103

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 some portion of that chapter devoted to the surgical treatment of primary cancer at that site. For example, Chapter 96 on breast disease primarily discusses the treatment of cancer because this is by far the predominant surgical disease in that organ. On the other hand, Chapter 49 on the small intestine has a much smaller proportion dealing with cancer as 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 103.1). 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 vary among different antineoplastic agents, but specific side effects most commonly seen are bone marrow suppression, gastrointestinal toxicity, or neurotoxicity, which 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 differs from the target organ of drug toxicity, the therapeutic index is improved if technical means exist to allow the successful delivery of 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 which cannot be readily achieved systemically (Table 103.2). 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, such as external-beam radiation therapy, is a local treatment as the therapy is only delivered to the sites where laser light of a defined wavelength is directed; this is discussed in detail in the section on intracavitary treatments.[4-6] 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, deliver antiangiogenic therapies, or utilize virus that cause lysis selectively in tumor cells.[7,8] However, this type of treatment,

TABLE 103.1. 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

which has been shown to be effective in vitro to reverse malignant phenotypes, often cannot be translated into in vivo therapies because the vector cannot be delivered successfully to the sites of cancer. Regional delivery techniques may provide an opportunity to ameliorate the current deficiencies of systemic genetic vector administration.[7,9]

The two categories of regional therapy, intravascular therapy and intracavitary therapy, are discussed generally, and then specific clinical experience for each treatment is discussed (Table 103.3). New techniques or treatments that are in development are also 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 an extremity. Within the category of regional vascular treatment are two general categories differentiated 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 is often 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 because of 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.[10,11] 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 devise applied to temporarily decrease the normal vascular inflow to that site.[12,13] 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[13] as well as regions to the body such as an extremity.[14] Thompson and colleagues have promoted isolated limb infusion (ILI) as a similar and less costly procedure than isolated limb perfusion (ILP) for advanced extremity melanoma.

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 which allows continuous recirculation of antineoplastic agent into that area of the body. This technique is advantageous as it not only eliminates the target 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 upon the technological advance of extracorporeal bypass that was designed primarily to facilitate cardiac operations. With the develop-

TABLE 103.2. 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, Foscan in pleural cavity
Gene therapy	Wild-type p53 gene into hepatic artery, TK suicide gene in intrapleural treatment

TABLE 103.3. Categories of Regional Treatment of Cancer.

Area of treatment	*Procedure*	*Target disease*
Limb	Isolated limb perfusion	In-transit melanoma
	Isolated limb infusion	Extremity sarcoma
Liver	Hepatic artery infusion pump	Colorectal metastases, other metastatic tumors
	Isolated hepatic perfusion	
	Percutaneous hepatic perfusion with hemofiltration	Hepatomas
	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
	Photodynamic therapy	
	Gene therapy	Sarcomatosis
Pleural cavity	Photodynamic therapy	Mesothelioma
	Gene therapy	Lung cancer Metastatic cancer

ment of this technology in the midpart of the twentieth century, surgical oncologists recognized the ability to apply extracorporeal bypass to regional vascular perfusion.[15] In this initial experience, many areas of the body were attempted to be treated with isolation perfusion.[16–18] 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 accepted as a standard procedure. 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 103.3). Specifically, isolation perfusion procedures of the liver[19,20] and lung,[21,22] which had been reported as failures as a result of technical difficulties and low response rates, are being actively studied once again. Additional work has been performed on isolation perfusion procedures of the pelvis[23,24] as well as the kidney.[25] 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 other areas is also mentioned.

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 (Table 103.3). 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.

Many tumors have a natural history in which there is widespread disease in the peritoneal cavity without any evidence of hematogenous or even lymphatic spread.[26,27] Carcinomatosis from either primary ovarian tumors[28,29] or gastrointestinal tumors, including colorectal, appendiceal, gastric, and pancreatic cancers, constitute adenocarcinomas that spread in this manner.[30–32] Sarcomatosis from either primary gastrointestinal stromal tumors[33] or retroperitoneal sarcoma[34] comprise the second major group of tumors that spread in this way. There is no effective standard treatment available for peritoneal carcinomatosis and sarcomatosis, and tumor progression in these patients inevitably leads to considerable morbidity and eventual death.[35] Peritoneal carcinomatosis represents direct extension into a contained cavity with a complex surface where malignant cells may implant on any available surface and form nodules or plaques as well as causing ascites.[27,28] Ovarian tumors gain access to the peritoneal cavity as 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 consequence of microscopic seeding throughout other surfaces that cannot be appreciated at the time of surgery. 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.[33] 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.[36] 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 it can be removed 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.[37,38] 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 caused by gastrointestinal tumors. Ovarian cancers are more chemoresponsive, but once gross peritoneal carcinomatosis is present (i.e., stage 3 disease), this tumor is almost never cured. This lack of efficacy stems from the general failure of available antineoplastic agents against solid malignancies at any location and is compounded by the inability of intravascular drug delivery to reach peritoneal disease that 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 regional infusional therapy.[39] 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 and locally advanced lung cancers. Pleural mesothelioma, as is peritoneal carcinomatosis, is typically considered incurable but often is a relatively isolated disease at the time of diagnosis.[40] 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, 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) in certain patients with metastatic disease, and these are also discussed.

Extremity Procedures

Although the number of patients with diffuse in-transit melanoma of the extremity who are 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 clinical trials have evaluated the addition of tumor necrosis factor and extended this application from in-transit melanoma to unresectable extremity sarcomas and other soft tissue neoplasms of the limb.[41,42] 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 ILP, the results in melanoma both for adjuvant and therapeutic perfusion, and the results for soft tissue sarcoma are discussed.

Technique of Isolated Limb Perfusion

Anatomically the extremities are excellent areas for isolation perfusion procedures 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, placing a tourniquet at the root of the extremity, and 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 brachial 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, body habitus, or anatomic 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 which 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. 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 skeletonization 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 which 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, which 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 lead 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.[41] 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 tumor necrosis factor (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.[43] This assessment is both quantitative and continuous, allowing the surgeon to react to changes almost immediately to control a perfusate leak.

