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Regional Therapy of Cancer

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Surgical resection is the primary treatment and typically the only curative therapy for most solid malignancies. Throughout this surgical textbook, virtually all chapters dealing with individual organs have a variable portion of that chapter devoted to the surgical treatment of primary cancer at that site. For example, Chapter 78 on breast disease primarily discusses the treatment of cancer as this is by far the predominant surgical disease in that organ. On the other hand, Chapter 31 on the small intestine has a much smaller proportion concerned with cancer because primary malignancies comprise a smaller fraction of the surgical diseases involving the small intestine. A specialized type or category of surgical treatment for cancer can be categorized as regional therapy. As opposed to straightforward surgical resection, in this type of therapy a specific region or area of the body is treated. Regional therapy is primarily applicable to metastatic disease limited to one site or area of the body. There are two broad categories of regional therapy of cancer: (1) vascular-based treatments and (2) intracavitary treatments. The most successfully treated areas of the body by vascular means are the extremities and the liver. There is also potential to treat other sites such as the lung or pelvis. The peritoneal cavity and the pleural cavity are areas amenable to intracavitary treatments.

The theoretical advantage of regional therapy lies in the ability to have either a significant dose escalation of an antineoplastic agent to increase the therapeutic index or a specific targeting of treatment to one region (Table 85.1). The majority of regional treatment strategies use standard chemotherapeutic agents. For most antineoplastic drugs, dose escalation to the maximally tolerated level leads to the optimal response rate for that agent. Dose-limiting toxicities are variable between different antineoplastic agents, but specific side effects most commonly seen are bone marrow suppression, gastrointestinal toxicity, or neurotoxicity, and provide well-defined limits beyond which it is unsafe to administer any more systemic treatments. If a patient has tumor that is only in one region of the body such as an extremity or in one organ such as the liver, delivery of drug only to that site may allow dose escalation to achieve tissue levels well beyond what can be achieved with maximal systemic drug delivery. When the location of the metastatic cancer is different from the target organ of drug toxicity, the therapeutic index is improved if technical means exist to allow regional therapy.

Although a large proportion of regional therapies of cancer deliver standard chemotherapeutic agents that have well-characterized responses and toxicities via systemic administration, regional approaches facilitate the use of other potential tools against cancer that cannot be readily achieved systemically (Table 85.2). Examples of alternative agents or techniques to treat cancer that can be used in conjunction with regional treatment include hyperthermia, photodynamic light therapy, and cancer gene therapy. Malignant cells are known to be more sensitive to hyperthermia than nontransformed cells.[1–3] The ability of the entire body to withstand temperatures that are in the range that would have a significant effect against cancer may produce unacceptable systemic toxicity. By applying hyperthermia regionally, this therapy can be tolerated with fewer untoward effects.[2] Also, hyperthermia has been shown to act synergistically with both standard chemotherapeutic agents as well as biological agents.[3] Photodynamic therapy, like external-beam radiation therapy, is a local treatment as the therapy is only delivered to the sites where laser light of a certain wavelength is directed; this is discussed in detail in the section on intracavitary treatments.[4,5] Gene therapy of cancer is a topic of intense investigation with multiple strategies that can be employed to target genetic mutations in tumor suppressor genes and proto-oncogenes, deliver suicide genes, or even deliver antiangiogenic therapies.[6,7] However, this type of treatment, which has been shown to be effective in vitro to reverse malignant phenotypes, often cannot be translated into in vivo therapies due to the inability to delivery the vector successfully to the sites of cancer. Regional delivery techniques may provide an opportunity to ameliorate the current deficiencies of systemic genetic vector administration.[6,7]

The two types of regional therapy, intravascular therapy

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TABLE 85.1. Advantages and Disadvantages of Regional Therapy.

Advantages
Dose escalation at treatment site
Limited toxicity
Ability to add hyperthermia
Disadvantages
Regional treatment for a potentially systemic disease
Complicated procedure to deliver therapy
Other single treatment possible

TABLE 85.2. Agents/Modulation Utilized in Regional Cancer Therapies.

Agents/modalities	*Examples*
Chemotherapeutics	Melphalan in isolated limb perfusion; FUDR in hepatic artery infusion; cisplatin/mitomycin in peritoneal perfusion
Biological agents	Tumor necrosis factor in isolated limb perfusion and isolated liver perfusion
Hyperthermia	Isolated limb perfusion, isolated liver perfusion, continuous hyperthermic peritoneal perfusion
Photodynamic therapy	Photofrin in peritoneal cavity and pleural cavity
Gene therapy	Wild-type p53 gene into hepatic artery, TK suicide gene in intrapleural treatment

and intracavitary therapy, are discussed generally and then the specific clinical experience of treatment for each is discussed (Table 85.3). New techniques or treatments that are in development will be described.

Intravascular Regional Treatment

Intravascular regional therapy of cancer is based on delivering antineoplastic treatments via the bloodstream, targeting a specific organ such as the liver or a specific region of the body such as the extremity. Within the category of regional vascular treatment, there are two general categories delineated by the mechanism of drug delivery: (1) regional vascular infusion, and (2) isolated vascular perfusion. Regional infusion is technically more straightforward than isolation perfusion and often is a procedure performed by an interventional radiologist working in conjunction with medical oncologists. However, the degree of advantage gained in improving the therapeutic index based on regional infusion compared to systemic intravascular delivery is much less than can be achieved by isolated perfusion. By far the most important site of treatment for regional intravascular infusion is the liver. The ability of infusion to be effective in this location is predominantly due to the role the liver plays in drug metabolism. This ability to metabolize drug allows the liver to clear certain agents on the first pass through the liver parenchyma, which is not applicable to other areas or regions of the body.[8,9] A variation of regional intravascular infusion that has been applied to other areas besides the liver is a stop flow technique in which an antineoplastic drug is infused into an organ or region with a balloon device applied to temporarily decrease the normal vascular inflow to that site.[10,11] By blocking the normal inflow at the time of infusion, the level of drug exposure is improved as there is less rapid drug washout. Also, tissue ischemia is generally produced to some degree by blocking normal arterial inflow and this may augment the response. This technique has been applied to situations such as tumors of the pancreas[11] as well as regions of the body such as the extremity.[12]

The second type of vascular regional treatment is isolation perfusion. Isolation perfusion is a surgical procedure in which control of the inflow and outflow vessels to and from an organ or region of the body is achieved by operative dissection. That area of the body is then perfused using an extracorporeal bypass circuit that allows continuous recirculation of antineoplastic agent into that area of the body. This technique is advantageous as it not only eliminates the tar-

TABLE 85.3. Categories of Regional Treatment of Cancer.

Area of treatment	*Procedure*	*Target disease*
Intravascular treatment		
Limb	Isolated limb perfusion	In transit melanoma
	Isolated limb infusion	Extremity sarcoma
Liver	Hepatic artery infusion pump	Colorectal metastases, other metastatic tumors, Hepatomas
	Isolated hepatic perfusion	
	Percutaneous hepatic perfusion with hemofiltration	
	Gene therapy	
Lung	Isolated lung perfusion	Metastatic lung cancer (sarcoma, renal cell cancer), primary lung tumor
	Isolated lung infusion	
Pelvis	Isolated pelvic infusion	Recurrent rectal cancer
Kidney	Isolated renal perfusion	Multifocal renal cancer
Intracavitary treatment		
Peritoneal cavity	Continuous hyperthermic peritoneal perfusion	Carcinomatosis from gastric, colorectal, appendiceal, pancreas and ovarian cancer
	Photodynamic therapy	
	Gene therapy	Sarcomatosis
Pleural cavity	Photodynamic therapy	Mesothelioma
	Gene therapy	Lung cancer
		Metastatic cancer

get organ of toxicity for a particular drug but also may eliminate the organ of metabolism for that drug such that the area under the curve of drug exposure during the time of isolation perfusion is markedly increased. The ability to perform isolation perfusion was dependent on the technological advance of extracorporeal bypass or the so-called heart-lung machine that was designed primarily to facilitate cardiac operations. With the development of this technology in the midpart of the twentieth century, surgical oncologists recognized the ability to apply extracorporeal bypass to regional vascular perfusion.[13] In this initial experience, many areas of the body were attempted to be treated with isolation perfusion.[14–16] Only treatment of the extremities primarily for in transit melanoma produced results with positive objective antitumor responses and acceptable toxicity such that the operation became generally applied. Recently, partly because of improved technical aspects of complex surgical procedures as well as the availability of alternative treatment agents, isolation perfusion has been applied to other organs that were abandoned by the earlier investigators 30 to 40 years ago (see Table 85.3). Specifically, isolation perfusion procedures of the liver[17,18] and lung,[19,20] which had been attempted decades earlier and reported in the surgical literature, have been recently resurrected. Additional work has been performed on isolation perfusion procedures of the pelvis[21] as well as the kidney.[23] Because of the multiple areas of vascular inflow and areas of vascular outflow in the pelvis, this has not been as successful as isolation perfusion of the limb or liver. Isolation perfusion of the kidney is technically easier but is limited by the lack of clinical situations in which isolation perfusion would be an optimal outcome as compared to unilateral nephrectomy or renal wedge resection. The application of intravascular regional therapy to the extremities and liver is discussed here in great detail, and experience with isolated perfusion of the other areas is also discussed.

Intracavitary Treatment

The second broad category of regional therapy is intracavitary treatments. The two sites that are potentially treatable are the peritoneal cavity and the pleural cavity (see Table 85.3). The bladder also provides an area for potential intracavitary treatment, but this is different in that it is typically applied to superficial bladder cancer as a primary neoplasm in an organ that has a contained accessible lumen. Regional therapies for the peritoneal cavity and the pleural cavity primarily target metastatic disease or diffuse primary malignancies such as mesothelioma of the pleura or peritoneum.

