Cancer Regional Therapy

HAI, HIPEC, HILP, ILI, PIPAC and Beyond

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ISBN 978-3-030-28890-7 ISBN 978-3-030-28891-4 (eBook)
https://doi.org/10.1007/978-3-030-28891-4

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

This book is dedicated to the memory of Chen Ling Kou (November 5, 1963–April 6, 2019), who passed away after bravely battling pancreatic cancer for nearly 4 years. Her cancer was confined to the peritoneal cavity. Her disease is what the therapies in this book are designed to address. Mrs. Kou accepted many experimental cancer treatments in the hope that it would help others suffering from cancer. She epitomizes the countless patients who enroll in research studies to help prolong the lives of many other patients and to lead us one step closer to one day finding a cure.

Every time Chen Ling spoke of her three children, she would beam with pride. Every time the disease or her treatments would cause her pain, she was as worried for her family's suffering as for her own. Treating her reminded me that illness is a family matter. In treatment of cancer, we must care not only for the well-being of the patient but also of her family and her community.

Chen Ling is survived by her husband and their three children. She was truly a beautiful person inside and out. She will forever be remembered as a great mother, a great wife, and a great friend.

In your memory Chen Ling, we dedicate this book to help educate practitioners of cancer therapy. We also dedicate our future research striving for more effective treatments of peritoneal malignancies and for a future cure for these deadly diseases.

Foreword

Dose Intensity Versus Perplexing Access

Over the last 30+ years at the Washington Cancer Institute, I have been determined to optimize the management of peritoneal metastases using combinations of surgery, regional (intraperitoneal) chemotherapy, and systemic chemotherapy. After maximizing the benefits of cytoreductive surgery using peritonectomy procedures and visceral resections, a second goal in this endeavor was to describe the optimal perioperative (HIPEC and EPIC) chemotherapy through pharmacologic studies [1, 2]. 2043 patients have endured our Washington Cancer Institute protocols with greatly variable results. One aspect of cancer care I have repeatedly recognized as an absolute requirement for long-term benefit is local control of disease. For peritoneal metastases, regional chemotherapy is, in selected patients, an absolute requirement to achieve the first and foremost of all needs for treatment with curative intent.

The requirement for a regional approach to chemotherapy delivery is a consequence of lack of benefit from systemic chemotherapy. The DOSE INTENSITY of regional chemotherapy may provide control that systemic drugs cannot achieve. Increasing the drug concentrations in the regional tissues may result in significantly larger response rates and even complete response. A natural consequence of this rationale for a regional approach is a diminished or even absent need for regional chemotherapy as systemic chemotherapy improves. For example, limb perfusion for *in-transit* dermal metastases from malignant melanoma has increasing limited applications. When satellite or in-transit metastases are observed, this indicates that the disease has the ability to metastasize. Currently, the treatment is early systemic intervention with the local-regional lesions being used as an indicator of effective treatment [3]. Isolated limb perfusion or infusion remains an option only in selected patients with systemic treatment failure and extensive progression limited to the extremity. Somewhat counterintuitive, systemic treatment that halts the progression of metastatic disease may encourage local-regional efforts [4]. Radical surgery may benefit if metastases are symptomatic and especially if the intervention makes the patient clinically disease-free.

The possible benefits of regional cancer treatments come with a price. The major obstacle is ACCESS. Ports, pumps, laparoscopy, abdominal and/or pelvic surgery, and arterial and venous cannulation are required for single or

repeated access. This access for regional chemotherapy is expensive and carries a definite morbidity and mortality defined by a learning curve. Regional chemotherapy access is far more complex and problematic than systemic drug administration through an implanted intravenous port. Although regional therapies may be safe (with experience) and show benefit (with proper patient selection), they are INCONVENIENT. For patient and oncologist, they usually add complexity, cost, and complications to patient care. Regional chemotherapy at some institutions may be repeatedly safe and effective but not available at other nearby cancer centers. To be successful, there is a requirement for an interdisciplinary team of surgeon, radiation therapist, medical oncologist, interventional radiologist, and nuclear medicine physician. Quite a complex team!

For regional chemotherapy to be considered, there are several requirements for success. The cancerous process treated by regional chemotherapy is not localized and amenable to local treatment by resection and/or radiation. Also, it is not reasonable to treat systemic metastases by regional chemotherapy. The target is an intermediate stage of cancer dissemination. In almost all instances the malignancy must be limited to the anatomic site that will be flooded by regional chemotherapy. Some cancers may remain confined to a single anatomic site throughout their natural history (malignant peritoneal mesothelioma). In other diseases, regional chemotherapy may control the disease at a single site for a prolonged period of time before systemic metastases appear (ovarian cancer). That anatomic site needs to have uniform access to drugs for single or preferably repeated drug instillation. A prominent reason why regional cancer treatments fall short is a limited number of treatments. For example, hyperthermic intraperitoneal chemotherapy (HIPEC) is limited to a single event. This limitation of HIPEC has led to its characterization as a necessary but not a sufficient local-regional treatment for peritoneal metastases [5]. In patients whose peritoneal metastases cannot be completely (by visual inspection) resected, pressurized intraperitoneal aerosol chemotherapy (PIPAC) may be more beneficial in that repeated treatments are possible [6].

There are consequences for these two realities of regional chemotherapy administration. First reality, we are treating an intermediate stage of cancer progression. Second reality, all too often there is a limited time for cancer to remain confined to a single anatomic region. This means that complete success of regional therapy will often occur in patients who eventually develop systemic disease and cancer death. The consequence is that we are providing with regional cancer treatment a prolongation of disease-free survival for our patients but infrequent cure. If this prolongation of survival can be accomplished with the preservation of quality of life, it is of great value. If we initiate regional cancer treatments from which patients do not fully recover, they are unacceptable.

A second requirement is a pharmacologically appropriate drug. The intrinsic chemical and biologic properties of the drug instilled, perfused, or recirculated must be carefully selected and properly dosed to result in optimal benefit. For example, drugs with cell cycle requirements for cytotoxic effects

will not be appropriate for a treatment that lasts only 1–2 hours. These drugs, such as 5-fluorouracil and paclitaxel, are appropriate for repeated instillation over several days. For a limb or organ perfusion over approximately 1 hour, the acute cytotoxic effects of melphalan may be appropriate [7].

A third requirement for the oncologist regards avoidance of local-regional toxicities. The local dose intensity which may result in cancer control may exceed tissue tolerance and result in a major long-term complication. Drug-induced fibrosis or intravascular sclerosis may lead to organ dysfunction and reduced quality of life or reduced survival. Knowledgeable monitoring of patients for toxicities induced by the regional cancer therapies must occur. These local-regional toxicities may not be readily apparent and are only discovered by long-term follow-up and a high index of suspicion. For example, sclerosing encapsulating peritonitis from an overdose of intraperitoneal doxorubicin may not become clinically apparent for many months after treatment [8]. Of course, underdosing may be equally destructive in that maximal local cancer control will not be achieved. Underdosing may be occurring far too frequently with regional chemotherapy.

Finally, a requirement for regional cancer treatment success is proper integration/sequencing with systemic chemotherapy, especially neoadjuvant chemotherapy. For example, if a maximal cell kill has been achieved by FOLFOX chemotherapy, peritoneal metastases will have acquired drug resistance for oxaliplatin. Responsive cancer cells have been destroyed and only resistant clones remain. Even if used with heat, HIPEC with oxaliplatin would not be expected to add benefit after neoadjuvant FOLFOX [9]. Some data may suggest that adequate hyperthermia can, at least in part, reverse natural or acquired drug resistance [10]. Perhaps a major gap in the optimal use of regional chemotherapy is a failure to integrate systemic and regional treatments for the cancer patients' best advantage.

In conclusion, regional cancer treatments allow a regional dose intensity that can be exploited for the great benefit of the patient. It requires access to the body compartment involved by cancer. This access is at least inconvenient and at worst results in serious complications. Not only proper patient selection but also pharmacologically appropriate chemotherapy agents at an optimal dose must be selected. All of this must be integrated with systemic treatments.

The many strategies currently in use are magnificently presented in this cancer regional therapy textbook. The coverage of this subject is comprehensive. The indications for treatment and the difficult problems with patient selection for regional cancer treatment are provided for each disease process. The expectations for long-term benefit are presented in a balanced perspective. This textbook will be of great use for many years to come and provide a source of information on the state of the art in 2019 for regional cancer treatments.

Washington, DC, USA Paul H. Sugarbaker

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Preface

Regional Therapy: Evolution from "Only Thing We Can Do" to "Best Thing We Can Do"

The practice of regional therapies is based on the following: (1) certain disseminated cancers are still restricted to a single compartment in the body, (2) cytoreduction within that compartment improves survival and/or symptoms, (3) delivering chemotherapy and other tumoricidal agents to the affected compartment increases the therapeutic doses to tumor sites while reducing toxicities, and (4) combining cytoreduction and regional-systemic tumoricidal agents improves clinical outcome. In this regard, regional therapies have been used for liver, limbs, peritoneal cavity, pleural cavity, and cerebral ventricular space. Such were the origins of isolated hepatic perfusion (IHP), isolated hepatic infusion (IHI), isolated limb perfusion (ILP), isolated limb infusion (ILI), hyperthermic isolated peritoneal chemotherapy (HIPEC), isolated thoracic perfusion (ITP), intraventricular infusion therapy (IIT), and early postoperative intraperitoneal chemotherapy (EPIC).

This alphabet of therapies originated because few effective systemic therapies were available 3–4 decades ago. Imaging was primitive. Surgical planning was often done with our patients already in surgery as we encountered the cancer. Surgical cytoreduction often carried significant morbidity. Regional delivery of cytotoxic agents allowed dose intensification at the sites of cancer. At that time, these were always delivered surgically because the fields of interventional radiology and image guidance were in their infancy. We started down the path of surgical regional cytoreduction and surgical regional chemotherapies because it worked and we had nothing better.

The regional oncologic therapy field has evolved significantly in the last decades. Surgical cytoreduction has become much safer. Liver resection is now associated with low mortality [1] and is even evolving to outpatient surgery [2]. Peritoneal cytoreduction can now be performed safely at many centers. Thermal- [3] and radio-ablative [4] techniques also allow for additional options for cytoreductive therapy at minimum morbidity. Interventional radiologic techniques now allow delivery of regional cytotoxic therapies without the morbidity of isolated surgical perfusions. Many novel agents are now also found to have great first-pass extraction, allowing addition of effective agents for regional cancer therapy. Finally, the lengthening of the survival curve by effective systemic therapy and the increasing safety of

cytoreductive therapies has altered the risk-benefit ratios of regional therapies, especially in patients that over prolonged follow-up prove to have single compartment-dominant disease.

With these changes, there has been a revival of regional cancer therapies. There has also been the birth of new surgical MIS regional therapies, such as pressurized intraperitoneal aerosol chemotherapy (PIPAC), and image-guided MIS therapies, such as ILI, that have greatly reduced the procedural morbidity and allow repeated treatment. New biologic scans for cancer for assessing tumor burden and response to therapy also allow better treatment planning. Finally, many new agents, including viruses, cells, and antibody fragments, hold biologic rationale for regional delivery. The field has evolved to a field of novel procedures, a field of novel agents, and a field of novel correlative imaging and markers.

Understanding concepts underlying these regional therapies, as well as devices and procedures available for regional delivery of oncologic agents, will be important for both the experimental and clinical oncologist.

The goals of this book are (1) to review the theory and practice of cancer regional therapies including pharmacology, devices, techniques, and workflow, (2) illustrate the most common procedures performed in the interventional and operating rooms, and (3) discuss data supporting use of cancer regional therapy (CRT). This is meant to be a definitive text on the theory and practice of CRT. The current book summarizes the history, current technology, common procedures, and future prospects in this field of CRT. It will include procedures from many surgical and interventional radiologic disciplines.