Natural History of In-Transit Melanoma

Isolated limb perfusion (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.[44] The entire limb is at risk for this pattern of spread, including areas distal to the site of the primary (Fig. 103.1). Because this represents intralymphatic spread, it is considered stage III disease, with in-transit nodules being N3 disease (AJCC stage 3C). 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 an intermediate and high-risk primary melanoma (>1.5 mm) (Table 103.4). 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.[45] 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.[46] 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.[47] Therefore, an effective therapy to treat the entire limb may be beneficial for this patient population. Some investigators have postulated an increase in in-transit melanoma in the past 10 years since the practice of sentinel lymph node biopsy has been widely used.[48,49] Theoretically, the specific ligation of the primary draining lymphatic vessels may cause more in-transit disease. However, analysis of a large series of cases at John Wayne Cancer Institute showed no increase with sentinel lymph node biopsy, and it was an excellent demonstration of the expanded incidence of in-transit disease.

TABLE 103.4. Incidence of In-Transit Melanoma of the Extremity.

Group	*n*	*Incidence of in-transit disease (%)*
Total population	3832	171 (4.46%)
Incidence based on Breslow levels		
<1.0 mm	1891	30 (1.59%)
1.01–2.0 mm	1074	41 (3.82%)
2.01–4.0 mm	610	55 (9.02%)
>4.0 mm	257	23 (8.95%)
Incidence based on surgery of lymph nodes		
Wide local excision only	2771	93 (3.36%)
Sentinel lymph node biopsy	1061	37 (3.64%)
Elective lymph node dissection	625	41 (6.56%)

Source: Adapted from Kang JC, Wanek LA, Essner R, Faries MB, Foshag LJ, Morton DL. Sentinel lymphadenectomy does not increase the incidence of in-transit metastases in primary melanoma. J Clin Oncol 2005;23:4764–4770.[48]

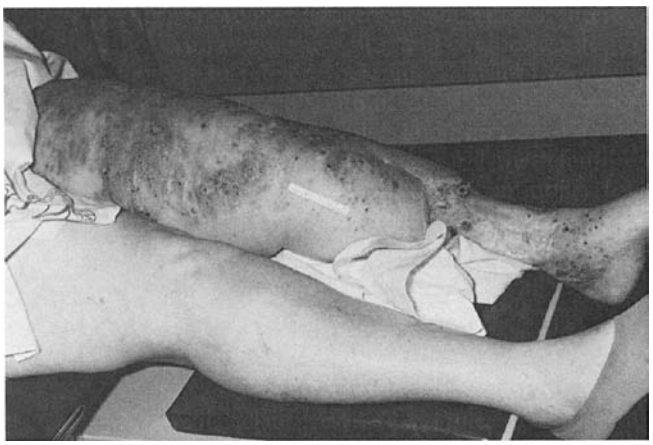

FIGURE 103.1. Patient with extensive in-transit melanoma from a calf primary. Note the extent of surgical resection of the distal calf, yet recurrent melanoma both distally and extensive disease proximal to that resection site. At the time of this photograph, the patient had no evidence by radiologic studies or physical examination of any extraextremity disease.

Adjuvant Isolated Limb Perfusion 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. 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.[50] Although individual investigators who believe in the benefit of ILP applied this regional technique after resection of high-risk primary lesions (typically primary melanomas more than 1 or 1.5 mm thick), both retrospective case-controlled studies and prospective randomized studies have failed to verify a benefit for this use of ILP.[51,52] A small study from Germany published in the 1980s reported a significant improvement in survival after adjuvant ILP. However, the numbers of patients treated were small, and the outcome in the control group was

TABLE 103.5.
Prospective Randomized Trials of Adjuvant Isolated Limb Perfusion (ILP) for Resected High-Risk Primary or In-Transit Melanoma.

Stage II primary melanoma (45):

	Excision alone	*Excision + ILP*
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 (53):

	Excision Alone	*Excision + ILP*
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%

so much worse than expected compared to historical controls that this trial is not to be utilized in arguing for adjuvant ILP. The best information regarding adjuvant ILP for resected high-risk primary extremity melanoma comes from a recently published very large prospective randomized study[45] (Table 103.5). With almost 400 patients in a wide local excision-alone group or a 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. 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 ILP 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.[53] 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.[51,52] The best adjuvant isolated limb perfusion trial for resected in-transit disease comes from Sweden; there was a significant improvement in local control in the perfusion field, but this did not translate into improvement in overall survival[53] (see Table 103.5). Again, only small numbers of patients (fewer than 40 per arm) were studied, and with larger numbers there may have been a significant 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 Isolated Limb Perfusion for Extremity Melanoma

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.[41,45,54] 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%. These response rates should be placed in context of the responses seen with systemic chemotherapy. The best combination systemic chemotherapy gives a 25% to 40% response rate and a 0% to 5% complete response[44] (Table 103.6). Interleukin 2 treatment results in an 18% to 25% overall response rate and a 7% complete response.[44] There have never been any randomized clinical trials comparing melphalan ILP to systemic treatments because of this clear difference in response.[55,56] What is not known is whether this difference in regional response translates into any improvement in survival. 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.[57] 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. Even with melphalan dosing based on limb volume, recent studies have shown highly variable perfusate in tissue drug levels, possibly contributing to variable response rates.[58]

The two best current studies of the objective response rates that can be achieved with melphalan ILP come from northern Europe. One is a multiinstitutional study of more than 100 patients reporting a complete response rate of 54% and an overall response rate of 85%.[59] The median duration of response was slightly more than 9 months. A more updated study from two centers in the Netherlands reported a complete response rate of 45% with melphalan ILP and time to complete response of 3 months. Median limb recurrence-free survival was 14 months, limb salvage rate was 96%, and overall 5-year survival was 29%.[60]

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

TABLE 103.6. Objective Treatment Response for Metastatic Melanoma.

	Complete response rate	*Overall response rate*
DTIC	0%–2%	20%
Combination chemotherapy	5%–15%	13%–55%
IL-2	8%	20%–30%
ILP-melphalan	54%–65%	79%–95%
ILP-melphalan + TNF	78%–90%	95%–100%

TNF, tumor necrosis factor; DTIC, dacarbazine.