The natural history of many tumors, particularly in the peritoneal cavity, is such that patients frequently have widespread disease at that site without any evidence of hematogenous or even lymphatic spread.[24,25] Carcinomatosis from either primary ovarian tumors[26] or gastrointestinal tumors including colorectal cancers, appendiceal cancers, gastric cancers, and pancreatic cancers comprise adenocarcinomas that spread in this manner.[27–29] Sarcomatosis from either primary gastrointestinal stromal tumors[30] or retroperitoneal sarcomas[31] comprise the second major group of tumors that spread in this way. There is no effective treatment available for peritoneal carcinomatosis and sarcomatosis, and tumor progression in these patients inevitably leads to considerable morbidity. Even without hematogenous spread, patients afflicted with this pattern of disease eventually succumb to their disease. The pathology as well as the development of this pattern of disease is one in which a contained cavity with a complex surface is exposed to malignant cells that may implant on any available surface and form nodular disease.[24,25] Ovarian tumors gain access to the peritoneal cavity because they represent free organs within the peritoneum, and this is the most common pattern of spread for that histology. Similarly, the pancreas although retroperitoneal in location may have direct seeding of the peritoneal cavity from tumors on the surface of the pancreas. Cancers of the colon, appendix, stomach, bile duct, and gallbladder uniformly start on the inner surface or mucosal layer, but can have transmural invasion such that cells are seeded into the peritoneal cavity.

Standard oncological therapies including surgical resection, radiation therapy, and systemic chemotherapy uniformly fail in patients afflicted with this pattern of disease. Although all grossly visible surgical implants may be technically resected, recurrent disease always develops as a result of microscopic seeding throughout other surfaces that cannot be appreciated at the time of resection. To attempt to improve these results, more aggressive surgical procedures called peritonectomy procedures have been advocated, as the peritoneal lining is often a barrier against this disease because tumor implants spread on the surface but do not invade through the peritoneum.[32] Although peritonectomy including stripping of the lining of the diaphragms, pericolic gutter, anterior abdominal wall, and pelvis is technically possible, the extensive operation removes less than half the potential surfaces available for contamination with intraperitoneal spread. Specifically, the capsule of the liver and the capsule of the spleen cannot be completely stripped without leading to life-threatening blood loss. Similarly, the serosa of the stomach, small bowel, and colon cannot be excised, and these are frequently sites where tumor implants will grow. Finally, the mesenteric peritoneum for the small intestine and the transverse mesocolon, although possible to remove in small areas, cannot be completely removed without considerable blood loss and potential ischemic injury to the intestine by damaging mesenteric vessels. Therefore an effective adjuvant therapy to add to peritonectomy or tumor debulking is needed.

Radiation therapy of the entire peritoneal cavity has been utilized as an adjunct in certain situations including treatment of ovarian tumors and others.[33,34] However, the dose of radiation that can be administered to the entire abdominal cavity is limited by normal tissue toxicity to a level that is not generally cytotoxic. Finally, standard systemic chemotherapy is generally ineffectual against intraperitoneal disease. This lack of efficacy stems from the general failure of available antineoplastic agents against solid malignancies at any location. This lack of efficacy is compounded by the inability of intravascular drug delivery to reach peritoneal disease, which may be poorly vascularized. Intraperitoneal chemotherapy given via one or even more catheters placed at the time of an operative procedure has been attempted as a regional infusional therapy.[35] However, after any surgical procedure, particularly when malignancy is involved, the contents of the abdominal cavity become densely adherent to one another creating multiple isolated areas of peritoneal surfaces. Therefore, intraperitoneal drug delivery even when multiple catheters are used does not allow distribution of the treatment to all surfaces of the peritoneum that are at risk for tumor.

Two types of surgical peritoneal treatments are discussed, hyperthermic peritoneal perfusion and photodynamic therapy of the peritoneal cavity. Intraperitoneal gene therapy is also in initial clinical trials as an innovative approach using a different treatment agent against this pattern of disease.

The second area of the body in which intracavitary treatment may be applied for extensive disease is the pleural cavity. Intrapleural treatments are primarily directed against mesothelioma. Pleural mesothelioima like peritoneal carcinomatosis is typically considered incurable but often is a relatively isolated disease at the time of diagnosis.[36] There is no currently available surgical and chemotherapy treatment to obtain a complete response. Primary lung carcinomas often may have intrapleural effusions and recurrences; however, the application of intracavitary treatments to that histology is limited by the fact that the majority of patients develop both lymphatic and hematogenous metastases simultaneously with intrapleural recurrences. In other words, as opposed to patients with carcinomatosis and sarcomatosis, patients with widespread intrapleural lung cancer generally do not have disease limited only to that site. Similar intracavitary approaches have been applied to the pleural space (photodynamic therapy, gene therapy) to certain patients with metastatic disease and these are discussed.

Extremity Procedures

Although the number of patients with patterns of disease eligible for isolated limb perfusion is relatively small, the technical ease of the procedure and the early success rates of this procedure for extremity melanoma made this the most accepted and widely applied isolation perfusion procedure. Recent advances in the treatment regimen specifically adding tumor necrosis factor (TNF) has extended this application from in transit melanoma to extremity sarcomas and other soft tissue neoplasms of the limb.[37] An additional procedure that has recently been reported with favorable objective response rates is isolated limb infusion, which is a nonsurgical intervention for in transit melanoma. The technique of isolated limb perfusion (ILP), the results in melanoma both for adjuvant and therapeutic perfusion, and the results for soft tissue sarcoma will be discussed.

Technique of Isolated Limb Perfusion

Anatomically the extremities are excellent areas for isolation perfusion because of the straightforward vascular anatomy. For both the upper and lower extremity, there is essentially one artery into the extremity and one vein out of the extremity. The exception is the upper extremity, where there may be multiple axillary veins, but typically these run in parallel and there is one dominant vessel. Isolated limb perfusion involves cannulating an artery leading to the extremity and a vein leading from the extremity, ligating collateral vascular branches, and placing a tourniquet at the root of the extremity; by these maneuvers, there is control over the circulation to that portion of the body. This cannulation can be performed at multiple sites in both the upper and lower extremities. The potential levels for cannulation in the lower extremity are the external iliac vessels via a retroperitoneal approach, the common femoral vessels, and the popliteal vessels. Options for cannulation of the upper extremities are the axillary vessels and the bracheal vessels just above the elbow. The level of cannulation is dictated by the disease that is being treated and other factors such as previous surgical dissection or anatomical variations. For in transit melanoma in which the entire extremity is at risk for disease, the most proximal technically possible cannulation site is utilized. This site is always the axillary vessels for the upper extremity and typically the external iliac vessels for the lower extremity. For soft tissue tumors such as single large extremity sarcomas, the most distal site that can perfuse the entire tumor is utilized as this histology tends not to spread via intradermal lymphatics. An exception to this rule is multifocal sarcomas that act as melanoma, such as epithelioid sarcomas and angiosarcomas in which proximal perfusion is indicated.

One of the most important technical aspects of isolated limb perfusion is gaining vascular control to prevent leak of the perfusate with the antineoplastic agents to the systemic circulation. With the use of high-dose tumor necrosis factor at several times the lethal systemic dose level, this problem has been magnified.[37] There is much greater potential for leak from the extremity to the rest of the body in isolated limb perfusion compared to isolated organ perfusions, including the liver, lung, and kidney in which the dissection can completely isolate that organ and obviate any significant leak. The cross-sectional area of the lower extremity at the pelvis is quite large, and significant potential collaterals exist posteriorly in the gluteal and pudendal vessels and centrally in the obturator vessels. An upper-extremity perfusion is more easily controlled as the cross-sectional area of the arm at the shoulder is much smaller and more complete control can be obtained. The maneuvers utilized to achieve vascular isolation of the lower extremity at the external iliac vessels are complete skeletinization of the external iliac artery and vein down into the proximal common femoral vessels ligating all branches circumferentially. The internal iliac artery is dissected and clamped and the obturator artery is tied. Either the main internal iliac vein or branches of that vein that appear to be going inferiorly to the leg can also be encircled and either tied or clamped. Finally, a tourniquet is placed around the root of the extremity, typically using an Esmarch tape placed in the medial groin crease and controlled laterally with a Steinmann pin in the anterior superior iliac spine. Approaching the lower extremity via the common femoral vessels utilizes a similar application of a tourniquet but does not control the branches above the inguinal ligament and therefore has a greater potential for leak of the perfusate to the systemic circulation. Cannulation via the popliteal vessels utilizes a pneumatic cuff tourniquet in the proximal thigh at 300 mmHg, and this leads to virtual total isolation of that lower portion of the extremity. For upper-extremity perfusions, dissection of all the axillary artery and vein branches and placement of an Esmarch tourniquet around the axilla secured with a small Steinmann pin in the head of the humerus leads to almost complete control of perfusate leak. In fact, the greatest problem with upper extremity ILP is to avoid causing brachial plexus trauma with excessive tightness in the tourniquet.