The book will begin with a summary of the history; technical principles that underlie regional therapy will be presented. The following parts will discuss current data and practice in peritoneal, liver, limb, pleural, and other sites. Included in the practice will be considerations of workflow and financial issues revolving around CRT. Novel techniques and therapies under investigation will be presented to inform the direction of the field.

This book is intended to summarize the field for current and future practitioners at all levels. It is meant to be a guide for residents and fellows entering the field. It is meant to summarize the current state of the art for the surgeons and interventional radiologists active in CRT development and research. It is meant as a primer for senior surgeons and radiologists adapting newer technologies to their current practice. We hope that our audience of surgeons, oncologists, and interventional radiologists find this useful.

A work like this is only possibly because of the contributions of many. The authorship of this work includes experienced surgical oncologists, general surgeons, thoracic surgeons, gynecologic oncologists, urologists, and interventional radiologists. We thank them for their contributions and efforts to collaborate in the creation of this comprehensive and special work.

We also thank our teachers, residents, clinical fellows, and colleagues who have shared their knowledge and experience with us. We thank our patients who inspire us to be superior clinicians and to constantly strive to improve the

field. We thank our editor at Springer Barbara Lopez-Lucio. Finally, we thank our families, for the patience and support they have given us daily for our clinical work and then to complete a work such as this.

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Part I

Background

1 The Basis of Regional Therapy, Pharmacology, Hyperthermia, and Drug Resistance

Kim Govaerts, Kurt Van der Speeten, Lana Bijelic, and Jesus Esquivel

The Basis of Regional Therapy

The peritoneal surface is a common failure site for most gastrointestinal and gynecologic malignancies, providing a strong incentive for studying regional approaches to chemotherapy delivery. The relative accessibility of the peritoneal cavity is another reason intraperitoneal chemotherapy, either as part of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) or as catheter-based repeated instillations, is the most commonly studied form of regional therapy.

The Peritoneal-Plasma Barrier

Intraperitoneally administered chemotherapy (IPC) enters the systemic circulation either by diffusion into the vascular compartment or by absorption through peritoneal lymphatics.

The rationale for this route of administration is based on the knowledge that the peritoneal membrane acts as a relative transport barrier between the peritoneal cavity and the systemic circulation. Contrary to intuitive thinking, resection of the mesothelial lining, like is done during peritonectomy in cytoreductive surgery, does not seem to affect transport of agents between the peritoneal cavity and the systemic circulation. This was shown by Flessner et al. in 2003 who demonstrated that neither removal of the stagnant peritoneal fluid layer nor resection of the mesothelial lining influenced the mass transfer coefficient (MTC) in a rodent model [1]. Similarly, the extent of parietal peritonectomy does not seem to influence IP chemotherapy pharmacokinetics in humans [2–5]. This is explained by the fact that the principal barrier for clearance of solutes from the abdominal cavity consists of the submesothelial blood capillary walls and the surrounding ECM rather than the mesothelial lining.

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Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_1

Compartment Model for IP Drug Delivery

The tissue surrounding the peritoneal cavity can absorb almost all agents [6, 7]. Subperitoneal tissues mediate the transfer of IP fluid and solutes via lymphatics or blood flow into the circulation. Even though within 24 hours the entire peritoneal surface will make contact with an IP-administered solution, only a fraction (approximately 30%) is typically in contact at any given time. The volume of the solution, adhesions, the size of the patient, and the patient's position all affect the peritoneal contact area. Pharmacologic studies of IP chemotherapy typically simplify this complex clinical situation by considering the peritoneal cavity to be a single compartment separated by an effective membrane (peritoneum) from another single compartment, plasma [8]. Fick's law of diffusion to transperitoneal transport can be applied. Transfer of a drug from the peritoneal to the systemic circulation occurs across the peritoneal membrane, governed by the permeability-area product (PA). The latter is calculated by measuring the rate of drug disappearance from the cavity divided by the overall concentration difference between the peritoneal cavity and plasma.

$$\text{Rate of mass transfer} = \text{PA}\left(\text{CP} - \text{CB}\right).$$

The importance of the effective contact area is highlighted this way, but its value in actual transfer across the membrane is not determined in this model.

Dedrick Diffusion Model

The pharmacokinetic rationale for IPC is based on "dose intensification" achieved by the peritoneal-plasma barrier [9]. Dedrick et al. concluded from peritoneal dialysis research that the peritoneal permeability of a number of hydrophilic drugs may be considerably less than their plasma clearance [10]. After IP administration, peritoneal clearance is inversely proportional to the square root of the drug's molecular weight. Once the drug enters the systemic circulation, it undergoes rapid metabolism limiting its systemic toxicity. This leads to a significantly higher concentration in the peritoneal cavity compared to the plasma. Simplified, this means that when the concentration of intraperitoneally administered drug in the peritoneal solution is plotted over time, the area under the curve (AUC) provides an idea of the efficacy of the treatment. On the other hand, when after IP administration of chemotherapy its IV concentration is plotted over time, the AUC will provide an idea of the toxicity of the treatment. The difference in drug concentration between the peritoneal cavity and the systemic circulation attributed by the peritoneum-plasma barrier has been called the pharmacokinetic advantage. This dose intensification is expressed as the AUC ratio of intraperitoneal (IP) versus plasma (IV) concentrations. Practically, this means that after CRS, this concentration difference enables exposure of residual tumor cells to high doses of chemotherapeutic agents, while reduced systemic concentrations limit systemic toxicity.However, two important factors must be taken into consideration regarding this simplified model. Firstly, exposure of residual tumor cells to increased drug levels by increasing drug concentration at their surface (achieved by changing pharmacokinetic variables) does not necessarily lead to increased uptake and thus high intratumoral concentration. The ideal drug for IP administration should not only be retained in the peritoneal cavity for a prolonged period but also be able to penetrate in high concentrations into tumoral tissue.

Secondly, recent publications indicate factors other than systemic absorption may influence the AUC ratio such as the timing of the last measurement of plasma AUC, the instillation time, and the grade of drug distribution in the body (the distribution of drug into the peripheral compartment) [11]. The latter has also been shown by Lemoine et al. who observed an additional peak in the plasma AUC with elongation of measurements after IP instillation due to remobilization of the drug out of the peripheral compartment.

Peritoneal Carcinomatosis: Changed Barriers

Malignant invasion of the peritoneum often causes at least partial destruction of the normal peritoneum. This results in lack of a mesothelial layer over the tumor, an altered interstitium, hyperpermeable microcirculation, and the lack of lymphatics which can all affect intraperitoneal chemotherapy.

Neoplastic Peritoneum

The loss of mesothelial cells in the neoplastic peritoneum leads to lack of a smoothly gliding peritoneal surface, promotes formation of adhesions, and decreases the function of the immune system. Furthermore, it allows macromolecules to pass through. This has been shown by the ability of viral vectors containing antisense RNA to penetrate through cancerous peritoneum but not normal peritoneum [12].

Lymphatics

In peritoneal carcinomatosis, the subdiaphragmatic as well as the visceral lymphatics may be obstructed, leading to disturbed protein clearance and ascites [13, 14]. Supradiaphragmatic lymph nodes may be overwhelmed by tumor cells, providing a metastatic route to the systemic circulation. However, if these pathways are still functional at the time of IP therapy, they may provide a direct route for the drug into the systemic circulation (especially in case the drug has a molecular weight greater than that of albumin).

Tumor Microenvironment

The tumor microenvironment consists of two components: the extracellular fluids (blood, lymph, interstitial fluid) and solids (connective tissue proteins and mucopolysaccharides). The fluids are subdivided into the vascular and the interstitial space, separated by the vascular wall. A tumor can thus be seen as a three-compartment model consisting of the malignant cells, the vessels, and the interstitial water space.

Microvasculature

The normal capillary wall consists of the endothelium lined by a glycocalyx which is more pronounced at the level of interendothelial clefts to provide passage to only small molecules (e.g., insulin 5500 Da). Elsewhere, a limited number of gaps with less dense glycocalyx exist to permit protein leakage [15]. It is the glycocalyx surrounding the endothelium that provides most of the barrier to solute transfer. Inflammation and certain drugs can cause degradation of the glycocalyx, thereby increasing the capillary permeability [16]. Furthermore, neo-angiogenesis that accompanies malignancy results in the formation of vessels that contain no or minimal glycocalyx and are unevenly distributed [17]. Although these leaky neo-capillaries might provide rapid clearance of drugs from the systemic circulation into the tumor, the high interstitial pressures limit effective drug penetration.

Interstitium

Alterations in the interstitial pressure change the interstitial water space and thus the tissue available for solute transport [18]. It has been shown that the malignant interstitium is markedly expanded in comparison to the interstitial water space of normal tissue [17, 19]. Despite this, malignant interstitium seems to be more resistant to transfer of molecules compared to normal interstitium. Furthermore, an increased interstitial water space implies a greater distance between the vessels and tumor cells contributing to “metabolic death” and difficulty of IP chemotherapeutic to get access to malignant cells. The malignant interstitial pressure can reach up to 45 mmHg, with increased pressures present

within the first millimeter of tumor tissue below the peritoneal surface which limits convection of IP drugs [15–20]. The upper limit of IP pressure tolerated by an ambulatory patient is 8–10 mmHg. Anesthetized and mechanically ventilated patients can tolerate higher IP pressures; however, values >15 mmHg might impair portal circulation or respiration [17, 20–22].In conclusion, multiple characteristics of the neoplastic interstitium may negatively impact the ability of intraperitoneal drugs to reach and penetrate malignant cells.

Pharmacology

The pharmacology of IP chemotherapy can be subdivided into pharmacokinetics and pharmacodynamics. Pharmacokinetics evaluates what the body does to the drug by analyzing what happens between the moment of administration of the IP chemotherapy and the drug showing up at the level of the tumor nodule. Pharmacodynamic studies focus on delivering the chemotherapy in the most efficient way possible at the level of the tumor nodule. Concentration over time graphs is used for illustration of pharmacokinetic properties. Pharmacodynamics describe what the drug does to the body, looking at the effect the chemotherapy really has on the tumor illustrated by effect over concentration graphs. Table 1.1 summarizes the most important Pk and Pd variables characterizing pharmacology of IPC.

Table 1.1 Pharmacokinetic and pharmacodynamic variables of IPC

Pharmacokinetic variables (Pk)	Pharmacodynamic variables (Pd)
Dose	Temperature
Volume	Size residual tumor nodule
Duration	Density
Carrier solution	Binding
Pressure	Interstitial fluid pressure
Vasoactive agents	Charge
Macromolecular vehicles	Vascularity

Pharmacokinetics

Dose: BSA-Based Versus Concentration-Based

Due to the multitude of perioperative cancer therapy centers worldwide, different schedules of chemotherapeutic agents, concentrations, and doses have been developed. The current dosing regimens of IP chemotherapy can be divided into body surface area (BSA)-based and concentration-based.

Most groups use a drug dose based on calculated BSA (mg/m2) in analogy to systemic chemotherapy regimens. These regimens take BSA as a measure for the effective peritoneal contact area. However, Rubin et al. demonstrated there is an imperfect correlation between actual peritoneal surface area and calculated BSA [23]. Furthermore, females have a 10% larger peritoneal surface in relation to their body size which probably affects absorption. BSA-based IP chemotherapy will result in a fixed dose (BSA-based) diluted in varying volumes of perfusate, implicating different concentrations. From the Dedrick formula, we know that peritoneal concentration and not peritoneal dose is the driving diffusion force. The importance of this finding has been discussed by Elias et al. in a clinical investigation where 2, 4, and 6 liters of chemotherapy solution were administered with a constant dose of chemotherapy solution [24]. A more dilute IP chemotherapy concentration retarded the clearance of chemotherapy and resulted in less systemic toxicity [25]. Therefore, it can be assumed that by the diffusion model, less concentrated chemotherapy would penetrate to a lesser extent into the cancer nodules and normal tissues. To increase the accuracy of predicting systemic drug toxicity, the volume of chemotherapy solution should also be determined by the BSA, resulting in a constant chemotherapy dose as well as its concentration.