Source: Data from references 44, 54, 56, 59, 60.

range of 50% to 60% objective response rates, and this agent when used in ILP is complicated by peripheral neuropathy.[54] The most successful systemic treatment agent for melanoma is DTIC but used in regional perfusion this agent leads to minimal responses.[61]

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 causes complete necrosis of established 1-cm subcutaneous sarcomas in mice with a single treatment.[62] 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.[63] 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. 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 systemic administration, TNF was utilized in regional perfusion.[64] In this setting, the equivalent intravascular levels that led to responses in mice (1–3 μg/ml) could be achieved in the perfusate. TNF alone in ILP for melanoma led to minimal antineoplastic effects that were not sustained.[65] However, 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[66,67] (Table 103.7). There was also a suggestion that the duration of response was improved.[66] 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.[68] 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 seen at 78% instead of 90%.[68]

TABLE 103.7.
Results of ILP Trials Using TNF to Treat In-Transit Melanoma of the Extremity.

Reference	*Type of trial*	*Treatment regimen*	*n*	*Percent CR*
67	II	Melp/TNF/IFN	29	90%
70	II	Melp/TNF/IFN	26	76%
69	III	Melphalan	23	61%
		Melp/TNF/IFN	20	80%
68	III	Melphalan + TNF	33	69%
		Melp/TNF/IFN	31	78%

CR, complete response; Melp, melphalan; IFN, interferon-γ.

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.[69] Patients with low tumor burden had equivalent complete response rates with melphalan alone (81%) and melphalan, TNF, and interferon-γ (87%) (see Table 103.7). However, in patients with high tumor burden, the addition of TNF and interferon increased response rates from 17% to 67%.[69] Figure 103.2 shows a patient with high tumor burden who had a sustained complete response after melphalan and TNF ILP. A follow-up randomized trial in North America compared melphalan alone to melphalan plus TNF. Preliminary results indicated no significant improvement in the experimental arm, and the trial was halted by the data safety

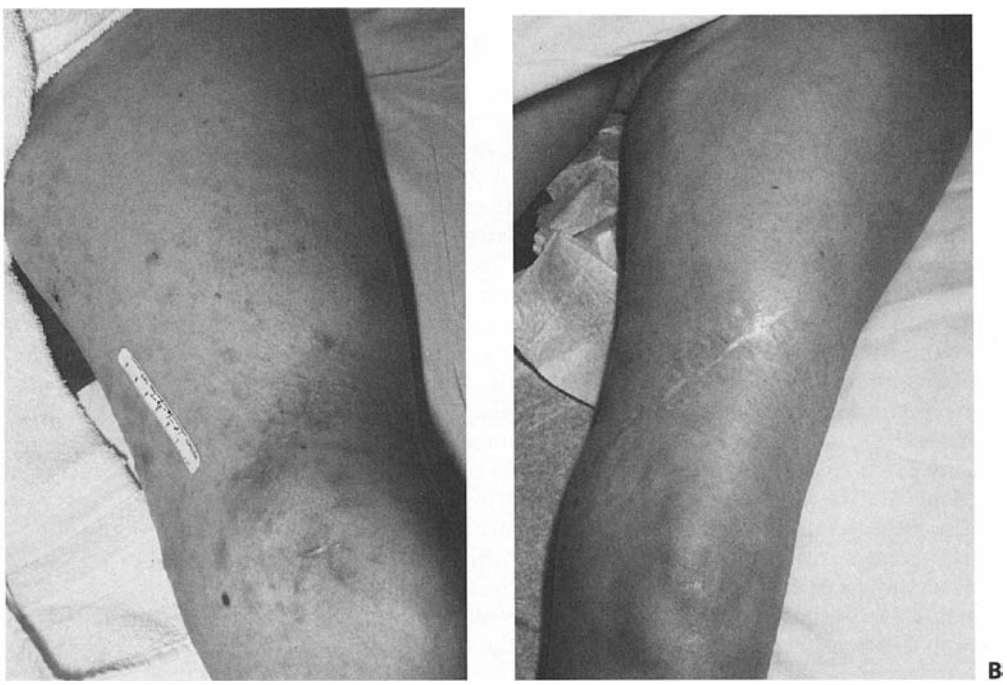

FIGURE 103.2. Patient with in-transit melanoma of the thigh. **A.** Preoperative photograph with multiple dermal and subcutaneous melanoma nodules. **B.** Same leg 1 year after an isolated limb perfusion with melphalan, tumor necrosis factor, and interferon-γ demonstrating a complete clinical response. This patient had a sustained complete response for more than 3 years, until she had systemic recurrence and succumbed to the disease.

and monitoring committee. The final results of this study have yet to be reported. In Europe, as TNF is an approved agent for ILP for unresectable extremity sarcoma, investigators use TNF selectively in melanoma for reperfusion after melphalan failure or for bulky disease. A phase I/II dose escalation study demonstrated no benefit for increased TNF levels but increased systemic and regional toxicity.[70]

In summary, all subsequent reports show that the response rate achieved with TNF and melphalan for melanoma are not as good as the initial complete response rates of 90%. However, there is value in the use of TNF in patients with bulky disease and in patients who have failed prior melphalan-alone ILP.[71] One study showed that the overall response rate achieved with melphalan plus TNF was 59%, and in a nonrandomized trial compared to their melphalan-alone perfusions there was no difference in recurrence rate or median limb recurrence-free survival. Another study of patients with very bulky disease and symptoms within the extremity[72] showed that TNF and melphalan achieved a complete response rate of only 13% but an overall response rate of 88%. Palliation of symptoms within the extremity occurred in 75% of the patients.[72,73] Evidence for the TNF effect includes enhanced response rates in bulky disease as well as responses in patients who have failed melphalan-alone isolated limb perfusion. As randomized studies have failed to demonstrate any significant improvement in duration of response or survival, TNF is unavailable in North America.

Toxicity of Isolated Limb Perfusion

Toxicity after ILP procedures can be categorized as side effects from systemic exposure of the drugs and side effects caused by 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 dose leads 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.[63,74] The side effects seen are those seen with systemic administration of TNF, including high fever, hypotension, and potentially acute respiratory distress syndrome (ARDS) and renal failure.[63] All these side effects are transient and are managed with appropriate resuscitative techniques.