An essential component of ILP is monitoring the perfusate leak to the systemic circulation and making adjustments during treatment to reduce that leak.[37] Techniques such as injecting fluorescein into the perfusate have been utilized but are highly imprecise and nonquantitative. Virtually all ILP circuits use a gravity return venous line to a reservoir such

that a visible assessment of the volume in the reservoir is possible. If the reservoir is decreasing in volume, it would indicate that perfusate is being lost into the systemic circulation. If the reservoir volume is rising, it would indicate that blood is leaking from the systemic circulation into the perfusion circuit. However, if there is a two-way leak of similar magnitude there would be no change in the reservoir yet considerable perfusate exposure. The standard of care, particularly in operations with high-dose TNF, uses a gamma counter over the precordium with radionuclide in the perfusion circuit that allows continuous readings and estimations of the leak of the perfusion solution into the systemic circulation.[38] This is both quantitative and allows the surgeon to react to changes almost immediately to control of perfusate leak.

Natural History of in Transit Melanoma

ILP has been applied most successfully against a pattern of disease spread called in transit melanoma metastases. This pattern of recurrence represents lymphatic spread in the dermal and subcutaneous tissue with multiple nodules appearing throughout the extremity.[39] The entire limb is at risk for this pattern of spread including areas distal to the site of the primary (Fig. 85.1). The incidence of in transit melanoma metastases from primary melanomas of the extremity is best demonstrated by clinical trials of adjuvant limb perfusion after resection of stage II (>1.5 mm thick) primary melanoma. Patients in the control arm of these trials who do not receive ILP therapy have an incidence of 9.9% in transit melanoma or local recurrence by satellite lesions.[40] The incidence of in transit melanoma for stage I primary lesions (<1.5 mm thick) is not as clearly known but would certainly be expected to be much less than the incidence for thicker melanoma. Local resection of in transit melanoma nodules is almost uniformly destined to fail as the entire extremity is at risk. Because in transit melanoma nodules are often quite some distance from the primary location, all the intervening tissue is at risk as well as any other area in the dermal and subcutaneous tissue of that extremity. Therefore, simple excision with narrow margins with primary closure is the most appropriate procedure for resection of in transit melanoma lesions instead of wide excision with split-thickness skin graft. Patients may develop very bulky disease in the extremity without evidence of systemic spread. Literature from a series of major limb amputations for extensive extremity melanoma report 25% to 30% 5-year disease-free survival rates indicating that even with regional disease remarkable enough to mandate an amputation systemic spread may not have occurred.[41] Therefore, an effective therapy to treat the entire limb may be beneficial for this patient population. Historically, the largest number of ILP procedures have been performed in the adjuvant setting, most commonly after resection of high-risk primary melanoma but also for resection of limited satellite or in transit metastases. A more important application is therapeutic ILP in which there is measurable disease treated within the limb.

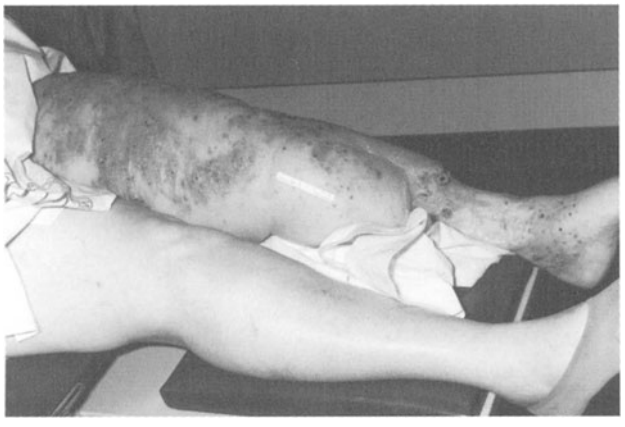


FIGURE 85.1. Patient with extensive in transit melanoma from a calf primary. Note the extent of surgical resection of the distal calf, yet recurrent melanoma both distally and extensive disease proximal to that resection site. At the time of this photograph, the patient had no evidence by radiologic studies of physical exam of any extraextremity disease.

Adjuvant ILP for Extremity Melanoma

An adjuvant ILP is one in which all gross disease has been resected from an extremity but there is a high risk of local recurrence. A great deal of the literature published on ILP for melanoma combines adjuvant perfusion with therapeutic perfusions, often with different regimens, making the interpretation of this data very difficult.[37] A large series from Tulane is representative of this problem, in which more than 1100 cases were reported with a median follow-up greater than 10 years yet no meaningful information can be gained about the true benefit of the procedure.[42] Although individual investigators who believe in the benefit of ILP applied this regional technique after resection of high-risk primary lesions (typically >1- or 1.5-mm-thick primary melanomas), both retrospective case-controlled studies and prospective randomized studies have failed to verify a benefit for this use of ILP.[37] A small study from Germany published in the 1980s reported a significant improvement in survival after adjuvant ILP.[43,44] However, the numbers of patients treated were small, and the outcome in the control group was so much worse than expected compared to historical controls that this trial is not to

TABLE 85.4.

Prospective Randomized Trials of Adjuvant Isolated Limb Perfusion (ILP) for Resected High-Risk Primary or In Transit Melanoma (Level I Evidence).

	Excision alone	*Excision + ILP*
Stage II primary melanoma[40]		
No. of patients	412	420
Incidence of Recurrent Disease (%)		
Local	3.3	2
In transit	6.6	1.5
Lymph nodes	16.7	12.6
Distant metastases	6	8
Overall survival	No difference	No difference
Resected in transit melanoma[46]		
n	36	33
Disease-free survival		
Overall (%)	17	33
Median (months)	10	17
Survival		
Overall (%)	44	55
Median (months)	39	57
Regional recurrence (%)	53	36
Distal recurrence (%)	16	18

be utilized in arguing for adjuvant ILP.[43,44] The best information regarding adjuvant ILP for resected high-risk primary extremity melanoma comes from a recently published, very large prospective randomized study[40] (see Table 85.4). With almost 400 patients in a wide local excision alone group or wide local excision plus isolated limb perfusion with melphalan group, there was a decrease in the regional recurrence rate but no increase in the systemic recurrence rate and no change in survival.[41] With the publication of this study as a negative trial, no adjuvant ILP should ever be performed after resection of primary melanoma.

A second setting for adjuvant isolated limb perfusion is for patients who have developed in transit metastases that have been excisionally biopsied. These patients are clearly at much greater risk for additional recurrences in the limb than patients with high-risk primary cutaneous melanoma who have not had a regional recurrence. One could argue that an adjuvant regional treatment would be beneficial in this setting. Again, there was a positive study reported from Germany, but the success rate with an adjuvant ILP with melphalan in that study was much greater than any other study reported in the medical literature with a small number of patients, and this study should not be trusted.[43,44] The best adjuvant isolated limb perfusion trial for resected in transit disease comes from Sweden in which there was a significant improvement in survival in the perfusion field, but this did not translate into improvement in overall survival[45,46] (Table 85.4). Again, only small numbers of patients (<40 per arm) were studied, and with larger numbers there may have been a signifciant benefit. At the present time, adjuvant ILP should never be used for high-risk primary disease that has been resected and should be utilized for resected in transit metastases only in the setting of a clinical trial.

Therapeutic ILP is defined as procedures that treat measurable disease in the extremity. The response rates that are obtained with ILP are considerably higher than any other systemic therapy for this type of tumor. Although melphalan has very limited activity given systemically against melanoma, it is the optimal chemotherapeutic drug for ILP.[37,46] Objective response rates with melphalan ILP under either normothermic (37°C) conditions or with mild hyperthermia (38.5°–40°C) have been reported as high as 90% to 100% with complete response rates between 54% and 65%.[37] The median duration of responses in extremity ILP is approximately 9 months, with a subset of patients who have long-term disease control with this regional therapy.[46] These response rates should be placed in context of the responses seen with systemic chemotherapy. The best systemic combination chemotherapy gives 25% to 40% response rate and 0% to 5% complete response[39] (Table 85.5). Interleukin-2 treatment results in 25% overall response rate and a 7% complete response.[39] The optimal dose of melphalan is calculated based on limb volume because basing melphalan dose on patient weight may undertreat or overtreat an individual dependent on body habitus. Limb volume measurements either with water displacement or sequential circumferential measurements can be obtained with lower extremities treated with 10 mg melphalan/l limb volume and upper extremities treated with 13 mg melphalan/l limb volume.

TABLE 85.5. Objective Treatment Response for Metastatic Melanoma.

	Complete response rate (%)	*Overall response rate (%)*
DTIC	0–2	20
Combination chemotherapy	5–15	13–55
IL-2	7	20–30
ILP, melphalan	54–65	79–95
ILP, melphalan + TNF	78–90	95–100

Source: Adapted from Fraker,[37] Balch et al.,[40] and Lienard et al.[56]

Other standard chemotherapeutic agents used in therapeutic ILP for melanoma have yielded either much lower subjective response rates or, if responses are seen, the toxicity is much greater. The most successful alternative would be cisplatin, but the response rates are somewhat lower, in the range of 50% to 60% objective response rates, and this agent used in ILP is complicated by peripheral neuropathy.[47] The most successful systemic treatment agent for melanoma is DTIC but used in regional perfusion this agent leads to minimal responses.[48,49]

Tumor Necrosis Factor in Isolated Limb Perfusion

Tumor necrosis factor (TNF) is a protein derived from multiple cellular sources believed to be a mediator of the inflammatory cascade in acute sepsis as well as in chronic autoimmune diseases. This protein received its name from the observation that serum containing TNF led to complete necrosis of established 1-cm subcutaneous sarcomas in mice with a single treatment.[50] The systemic use of recombinant TNF in patients did not translate into the responses seen in the preclinical murine models. In fact, virtually no patients responded to TNF in multiple phase I and phase II clinical trials of advanced cancer.[51] The dose-limiting toxicity is universally hypotension, and serum levels of TNF at maximal doses in patients are 100 fold lower than levels achieved in mice (Table 85.6).

