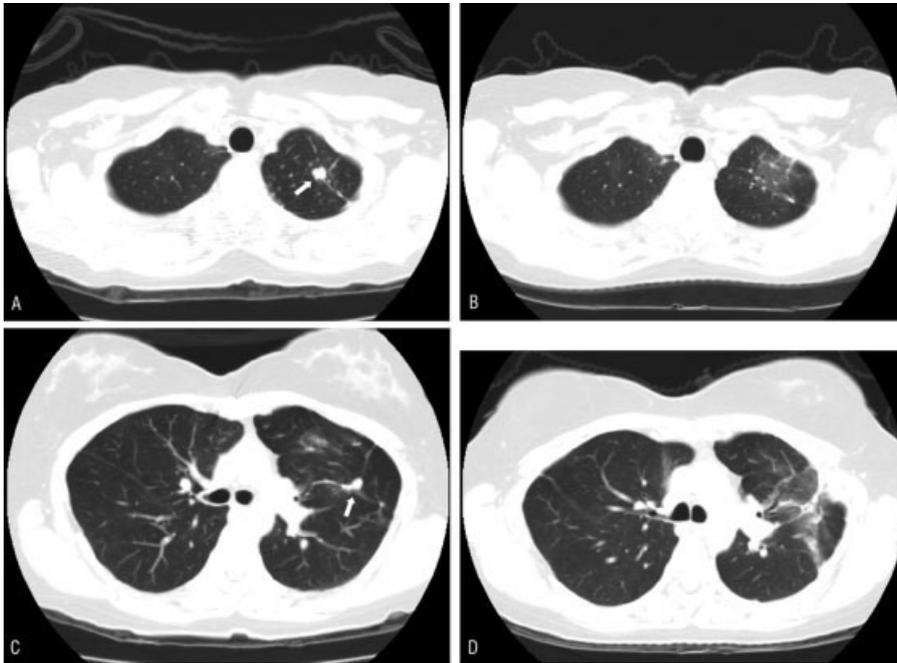
**FIGURE 6.** Case Example of Stereotactic Body Radiotherapy (SBRT) for Lung Metastases in a 42-year-old Woman With Metastatic Adenoid Cystic Carcinoma to the Lung With a Controlled Orbital Primary Tumor. The patient underwent several wedge resections within both lungs previously for metastases over a 10-year period. She presented with a new nodule in the left upper lobe and a suture line recurrence of a left upper lobe lesion. She received SBRT to both lesions using 54 grays in 3 fractions to each lesion. (A) Axial pretreatment computed tomography (CT) image of the left upper lobe tumor (white arrow). (B) A 9-month post-SBRT CT image of the left upper lobe tumor. Fluffy posttreatment alveolar infiltrate was present but the patient was asymptomatic. (C) Axial pretreatment CT image of the suture line recurrence (arrow). (D) A 9-month post-SBRT CT image of the suture line recurrence in which more dense posttreatment fibrosis was noted.

## Conclusions and Future Directions

Although the goal of cancer therapy research is to cure cancer, the idea of finding a treatment capable of delivering a "knockout punch" for all patients appears less probable due to the heterogeneous nature of human cancers. Instead, the effectiveness of therapies will improve differentially among different cancer types. Whether all tumor cells hiding in the body will be eradicated remains to be seen. It is possible that cancer will first be converted into a chronic disease, hopefully with a low tumor burden below which would cause symptoms affecting quality of life. Local therapies may be very useful in future treatment strategies to deal with residual macroscopic disease

more effectively or to treat symptomatic disease recurrences when they arise. As such, with improvements in the effectiveness of systemic therapy, there may be an expanding role for local therapies in the management of metastatic cancer.

Human cancers arise from the host's own tissues. As such, and unlike infections attacking from the outside, the body's natural immune system does not always recognize the distinction between normal cells and tumor-bearing tissues that would allow an effective immune response. With a better understanding of the immune failure that occurs with the formation of cancer, steps may be taken to redirect the immune response in such a way that might eliminate metastatic cancer. In one scenario, local therapies might be helpful at presenting tumor antigens in a more efficient fashion. In particular, thermal ablative or SBRT techniques, which do not physically remove the tumor tissue, might be coupled with immune-stimulating agents to activate the immune response.[172-174]

It will be essential that local treatments for metastatic disease avoid toxicity. Efforts to use less and less invasive technology or techniques, avoid long recovery requirements, and combine therapies prudently are being scrutinized in clinical trials. The winner among local therapies will likely depend on the site of tumor involvement and disease status. Collectively, surgical metastectomy, RFA, and SBRT are demonstrating considerable ongoing promise in treating metastatic cancers. ■

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