The most important toxicities in ILP are the regional effects in the extremity.[41,59] 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, with areas of blistering and subcutaneous edema in virtually all patients.[75–77] The skin changes as well as this edema universally return 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, which 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 Isolated Limb Perfusion 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.[78] 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 is different than from the outcome in in-transit melanoma.[79]

When the benefit of TNF when added to melphalan in ILP for bulky melanoma was seen, this same regimen was applied to sarcoma.[66] 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 option[80–82] (Table 103.8). The overall approach with large extremity sarcomas that have no local resection options because of 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 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 were 17% complete response rates and 54% partial response rate.[81] When patients do not undergo the secondary resection, there is a high incidence of local recurrence.[66] Other groups have similar although not quite so dramatic response rates. A group from Amsterdam of 48 evaluable patients had a complete response rate of 2% and partial response rate of 47% based on standard size criteria. When they incorporated pathological responses, this increased to

TABLE 103.8.

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

Reference	*No. of patients*	*CR (%)*	*PR (%)*	*Overall response (%)*	*Limb salvage*
81	186	18%	57%	75%	82%
87	43	27%	32%	59%	58%
82	35	37%	54%	91%	85%
85	53	42%	46%	88%	82%
86	30	20%	50%	70%	65%

CR, complete response; PR, partial response.

8% complete response rate and 57% partial response rate.[83] However, because high-grade sarcomas often have a large degree of necrosis without any treatment, it is hard to differentiate tumor necrosis resulting from rapid growth from that induced by the regional therapy. A study from France has questioned whether the dose of tumor necrosis factor used in perfusion for sarcoma is too high. They performed a clinical trial with four doses of TNF (0.5, 1, 2, and 3 or 4 mg).[84] The response rates of extremity sarcoma in these four dose groups were 68%, 56%, 72%, and 64%, respectively, showing absolutely no dose effect, and none was significantly different from another. The long-term overall survival and disease-free survival were no different. The authors did comment that the systemic toxicity seen in this patient population was always higher in the higher TNF groups and questioned whether a lower dose may be equally effective but safer.

A separate group of sarcoma patients are those in which multifocal disease behaves more as in-transit melanoma metastasis than a single bulky sarcoma; examples include angiosarcoma, epithelioid sarcoma, and multifocal malignant fibrous histiocytoma. In a series published from Europe, 64 isolated limb perfusions were performed on 53 patients with multifocal disease.[85] The overall response rate was 88% with 42% complete response rate and a 46% partial response rate. In this same group of patients, single large lesions had an overall response rate of 69% (see Table 103.8). Just as for melanoma, this perfusion strategy seems to achieve better results when administered for smaller volume, but multifocal, disease. A second clinical situation that often rises in extremity sarcoma is local recurrence after initial resection with maximal radiation therapy. In these situations, the local recurrence often grows in a way in which repeat excision is not possible and, as there is no way to deliver additional radiation therapy, amputation may be the only option. A group of 30 isolated limb perfusions were performed for this indication, with a response rate of 70% with 20% complete responses and 50% partial responses.[86] The overall limb salvage was 65%. There was no increased toxicity seen in this patient group compared to the patients who have not had radiation therapy.

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.[64] The success rate has varied from an 80% to 85% limb salvage rate in European studies to a 65% limb salvage rate in North American trials[87] (see Table 103.8). As opposed to melanoma, the addition of TNF to a melphalan ILP has demonstrated a clear improvement in tumor response and benefit in terms of limb salvage. For these reasons, TNF is approved and available for ILP for extremity sarcoma in Europe.

In addition to treatment of 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.[88] Again, as this treatment acts via an apparent antiangiogenic mechanism, it may be applicable against all solid malignancies with a target tissue of the tumor endothelium that is similar across several histologies.

Isolated Limb Infusion

Although the success rate with isolated limb perfusion (ILP) is significant, this treatment requires a surgical procedure, one that generally lasts 4 to 5 h 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.[71] An alternative regional treatment for extremity melanoma that has been proposed by Thompson from Australia isolated limb infusion (ILI).[14,89] In this setting, a radiologic procedure in which balloon cannulas are utilized is essentially a stop-flow infusion into an extremity with a tourniquet, which 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 reperfusion.[14] The Sydney Melanoma Group has furthered this field of isolated limb infusion by developing a salvage regimen. They treated patients who have failed one or more ILIs with melphalan in whom amputation was the only other treatment option with ILI with fotemustine after systemic chemosensitization with DTIC.[90] They treated 13 of these patients; 4 had a complete response and 8 had a partial response. However, the median duration of the response was only 3 months, resulting in limb salvage in 5 of 12 assessable patients; this is a very good response rate in a heavily pretreated patient population.

Isolated limb infusion is just now being investigated at select centers in the United States, and the ability to achieve similar response rates as seen in the Australian experiments has yet to be reported. This is a less expensive technique than isolated limb perfusion, but the early reports of toxicity are no different. If there are not equal or improved response rates, then this technique would be inferior to isolated limb perfusion. Furthermore, the conduct of this treatment does not allow regional therapy to the proximal one-third to one-half of the thigh and, because of the pattern of spread of the in-transit melanoma, there will be a patient population that will be not eligible as a consequence of proximal disease spread. Ongoing trials will determine the role of this procedure in the regional treatment of extremity melanoma.