Because the preclinical evidence that TNF is an effective antineoplastic drug is overwhelming and because the doses that led to responses in mice could not be achieved with sys-

TABLE 85.6. Response Rate with Regional and Systemic Treatment with Tumor Necrosis Factor (TNF).

	Systemic murine treatment	*Systemic human treatment*	*Isolated limb perfusion*
Maximally tolerated dose	10–15 mcg	250–400 mcg	4000 mcg
Maximal serum level TNF	1–2 mcg/ml	10–15 ng/ml	2–3 mcg/ml
Complete response rate	80% (in a MethA sarcoma)	0	80%–90%[a]

[a]Response in ILP in combination with melphalan.

TABLE 85.7.
Results of ILP Trials Using TNF to Treat in Transit Melanoma of the Extremity.

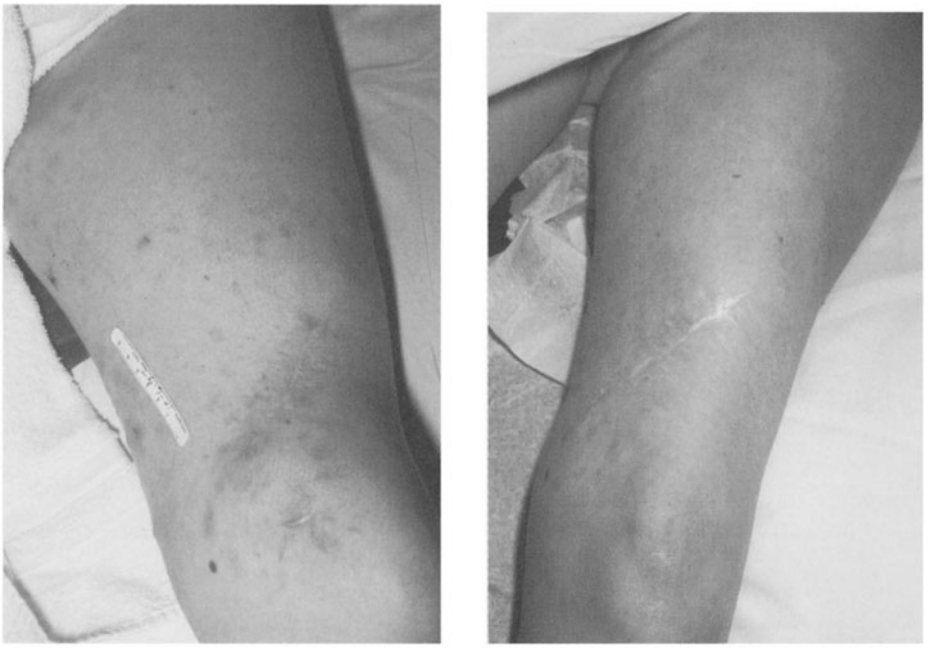
Author	*Type of trial*	*Treatment regimen*	n	*CR (%)*
Lienard et al.[55]	II	Melp/TNF/IFN	29	90
Fraker et al.[58]	II	Melp/TNF/IFN	26	76
Fraker et al.[57]	III	Melphalan	23	61
		Melp/TNF/IFN	20	80
Lienard et al.[56]	III	Melphalan + TNF	33	69
		Melp/TNF/IFN	31	78

TNF, tumor necrosis factor; Melp, melphalan; IFN, interferon-γ.

temic administration, TNF was utilized in regional perfusion.[52] In this setting, the equivalent intravascular levels that led to responses in mice (1–3 mcg/ml) could be achieved in the perfusate (Table 85.6). However, TNF alone in ILP for melanoma led to minimal antineoplastic effects that were not sustained.[53] High-dose TNF combined with a standard dose of melphalan seemed to augment the response, with the initial phase II trial reporting a 90% complete response rate and a 100% overall response rate[54,55] (Table 85.7). There was also a suggestion that the duration of response was improved.[54] These initial trials of TNF also incorporated low-dose preoperative subcutaneous interferon-γ and low-dose interferon-γ in the perfusion. A phase III trial in Europe comparing melphalan plus TNF with or without interferon-γ demonstrated that the addition of interferon resulted in marginal benefit.[56] Also, in the setting of a multiinstitutional study, the initial phase II results were not reproduced with complete response rates with melphalan, TNF, and interferon at 78% instead of 90%.[56] A North American trial comparing melphalan alone to melphalan, TNF, and interferon-γ demonstrated some benefit with TNF for patients with high tumor burden but showed equivalent results when patients with low tumor burden or small tumors were treated with either of these two regimens.[57] Patients with low tumor burden had equivalent complete response rates with melphalan alone (81%) and with melphalan, TNF, and interferon-γ (87%) (Table 85.7). However, in patients with high tumor burden, the addition of TNF and interferon increased response rates from 17% to 67%.[57] Figure 85.2 shows a patient with high tumor burden who had a sustained complete response after melphalan and TNF ILP. The role of TNF in isolated limb perfusion for extremity melanoma is currently under investigation in ongoing randomized trials in the United States and Europe.[58–61]

Toxicity of ILP

Toxicity after ILP procedures can be categorized as side effects from systemic exposure of the drugs and side effects due to the regional effects of high-dose exposure. The systemic exposure depends on the adequacy of the isolation in the perfusion circuit. Perfusate leak with melphalan at the doses utilized in limb perfusion can be tolerated up to a 10% to 20% leak in which patients receive what would be a typical systemic bolus dose of melphalan; this would lead to early postoperative nausea and vomiting and a delayed bone marrow suppressive effect that is transient. The use of high-dose TNF at levels 10 times the maximally tolerated systemic intravenous bolus dose limits the acceptable leak rate to 10% in ILP use with TNF.[51] The side effects seen are those seen with systemic administration of TNF including high fever, hypotension, and potentially ARDS and renal failure.[51] All these side effects are transient and are managed with appropriate resuscitative techniques.



A B

FIGURE 85.2. Patient with in transit melanoma of the thigh. **A.** Preoperative photograph with multiple dermal and subcutaneous melanoma nodules. **B.** Same leg 1 year after an isolated limb perfusion with melphalan, tumor necrosis factor, and interferon-γ demonstrating a complete clinical response. This patient had a sustained complete response for more than 3 years, until she recurred systemically and succumbed to the disease.

The most important toxicities in ILP are the regional effects in the extremity.[37,47] All tissues of the extremity including skin, muscle, bone, and peripheral nerve are exposed to the same additions of chemotherapy concentration and temperatures to which the tumors within the extremities are exposed. The toxicities seen with melphalan are skin erythema and with areas of blistering and subcutaneous edema in virtually all patients.[62–64] The skin changes as well as this edema universally returns to baseline after several months. The most important toxicities are the effects on muscle and peripheral nerve. Myopathy can be seen with mild muscle discomfort and in the worst situation causes compartment syndrome with potential muscle necrosis and subsequent limb loss. Peripheral neuropathies lead to transient electrical shock sensations in more than half the patients treated that typically resolve. Approximately 5% to 10% of the patients have significant long-term discomfort in their extremity after ILP. The addition of TNF to melphalan appears to add virtually nothing to the regional side effects.

Use of ILP in Nonmelanoma Tumors

Although by far the most widespread use of ILP is for extremity melanoma, this procedure was also applied to other tumors in the extremity, most commonly soft tissue sarcomas in the 1960s and 1970s. The early experience with treatment of soft tissue sarcomas showed minimal objective responses, and this application was not generally utilized by most investigators after the initial disappointing results. An initial series by Krementz reported a 33% objective response rate in 39 patient treated with ILP.[65] Also, it was more acceptable to undergo an extremity amputation for a soft tissue tumor than for diffuse in transit melanoma. Recently, alternative strategies for limb preservation by compartmental excisions with preoperative or postoperative radiation therapy were able to provide adequate local control for most extremity sarcoma, which differs from the outcome in in transit melanoma.[66]

When the benefit of TNF when added to melphalan in ILP for bulky melanoma was seen, this same regimen was applied to sarcoma.[54] The results were much more positive with this combination compared to melphalan alone, and several series have been published demonstrating limb preservation in patients deemed to have unresectable tumors with amputation as the only surgical options[67–69] (Table 85.8). The overall approach with large extremity sarcomas that have no local resection options because of their relationship to neurovascular and bony structures is to conduct an isolated limb perfusion with TNF and melphalan. This treatment generally results in significant tumor shrinkage by 8 to 12 weeks. At that point in time, a second procedure is undertaken to resect this smaller tumor. Objective response rates by size criteria in a large European trial of 186 patients is 18% complete response rates and 57% partial response rate.[67] When patients do not undergo the secondary resection, there is a high incidence of local recurrence.[54] Patients who have multifocal sarcoma, which acts like in transit melanoma, undergo an isolated limb perfusion but no secondary resective procedures.[67,68] These studies on bulky extremity sarcomas have demonstrated that the tumor necrosis factor is acting by targeting the tumor vasculature with fairly rapid elimination of tumor blood flow within days of the treatment to these tumors.[52] The success rate has varied from 80% to 85% limb salvage rate in European studies to 58% limb salvage rate in North American trials.[70] The best explanation for these different results is different patient selection with larger and more distal tumors treated in the United States series.

In addition to treatment of the melanoma and sarcoma, other more unusual tumors of the extremity such as Merkel cell carcinoma, which often spreads by in transit metastases within the limb, as well as eccrine adenocarcinoma and basal and squamous cell skin carcinoma have been reported to respond to ILP with melphalan plus tumor necrosis factor.[71] Again, because this treatment acts via an apparent antiangiogenic mechanism, it may be applicable against all solid malignancies, with a target tissue of the tumor endothelium, which is similar across several histologies.