Some groups use a dosimetry regimen based on concentration. The total amount of chemotherapy is mixed in a large volume of carrier solution. This regimen offers a more predictable

exposure of the tumor nodules to the IP chemotherapy by maintaining a constant diffusional force and thus cytotoxicity. Unfortunately, this also leads to unpredictable plasma chemotherapy levels and thus toxicity [11].

Currently, there is an ongoing randomized trial evaluating the pharmacology and morbidity of both dosing methods, entitled "concentration-based versus body surface area-based perioperative intraperitoneal chemotherapy after optimal cytoreductive surgery in colorectal peritoneal carcinomatosis treatment: randomized non-blinded phase II clinical trial" (COBOX trial) NCT03028155.

Volume

Target lesions or residual microscopic malignant cells can be present anywhere on the peritoneal surface and ideally should be reached by the chemotherapy solution during HIPEC. However, not only the body composition of the patients but also the methods of HIPEC administration (open versus closed) as well as determination of the perfusate volume (chosen arbitrarily, BSA-based, standard 2, 4, or 6 l) differ greatly. As descried in the previous paragraph, administration of variable volumes until the abdomen is full, to increase the contact area, is not a recommended practice due to the risk of over- or under-dosing, leading to unpredictable systemic toxicity.

Duration

After a drug is administered intraperitoneally, tumor cell kill will increase with time of instillation until it reaches its maximum effect at a certain moment, after which prolongation of the exposure will not offer any further cytotoxic advantage. Gardner et al. mathematically modeled dose-response curves and their dependency on exposure time [26]. Since a plateau in tumor cell kill is reached at a certain time, the most advantageous exposure time for IPC should be carefully weighed against accompanying systemic toxicity. Based on this rationale and understanding, depending on the drug used, the duration of HIPEC ranges from 30 to 120 minutes. However, the duration of IPC should be pharmacology-driven and not arbitrary.

Carrier Solution

The choice of carrier solution to deliver IPC has an impact on its efficacy and toxicity. Hypotonic, isotonic, and hypertonic solutions were explored with both low and high molecular weight chemotherapy molecules. The ideal carrier solution should provide the following: enhanced exposure of the peritoneal surface, prolonged high intraperitoneal volume, slow clearance from the peritoneal cavity, and absence of adverse effects to peritoneal membranes [27]. This is especially important in the setting of EPIC where maintenance of a high dwell volume of chemotherapy solution over a prolonged time period improves the distribution of the drug and the effectiveness of the treatment [28]. Mohamed et al. showed that an isotonic high molecular weight dextrose solution would prolong the intraperitoneal retention of the artificial ascites [29]. Several in vitro and animal studies suggested a pharmacokinetic advantage of hypotonic carrier solutions in a HIPEC setting [30, 31]. Elias et al. studied the pharmacokinetics of heated oxaliplatin with increasingly hypotonic carrier solutions in colorectal PC patients [32]. They reported no significant differences in absorption and intratumoral oxaliplatin but a very high incidence of unexplained postoperative bleeding (50%) and unusually severe thrombocytopenia in patients treated with hypotonic carrier solutions. Furthermore, oxaliplatin was initially considered unstable in chloride-containing media, resulting in the use of 5% dextrose as its carrier solution. This was based on extrapolation of systemic chemotherapy data. However, exposure of the peritoneum to 5% dextrose during perfusion times varying from 30 to 90 minutes is associated with serious hyperglycemia and electrolyte disturbances, resulting in significant added postoperative morbidity and mortality. Subsequent HIPEC-specific data demonstrate no such instability [33]. Furthermore, this degradation of oxaliplatin in normal saline only accounts for

less than 10% of the total amount at 30 minutes, as when applied during HIPEC. Moreover, oxaliplatin degradation was associated with the formation of its active drug form [33, 34].

Pressure

An increase in the intraperitoneal pressure causes increase of the extracellular space in the interstitium of the peritoneum, leading to increased effective tissue diffusivity [1, 8]. This can be derived from the Dedrick et al. formula postulating that the depth of drug penetration is equal to the square root of the ratio of tissue diffusivity and the rate constant for drug removal from the tissue, together with Flessner et al. describing an increase in the extracellular space due to increased IP pressure. Several animal models have confirmed these findings of increased intratumoral accumulation and cytotoxicity of drugs like cisplatin, oxaliplatin, and doxorubicin [8, 35–37]. However, the useful application of increased intra-abdominal pressure is limited by respiratory and hemodynamic intolerance. Proponents of the closed delivery method of HIPEC use the increased pressure of administration as one of the advantages over the open/coliseum technique (apart from less heat loss and a reduced chance of safety hazards). Currently, there are two clinical applications of administering IPC at raised IP pressure, being laparoscopic HIPEC (at 12–15 mmHg) and pressurized intraperitoneal aerosol chemotherapy (PIPAC).

Vasoactive Agents

There has been a lot of interest in the use of vasoactive substances to regulate peritoneal and tumor blood flow [8, 38–43]. Vasoconstricting agents may contribute to delayed clearance of the IPC since it is known that blood flow through the (sub-)peritoneal network plays an important role in the movement of fluids and solutes across the peritoneal barrier. Duvillard et al. observed better survival in a rat model in the animals treated with IP adrenaline and cisplatin compared to those treated with cisplatin alone [44]. The safe combination of IP adrenalin and cisplatin was shown in 18 patients by Loucon-Chabrot et al [43] In addition, Facy et al. showed adrenaline to be more effective than hyperthermia in increasing intratumoral drug concentrations of cisplatin in a rat model [40]. Lidner et al. observed a pharmacokinetic advantage of adding intravenous vasopressin administration to IP carboplatin and etoposide but not to 5-FU [42]. Considering very limited clinical experience, further studies on the routine used of these agents together with IPC as an attempt to improve effectiveness are required before its routine use.

Timing of IPC Administration in Relation to the Surgical Intervention

The most commonly used method of perioperative delivery of intraperitoneal chemotherapy is hyperthermic intraperitoneal chemotherapy (HIPEC). However, the application of IPC in clinical practice can occur at four timepoints which may have some impact on its effects.

Induction or Neoadjuvant IPC

In an attempt to reduce intraperitoneal disease burden and potentially test the response to the chemotherapeutic agent, IPC can be administered before definitive surgical cytoreduction. This could theoretically facilitate the surgery or increase the likelihood of complete cytoreduction. Radiological and clinical responses to neoadjuvant intraperitoneal and systemic chemotherapy (NIPS) in gastric cancer have been reported [45–47]. Possible disadvantages may include adhesions, extensive fibrotic response to IPC, and increased morbidity at the time of cytoreduction and HIPEC due to previous direct chemotherapeutic exposure. Further studies on the effectiveness of NIPS are warranted and currently under way for colon cancer.

Intraoperative

HIPEC is the most commonly adopted method in which heated IPC is administered immediately after surgical cytoreduction. The advantage of this method is the fact that tumor load and adhesions are minimized, increasing the likelihood of even distribution and exposure to IPC.

A subtype of HIPEC is bidirectional intraperitoneal chemotherapy (BIC)administration. Elias et al. first described the supplementation of IV

chemotherapy to IP chemotherapy to improve the cytotoxic efficacy [33]. The IV chemotherapy (5-FU) is given simultaneously or immediately prior to (15, 30, or 60 minutes) HIPEC. Within approximately 20 minutes, the peritoneal fluid becomes saturated with 5-FU, known as "pharmacologic sink phenomenon." Subsequently, this drug can only leave the peritoneal space by back diffusion. Due to rapid metabolization, only occurring in the liver and gastrointestinal tract mucosa, marked differences in peritoneal and plasma concentrations appear, which makes 5-FU an ideal drug for intraperitoneal administration with limited systemic effect [48, 49].

Early Postoperative Intraperitoneal Chemotherapy (EPIC)

After CRS with or without HIPEC, four drains and one Tenckhoff catheter are left in the abdomen. During the first 3–5 postoperative days, the abdominal cavity remains free from adhesions, and thus, a normothermic chemotherapeutic infusion can be instilled directly into the peritoneal cavity as a 23-hour dwell. In the treatment of CRC and appendiceal mucinous neoplasms, 5-FU is the most commonly used agent for this purpose because of its pharmacokinetic advantages. Given its cell-cycle-dependent activity, this is an ideal drug for repeated exposure. Furthermore, it is a small molecular weight molecule that moves rapidly out of the peritoneal cavity to the plasma where it is even more quickly metabolized by an enzyme that is only present in the liver and gastrointestinal tract mucosa, thereby lowering systemic toxicity. Paclitaxel has a favorable pharmacologic profile and mechanism of action for EPIC and is used for ovarian cancer and mesothelioma [50].

Pharmacodynamics

Until fairly recently, the pharmacologic efficacy of IPC was assessed by looking at the pharmacokinetics of the IP and IV compartment [51, 52]. However, Van der Speeten et al. in 2009 demonstrated a higher intra-tumoral doxorubicin concentration that could be predicted by simple IP/IV pharmacokinetics [53]. The penetration of cytotoxic drugs into the target peritoneal tumor nodules is a complex, multistep process dependent on multiple factors.

Density of the Tumor Nodules

In 2009, Van der Speeten et al. observed that the amount of doxorubicin measured in less dense diffuse peritoneal adenomucinosis (DPAM) subtype of appendiceal mucinous neoplasms was statistically significantly lower than in the denser peritoneal mucinous carcinomatosis nodules (PMCA) despite the same exposure to intraperitoneal drug [53].

Tumor Nodule Size

Results from experiments with multicellular models have shown that direct tissue penetration of most cytotoxic agents is very limited in space, four to six cell layers in doxorubicin, 0.5 mm in 5-FU, and maximally 2–5 mm in mitomycin C [52]. IPC effectiveness will therefore be limited to tumor nodules of a very small dimension. Since human cancers are known to obey the so-called Gompertzian growth kinetics, the presence of small tumor nodules will result in an additional advantage related to the population kinetics of tumor growth. This growth kinetics implies that instead of a continuous exponential growth, a plateau is reached when nutrient and oxygen supply no longer meet demands, resulting in a decline in growth when the tumor size increases. Small tumor nodules will have the largest growth fraction, and therefore, the fractional kill by chemotherapy will be much higher than later in the course of the disease [51].

Hyperthermia

The addition of hyperthermia to IP chemotherapy has been postulated to increase its effectiveness by several mechanisms. First, a direct antitumor effect of heat due to increased cell death has been reported. Mild hyperthermia seems to be selectively cytotoxic to malignant cells due to impaired DNA repair, protein denaturation, and inhibition of oxidative metabolism in the microenvironment of malignant cells, leading to increased acidity, lysosomal activation, and increased apoptosis

[54, 55]. Second, heat seems to work synergistically with selected drugs (doxorubicin, MMC, melphalan, platinum, docetaxel, gemcitabine, irinotecan) augmenting their cytotoxic effect by inhibition of intracellular detoxification pathways, disturbing DNA repair mechanisms, and damaging ATP transporters, leading to drug accumulation [56]. Finally, hyperthermia could increase penetration of chemotherapeutic agents in normal as well as malignant tissues [57].