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, so that an effective regional therapy may improve survival. 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 both 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 better drug delivery via the hepatic artery.[91,92] 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, extensive clearance of infused agents often occurs after a first pass through the hepatic vasculature, limiting systemic exposure with hepatic infusion.[10,11]

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 103.3). 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.[93] 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 in 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 complete resection, meaning there are approximately 37,000 new patients per year with colorectal metastases to the liver who are not resectable.[94] Historically, the first line of systemic therapy for metastatic colon cancer was fluorouracil (5-FU) plus leucovorin, with response rates in the range of 12% to 20% and duration of response less than 1 year. There has been tremendous progress in the treatment regimens available for colon cancer, with several new agents and several new treatment combinations reported over the past 5 to 10 years (Table 103.9). New standard antineoplastic agents such as irinotecan and oxaliplatin as well as targeted therapy such as an antivascular epithelial growth factor (anti-VEGF) antibody (Bevacizimab) and antiepidermal growth factor (anti-EGF antibodies) (Erbitux) have greatly improved the response rate and duration of response for metastatic colorectal cancer in the liver as well as elsewhere.[95] With this greatly improved systemic therapy, the role of regional treatment with intraarterial infusion therapy has greatly diminished in the past 5 years. The theory and results of hepatic arterial infusion therapy are reviewed briefly, and how this regional treatment may be incorporated into current protocols is discussed.

TABLE 103.9. Response Rates and Duration of Response for Metastatic Colon Cancer.

	Response rate	*Duration*
Systemic therapies:		
5-FU/leucovorin	11%–23%	3–5 months
IFL (irinotecan/5-FU/ leucovorin)	31%–35%	6.9 months
FOLFIRI (irinotecan/5-FU)	56%	8.5 months
FOLFOX (oxaliplatin/5-FU/ leucovorin)	54%	8.1 months
IFL + bevacizumab	45%	10.6 months
Intraarterial therapies:		
FUDR	42%–68%	8–10 months
FUDR + systemic oxaliplatin	90%	9.8 months
FUDR + systemic irinotecan	74%	8.1 months

5-FU, 5-fluorouracil; FUDR, fluorodeoxyuridine.

The initial regimen used for continuous intraarterial infusion therapy was floxuridine (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%.[10,11] 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 such as intraarterial FUDR on a daily basis continually, and these pumps replaced catheters placed percutaneously by radiologists.[96]

The initial phase II trials of hepatic arterial infusion therapy were 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%.[10,11] 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.[97] The complications of gastritis or duodenitis are prevented by a complete intraoperative dissection including cholecystectomy. 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. 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 progressive disease.[98] 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.[99] 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. Second, biliary sclerosis has been prevented 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 achieved by infusional FUDR were in the range of 50% to 78%.[99,100] At the time initial phase II trials were performed of hepatic arterial infusion therapy, the standard systemic therapy was 5-FU and leucovorin with response rates between 12% and 20%. This clinical situation was appropriately evaluated by several prospective randomized clinical trials in both the United States and Europe[98,101–105] (Table 103.10). In all these trials, the overall response rate achieved by infusional therapy was much higher than that with systemic therapy, but in the majority of trials this was not translated into improved survival. Reasons why the response rates were superior without survival benefit included crossover of patients from systemic therapy to infusional therapy, significant hepatotoxicity in the infusional therapy group, and systemic extrahepatic recurrences in the perfusion group. The response rates achieved with current combination systemic therapy regimens (also shown in Table 103.9) have improved so they are similar to those achieved with intraarterial infusion therapy.[95] Furthermore, these treatment regimens are systemic and would treat not only known hepatic disease but also any extrahepatic disease that is either present or in the microscopic stage. Finally, these therapies of course do not require any major abdominal procedure to administer and, for all these reasons, the utilization of intraarterial infusion pump treatment as an early-line treatment for metastatic colon cancer, even if liver-only disease, has diminished markedly.

New protocols are utilizing a combination of intraarterial FUDR with systemic agents that act by a different mechanism (see Table 103.9). The primary impetus from this comes from Memorial Sloan-Kettering Cancer Center where they have reported phase I/II trials combining hepatic artery FUDR plus systemic irinotecan and infusional FUDR plus systemic oxaliplatin. The maximally tolerated dose of irinotecan was 100 mg/m^2 weekly with concurrent FUDR at 0.16 mg/kg/day with dose-limiting toxicities of diarrhea and neutropenia. The response rate in evaluable patients was 76%.[106]

A subsequent trial combined FUDR intraarterially with systemic irinotecan for patients who had undergone complete resection of liver metastases from colorectal cancer (1072A). They were treated with six monthly cycles of FUDR and escalating doses of systemic irinotecan. The maximally tolerated dose levels were FUDR at 0.12 mg/kg/day for 14 days and irinotecan at 200 mg/m^2 every other week. Dose-limiting toxicities were diarrhea and neutropenia. With a follow-up time of 26 months, at 2 years the survival rate was 89%, and all 27 patients treated at the maximal dose level were alive.[107] The second phase I/II trial treated patients with established disease.[108] Two treatment groups were designed: one was given concurrent hepatic arterial therapy with FUDR plus systemic oxaliplatin plus irinotecan, and a second group received intraarterial FUDR plus systemic oxaliplatin and 5-FU and leucovorin. The overall response rate for the group receiving oxaliplatin plus irinotecan was 90%, and the complete overall response rate for the group receiving oxaliplatin plus systemic 5-FU was 87%.[108] These response rates compared to current systemic regimens incorporating oxaliplatin in the range of 35% to 45%, indicating that the addition of intraarterial FUDR may be beneficial in combination with these current systemic therapies (see Table 103.9).

A second regional therapy is as an adjuvant treatment after resection of hepatic disease or more recently in trials in which tumor debulking of gross tumors are treated by combination of resection plus ablative techniques. For patients who have metastatic disease to their colon who are eligible for resection, approximately half the recurrences will be in the remaining liver. In other words, microscopic disease will be present at the time of the resection that cannot be appreciated by palpation or preoperative imaging or intraoperative ultrasound. Two randomized trials evaluated patients who had complete resection and were randomized either to intraarterial FUDR or either systemic therapy or observation[109,110] (Table 103.11). Both these trials suggest improvement in local recurrences within the liver in the hepatic arterial infusion arm, but neither trial utilized currently available systemic agents in the control arm. Again, the progress in response rates with systemic requests has limited the use of intraarterial pump treatment in an adjuvant setting after liver resection. Also, other institutions have utilized intraarterial therapy in combination with ablative techniques.[111,112] Usage of radiofrequency ablation initially for primary hepatomas but also for metastatic colorectal cancer has been greatly increased. Ablative treatments can be done either alone or in combination with major lobar liver resections or wedge resections. In fact, the criteria for trying to eliminate gross disease in colorectal cancer has changed from a maximum of 3 or 4 separate nodules to sometimes up to 10 or more nodules that can be treated with this technique. Because these surgical resection and ablation procedures are open techniques, it is possible to place an hepatic arterial infusion pump. The protocols combining these two technologies show that it is safe but that the disease-free survival may be no different from that of patients who have adjuvant systemic therapy.