Isolated Limb Infusion

Although the success rate with ILP is significant, this treatment requires a surgical procedure, one that generally lasts 4 to 5 hours and has the disadvantage that it is quite difficult to administer a second treatment in a reoperative setting. Reperfusions using the ILP technique have been reported, but again this is more technically challenging and also there is some cumulative toxicity within the extremity.[59] An alternative regional treatment for extremity melanoma has been proposed by Thompson from Australia, which is an isolated limb infusion.[12] In this setting, a radiologic procedure in which balloon cannulas are utilized is essentially a stop flow infusion into an extremity with a tourniquet, and this allows a relatively acceptable dose of melphalan to be present within the extremity for 15 to 20 min. The objective response rates seen in gross disease in melanoma are significant considering the ease and dose of agent utilized in this technique. Complete response rates of 30% to 40% and overall response rates of 70% have been reported, and this technique has the advantage of being much easier for reports.[12] These results from the Australian series have yet to be reproduced in North America.

TABLE 85.8.

Response Rates and Limb Salvage in Phase II Trials of ILP to Treat Unresectable Soft Tissue Sarcomas of the Extremity.

Author	*No. of patients*	*CR (%)*	*PR (%)*	*Overall response (%)*	*Limb salvage (%)*
Eggermond et al.[68]	186	18	57	75	82
Fraker et al.[70]	43	27	32	59	58
Gutman et al.[69]	35	37	54	91	85

Regional Treatment of Liver Malignancies

The liver is the archetypal organ for regional treatment of cancer for several reasons. First, it is commonly the sole site of metastatic disease for a variety of malignancies such as colorectal cancer, gastrointestinal stromal tumors, gastrointestinal/pancreatic neuroendocrine tumors, and ocular melanoma. Also, as an essential organ as opposed to the extremity, liver failure is often the cause of death in patients with metastatic cancer from these primary lesions. Second, the liver is able to be dissected such that there is essentially no vascular connection to the remainder of the body except via bile duct collaterals. Third, the vascular anatomy favors regional intravascular therapy. Although the dual vascular supply of the hepatic arterial system and the portal vein would appear to complicate regional treatment of the liver to some extent, it offers advantages as well. The branching vasculature in and around the liver offers a straightforward cannulation site via cutdown on the gastroduodenal artery in most patients to allow simple access to the hepatic arterial system for either infusion or isolated hepatic perfusion. Also, studies have demonstrated that the majority of the blood supply from metastatic tumors growing in the hepatic parenchyma is parasitized from the hepatic arterial system as opposed to the portal venous system, which allows a better drug delivery via the hepatic artery.[72,73] The final reason why the liver is an excellent organ for regional perfusion is that as a central component of the body's system to metabolize drugs, there is often extensive clearance of infused agents after a first pass through the hepatic vasculature, limiting systemic exposure with hepatic infusion.[8,9]

The regional vascular treatments of liver metastases can be categorized as hepatic arterial infusion therapy, chemoembolization, isolated hepatic perfusion, and percutaneous hepatic perfusion with hemofiltration (see Table 85.3). Although isolated hepatic infusion can be delivered via radiologic catheters, the ability to have an indwelling pump with continuous flow has made this primarily a surgical procedure. The procedure of chemoembolization is clearly an interventional radiology procedure.[74] Isolated hepatic perfusion is a very extensive and complex surgical operation,[17,18] and isolated hepatic perfusion with hemofiltration is a percutaneous operation that has been primarily developed by surgical oncologists.

Colorectal Metastasis to the Liver and Regional Infusion Therapy

The most important metastatic tumor in the liver that is treated by regional therapy is metastases from colon or rectal primary adenocarcinomas. The incidence of adenocarcinoma of the colon/rectum has decreased recently in the United States, but there were still an estimated 139,000 cases in 1999. There will be an estimated 42,000 patients with metastases to the liver and approximately half these cases the liver will initially be the sole site of metastatic disease. It is estimated that only 10% of these patients would be eligible for resection, meaning there are approximately 37,000 new patients per year with colorectal metastases to the liver who are not resectable.[75] The natural history of metastatic colon cancer is shown in Fig. 85.3. The first line systemic therapy for this disease is a combination of 5-FU and leucovorin, and the best objective response rates are 25% to 30%. Furthermore, the median survival is relatively dismal, ranging between 10 and 13 months in most series.[76] A second-line chemotherapy available for patients with metastatic colorectal cancer who fail 5-FU is the topoisomerase I inhibitor CPT-11, but again the response rates at best are 20% to 30% and generally are short lived. Against this background response rate, the question is whether regional chemotherapy can improve on these systemic chemotherapy response rates and, more importantly, can any improved response be translated into an improved survival.

The initial regimen used for continuous intraarterial infusion therapy was FUDR. The reason for use of FUDR as opposed to 5-FU is that the extraction in the first pass through the liver with FUDR is in the range of 98% to 99% whereas with 5-FU it is 65% to 70%.[8,9] This increase in extraction raises local drug levels in the liver with FUDR and limits sys-

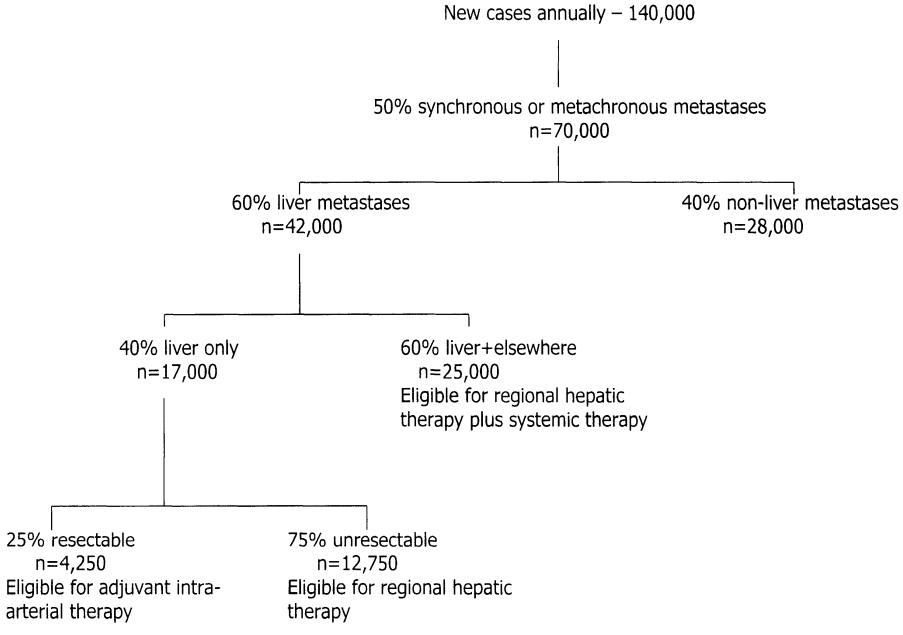


FIGURE 85.3. Flow diagram shows a rough estimate of the number of cases and patterns of metastases for colorectal cancer in the United States. Note the patient population eligible for either adjuvant regional therapy after liver resection, regional therapy for unresectable disease, and regional therapy in conjunction with systemic disease.

temic toxicity by limiting systemic exposure to the active chemotherapeutic agent. Although hepatic infusional FUDR can be delivered via percutaneous hepatic artery catheters placed with radiologic techniques, this percutaneous catheter has a high incidence of complications, does not achieve appropriate isolation, and requires an inpatient hospital stay during each treatment, which is quite expensive. More than 20 years ago, a device was developed that would serve as a subcutaneous pump which at body temperatures would infuse a small quantity of medication on a daily basis continually.[76] These indwelling pumps have many applications but one of the major uses for oncological treatment is as a hepatic intraarterial continuous infusion pump.

The initial phase II trials of hepatic arterial infusion therapy with FUDR at 0.3 mg/kg/day given as 2 weeks of treatment and 2 weeks off with reported response rates between 50% and 70%.[8,9] It became clear with this initial experience that there was toxicity to the normal liver, to the gallbladder via the cystic artery from the right hepatic artery, and to the lesser curvature of the stomach and duodenum via collateral branches. The complications of gastritis or duodenitis are prevented by a complete intraoperative dissection. It was apparent early in the experience of intraarterial infusional therapy that the gallbladder did not tolerate the infused chemotherapy, and thus a cholecystectomy became a routine part of this procedure.[76] The prevention of duodenitis and gastritis is done by complete arterial dissection such that there are no collateral branches from the hepatic artery feeding back to the stomach and duodenum, allowing delivery of chemotherapy to those areas. During placement of an intraarterial infusion catheter, fluorescein is injected via the pump, and under Wood's lamp evaluation the stomach and duodenum are inspected to see if there is any direct infusion from the pump into those areas. A more precise check occurs before the initial loading of the pump with chemotherapy with a macroaggregated albumin scan in nuclear medicine, again via the flush port of the pump again to look for perfusion of the stomach and duodenum. If a collateral vessel develops or a small vessel is missed at the time of the surgical dissection, this vessel can normally be occluded by coil embolization in radiology.

The most important side effect of hepatic arterial infusion therapy is chemical hepatitis, and in many cases this toxicity limits treatment more than does progressive disease.[77] This inflammation of the normal liver can lead to biliary sclerosis that in advanced cases causes liver failure with intrahepatic bile duct obstruction leading to overwhelming jaundice. Two advances have occurred in the past decade to circumvent this complication.[78] First, it was noted that addition of dexamethasone to the infusate limits this complication. A phase II trial reported improved response rates with the combination of dexamethasone plus FUDR and leucovorin, with a much lower rate of biliary sclerosis at 3% incidence. The second way biliary sclerosis has been prevented is by understanding and awareness of this side effect and using elevations of alkaline phosphatase as indicators to decrease the infused dose of drug or even hold therapy.