Multiple experimental studies have investigated the role of heating various IP chemotherapeutic agents. Piché et al. studied the effect of heat on IP-administered oxaliplatin in Sprague-Dawley rats. Besides increasing plasma concentrations of the drug proportionally to the IP-administered dose, they showed that heat not only enhanced peritoneal tissue concentration but also decreased its systemic absorption [58]. Concerning the effect of hyperthermia on IP-administered taxanes (paclitaxel and docetaxel), Muller et al. performed an in vitro study on human ovarian carcinoma cell lines but failed to observe any positive effect of heating these agents. Since other publications on heated taxanes have shown conflicting results, more studies on this matter are required [59]. The same lack of evidence exists for heating of IP mitomycin C. Klaver et al. randomly performed CRS, CRS/HIPEC, CRS with normothermic chemotherapy, and CRS with heated saline on WAG/Rij rats. They demonstrated the effectiveness of IP chemotherapy administration (normo- or hyperthermic) but failed to show any beneficial effect of hyperthermia [60]. However, hyperthermia exceeding 42 °C has been demonstrated to have a direct cytotoxic effect on normal as well as tumor cells [61, 62]. Sorensen drew the same conclusion after investigating the difference between normothermic and hyperthermic IP MMC administration in a rat model [63]. Further research in this area is mandatory before omitting this part of the procedure. However, since hyperthermia can be a logistic reason complicating widespread use of IP chemotherapy in many parts of the world, the suggested increased cytotoxicity of adding hyperthermia to IP chemotherapy observed by basic science needs urgent validation in clinical trials.

Drug Resistance

For chemotherapeutic agents to effectively kill malignant cells, the agents must first reach the target. The inability of the drug to reach the target is a basic mechanism of drug resistance that affects both intravenously and intraperitoneally administered agents. For targets on the peritoneal surface, IP administration allows dose intensification providing high concentrations of therapeutic agent right at the level of the tumor providing a better opportunity to reach the target.

However, as previously discussed, the high concentration of drug at the peritoneal surface and the AUC ratio itself may not directly translate into increased penetration to the tumor cellular level, and therefore, analysis specific to the tumor tissue itself is needed. This was emphasized in the following experiment: when comparing the AUC plasma, peritoneum, and tumor nodule curves for different chemotherapeutic agents used in the treatment of peritoneal carcinomatosis, differences in drug concentration within the tumor nodules of doxorubicin, cisplatin, or melphalan were observed despite the same peritoneal AUC curve (Fig. 1.1). Furthermore, Van der Speeten et al. observed a higher intra-tumoral doxorubicin concentration than could be predicted by simple IP/IV pharmacokinetics [53] (Fig. 1.2).

Another reason to use the tumor nodule as the pharmacological endpoint is provided by the finding of Van der Speeten et al. in their analysis (HPLC plasma, urine, and peritoneal fluid) of 145 peritoneal carcinomatosis patients treated with mitomycin C [5]. Mitomycin C is not a prodrug but is modified to its active state after entering the tumor cell. In 6 of these 145 patients (4%), the HPLC chromatogram showed no evidence of mitomycin C metabolites, suggesting that MMC was not metabolized in these patients. The patients had the same clinical and surgical factors as the other 139 patients, and until now, there is no known genetic or metabolic reason for this phenomenon. This might be an example of absolute drug resistance.

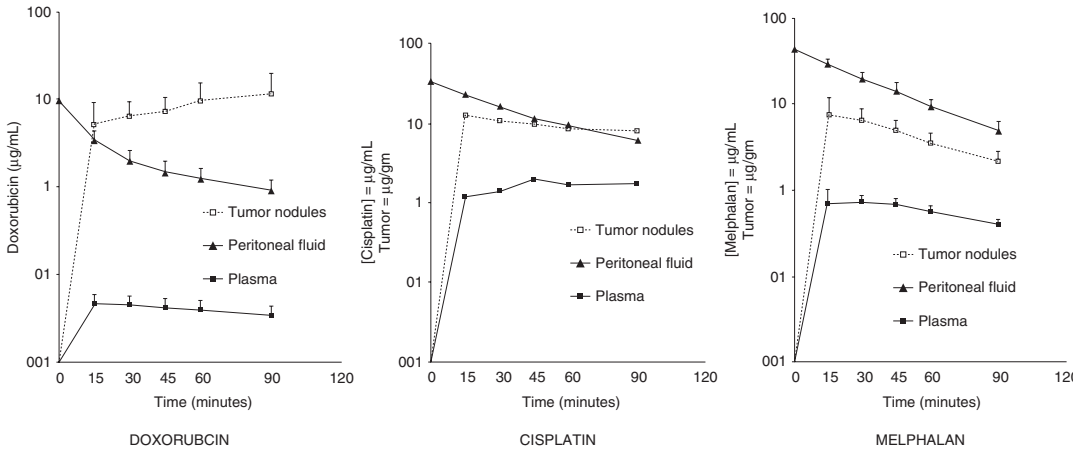

Fig. 1.1 Comparison of AUC of different IPC drugs

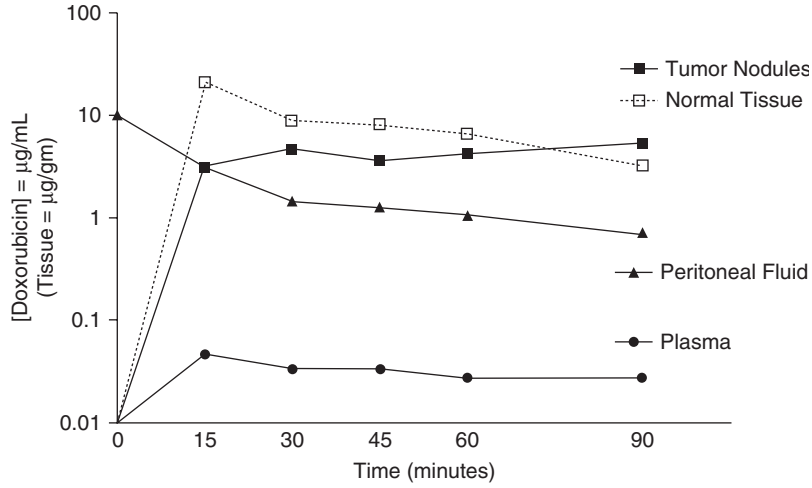

Fig. 1.2 Doxorubicin concentrations in plasma, peritoneal fluid, tumor nodules, and normal adjacent tissue in one patient

How to Select the Right IP Drug

Traditionally, the selection of drugs for intraperitoneal administrations has been based on beneficial pharmacokinetic and pharmacodynamic parameters, a good tolerance profile, and proven effectiveness with systemic administration as described in the previous paragraphs. However, the value of these parameters to predict what level of drug will be reached at the tumor cell level is likely limited. Furthermore, a more specific and personalized analysis of potential chemosensitivity aiming at increased effectiveness and limited toxicity will be needed in the future.

Individualized and Targeted Therapy

In Vitro: Chemosensitivity Testing

Chemosensitivity testing is an ex vivo way to determine the effect (endpoint can be cytotoxic-, cytostatic-, or apoptosis-inducing) of anticancer drugs on survival of cancer cells [64]. The clinical utility of chemosensitivity analysis for selecting a "personalized" HIPEC regimen is largely unknown. In 2013, the University of Uppsala demonstrated that the variability in ex vivo drug sensitivity in the CRC subgroup was large, rang-

ing from virtually no to total cell death [65]. In 2014, they showed in vitro drug sensitivity testing on samples obtained preoperatively to be clinically relevant in epithelial ovarian cancer. Furthermore, they used ex vivo drug sensitivity testing on samples obtained during CRS and HIPEC for patients with pseudomyxoma peritonei, showing a possible impact of IPC on PFS but not OS [66].

3D Culture

In vivo treatment response reflects not only properties intrinsic to the target individual malignant cells but also cell-to-cell interactions and extracellular components. For this reason, preserved 3D tumor-stroma structures from biopsy fragments may provide a more accurate model to predict treatment effect [67]. However, numerous limitations to this approach also exist: the influence of tumor resection, transport, and processing of cells for culture (either by mechanical or by enzymatic degradation) disturb the tissue, the ECM surrounding tumor cells is destroyed, and selective growth of subpopulations of cells may occur. In vitro growth rate usually is much faster than in vivo, leading to potential overestimation of chemosensitivity.

In Vivo: Tumor-Bearing Animal Models

The mouse (athymic, severe combined immunodeficient, or triple deficient) is a commonly used tumor-bearing model [64]. Human tumors can be grown subcutaneously as xenografts, and its growth can be studied by size measurements to construct growth curves and assess changes induced by treatment by various chemotherapy agents. Unfortunately, the correlation to treatment effects observed in patients has been variable, limiting the utility of this approach in clinical practice.

Molecular Basis of Chemosensitivity and Resistance

The current "one-treatment-fits-all" approach to chemotherapy treatment regimens, either systemic or locoregional, does not take any tumor nor patient-related variability into consideration which likely has a large impact on the cost-effectiveness. Studies to understand the molecular basis of drug effectiveness/resistance at the gene as well as the protein level have been crucial in the push for developing targeted therapies. It is important to point out that molecularly based drug resistance can exist at the onset of disease or be acquired after exposure to chemotherapy by developing escape mechanisms. In addition, tumors are known to be genetically dynamic, acquiring more genetic alterations as they evolve, leading to potential differences in chemosensitivity between the primary tumor and the metastases, explaining at least in part the phenomenon of heterogeneous response to treatment [68]. Two molecular approaches to studying prediction of treatment effect are currently used [69]:

Genomic Approach

Gene expression arrays have highlighted the great heterogeneity among cells with histologically similar appearance [70, 71]. Pharmacogenomics aim to accurately predict a patient's response to a drug in order to individualize treatment by focusing on genes that influence drug metabolism [72].

Cancer genomics refers to analysis of the cancer genome to identify specific genetic loci that are recurrently altered in specific cancer types. While many mutations have been shown to correlate with prognosis, a few examples of signatures that have also been predictive of outcomes with treatment exist [73].

For some drugs, chemosensitivity might be governed by mechanisms that are not readily revealed at the transcriptional level, such as posttranscriptional regulation, posttranslational

modification, proteasome function, or protein-protein interactions. In these cases, a proteomic approach could increase the predictive accuracy [72].

Proteomic Approach

In this analysis, protein markers are used for prediction of response to anticancer drugs which are more likely to reflect epigenetic influences as well as gene polymorphism. Addition of these studies (to genomic) will further facilitate the ability to a priori differentiate sensitive from resistant tumors. Simple IHC analysis of paraffin-embedded tissue can be used such as determination of MSI status in colorectal cancer and its association with response to immunotherapy.

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2 Novel Biological Therapies with Direct Application to the Peritoneal Cavity

Ulrich M. Lauer, Can Yurttas, and Julia Beil

Peritoneal Carcinomatosis: Background and Current Treatment Options

Peritoneal carcinomatosis (PC) is a rare type of cancer that occurs in the peritoneum, a thin layer of tissue that covers abdominal organs and surrounds the abdominal cavity. Several gastrointestinal and gynecological malignancies and also primary peritoneal malignancies have the potential to disseminate and grow in the peritoneal cavity, a condition which is often associated with disease progression, severe abdominal symptoms, and poor prognosis.

Despite overall improvements in the therapy of metastatic cancer, treating patients with PC has remained a significant challenge [1]. For decades, PC patients were treated with intravenous (i.v.) chemotherapy and/or cytoreductive surgery, a potentially curative procedure performed to remove all visible tumors from the abdomen. Conversely, systemic chemotherapy has shown only limited efficacy and traditionally has been regarded as palliative therapy [2].

Over the last two decades, surgical oncologists have made breakthroughs in treating PC with a combination of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) which now has become the gold standard for many cases of PC [3–6]. This combination of surgical resection of peritoneal metastases and subsequent intraperitoneal (i.p.) chemotherapy has been recognized to extend patients' life span and to improve their quality of life significantly [7–9]. Beyond that, i.p. chemotherapy was modified recently by developing the novel procedure of pressurized intraperitoneal aerosol chemotherapy (PIPAC), which constitutes a promising direction toward a minimally invasive, safe, and optimized regional drug delivery [10–13]. These methods were improved through multicenter studies and clinical trials yielding important insights and solutions.

With regard to symptom control, the trifunctional antibody catumaxomab has been approved for treatment of malignant ascites in patients with PC originating from gastrointestinal carcinomas [14–16]. Catumaxomab, however, is highly immunogenic due to its high mouse content and therefore only can be used in a single treatment cycle, which severely limits its clinical application

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Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_2

[14]. However, catumaxomab was voluntarily withdrawn from the US market in 2013 and from the EU market in 2017 for commercial reasons.