TABLE 103.10.
Randomized Trials of Intraarterial Chemotherapy for Colorectal Metastases to the Liver.

Reference	No. of patients	Objective Response (%)	Survival (median)
		IA vs. systemic	IA vs. systemic
98	110	42% vs. 10% ($P < 0.0001$)	NA–crossover
101	64	68% vs. 17% ($P < 0.003$)	22% vs. 15% (2-year survival)
102	99	50% vs. 20% ($P < 0.001$)	NA–crossover
103	69	48% vs. 21% ($P < 0.05$)	13 vs. 11 months
104	163	43% vs. 9%	15 vs. 11 months
105	100	NA	13.5 vs. 7.5 ($P < 0.05$)

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 (IHP) is complicated by the vascular activity of the liver. At the time when isolated limb perfusion was performed initially in the

TABLE 103.11.
Phase II and III Trials of Adjuvant Intraarterial Chemotherapy After Resection of Colorectal Metastases.

	MSKCC (109)		*SWOG/ECOG (110)*		*MSKCC*
	HAI + SYS + 5-FU	*SYS alone*	*HAI + SYS + 5-FU*	*No treatment*	*HAI + SYS + irinotecan*
n	74	82	53	56	46%
Two-year survival	85%	69%	80%	79%	89%
Phase	III		III		II
Hepatic DFS	89%	57%	85%	57%	88%
Overall DFS	55%	41%	58%	34%	47%
Overall 5-year survival	—	—	63%	32%	—

HAI, hepatic arterial therapy; SYS, systemic therapy; DFS, disease-free survival; MSKCC, Memorial Sloan Kettering Cancer Center; SWOG, Southwest Oncology Group; ECOG, Eastern Cooperative Oncology Group.

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."[16] Specifically, the dual blood supply as well as the reality that the inferior vena cava essentially passes through the posterior liver, with the hepatic veins being broad short structures, make this a much more complex situation than isolated limb perfusion. One recent strategy attempted in performing an isolated hepatic perfusion was 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 venovenous 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.[20,113] 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.[17,20] 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.[114] 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. A series of studies have evaluated isolated hepatic perfusion with melphalan either in combination with tumor necrosis factor,[115] alone, or with additional intraarterial hepatic infusion with FUDR and leucovorin. The initial study was a mixed group of tumors treated with melphalan and tumor necrosis factor with a 72% partial response rate and a 3% complete response rate occurring in an ocular melanoma patient. Subsequent follow-up studies have shown the response rates are between 71% and 77% for colorectal cancer; however, the median duration of response is 10 months[116] (Table 103.12). The addition of postisolated hepatic perfusion intraarterial FUDR did not appear to augment the response rate. Another tumor type that may be very appropriate for treatment with isolated hepatic perfusion is metastatic ocular melanoma. For unknown reasons, approximately 70% of patients with this tumor when it metastasizes have liver disease only. Furthermore, this tumor has been very resistant to treatment with standard agents that show benefit for cutaneous melanoma. A trial of melphalan isolated liver perfusion for ocular melanoma, showing a 10% complete response rate and a 52% partial response rate (see Table 103.12). For patients who had lactate dehydrogenase (LDH) in the mid- to low normal range, there was prolonged survival, but the overall duration of response was 9 months; this seemed to be greatly improved with the addition of tumor necrosis factor in the perfusate. Trials in Europe have generally reproduced these results in small series in the Netherlands and Germany. Typically, the response rates are in the range of 60% to 80% for melanoma, but the duration of response tends to be between 9 and 11 months.[116] In a recent report from the National Cancer Institute (NCI) of nine patients with primary hepatoma, a partial response rate of 67% (six of nine) was reported with a median time to progres-

TABLE 103.12.
Results of Clinical Trials with Isolated Hepatic Perfusion for Metastatic Cancers.

n	*Histology*	*Drug*	*Response rate*
29	Colorectal	Melphalan	17.2% (3%–4% CR, 13.8% PR)
22	Ocular melanoma	Melphalan ± TNF	62% (9.5% CR, 52% PR)
32	Colorectal	Melphalan + TNF	77% (0% CR, 77% PR)
19	Colorectal	Melphalan + ia FUDR	74% (0% CR, 79% PR)
29	Ocular melanoma	Melphalan	62% (10% CR, 52% PR)
9	Primary hepatic	Melphalan	67% (0% CR, 67% PR)
28	Colorectal + ocular melanoma	Melphalan (percutaneous perfusion with hemofiltration)	30% (7.1% CR, 23% PR)

CR, complete response; PR, partial response.
Source: Grover and Alexander,[116] Feldman et al.,[117] and Pingpank et al.[119]

sion of 7.7 months. Because of the complexity of this procedure, it has not been widely accepted, and efforts to streamline the operation by use of percutaneous catheter techniques are being studied.[117]

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.[118] 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. Two 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 technique treated patients with 5-FU, adriamycin, or melphalan.[118] Although the procedure was technically possible, there were only limited objective responses of very short duration following this treatment.

A recent phase I trial was reported using this type of technique from the group at the Surgery Branch at the NCI. A total of 74 percutaneous treatments were administered to 28 patients.[119] The drug used was melphalan initially at a dose of 2.0 mg/kg, escalating up to 3.5 mg/kg, with a treatment time of 30 min. The dose-limiting toxicity, seen at 3.5 mg/kg, was neutropenia and thrombocytopenia. The radiographic response rate overall was 30%, and in 10 patients with ocular melanoma a 50% overall response rate was seen with 20% (2 patients) having complete responses.[119] These results are much more promising than the earlier studies on this technique using other agents. This percutaneous technique is much less involved in terms of the technical aspects of the procedure than an open isolated hepatic perfusion performed surgically and allows retreatment. Further studies are needed to define the response rates in the patient population that will benefit from this regional treatment in light of the improved systemic therapies and alternative treatments for colorectal cancer. Perhaps this treatment may become a standard for the patient population with ocular melanoma who have limited alternative options.