The response rates that can be achieved with infusional chemotherapy to the liver are significantly greater than those achieved with systemic therapy. The response rates in several phase II studies with variable regimens of intraarterial therapy ranged between 50% and 78%.[78,79] Again, the optimal regimens given systemically have objective response rates of at best 25% to 30%.[75] Furthermore, with the exception of biliary sclerosis and if there are no technical complications regarding infusing the stomach and duodenum, the side effects that patients perceive during intraarterial infusion therapy are minimal compared to the side effects from systemic therapy because most of the drug is metabolized by the first pass through the liver and the remainder of the body does not receive any active agent.

TABLE 85.9.
Randomized Trials of Intraarterial (IA) Chemotherapy for Colorectal Metastases to the Liver (Level I Evidence).

Author	No. of patients	Objective response (%), IA versus systemic	Survival S(median), IA versus systemic
Hohn[77]	110	42% vs. 10% ($p < 0.0001$)	NA (crossover)
Chang[80]	64	68% vs. 17% ($p < 0.003$)	22% vs. 15% (2-year survival)
Kemeny[81]	99	50% vs. 20% ($p < 0.001$)	NA (crossover)
Martin[82]	69	48% vs. 21% ($p < 0.05$)	13 vs. 11 months
Rougier[83]	163	43% vs. 9%	15 vs. 11 months
Allen-Mersh[84]	100	NA	13.5 vs. 7.5 ($p < 0.05$)

Despite these improved response rates, there has not been a clear demonstration of improvement in survival with the use of intraarterial therapy compared to systemic therapy for metastatic colorectal cancer. Several prospective randomized trials have been appropriately performed comparing these two types of treatment[77,80–84] (Table 85.9). Again, the difference in response rate is universally present in these studies showing significant better response with regional treatment compared to systemic treatment. The reasons for the failure of improved survival are multiple. First, many of the initial trials had a crossover design such that when patients on systemic therapy failed and still had liver-only disease, they "crossed-over" to the intraarterial treatment and therefore long-term survival could not be followed.[77] Also, the initial regimens without dexamethasone and with a higher dose of FUDR used in these studies frequently led to biliary sclerosis that in many patients impacted on their longevity and led to treatment-related deaths as opposed to disease progression deaths.[77,80,81] In some trials, treatment was halted more frequently for hepatic toxicity than for tumor progression.[77,80] Third, the intraarterial therapy is a regional treatment for what is a potentially systemic metastatic disease, and there are clearly certain patients in which control of the liver disease may not impact on the overall survival. Table 85.9 shows the results of prospective randomized trials comparing the intraarterial therapy to systemic chemotherapy.

A new cooperative group trial has been initiated over the past few years to attempt to obviate these problems. This trial first utilizes dexamethasone and a lower dose of FUDR (0.18 mg/kg/day) to limit biliary sclerosis. Also, there are strict guidelines regarding dose deescalation based on elevations in alkaline phosphatase over baseline to prevent liver toxicity. Finally, this trial does not allow a crossover such that patients who are randomized to systemic therapy at least per the protocol design would not be allowed to have an intraarterial

TABLE 85.10.
Phase III Trials of Adjuvant Intraarterial Chemotherapy After Resection of Colorectal Metastases (Level I Evidence).

	MSKCC[86]		*SWOG/ECOG*[87]	
	HAI + SYS	*SYS alone*	*HAI + SYS*	*No treatment*
n	74	82	53	56
2-year survival	85%	69%	80%	79%
Hepatic DFS	89%	57%	85%	57%
Overall DFS	55%	41%	58%	34%
Overall 5-year survival	—	—	63%	32%

HAI, hepatic arterial therapy; SYS, systemic therapy; DFS, disease-free survival.

pump placed. If this trial was able to achieve its accrual goal, it may answer definitively the question whether the improved response rates with hepatic infusional therapy can translate into improved survival.[85]

New directions with hepatic infusional therapy are use of this technique in an adjuvant setting as well as combining intraarterial therapy with chemotherapy. Recent trials demonstrated that after hepatic resection, intraarterial infusion therapy led to a significant improvement in overall survival compared to systemic therapy, with a follow-up of 2 to 3 years.[86,87] Most patients who undergo successful hepatic resection of all gross disease for metastatic colon cancer recur in the liver and theoretically infusional therapy with better response rates would limit that recurrence and possibly improve outcome. Results of these recent prospective randomized studies are shown in Table 85.10.

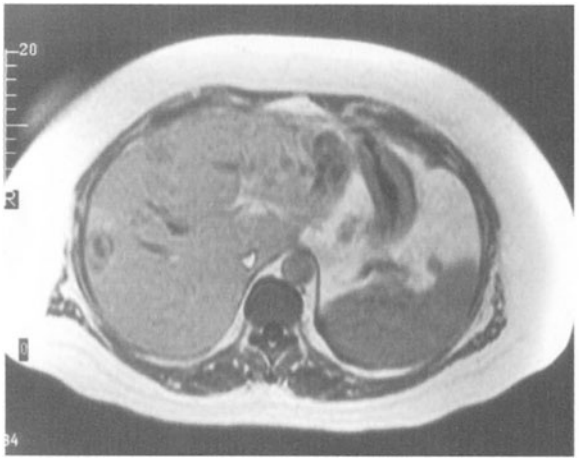
A variation on use of intraarterial therapy as an adjuvant is to combine this treatment with direct ablative techniques. Ablation techniques treat malignant nodules by direct destruction with either thermal or chemical methods. Cryosurgery utilizes a probe cooled to the temperature of liquid nitrogen to directly freeze tumors.[88] This technique has been studied for more than 10 years, and when appropriate size lesions are treated long-term control is achieved. Complications of cryosurgery for liver lesions are bleeding and postoperative "cryo-syndrome" consisting of pain and fevers. A newer technology uses heat to destroy tumors, delivering radiofrequency energy.[89] This technique of radiofrequency thermal ablation appears to have fewer side effects than cryosurgery and costs less in terms of equipment, but does not have long-term follow-up as yet to determine efficacy.[90] Percutaneous ethanol injection has benefit mostly in primary hepatomas as colorectal metastases are so firm and schirrous that it is impossible to inject substances into them. Phase II protocols combining hepatic arterial pump chemotherapy after cryoablation or radiofrequency thermal ablation of hepatic lesions are currently under way.

A second use of intraarterial therapy is combination with systemic therapy for both liver-only disease with colorectal metastases or liver-predominant disease. When the only approved agent for systemic treatment was 5-FU, the combination of intraarterial FUDR and systemic 5-FU led to accumulative overlapping toxicities and decreased ability to administer target drug leak. With the approval of a second-line chemotherapy (CPT-11), which acts by a different mechanism and has different toxicities, a phase I trial combining systemic CPT-11 and intraarterial FUDR is under way at Memorial Sloan-Kettering.[91]

Isolated Hepatic Perfusion

Although there are many advantages to the liver both anatomically and by its drug metabolism for hepatic arterial infusion, the technique of isolated hepatic perfusion is complicated by the vascular activity of the liver. At the time when isolated limb perfusion was performed initially in the 1950s, isolated hepatic perfusion was also attempted, but as stated by Dr. Chung "the technique for complete isolation of the liver is a relatively complicated procedure because of its anatomic peculiarity."[14] Specifically, the dual blood supply as well as the reality that the inferior vena cava essentially passes through the posterior liver with hepatic veins being broad, short structures makes this a much more complex situation than isolated limb perfusion. One recent strategy that was attempted in performing an isolated hepatic perfusion (IHP) was using a double-lumen cannula that allowed inferior vena cava blood returning from the lower extremities and kidney to pass behind the liver at the same time that hepatic venous return was collected in a recirculating system. A major advance for IHP was the application of a veno–venous bypass extracorporeal circuit to shunt both the portal venous flow and the inferior vena cava flow below the level of the liver back to the axillary vein.[17,92] This circuit is utilized in liver transplantation when patients are anhepatic, and while the liver is completely isolated it can be used to shunt blood flow peripherally. The hepatic artery can be cannulated via the gastroduodenal artery as in hepatic infusional therapy. The retrohepatic vena cava can be cannulated directly for venous return and with a complete dissection including ligation of phrenic veins and the right adrenal vein, the entire liver is completely isolated.[17,18] The only connection that does not allow complete vascular control is the bile duct, and the amount of blood flow there is minimal.