In this context, there is an urgent need for new treatment options in the field of PC, which will help to improve the previously limited success in the palliation of these cancer manifestations and, in addition, open up potential new curative perspectives.

Alternatives for the Treatment of Peritoneal Carcinomatosis

Regional Drug Delivery

Over recent decades, multiple therapeutic approaches have been explored for the improved management of peritoneal carcinomatosis. Particularly, the i.p. route of administration can be used to achieve elevated local concentrations and extended half-life of drugs in the peritoneal cavity to improve their anticancer efficacy. However, i.p. administered chemotherapeutics have a short residence time in the peritoneal space and usually are not tumor selective. The ideal drug for i.p. administration should remain active in the peritoneal cavity for a prolonged period of time to avoid any systemic absorption and thereby systemic toxicity. In addition, such drugs should be selective in targeting the tumor cells growing on the peritoneal lining with deep penetration into tumor nodules [17]. So far, most HIPEC and PIPAC procedures are using i.v. formulations of conventional chemotherapeutic agents. However, major method development has been made lately through nanomedicine, specifically nanoparticles.

Recent progress in nanotechnology has shown that nanoparticles (structures smaller than 100 nm in at least one dimension) have a great potential as drug carriers. Due to their small sizes, the nanostructures exhibit unique physicochemical and biological properties (e.g., an enhanced reactive area as well as the ability to cross cell and tissue barriers) that make them favorable delivery tools for currently available bioactive compounds [18]. In detail, nanostructures including liposomes, polymers, dendrimers, silicon or carbon materials, and magnetic nanoparticles have been tested already as carriers in drug delivery systems [19]. Cell-specific targeting can be accomplished by designing carriers with various forms of drug attachment.

With regard to the treatment of PC, a multitude of nanocarrier conjugates, e.g., with chemotherapeutics, immunotherapeutic agents, tumor-homing peptides, and antibodies, are currently under investigation in preclinical as well as in clinical studies.

One important example is Abraxane®, a nanoparticle albumin-bound paclitaxel (nab-paclitaxel), which is already approved for i.v. treatment of metastatic breast cancer and locally advanced or metastatic non-small cell lung cancer and indicated for first-line treatment of patients with metastatic adenocarcinoma of the pancreas [20–22]. Abraxane® has been demonstrated to be superior to an equitoxic dose of standard paclitaxel with a significantly lower incidence of toxicities which is why this albumin-stabilized nanoparticle formulation is also being studied in the treatment of other types of cancer, e.g., peritoneal carcinomatosis.

Currently, clinical studies are evaluating the use of i.p. administration of nanocarrier conjugates alone, without induction of hyperthermic conditions. For example, in a phase I trial, the side effects and best dosing of i.p. paclitaxel albumin-stabilized nanoparticle formulation (Abraxane®) in treating patients with advanced cancer of the peritoneal cavity are investigated (NCT00825201). In addition, a further phase I study evaluated the safety, tolerability, pharmacokinetics, and preliminary tumor response of a nanoparticle formulation of paclitaxel called Nanotax® which is prepared by a special continuous supercritical fluid process and which is administered i.p. for multiple treatment cycles in patients with solid tumors predominantly confined to the peritoneal cavity (NCT00666991). Data of this study support the assumption that compared to i.v. paclitaxel administration, i.p. administration of Nanotax® provides higher and prolonged peritoneal paclitaxel levels with minimal systemic exposure and reduced toxicity [23].

Looking to the future, the combination of nanotherapy with hyperthermic intraperitoneal and/or pressurized intraperitoneal aerosol chemotherapy potentially further enhances cancer treatment and represents an important step in the evolution of PC treatment [24]. With this perspective, the PIPAC nab-pac study, which currently is recruiting patients (NCT03304210), is designed to examine the maximum tolerated dose of albumin-bound nanoparticle paclitaxel (nab-pac, Abraxane®) administered with repeated pressurized i.p. aerosol chemotherapy (PIPAC) to patients with PC, in a multicenter, multinational phase I trial.

Biological Cancer Therapies: Immunotherapy

In general, biological therapies involve the use of living organisms, substances derived from living organisms, or laboratory-produced versions of such substances to treat all kinds of diseases. More specifically, biological therapies for cancer are used in the treatment of many tumor types to prevent or slow tumor growth and to also prevent the spreading of malignant cells. Notably, biological cancer therapies often cause fewer toxic side effects than other, e.g., chemotherapeutic, regimes, because they often are nongenotoxic in nature, but "only" aim at a stimulation of the body's immune system to act against cancer cells. Mostly, this approach is tolerated quite well, even in advanced stages of malignancies. However, these types of biological therapies do not target cancer cells directly. In contrast, other biological therapies, such as antibodies, do target cancer cells directly and the immune system "only" becomes activated consecutively. All of these biological cancer therapies with involvement of the immune system are collectively referred to as immunotherapy.

Intraperitoneal immunotherapy represents a novel strategy for the management of PC. From Coley's toxins to immune checkpoint inhibitors (ICIs), the wide variety of anticancer immunotherapeutic strategies is now garnering attention for the control of regional diseases of the peritoneal cavity. A multitude of early clinical studies with immune-modulating agents, monoclonal antibodies (mAb), and immune checkpoint inhibitors (ICIs) are being performed, showing promise for the control of peritoneal spreading and induction of long-lasting anticancer immunities (Table 2.1).

As an example of immune-modulating agents, IMP321 should be mentioned. IMP321 is a soluble version of the immune checkpoint molecule LAG3 and a highly potent activator of antigen-presenting cells [25]. Up to now, IMP321 is solely administered subcutaneously, and the main indication for the drug is metastatic breast cancer. In a phase I trial, the potential enhancement of IMP321 immune-activating effects by new routes of administration is investigated. Among other application routes, the investigators will explore if an i.p. therapy represents a feasible alternative by means of delivering high drug concentrations directly to tumors located in the peritoneal cavity (NCT03252938).

The use of mAb in cancer therapy is based on the idea of selectively targeting tumor cells that express tumor-associated antigens. The first cancer patient who was treated with mAb had been a patient with non-Hodgkin's lymphoma [26]. Since then, considerable progress has been made in this area. Various mAb against cancer-associated antigens have been investigated in preclinical and clinical studies, and mAb have become one of the biggest classes of new drugs approved for the treatment of cancer. Furthermore, the already approved mAb bevacizumab (Avastin®) and cetuximab (Erbitux®) are now intensively examined in several clinical trials with the focus on treatment of PC either as monotherapy or in combination with chemotherapies. For instance, in a phase I study, the drug combination of i.p. oxaliplatin and paclitaxel plus i.v. paclitaxel and bevacizumab is investigated in patients with advanced PC (NCT00491855). In this toxicity trial, the maximum tolerated doses of i.p. oxaliplatin and i.p. paclitaxel were defined, and stable disease could be observed in 7 (58%) out of 12 patients after 2 months [27].

Therapies with immune checkpoint inhibitors (ICIs) represent currently the most promising

Table 2.1 Trials of intraperitoneal immunotherapies[a]

Immunotherapy	Clinical study	Conditions	Treatment strategy	NCT number
Immune-modulating agent	Phase I	Solid tumors involving the peritoneum	Immunotherapy with IMP321—testing different routes of administration (including i.p.)	NCT03252938
Immune-modulating agent + neoadjuvant chemotherapy	Phase II	Metastatic gastric cancer	Immunotherapy with interleukin-2 (i.p.) + chemotherapy with cisplatin +5-FU	NCT02976142
Immune-modulating agent + neoadjuvant chemotherapy	Phase I/II	Recurrent ovarian cancer	Chemoimmunotherapy with cisplatin and rintatolimod (i.v.) + immunotherapy with pembrolizumab	NCT03734692
Immune-modulating agent	Phase I/II	Colorectal neoplasms	Immunotherapy with immunotoxin MOC31PE (i.p.)	NCT02219893
Immune-modulating agent + tumor-specific DC-vaccine + neoadjuvant chemotherapy	Phase I/II	Recurrent ovarian cancer	Chemoimmunotherapy with cisplatin and tumor-specific DC-vaccines +/− drug combination: Rintatolimod (i.p.), IFN alpha-2b (i.p.), celecoxib (p.o.)	NCT02432378
Radiolabeled monoclonal antibody + chemotherapy	Phase I	Primary peritoneal cancer; ovarian cancer	Radioimmunotherapy with lutetium LU 177 mAb CC-49177 (LU-CC49) or yttrium Y 90 mab CC49 (90Y-CC49) (i.p.) + IFN alpha-2b (s.c.) + chemotherapy with paclitaxel or topotecan	NCT00002734
Radiolabeled antibody	Phase I	Desmoplastic small round cell tumors (DSCRT); solid tumors involving the peritoneum	Radioimmunotherapy with 131I-8H9 (i.p.)	NCT01099644
Activated monocytes	Phase I	Recurrent or refractory ovarian cancer; fallopian tube cancer; primary peritoneal cancer	Immunotherapy with autologous monocytes (i.p.) + peg-IFN alpha-2b (i.p.) + IFN gamma-1b (i.p.)	NCT02948426
CAR-T cells	Phase I	CEA-expressing adenocarcinoma with peritoneal metastases or malignant ascites	Immunotherapy with anti-CEA CAR-T cells (i.p.)	NCT03682744
CAR-T cells	Phase I	Advanced gastric cancer with peritoneal metastasis	Immunotherapy with anti-EpCAM CAR-T cells (i.p.)	NCT03563326
Immune checkpoint inhibitor	Phase I	Peritoneal carcinomatosis; gynecologic cancers	Immunotherapy with nivolumab +/− ipilimumab (i.p.)	NCT03508570

[a]Selection of studies does not claim to be complete

approaches in cancer and are in the focus of a multitude of preclinical and clinical developments. In order to understand how ICIs develop their effectiveness, one must first take a closer look at the complex oncoimmunological mechanisms. Tumor cells in a solid tumor are embedded in the tumor stroma together with microvasculature and immune cells. The immune cell component consists on the one hand of a mixture of cell types that suppress the immune activity against the tumor and on the other hand of cytotoxic T lymphocytes that may attack tumor cells. Immune checkpoint proteins such as the cytotoxic T-lymphocyte-associated-4 protein

(CTLA-4) and the programmed cell death protein 1 (PD-1) constitute receptors which are expressed on the surface of cytotoxic T lymphocytes that interact with their ligands, e.g., programmed death ligand-1 (PD-L1) on antigen-presenting cells (APCs), which helps the cancer cell to evade T-cell-mediated cell death. Immune checkpoint inhibitors prevent the receptors and ligands from binding to each other, thereby disrupting the immune signaling; in this way, ICIs release the "brakes" of the immune system, and T lymphocytes are now capable to kill cancer cells [28–30]. Ipilimumab (anti-CTLA-4), nivolumab (anti-PD-1), and pembrolizumab (anti-PD-1) are modulating ICI drugs which are already approved for i.v. injection as single-agent therapy or in combination with other therapeutic interventions for many different immunogenic tumor entities, such as malignant melanoma, metastatic non-small cell lung cancer (NSCLC), renal cell carcinoma, and many others [31]. To investigate the safety and efficacy of these ICIs for i.p. application, currently a phase I study is initiated where a combination of ipilimumab and nivolumab is given by an i.p. infusion to patients with recurrent or high-grade gynecological cancers with metastatic PC (NCT03508570).

The field of cancer immunotherapy is tremendously manifold and, step by step, new therapeutic modalities are being developed and validated in a large number of clinical studies. Nonetheless, every modality has its hurdles and limitations to overcome. On the one hand, this can be achieved through intelligent combination strategies with already approved cancer therapies, but on the other hand, it still remains necessary to develop novel drugs that overcome these hurdles or circumvent them, possibly through a diverse mechanism of action.