Isolated Lung Perfusion

If the extremities are straightforward in terms of anatomic 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, although for the histologies listed here the primary set of metastasis is often the lung, it is more likely than with other malignancies to have extrapulmonary spread as well. A series of publications were reported from Pass from the National Cancer Institute[21] on the preclinical models of isolated lung perfusion and a subsequent clinical trial. This trial utilized escalating high-dose tumor necrosis factor (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.[21]

A different strategy was employed by investigators at Memorial Sloan-Kettering Cancer Center in which an isolated lung infusion was performed.[120] 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 already 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 has also 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/de-

bulking operation.[121] 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.[122–124] 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.[125] 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.

Two recent studies from Japan have been reported randomizing patients to receive hyperthermic peritoneal perfusion after resection of primary gastric cancer for T2 through T4 primary lesions. The results are variable, as one study reported a positive benefit and the other did not. The negative trial was not randomized, but included patients of younger age and better performance status who received the hyperthermic perfusion and patients who were older or had decreased performance status or major organ function who received surgery alone. A total of 124 patients were treated, 45 patients in the peritoneal perfusion group and 79 in the nonperfusion group.[126] The tumor characteristics including depth of penetration and nodal status were no different between the two groups. Patients received a combination of mitomycin C, cisplatin, and etoposide hyperthermic peritoneal perfusion following resective surgery. The 5-year survival rate for the perfusion group was 49% and for the nonperfusion group was 56%.[126] Again, this was not a randomized study, but the tumor characteristics were similar, and because the performance status was better in the perfusion group, one could argue that they would be expected to have an improved outcome. This trial would then argue against any benefit from prophylactic CHPP. A second study recently reported was a true randomized trial for patients with T2 through T4 primary gastric cancers but no evidence of peritoneal carcinomatosis.[127] One hundred and thirty-nine patients were randomized to either surgery alone, surgery plus a normothermic peritoneal perfusion with mitomycin C, or surgery plus a hyperthermic peritoneal perfusion with mitomycin C. In this trial, a positive result with 5-year survival rates for surgery alone were 42%, surgery plus normothermic peritoneal perfusion 43%, and surgery plus hyperthermic perfusion were 61%.[127] This trial achieved statistical significance, and the authors conclude that this is beneficial only when given as a hyperthermic peritoneal perfusion in this patient population. They did notice increased toxicity with peritoneal perfusion of either type, not dependent on temperature.

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[128,129] (Table 103.13). Investigators at Bowman Gray University[120] as well as M.D. Anderson have utilized mitomycin C as the primary chemotherapeutic agent with this technique. At the Surgery Branch of the National Cancer Institute,[130] 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 antimetabolites such as 5-FU. These trials varied 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 MD 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.[128]

The results of the initial phase I studies of CHPP report toxicity and pharmacokinetics.[121] 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%.[130] 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 1 patient who recurred at 20 months and 1 who is free of disease 42 months after treatment. Also, benefit was seen in

TABLE 103.13.
Phase I/II Trial of Continuous Hyperthermic Peritoneal Perfusion for Advanced Peritoneal Disease.

	NCI, Surgery Branch (130)	*Bowman Gray (120)*	*NCI (128)*
n	27	34	49
Agents	Cisplatin 100–350 mg/m^2 TNF 0–3 μg/L	Mitomycin C 30 mg initial + 10 at later time	Cisplatin + 5-FU trial
Inflow temperature	48°C	42°C	42°C
Peritoneal temperature	41.5°–43°C	40°–40.5°C	41.5°–43°C
Duration of treatment	90 min	120 min	90 min
Tumor type	Mixed	Gastric	Mesothelioma
Outcome	1-year survival 49%	1-year survival 75% 2-year survival 48% 75% ascites controlled	17 months progression-free survival; 92 months median overall survival

patients with primary peritoneal mesothelioma with recurrence at 3, 5, 24, and 31 months.[130] The field has matured enough that individual investigators are now accumulating significant follow-up for specific types of cancer. The group at Wake Forest has reported studies evaluating experience with gastric cancer as well as colorectal cancer.[131] In 34 patients with gastric cancer treated with hyperthermic peritoneal perfusion with mitomycin C for carcinomatosis and compared to a historical population, the overall survival rate was 11.2% versus 3.3%, with a 2-year survival rate of 45% versus 8%.[131] Again, this was not a randomized trial but a historical comparison against patients who have a very poor prognosis. This same group reported on 77 patients with colorectal cancer and peritoneal carcinomatosis.[132] In this patient group, the 2-year survival rate after tumor debulking and hyperthermic peritoneal perfusion was 25% and the 5-year survival rate was 17%. Bowel obstruction, malignant ascites, and incomplete debulking were all correlated with poor outcomes. The Loggie group has reported using hyperthermic peritoneal perfusion with mitomycin in 109 patients with carcinomatosis. For patients who could have complete debulking of all gross tumor, the median survival was 15.5 months with a 5-year survival of 13%. For patients who did not achieve complete debulking, the median survival was 7.9 months with a 2% 5-year survival. Conclusions from these studies would be that in select patient populations that have fairly minimal disease, this strategy may have some benefit in achieving long-term survival in a subset of the population.[133] Patients who had more bulky disease in which gross disease is being treated with hyperthermic peritoneal perfusion do not do as well. However, one could also interpret that the patients who achieved complete debulking had fairly nonaggressive tumors and may benefit from the surgical procedure alone as there has been no randomized trial comparing surgery alone in this patient population to surgery plus hyperthermic peritoneal perfusion.

A disease type that has no other reasonable treatment options is peritoneal mesothelioma. The group at the NCI[134] has reported remarkable results for this patient population with cisplatin hyperthermic peritoneal perfusion with or without a postperfusion treatment with Taxol plus 5-FU. In 49 patients with peritoneal mesothelioma treated in this study, there was a 17-month median disease-free survival and a remarkable 92-month overall median survival in patients who historically did not have good results even with surgery alone or surgery plus systemic therapy[134] (see Table 103.13).