The initial trials of isolated hepatic perfusion reported recently used mitomycin C, which led to significant objective responses but were complicated by life-threatening venoocclusive disease, and this dose-limiting toxicity made this treatment impractical.[93] Even though melphalan is not an active agent against colorectal adenocarcinoma given systemically, because it is an excellent perfusion drug with outstanding tissue levels as seen with isolated limb perfusion, it was utilized in isolated hepatic perfusion. Initial reports demonstrated a response rate in the range of 60% with acceptable hepatic toxicity. Lesions appeared to lose any evidence of blood flow following isolated hepatic perfusion (Fig. 85.4). A trial combining melphalan plus tumor necrosis factor at optimal doses led to a response rate of 78% in heavily



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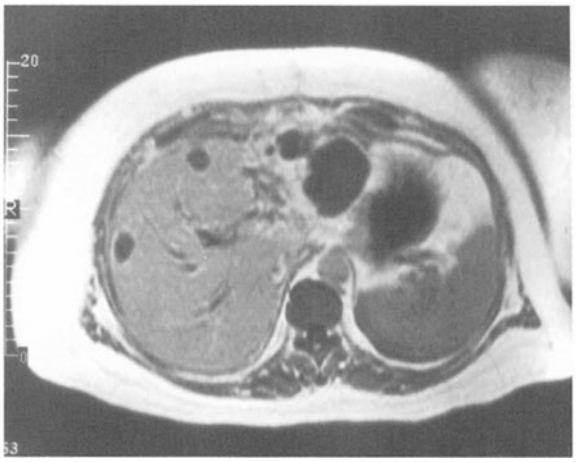

B

FIGURE 85.4. Preoperative (**A**) and postoperative (**B**) MRI scans of of a patient with bilobar colorectal metastases to the liver. Note in the preoperative photograph a very large enhancing left lateral segment nodule as well as a right lateral and central superior lesion. This disease is clearly seen in the postoperative MRI scan taken 4 weeks after isolated hepatic perfusion with tumor necrosis factor and melphalan. The lesions in **B** appear as dark, almost cystic lesions with no evidence of any viable tissue or blood flow.

pretreated patients.[17] Because of the complexity of this operation, this is universally a single treatment and because of the extent of disease there are frequent regional recurrences. With the median follow-up of 10 months, approximately one-third of the patients recurred within the liver, one-third of the patients recurred systemically, and one-third of the patients had ongoing responses.[17] Just as with use of adjuvant intraarterial chemotherapy after liver resection and after direct ablative techniques, trials are under way combining intraarterial therapy with isolated hepatic perfusion.

As opposed to hepatic infusional therapy, which utilizes a chemotherapeutic regimen that has been shown to be effective only against colorectal metastases, isolated hepatic perfusion has a potential application against other malignancies as well. In the initial phase I trials of isolated hepatic perfusion with TNF alone, and then isolated hepatic perfusion with TNF plus melphalan, responses were seen in ocular melanoma, neuroendocrine tumors, and GI sarcomas.[94] The available alternative treatments toward these histologies have minimal efficacy compared to colorectal metastases, and development of this technique may be beneficial for these less common tumors.

Percutaneous Perfusion with Hemofiltration

A variation on isolated hepatic perfusion that is much less invasive is percutaneous hepatic perfusion with hemofiltration. This technique uses a percutaneous arterial catheter into the common hepatic artery.[95] A double balloon inferior vena cava catheter collects the hepatic venous effluent, and then this collected blood is recirculated externally into a large-bore cannula into the subclavian vein. Although significant problems exist with this percutaneous technique compared to the open isolated hepatic perfusion technique. First, the portal venous flow is not controlled, and therefore the majority of the blood coming through the liver does not contain chemotherapeutic drug and a large outflow from the hepatic veins is from this portal system. Second, the type of drug in the dose escalation is limited by the ability of the extracorporeal charcoal filter system to remove the agent before reinfusion into the subclavian vein. Technological limitations on this clearance at rapid flow rates limit the ability to significantly escalate the drug as can occur in isolated hepatic perfusion. Third, the isolated hepatic perfusion uses hyperthermia by heating the perfusate. Again, in this closed technique it would be technically impossible to successfully utilize hyperthermia to augment chemotherapy response. The initial use of this approach was to treat patients with 5-FU, adriamycin, or melphalan.[95] Although the procedure was technically possible, there were only limited objective responses of very short duration following this treatment.

Isolated Lung Perfusion

If the extremities are straightforward in terms of anatomical considerations to perform isolation perfusion and the liver is a challenge, isolation perfusion of the lung provides another level of technical difficulty. The pulmonary artery and vein have an extremely high flow rate as each lung receives approximately half the total cardiac output at any one time. These are large short vessels that may be fragile in terms of cannulation, and to perform perfusion in an isolated way is a technical challenge. The other considerations that limit the use of this technique are the bronchial vessels, which provide a second source of blood flow that is difficult to control. Another limitation is that of a clinical indication for this treatment and whether this induction justifies the complexity of the procedure. Although the lung is often the sole site of metastatic disease in patients with soft tissue sarcomas as well as renal cell carcinomas and occasionally melanoma, the metastatic spread is typically to both the right and left lung. Therefore, not only is it a complex procedure needed to perfuse the one lung, but a second procedure is necessary to provide the patient with a complete therapy for their metastatic disease in this clinical situation. Also, for the histologies listed the primary site of metastasis is often the lung and it is more likely than with other malignancies to have extrapulmonary spread as well. A recent clinical trial was reported by Pass from the National Cancer Institute[19] on the preclinical models of isolated lung perfusion and a subsequent clinical trial. This trial utilized escalating high-dose TNF

(0.3–6.0 mg) and lower dose interferon-γ. Although this study showed isolated lung perfusion was technically possible by a skilled thoracic surgeon, there were only 3 partial responses in 16 patients treated and all these responses were of short duration.[19]

A different strategy was employed by investigators at Memorial Sloan-Kettering Cancer Center in which an isolated lung infusion was performed.[96] In this preclinical model, direct infusion into the pulmonary artery was performed with infusion of a catheter without a recirculation perfusion. This technique applied in a preclinical model of a rat with sarcoma metastasis led to improved response rates but has yet to be utilized to any large extent in clinical trials.

Intracavitary Treatments

As described, several types of malignancies spread within the generalized body cavity in which they originate. Two surgical techniques have been applied to the problem of diffuse peritoneal disease, and one of these techniques has also been applied to advanced disease of the pleural cavity. The first procedure is tumor debulking from the peritoneum with hyperthermic peritoneal perfusion at the time of operation with high-dose chemotherapy. The second procedure is photodynamic therapy for intraperitoneal disease, and this also has been evaluated in clinical trials for the pleural cavity. The rationale behind these experimental approaches, the technical considerations, and the results of these regional therapies are discussed.

Continuous Hyperthermic Peritoneal Perfusion of the Abdominal Cavity

The concept of continuous hyperthermic peritoneal perfusion (CHPP) was developed as an intraoperative technique to circumvent the problem of poor drug distribution with postoperative intraperitoneal therapy. This treatment may be given to patients who have demonstrated advanced intraperitoneal disease or as an adjuvant treatment based on the natural history of a specific tumor (e.g., ovarian cancer, gastric cancer). This approach provides excellent drug distribution as the treatment is done at the conclusion of a tumor resection/debulking operation. Another advantage of this approach is that there is a significant decrease in the tumor burden immediately before the treatment. The initial application of this technique was done in Japan in conjunction with gastrectomy for advanced disease.[97,98] A follow-up prospective randomized trial treated 60 patients undergoing gastric resection with curative intent who were then treated in an adjuvant manner with either mitomycin C at 8 to 10 mg/l perfusate with significant hyperthermia versus no further treatment.[99] In the 47 patients in this study who had evidence of serosal invasion, the survival rate was improved in the CHPP group, with 83% 3-year survival compared to the control group, with 67% 3-year survival.

The North American experience with CHPP has been almost exclusively treating advanced disease as opposed to adjuvant treatment after resection of high-risk primary lesions.[100] Investigators at Bowman Gray University[101] as well as MD Anderson[100] have primarily utilized mitomycin C as the primary chemotherapeutic agent with this technique. At the Surgery Branch of the National Cancer Institute,[102] cisplatin has been primarily studied as the chemotherapeutic agent. Both these drugs are alkylating agents and are much more suitable for a short-term, high-dose treatment such as CHPP than drugs that are antimetabolates, such as 5-FU. These trials vary in terms of the perfusate inflow temperature and the target intraperitoneal temperature. The study from Bowman Gray utilizes an inflow temperature of 42°C with a target intraperitoneal temperature between 40° and 40.5°C. The inflow perfusion temperature at M.D. Anderson is 44.5°C, also seeking a target temperature between 40° and 41°C in the peritoneum. The NCI studies utilize a higher inflow temperature of 48°C with a target temperature between 41.5° and 43°C intraperitoneally.[100]

TABLE 85.11.
Phase I/II Trial of Continuous Hyperthermic Peritoneal Perfusion for Advanced Peritoneal Disease.

	NCI, Surgery Branch[102]	*Bowman Gray*[101]
n	27	34
Agents	Cisplatin 100–350 mg/m^2 TNF 0–0.3 mcg/l	Mitomycin C 30 mg initial + 10 at later time
Inflow temperature	48°C	42°C
Peritoneal temperature	41.5°–43°C	40°–40.5°C
Duration of treatment	90 min	120 min
Outcome	1-year survival 49%	1-year survival, 75% 2-year survival, 48% 75% ascites controlled

The results of the initial phase I studies of CHPP report toxicity and pharmacokinetics. Partly because the initial reports are phase I trials and partly because the intraperitoneal disease after debulking is generally not detectable by any standard imaging study, it is very difficult to ascertain the response rates or benefit from this regional treatment. In a recent report of the NCI phase I trial of cisplatin with or without tumor necrosis factor with a median follow-up time of 12.3 months, the 1-year survival rate was 49%[102] (see Table 85.11). Patients with colorectal carcinoma recurred at a median time interval of 3 months. Patients with sarcoma recurred at a median time of almost 3 months as well. Patients with low-grade pseudomyxoma type lesions such as appendiceal carcinoma include one patient who recurred at 20 months and one who is free of disease 42 months after treatment. Also, benefit was seen in patients with primary peritoneal mesothelioma with recurrence at 3 months, 5 months, 24 months, and 31 months.[102] The two mesothelioma patients who had benefit with prolonged disease-free survival underwent repeat treatment and both were still free of disease. There are no randomized studies comparing this type of CHPP treatment with other therapies or simply surgery alone. The randomized studies reported from Japan are in the setting of adjuvant treatment and have not been reproduced in the North American or European trials. Therefore, it is difficult to say with certainty that there is any benefit from the intraperitoneal treatment as opposed to the aggressive debulking surgery.