Novel Biological Cancer Therapies: Oncolytic Virotherapy

Promising candidates of novel biological therapeutics are oncolytic viruses. The idea of using viruses for the treatment of cancer is based on observations made in the early nineteenth century, which—in individual cases—documented a regression of tumors, in parallel with a natural viral infection that occurred coincidentally in cancer patients at the same time [32]. However, due to the often severe pathogenicity of naturally occurring viruses and their associated toxicities, early therapeutic trials on cancer patients with such naturally occurring viruses, only being at hand at these times, had to be quickly halted. Only emerging developments in the field of genetic engineering and molecular virology, which now allow targeted modification and thereby on the one hand attenuation of viral properties in terms of their safety and on the other hand improvement of antitumoral efficiency, brought virotherapy back to the track [32].

In the course of their ongoing transformation process, tumor cells inevitably must accumulate mutations that prevent them from detection and control by the immune system by making them in a way "invisible" to immune cells. In contrast to healthy, nonmutated body cells, this characteristic of tumor cells "unintentionally" also creates the best conditions for an unrestrained replication of oncolytic viruses, thus leading to exhaustion of virus hosting tumor cells and thereby to a subsequent massive oncolysis [33]. For example, mutations in the interferon (IFN) signaling pathway of tumor cells lead to a significant attenuation of the antitumoral immune response. However, this IFN deficiency likewise abrogates the antiviral defense mechanisms in tumor cells [34]. Furthermore, the overexpression of virus receptors on cancer cells (e.g., the CD46 receptor for measles vaccine viruses) can also play an important role in the natural and therefore inherent tumor selectivity of oncolytic viruses [33].

There are now a variety of ways to genetically modify oncolytic viruses and thus further increase their selectivity toward tumor cells and also their oncolytic efficiency [35]. A prime example of this is the genetically modified herpes simplex virus T-VEC, which encodes and expresses the human granulocyte macrophage colony-stimulating factor (GM-CSF). Based on a successful phase III study, T-VEC was approved in 2015 as the world's first viral drug (Imlygic®) in the USA and Europe for a virus-based

immunotherapy of patients with unresectable, locally, or distant metastatic melanoma [36].

The antitumoral effect of oncolytic viruses is mediated via a direct as well as an indirect mechanism. Once an oncolytic virus infects a tumor cell, it usually takes complete command of the transcription and translation machinery of the tumor cell, with the sole aim of producing the largest possible number of progeny virus particles. If the cellular viral load is too large, it will lead to a metabolic break down and subsequent oncolysis and as a result to a massive release of newly formed infectious virus particles. At the same time, tumor cell bursting also releases (i) tumor cell-associated antigens, (ii) viral antigens, and (iii) a variety of inflammatory factors, a process called "immunogenic cell death (ICD)" [37]. While the released virus particles in turn infect new hitherto uninfected neighboring tumor cells, a tumor antigen-specific immune response is triggered in the inflammatory tumor micromilieu, which subsequently mediates a targeted destruction of the remaining uninfected tumor cells throughout the body [38]. Thus, virotherapeutics can be considered as biological adjuvants that can enhance a hitherto insufficient antitumoral immune response ("converting cold tumors into hot tumors"), resulting in a sustainable T-cell-mediated systemic tumor therapy.

More than ten different types of oncolytic viruses are currently being developed into clinically useful viral therapeutics with adenoviruses (AD), reoviruses (REO), Newcastle disease viruses (NDV), herpes simplex viruses (HSV), vaccinia viruses (VACV), and measles vaccine viruses (MV) among the best studied [35, 39, 40].

Oncolytic Virotherapy in Peritoneal Carcinomatosis

Oncolytic virotherapy is a very promising treatment concept for the treatment of PC. Because of their (i) inherently high levels of tumor selectivity, (ii) their direct cytolytic potency, and (iii) their strong immunostimulatory effects, oncolytic viruses represent an optimal system for attacking tumor nodules in the abdomen, especially after direct i.p. application. Several oncolytic viruses are currently under investigation in clinical trials regarding their potency in PC (Table 2.2).

For example, two different Edmonston vaccine strains of measles virus (MV) were tested in phase I trials in patients with recurrent ovarian cancer. MV-CEA [41] (MV engineered to express carcinoembryonic antigen (CEA)) and MV-NIS [42] (MV engineered to express the sodium iodide symporter gene (NIS)) were both administered i.p. every 4 weeks for up to six cycles. In both studies, MV treatment was well tolerated and associated with promising median overall survival rates in patients with heavily pretreated ovarian cancer. Furthermore, no dose-limiting toxicities were observed. In addition, immune monitoring posttreatment with MV-NIS showed an increase in effector T cells recognizing tumor antigens, suggesting that an immune mechanism might be responsible for the observed antitumor effects [42].

In another phase I/II combined clinical trial, the safety and tolerability of i.v. and i.p. administration of wild-type reovirus (REOLYSIN®) are determined in patients with metastatic ovarian epithelial cancer, primary peritoneal cancer, or fallopian tube cancer (NCT00602277). In this study, patients receive reovirus i.v. over 60 minutes on days 1–5 in course 1, followed by insertion of an i.p. access port. Beginning in course 2, patients receive reovirus i.v. over 60 minutes on days 1–5 and reovirus i.p. over 10 minutes on days 1 and 2. Treatment over both application routes repeats every 28 days in the absence of disease progression or unacceptable toxicities. Thus far, the study has concluded that there is evidence of a selective reovirus penetration in peritoneal tumors and no dose-limiting toxicities (DLTs) have been observed up to now [43].

Oncolytic vaccinia virus (VACV) represents another promising virus strain for the treatment of peritoneal carcinomatosis. In a recent phase I clinical study, GL-ONC1, a GMP-grade preparation of oncolytic VACV GLV-1 h68 [44], was first tested in nine patients with advanced-stage PC or advanced peritoneal mesothelioma. Virotherapeutic treatment was performed by direct i.p. infusion of GL-ONC1 via an indwelling catheter every 4 weeks for up to four cycles at three different dose

Table 2.2 Trials of intraperitoneal viral therapies[a]

Oncolytic virotherapy	Clinical study	Conditions	Treatment strategy	NCT number
GL-ONC1 (vaccinia virus)	Phase I/II	Recurrent or refractory ovarian cancer; peritoneal carcinomatosis	i.p. virotherapy with GL-ONC alone or in combination with chemotherapy +/− bevacizumab	NCT02759588
GL-ONC1 (vaccinia virus)	Phase I	Peritoneal carcinomatosis	i.p. virotherapy with GL-ONC1	NCT01443260
Talimogene laherparepvec (T-VEC) (herpes simplex virus)	Phase I	Peritoneal surface dissemination from gastrointestinal or recurrent, platinum-resistant ovarian cancer	i.p. virotherapy with T-VEC after prior vaccination	NCT03663712
MV-CEA; MV-NIS (measles vaccine virus)	Phase I	Progressive, recurrent, or refractory ovarian epithelial cancer; primary peritoneal cancer	i.p. virotherapy with MV-CEA or MV-NIS	NCT00408590
MV-NIS (measles vaccine virus)	Phase II	Ovarian, fallopian, or peritoneal cancer	i.p. virotherapy with MV-NIS vs. investigator's choice chemotherapy	NCT02364713
MV-NIS-infected mesenchymal stem cells (measles vaccine virus)	Phase I/II	Recurrent ovarian cancer; primary peritoneal cancer	i.p. virotherapy of MV-NIS + MV-NIS-infected mesenchymal stem cells	NCT02068794
REOLYSIN® (wild-type reovirus)	Phase I	Recurrent ovarian cancer; fallopian tube cancer; primary peritoneal cancer	Virotherapy with i.v. REOLYSIN® + i.p. REOLYSIN®	NCT00602277
Ad5-Delta 24RGD (adenovirus)	Phase I	Recurrent ovarian cancer; primary peritoneal cancer	i.p. virotherapy with Ad5-Delta 24RGD	NCT00562003

[a]Selection of studies does not claim to be complete

levels (10^7, 10^8, and 10^9 infectious viral particles). The indwelling catheter was also used for repetitive analyses of "liquid biopsies" by obtaining peritoneal fluids in a scheduled manner. Results of this study were published recently [45]. In short, i.p. administration of the virotherapeutic GL-ONC1 was well tolerated by all patients and adverse events were limited to grades 1–3, including transient flu-like symptoms and increased abdominal pain, resulting from treatment-induced viral peritonitis. No DLT was reported, and a maximum tolerated dose (MTD) was not reached. Furthermore, no signs of viral shedding were observed. Importantly, in eight out of nine study patients, effective i.p. infections, in-patient replication of GL-ONC1, as well as subsequent oncolysis were demonstrated in treatment cycle 1. All patients developed neutralizing antiviral activities against GL-ONC1 [45]. On the basis of these findings, an ongoing phase Ib/II study was initiated at Florida Hospital Cancer Institute and at Gynecologic Oncology Associates (Newport Beach, CA), where GL-ONC1 is now administered i.p. by multiple dosages, specifically in patients with PC originating from ovarian cancer (NCT02759588).

Future Perspectives with Oncolytic Viruses: Combination Therapies

As with other cancer therapies, oncolytic viruses have also revealed various hurdles and limitations in clinical trials that must be overcome in order to achieve a successful and sustained immunovirotherapy and consequently to get diverse viral therapeutics in a wide range of tumor indications clinically approved in the future. One hurdle, for example, is the early elimination of viral therapeutics by preexisting (e.g., after vaccination in early childhood) or by virus-specific antibodies (being generated directly after the first virotherapeutic application)

and by antiviral T cells [46]. In addition, there is increasing evidence that oncolytic viruses also can be largely inactivated by components of the complement system or by unspecific hemagglutination [47].

To date, there are many efforts to find or construct the "ideal" oncolytic virus, which overcomes all these hurdles known to date. However, it must be assumed that monotherapy with oncolytic viruses is most likely insufficient to adequately break through the sophisticated defense strategies of the diverse tumor types as well as of the immunosuppressive components of the immune systems of the respective tumor patients.

Therefore, a more recent approach is to combine virotherapy with well-established standard therapies such as chemotherapy, radiation, and the new antibody-based immunotherapies. Obvious advantages of such combinations are the already well-documented tolerability and the established administration routes of these combination partners. In addition, cross-resistances with the completely different biological principles of virotherapy can be largely excluded [48].

The combined use of virotherapy with immune checkpoint inhibitors is currently the most promising combination therapy in cancer treatment. First clinical data demonstrate that oncolytic viruses can break primary resistance of tumor cells to ICI antibody therapy, thereby helping to significantly enhance their antitumor efficacy even in primary ICI therapy failures. This is assumed by a shift in the quantitative and qualitative profile of tumor-infiltrating lymphocytes as well as by the induction of a sustained antitumoral T-cell response [49]. As a highly promising example, in a recently published phase Ib study, the viral drug T-VEC (Imlygic®) was administered intratumorally in combination with the i.v. administered anti-PD-1 ICI antibody pembrolizumab in patients with metastatic melanoma. An overall response rate of 62% was found for this combination of "Viro-ICI therapy," and one third of the combinatorial treated cancer patients showed a complete response. This response rate is significantly higher than what would have been expected for any monotherapy with ICI in this tumor indication (~35–40%) [50].

With regard to the treatment of PC, further clinical trials, investigating the combinatorial strategy of "Viro-ICI therapy," are urgently needed. Furthermore, it has to be investigated whether the combination of "Viro-ICI therapy" with previous cytoreductive surgery will have an additional positive effect on therapeutic efficacy in patients suffering from PC.

Summary and Conclusions

Peritoneal carcinomatosis is common in advanced tumor stages or disease recurrence of many tumor types. Since existing therapies are mostly ineffective, new therapeutic approaches are needed. One major lesson learned from current studies employing novel biological approaches, such as oncolytic virotherapy being applied directly to the peritoneal cavity, is that these should intervene early enough, preferably already in first- or second-line settings and going along with quite low tumor burdens, in order to provide enough time for a full execution of their profound antitumoral potencies. Beyond that, also adjuvant virotherapeutic interventions seem to be conceivable for PC patients subsequent to aggressive tumor mass reductions achieved by cytoreductive surgery plus HIPEC chemotherapy, meeting the requirement of low to very low tumor masses at the time point of virotherapeutic intervention.