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 upper abdomen and one in the pelvis.[128] 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 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 arising to above 40°C.[135] 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, as for 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 limits the utility of the indwelling cannulae.

Photodynamic Therapy

A second technique to address to the problem of surface malignancies throughout the peritoneum is photodynamic therapy (PDT).[4,5] As in CHPP, PDT combines a surgical debulking procedure with an additional procedure as treatment of 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 that lead to cell death. One potential limitation of this treatment is the depth of penetration of the light, which is variable depending on the wavelength of light used for a given sensitizer, typically 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 theoretical selectivity of the antitumor effect with PDT after systemic photosensitizer administration is in selective uptake and retention of the 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 primaries for reasons that are not clear.[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 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.[136,137] On the basis of these preclinical data, a phase I study was performed at the NCI alternating escalations of the dose of light energy and the dose of photosensitizer. The results of this phase I trial were published[138] and recently updated in abstract form.[139] 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 with gastrointestinal (GI) carcinomatosis. Nine of 39 patients remained disease free between 3 and 27 months later; 9 patients died of progressive tumor, and 21 were alive with disease with follow-up of approximately 1 year. Three patients with ovarian tumors were free of disease at 3, 4, 15, and 27 months after treatment. Three patients with GI tumors that were low-grade pseudomyxomas were free of disease at 8, 9, and 18 months, and 1 patient with sarcomatosis was free of disease at 20 months.[138,139]

A phase II trial was designed based on these data utilizing photofrin given at a dose of 2.5 mg/kg 48 h before debulking surgery. The inclusion criteria of this trial were disease confined to the peritoneal cavity with no evidence of hematogenous spread. To receive light treatments, the patient had to have tumors debulked down to 5 mm or smaller. Patients were divided into ovarian carcinomatosis, carcinomatosis from gastrointestinal tumors including stomach, pancreas, colon, and appendix, and sarcomatosis from gastrointestinal stromal tumors or retroperitoneal sarcomas. One hundred patients were entered in this trial, although only 71 could be debulked to a degree where light therapy was administered. All patients showed signs of recurrent disease typically within 3 to 4 months, but the median overall survival for this heavily pretreated population was 22.0 months for the ovarian carcinoma group, 13.2 months for the gastrointestinal group, and 21.9 months for the sarcoma group.[140] Tissue analysis suggested that, particularly for gastrointestinal tumors and sarcomas, there was no detected retention of the photosensitizer within the tumor compared to normal tissue contributing to the early recurrences. However, the fairly prolonged median survival in the patient population that at entry was very heavily pretreated indicates some essential benefit for this difficult disease.

New trials with second- and third-generation photosensitizers with either better optical properties or better tumor retention are being conducted.[141] Also, the way the light is administered and distributed in the complex peritoneal surface is being studied with measurements of light distribution at various locations within the peritoneum. Photodynamic therapy for endobronchial and esophageal lesions has been approved, but treatment for the peritoneal cavity is certainly considered investigational at present.

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.[6,142,143] A second treatment for pleural mesothelioma is with intracavitary gene therapy.[8,144] Mesothelioma is a tumor of the lining of the pleural cavity, and it often encases the lung at the time of presentation but has not spread outside of a single pleural cavity.[40] Surgery alone generally does not result in cure, and the tumor is relatively chemotherapy resistant, which provides an ideal setting for attempts at regional intracavitary therapy.

In many ways, the pleural spaces are better suited for photodynamic therapy than the peritoneum,[6,143] because of the relatively simple geometry of the surfaces in which there are no hidden areas between bowel loops and in the pelvis. An initial phase I trial of intraperitoneal PDT with photofrin II was conducted treating mesothelioma with escalating intraoperative light doses between 15 and 35 J/cm^2 48 h after receiving photosensitizer.[145] Forty-two patients were treated, and it established that the maximal 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.[145] 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.[142] 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 may provide benefit with this adjunctive regional therapy.

A phase II trial using Foscan, a second-generation sensitizer, has been recently reported from the group at Penn.[146] Four dose levels of Foscan were utilized in this study, and the maximal tolerated dose was 0.1 mg/kg injected 6 days before debulking surgery. The next higher dose level led to multisystem organ failure and capillary leak syndrome, and two of three patients at that dose level expired. As this was a phase I study, the clinical response results were not reported, but it was thought that this treatment deserved further study.

A recent clinical trial has been reported treating non-small cell lung cancer with pleural spread using intrapleural PDT.[147] The median survival rate for this patient population has historically been quite dismal, with most series reporting 6- to 9-month survival. This trial treated 22 patients with non-small cell lung cancer and, of the 22 enrolled, 17 were able to undergo complete debulking and photodynamic therapy. Fifteen of these 17 were available for response assessment. The local control of pleural disease at 6 months was achieved in 11 of 15 patients (73%).[147] Medial survival for the entire patient population entered on this trial was 21.7 months. For this disease, there were measurements of the tissue levels of photofrin and the ratio between tumor to normal tissue ranged between 1.19 and 22.4. These response rates, although not in a randomized trial, would argue strongly that there is significant benefit from photodynamic therapy for this difficult clinical problem compared to historical results. However, because very aggressive surgery is being performed that would otherwise not be indicated outside a clinical trial, one cannot at this time differentiate between the benefit achieved from the surgical intervention and the additional benefit from light treatment.

Regional Gene Therapy

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.[144] Twenty-one patients were treated with viral doses ranging from 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.

As the molecular genetics of malignancies have been defined as well as development of molecular techniques to alter gene expression with gene therapy, much preclinical work as well as clinical trials has 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 these susceptible to subsequent drug treatment. Other strategies include replacement of mutated tumor suppressor genes such as adenovirus vectors expressing wild-type p53 genes.[8]

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.[144] Similarly, intraperitoneal administration of wild-type p53 adenovirus vectors has been evaluated for ovarian carcinoma. In addition to the intracavitary treatments, intraarterial treatments are under investigation, primarily to the liver.[7] 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.[9] 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, it is hoped, provide meaningful improvements in disease-free survival for patients for whom there are no other effective therapies.

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