The technique of continuous hyperthermic peritoneal perfusion involves a laparotomy with the lysis of all adhesions to the anterior abdominal wall as well as between bowel loops. Tumor is debulked to the maximum possible degree, and then two large-bore catheters are placed, one in the up-

per abdomen and one in the pelvis.[100] The abdomen is filled with perfusate and the abdominal incision is closed. Multiple thermal probes are placed at various locations throughout the abdomen to monitor the temperature at those sites to ensure good distribution of treatment. The abdomen then is perfused with a volume of 2 and 6 l of perfusate that is recirculated with an extracorporeal circuit with a pump and heater. The setpoint of the inflow temperature of the perfusate will define the maximally achieved temperature as read by the thermisters. During the perfusion, the abdomen is gently manipulated and the table is turned side to side to ensure even distribution. At the conclusion of the treatment interval, generally either 90 or 120 min, the perfusate is washed out of the abdomen into a waste container. The abdomen is then reopened with removal of the thermisters and formal closure of the incision. Another key component in perfusing CHPP is to place ice around the extremities, chest, and head to prevent core body temperature rising above 40°C. This technique allows exposure to small-volume disease or microscopic disease on peritoneal surfaces to high concentrations of chemotherapeutic agent that may be augmented by hyperthermia. The major disadvantage of CHPP like all other surgical regional therapies is that this is limited to a single treatment. Some investigators leave intraperitoneal catheters behind at the time of surgery for additional postoperative treatment. However, shortly after an operation the formation of adhesions will limit the utility of the cannulae.

Photodynamic Therapy

A second technique to address to the problem of surface malignancies throughout the peritoneum is photodynamic therapy (PDT).[4,5] Like CHPP, PDT combines a surgical debulking procedure with an additional procedure as an additional treatment of the surface malignancies. Instead of using chemotherapeutic agents augmented by hyperthermia, PDT uses a laser light treatment of all surface areas. The three components of photodynamic therapy that are essential for cytotoxicity are light and specific wavelength, a photosensitizer retained by tumor cells, and oxygen.[4] When the photosensitizer is stimulated with the appropriate wavelength light, then the energy absorbed is transferred to oxygen and oxygen-free radicals are generated, which leads to cell death. One potential limitation of this treatment is the depth of penetration of the light, which varies depending on the wavelength of light used for given sensitizer and typically is in the range of 3 to 5 mm. Although this is a disadvantage because larger nodules of disease cannot be treated, it has an advantage as it protects normal tissues from toxic effects. The selectivity of the antitumor effect with PDT after systemic photosensitizer administration is in selective uptake and retention of photosensitizer within malignant cells to a greater degree than normal cells; this has been shown to be true for a variety of these porphyrin-derivative sensitizers that are retained in tumor and skin primary for unclear reasons.[4,5] The time interval between administration of photosensitizers and light delivery varies depending on the pharmacokinetics of the specific photosensitizer that is used. For the trials with the initial clinically sensitized hematoporphyrin derivative, the time interval is 48 h.

Initial preclinical data from a murine ovarian carcinomatosis model demonstrated benefit from treatment with intraperitoneal hematoporphyrin derivative and laser light therapy.[103,104] On the basis of this preclinical data, a phase I study was performed at the National Cancer Institute alternating escalations of the dose of light energy and the dose of photosensitizer. The results of this phase I trial have been published[105] and have been recently updated in an abstract form.[106] In an initial report, 56 patients were entered and received photosensitizer. Two patients had no evidence of disease at operation and 15 patients had tumors that could not be debulked below 5 mm as required by the protocol. Therefore, only 39 patients were treated including 21 with ovarian cancer, 12 with sarcomatosis, and 6 patients with GI carcinomatosis. Nine of 39 patients remained disease free between 3 months and 27 months; 9 patients died of progressive tumor and 21 were alive with disease with follow-up of approximately 1 year; 3 patients with ovarian tumors were free of disease at 3 months, 4 months, 15 months, and 27 months after treatment; 3 patients with GI tumors that were low-grade pseudomyxomas were free of disease at 8 months, 9 months and 18 months; and 1 patient with sarcomatosis was free of disease at 20 months.[105,106]

Again, the same limitations apply to the photodynamic therapy as to continuous hyperthermic peritoneal perfusion. That is, the patients undergo a very extensive and complex surgical procedure and have only essentially one treatment of this complex surface as there are no easy nonsurgical or minimally invasive options for scheduled repeat treatment. Therefore, any area that did not receive treatment or failed treatment for any reason can lead to a regional recurrence as is often seen in both types of treatment. Again, the few successes that are available from initial reports may be caused more by surgical resection or the biology of the tumor than to the success of the adjuvant treatment following maximal surgical debulking.

New second-generation photosensitizers exist that have better selective retention tumor tissue and are excited at wavelength of light with greater depth of penetration.[107] Photodynamic therapy is theoretically an ideal treatment for the peritoneal surface as the complexities of the surface shape and areas are addressed by the ability of light to diffuse throughout all areas of the abdomen. The results available with the current photosensitizers and at the current light energies appear to be inadequate to provide significant benefit to most patients, but new photosensitizers may offer more benefit.

Intrapleural Treatments

Two types of regional therapy have been applied to the pleural cavity primarily for mesothelioma. One is analogous to the PDT that has been utilized and described for intraperitoneal diseases.[108] A second treatment for pleural mesothelioma is with intracavitary gene therapy.[109] Mesothelioma is a tumor of the lining of the pleural cavity; it often encases the lung at the time of presentation but has not spread outside of a single pleural cavity.[36] Surgery alone generally does not result in cures, and the tumor is relatively chemotherapy resistant. This provides an ideal setting for attempts at regional intracavity therapy.

In many ways, the pleural spaces are better suited for photodynamic therapy than the peritoneum, because of the rel-

atively simple geometry of the surfaces in which there is no hidden areas between bowel loops and in the pelvis. An initial phase I trial of intraperitoneal photodynamic therapy with photofrin II was conducted treating mesothelioma with escalating intraoperative light doses between 15 and 35 J/cm^2 48 h after receiving photosensitizer.[110] Forty-two patients were treated and it was established that the maximally tolerated light dose was 30 J/cm^2. This phase I trial was then followed by a phase II trial comparing maximally debulking of mesothelioma with postoperative cisplatin, interferon-α, and tamoxifen with or without PDT.[110] Forty-eight patients were randomized to receive PDT or not and there was no difference in median survival, median disease-free survival, and sites of first recurrence.[108] The conclusions from this study were with the first-generation sensitizers available, and although the treatment could be technically delivered, there was no benefit over surgery plus chemotherapy. Again, second-generation sensitizers with more selective uptake into tumor tissue as well as depth of penetration will hopefully provide benefit with this adjunctive regional therapy. A phase II trial using Foscan is currently underway at the University of Pennsylvania in this patient population.

This same patient population with regional advanced pleural mesothelioma has also been studied in a gene therapy trial. A phase I trial used adenovirus to deliver herpes simplex virus thymidine kinase gene with follow-up treatment with ganciclovir.[109] Twenty-one patients were treated with viral doses ranging between 1×10^9 up to 1×10^{12} by forming units. Dose-limiting toxicity was not reached in this trial. Patients underwent thoracoscopic pleural biopsies, which demonstrated strong gene transfer and expression as well as an intratumor immune response with this adenoviral vector. These studies of gene therapy into the pleural cavity are in their infancy and may serve as a proof of principle concerning the ability to administer viral vectors to an intracavitary space. No data regarding response or regression of tumor are available with current studies.

Regional Gene Therapy

As the molecular genetics of malignancies have been defined, as well as development of molecular techniques to alter gene expression with gene therapy, a large amount of preclinical work as well as clinical trials have been performed utilizing gene therapy for treatment of malignancy. The most commonly used transgene is a thymidine kinase gene or suicide gene that if expressed in malignant tissues make them susceptible to a subsequent drug treatment. Other strategies include replacement of mutated tumor suppressor genes such as adenovirus vectors expressing wild-type p53 genes.

One of the major obstacles in gene therapy even if an effective agent were available would be a systemic distribution to all sites of malignant disease. In the application of this technology, often the regional treatment is the most optimal mode of effective delivery. For example, intrapleural administration of adenoviral vectors expression suicide genes has been studied for treatment of mesothelioma.[109] Similarly, intraperitoneal administration of wild-type p53 adenovirus vectors[7] have been evaluated for ovarian carcinoma. In addition to the intracavitary treatments, intraarterial treatments are under investigation, primarily into the liver.[6] In many cases, surgical oncologists are either the principal investigators or important coinvestigators as these early trials of gene therapy generally rely on regional delivery systems.[7] Many of the clinical scenarios mentioned here may provide suitable clinical models for either intracavitary or intravascular gene therapy in the next decade.

In summary, surgical oncologists have played a major role in designing treatment strategies that target regions or specific areas of the body primarily to treat metastatic disease. Again, the opportunity to employ these treatments depends on the natural history of a particular malignancy in terms of having locally advanced disease with limited or no systemic spread. The surgical strategies combining debulking operations in some cases or vascular isolation in other cases may provide meaningful improvements in disease-free survival for patients in which there are no other effective therapies.

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