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3 Y-90 Radiomicrosphere Therapy: Principles and Clinical Use in Colorectal Cancer Liver Metastases

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Principles of Y-90 Radiomicrosphere Therapy

Y-90 RMT refers to intrahepatic arterial administration of Y-90 radiomicrospheres. Yittrium-90 (Y-90) is a high-energy beta particle-radiating radioisotope. It is incorporated in biocompatible microspheres measuring 30–40 microns. The intellectual basis of Y-90 radiomicrosphere treatment is the preferential distribution of microspheres, when injected hepatic arterially, yielding much higher concentrations in the tumor compartment than the normal liver parenchyma. This selectivity is due to the fact that the tumor blood supply is overwhelmingly derived from the hepatic artery, since the neovasculature of angiogenesis is rooted from the hepatic artery branches. Intrahepatic arterially administered Y-90 microspheres are entrapped in the microvasculature and release beta radiation (energy maximum, 2.27 MeV; mean, 0.9367 MeV) with an average penetration range of 2.5 mm and a maximum range of 11 mm in tissue. Y-90 has a physical half-life of 64.2 hours (2.67 days). In therapeutic use, 94% of the radiation is delivered over 11 days. The high tumor-to-liver concentration ratio of Y-90 radiomicrospheres results in an effective tumoricidal radiation-absorbed dose while limiting the radiation injury to the normal liver. Within the atumoral liver parenchyma, the microsphere distribution is confined to the portal tracts. Because of this unique localization pattern of the microspheres, even though the maximum range of β-particles in the liver is approximately 11 mm (5–10 times the lobule width), a significant fraction of absorbed dose is delivered within the portal tract domain. This dose absorption pattern explains the difference between the external beam RT-associated RILD and RMT-associated RMILD, in favor of the latter. A radial dose function analysis and spherical Monte Carlo modeling demonstrated a rapid fall in the absorbed dose within a short distance from the microsphere in a lobular Monte Carlo lattice geometry model [1] (Fig. 3.1).

The first report of Y-90 microsphere treatment in patients with colorectal cancer liver metastases (CRCLM) was published in 1964 by Ariel, a New York surgeon who was among the first to use radioisotopic techniques in clinical diagnostics and therapy [1]. Ceramic or resin Y-90 microspheres were injected in the aorta at the level of the celiac axis using transfemoral catheter access or in the hepatic artery via retrograde catheterization of the gastroepiploic artery using direct surgical access. Selective internal radiation treatment given with concomitant chemotherapy resulted in better objective and subjective response rates than either treatment alone. The Ariel group later

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Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_3

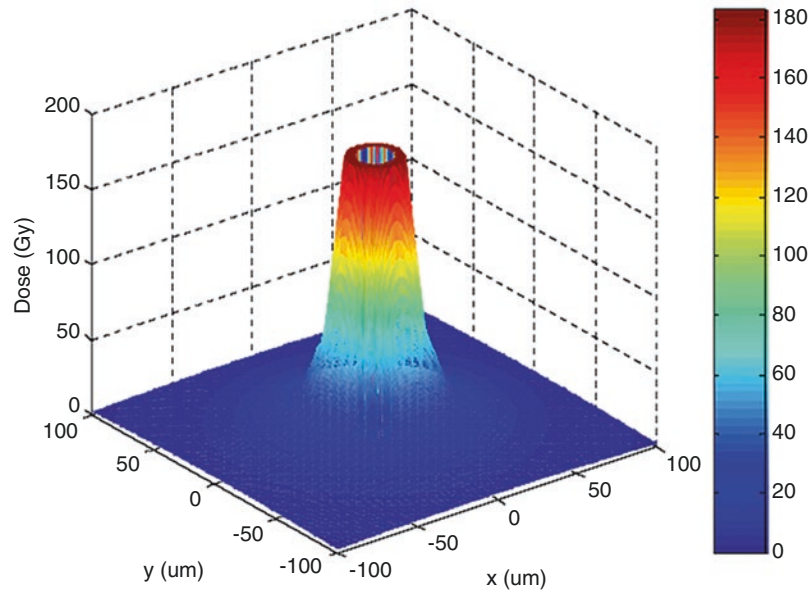

Fig. 3.1 Hepatic structural dosimetry in Y-90 microsphere treatment: dose distribution using a Monte Carlo modeling approach based on lobular microanatomy

published two subsequent studies reporting combined use of SIRT with 5-fluorouracil (5-FU) in symptomatic and asymptomatic patients with CRCLM. The mean administered activity in these studies was 3.7 GBq, which was well tolerated by the liver. Chemo-SIRT tripled the life span of patients with asymptomatic metastases to an average of 28 months compared with the historic control [2].

The second stage in the development of Y-90 microsphere technology involves systematic experimental studies designed by Gray et al. exploring the intrahepatic and intratumoral distribution kinetics of different sizes and concentrations of microspheres. Animal studies demonstrated that the concentration of arterially administered microspheres with diameters of 15–35 μm in tumor tissue was three times that of the ambient normal liver tissue. In contrast, microspheres with a diameter of 50 μm or larger had lower concentrations in tumor tissue than in normal liver tissue. The homogeneity of distribution, on the other hand, improved with larger diameters. The optimal therapeutic microsphere size based on these observations was determined to be approximately 30–35 μm. Microspheres of this size distribute more homogenously within the vascular bed, yet provide a higher concentration in the tumor tissue. Further animal experimentation demonstrated that to achieve maximum homogeneity in distribution, 4000 microspheres per gram of liver tissue was required. Gray et al. also studied the radiation dose delivered to tumor and liver parenchyma using an intraoperative solid-state radiation detection probe in patients who were treated with Y-90 microspheres. Radiobiologic effects were evaluated by liver function tests and by histologic changes in liver biopsy specimens [3–5].

There are currently two commercially available Y-90 radiomicrosphere products in the USA: glass microspheres (Thera-Sphere; MDS Nordion, Ottawa, Ontario, Canada) and resin microspheres (SIR-Spheres; Sirtex Medical, Sydney, Australia). Both microspheres have relatively consistent size ranging from 20 to 40 microns, and neither is metabolized or excreted, but they remain in the liver permanently. The main differences are in the density (g/cc) and specific activity (activity/sphere). The glass microspheres are 3 times heavier per volume and carry 50 times more activity per weight than resin microspheres. In the USA, for CRCLM indication, the resin microspheres have been FDA-approved since 2002. The glass microspheres are, at present, used under a humanitarian device exemption (HDE) protocol.

Pretreatment Evaluation

Evaluation of Liver Function/Reserve

Liver reserve might be (often is) affected due to neoplastic replacement and prior hepatotoxic treatments. ALT/AST and alkaline phosphatase/GGT are the markers for acute and subacute hepatocellular and bilio-canalicular injury, respectively. More difficult to evaluate is the real "functional volume" in the anatomically intact appearing liver region(s). Bilirubin is a composite marker of liver reserve and has been widely used in many classification systems as a predictive measure. A bilirubin level above 2 mg/dl in the absence of correctable obstructive etiology precludes RMT [6].

Multiphase Liver Scan: CTA and FDG-PET/CT

Currently, the optimal imaging protocol for Y-90 radiomicrosphere workup is combined and contrast-enhanced CT. A comprehensive protocol includes FDG-PET/CT where FDG serves as a "metabolic contrast" and a three-phase (arterial, portal, equilibrium phases) contrast-enhanced CT. The traditional evaluation of metastatic disease in colorectal cancer, including selection of patients for surgical treatment or systemic chemotherapy, is largely based on cross-sectional imaging criteria. These criteria include definition of number and size of the lesions and their anatomic distribution characteristics. PET imaging using ^{18}F-FDG has become an indispensable staging modality for colorectal cancer. ^{18}F-FDG enhances the detection of metastatic lesions, resulting in more complete evaluation of extent of disease. The role of ^{18}F-FDG in the evaluation of patients with colorectal cancer extends beyond definition of extent of disease. The quantitative evaluation of ^{18}F-FDG uptake, in routine clinical practice, is performed by SUV determination. More informative parameters that can be incorporated in functional evaluation of tumors are FTV and TLG. FTV refers to the size of tumor(s) that have any ^{18}F-FDG uptake above the surrounding normal tissue uptake. TLG is defined as the product of the functional volume and mean or maximum tumor SUV. The pretreatment FTV and TLG levels are predictive of survival. The FTV and TLG changes are early predictors of anatomic tumor volume changes. The metabolic response in the tumors is evident as early as 4 weeks posttreatment. The early (4-week) metabolic response documented by PET/CT evaluation is a function of decrease in viable tumor cell volume rather than temporary metabolic suppression, and the differential in TLG is predictive of survival [7].

Angiography

Angiography has a paramount importance in the planning and administration of the RMT. All patients undergo a standard mesenteric angiography which involves an abdominal aortogram, a superior mesenteric angiogram, and a celiac angiogram followed by a common hepatic angiogram. This initial step allows assessment of first- and second-order anatomy and variations. The second step of angiography involves selective catheterization of left and right hepatic branches. The assessment of segmental blood flow and third-order vascular anatomy is then performed with identification of smaller GI branches such as falciform, phrenic, right, or accessory gastric arteries and supraduodenal, retroduodenal, retroportal, and cystic arteries. An aggressive prophylactic embolization of vessels before therapy is highly recommended, such that any and all hepaticoenteric arterial communications are completely disconnected. The flux of Y-90 radiomicrospheres into unrecognized collateral vessels results in clinical toxicities if proper angiographic protocols are not followed. These might include gastrointestinal ulceration, pancreatitis, cholecystitis, esophagitis, and skin irritation.

TC-99 M MAA Hepatic Scintigraphy

Macroaggregate albumin (MAA) is a particulate form of albumin with an average size of 20–40

micron. Its density is close to that of resin microspheres, and the number of particles per unit volume can be adjusted to a desirable range. Labeled with Tc-99 m, MAA constitutes a reasonable surrogate diagnostic radiopharmaceutical to simulate Y-90 radiomicrosphere distribution when injected in the hepatic artery. Tc-99 m MAA is injected via the hepatic arterial catheter at the completion of the visceral angiography. Shortly after the administration, anterior-posterior planar images of chest and abdomen and SPECT images of liver are obtained. There are three objectives of Tc-99MAA study. First and foremost is the detection and quantitation of intrahepatic shunting that would result in escape of radioactive particles to the lungs. Hepatocellular carcinoma and hypervascular metastases may be associated with intrahepatic arteriovenous shunting. Fortunately, the incidence and degree of shunt is less than 5% with no shunting occurring in majority of patients. Shunt fraction is determined by ROI analysis on Tc-99 m MAA planar images. Second objective of Tc-99 m MAA imaging is the identification of extrahepatic GI uptake which might be caused by an unrecognized hepatofugal vascular runoff. This finding, depending on its size, might preclude further treatment with Y-90 radiomicrospheres unless a safe interventional plan for prevention of extrahepatic flux can be made. The third use of Tc-99 m MAA hepatic scintigraphy is the determination of blood flow ratio between the tumor and normal hepatic parenchyma, which is the major determinant of degree of "selectivity" of RMT [6] (Fig. 3.2). The commercially available MAA particles have been successfully labeled with Ga-68 for PET/CT quantitative imaging and dosimetry, awaiting clinical studies [8].

Treatment Technique

The administration of the Y-90 radiomicrospheres is performed in an angiography suite. The catheter is usually positioned in a position determined by the choice of the treatment mode (whole liver, lobar, or segmental). Both Y-90 radiomicrosphere products have their own dedicated apparatus designed to facilitate the administration. Because the resin microspheres have much higher number of microspheres per unit dose, there is an embolic tendency, especially toward the last stages of the administration, which is performed in a manually controlled manner with angio-fluoroscopic guidance. Observation of increasing reflux is a sign of increased risk for hepatofugal flux, therefore might be an indication to discontinue the administration. Strict adherence to radiation safety guidelines is critically important in patient and personnel safety [9].

The administration of Y-90 resin microspheres via hepatic arterial pump has been evaluated in vitro and demonstrated to be feasible. However, the clinical experience is limited [10].

Y-90 radiomicrosphere treatment usually is an outpatient treatment. Patients who experience moderate embolic syndrome could be admitted for under 24 hours. Symptomatic treatment might be indicated for pain or nausea. Routine prophylactic use of antibiotics, proton pump inhibitors, or steroids is not indicated. Patients are provided with radiation safety instructions upon discharge.

Complications of RMT

In approximately one-third of patients, administration of RMT causes mild short-term abdominal pain requiring narcotic analgesia. This side effect is more common with increasing number of microspheres administered. Post-RMT treatment lethargy is also common symptoms and can last up to 10 days and may require medication. Most patients develop a mild fever for several days following RMT administration that does not require treatment. Distant organs are not subjected to beta radiation due to the short range of beta particles. Radiation doses to the gonads are unlikely, given the distance to the liver and very short range of beta particles of Y-90. The most serious complications are gastric/duodenal ulcer, resulting from reflux of Y-90 radiomicrospheres into the GI vascular bed, and radiation hepatitis, resulting from a radiation overdose to the normal liver parenchyma.

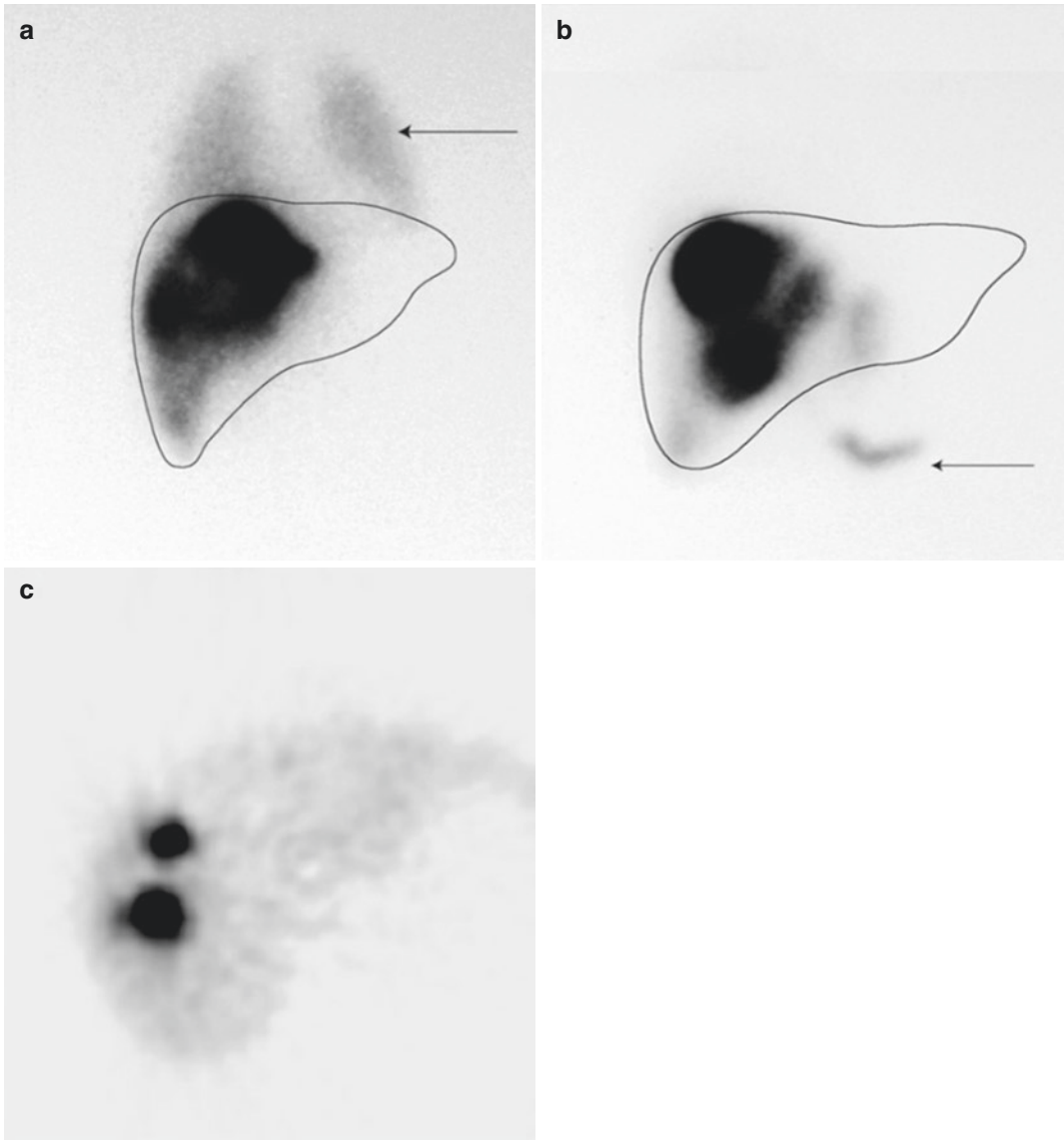

Fig. 3.2 The MAA imaging is performed to evaluate for lung-shunt fraction (**a**), extrahepatic gastrointestinal uptake (**b**), and determination of expectant tumor-to-liver ratio for microsphere distribution (**c**)

GI Complications

The most common GI complication is gastroduodenitis and gastroduodenal ulcers (5%). This is related to reflux of radiomicrospheres into hepatofugal branches, primarily gastroduodenal artery and right gastric artery. Cystic artery could also be involved. Subclinical cholecystitis is probably more common than it is thought, but severe, surgical treatment requiring cholecystitis is rare. Pancreatitis has been listed as a potential complication, but it is even more uncommon than cholecystitis.

RMT-Induced Liver Disease

The pathogenesis of radiation damage to the liver from conventional external beam radiation is dominated by vascular injury in the central

vein region. Early alterations in the central vein caused by external beam radiation are an intimal damage which leads to an eccentric wall thickening. This process, when diffuse and progressive, results in clinical "veno-occlusive disease" characterized by the development of portal hypertension, ascites, and deterioration in liver function [11]. RMT-associated radiation injury has a different pattern. Radiation from microspheres is deposited primarily in the region of the portal triad and away from the central vein, thus minimizing the damage pattern seen in radiation hepatitis from external beam sources [3]. Macroscopically, there are infarction necrosis and fibrosis with nodularity and firmness. Microscopically, RMTILD is characterized by microinfarcts and a chronic inflammatory infiltrate dominating at the portal areas. The radiation dose to healthy liver parenchyma is determined by number of microspheres present, the distance from microspheres from one another, and the cumulated activity of the microspheres implanted. Microspheres lodge preferentially in the growing rim of the tumor, as the center may become necrotic and avascular as the tumor size increases. The highest dose exposure is at the zone immediately surrounding the tumor. The damage to this area of parenchyma is unavoidable. The remainder of the liver receives less radiation than would be predicted from assuming a homogeneous distribution of radiation dose throughout the parenchyma. Clinical veno-occlusive disease is uncommon with RMT.

Radiation Pneumonitis

The second organ of concern is the lung, as a fraction of microspheres might shunt through the liver and into the lung. It is important to ensure that the radiation dose to the lung is kept to a tolerable limit and this can be calculated from the hepatic MAA scintigraphy. Radiation pneumonitis has been reported to occur at an estimated lung dose level of 30 Gy [12].

The Role of RMT in the Contemporary Management of CRCLM

The natural course of untreated metastatic liver disease is poor. Data from the 1960s and 1970s show that the median survival of patients receiving no treatment ranges between 3 and 12 months with an overall median survival of 7 months [13, 14]. Liver resection provides the most favorable outcomes in appropriately selected patients. With the advances in surgical, anesthetic, and perioperative care, and in medical imaging which allowed better patient selection and surgical planning, liver resections have become accepted as standard therapy [15]. Increasingly, aggressive resections are being performed with an operative mortality less than 5%. At many centers, more than two-thirds of resections now consist of major hepatectomy procedures. While the liver resection has been accepted to be the only treatment with a chance of long-term survival in patients with CRCLM, the resectability rate of metastases at the time of diagnosis has been low, accounting for the low proportion of patients who may benefit from a surgical approach. Until recently, patients initially considered as unresectable were treated by palliative chemotherapy, with poor response rates and obviously little chance of 5-year survival. Chemotherapy as a first-line treatment of metastatic colorectal cancer has greatly changed within the last decade. Oxaliplatin- and irinotecan-based combination regimens not only have improved the efficacy of systemic treatment allowing increased patient survival in a palliative setting but have also offered a possibility of cure to previously unresectable patients with liver surgery after tumor downsizing [16–18]. By reconsidering the initial unresectability of patients who strongly respond to chemotherapy, Adam et al. have shown that survival could be achieved by liver resection in a significant proportion of patients otherwise destined to a poor outcome [19]. This group analyzed a consecutive series of 1439 patients with CRLM managed in a single institution during a

11-year period (1988–1999). Metastatic disease was determined to be resectable in 335 (23%) of the patients at initial presentation. Remaining 1104 (77%) were treated by chemotherapy, involving new-generation protocols. Among 1104 unresectable patients, 138 (12.5%) underwent secondary hepatic resection after an average of 10 courses of chemotherapy. Seventy-five percent of procedures were major hepatectomies. Portal embolization and ablative treatments were liberally used as adjunct modalities. Currently, an average 5-year overall survival rate of 33% has been achieved with a wide use of repeat hepatectomies and extrahepatic resections. These results indicate that multimodality approach with aggressive surgical and nonsurgical interventions can be justified toward the goal of improving the survival of patients with CRCLM. Also, a significant number of patients can be downsized for a potentially curative resection provided that a successful neoadjuvant strategy can be employed.

At present, the systemic treatment for unresectable CRCLM involves oxaliplatin- and irinotecan-based chemotherapy regimens combined with targeted therapies such as bevacizumab (Avastin™) and cetuximab (Erbitux™). Radiation therapy, traditionally, is not considered a viable treatment modality due to its unacceptably high hepatic toxicity and the long-standing dogma that chemoradiation cannot be an oncological strategy for a stage IV disease. Selective internal radiation treatment with Y-90 radiomicrospheres has emerged as an effective liver-directed therapy with a favorable therapeutic ratio. Since its early clinical trials, it has demonstrated an improved response rates when used in conjunction with systemic or regional chemotherapy.

Clinical Studies in Colorectal Cancer with Y-90 RMT

Selective targeting of metastases with RMT induces substantial objective responses as measured by decrease in functional (by FDG-PET/CT) and anatomic (by CECT or MRI) tumor volume in the liver and significantly prolongs time to progression (TTP), progression-free survival (PFS), and overall survival (OS). RMT in CRCLM can be administered as a stand-alone treatment in a salvage setting or can be administered in conjunction with systemic chemotherapy. The efficacy of the treatment has been demonstrated in both settings.

Chemo-RMT

There have been a number of structured clinical trials with RMT using Y-90 resin microspheres which have been fully executed and have published their final analyses. These include a randomized phase III study using hepatic artery chemotherapy with FUDR, a randomized phase II trial comparing systemic chemotherapy with 5-FU/LV with or without SIR-Spheres™, a phase I/II dose escalation study with oxaliplatin, a phase I/II dose escalation study with irinotecan, and a phase II study with FOLFOX-6 or FOLFIRI regimens [20–24]. The pivotal phase III trials comparing chemotherapy alone and chemotherapy combined with Y-90 RMT (SIRFLOX, FOXFIRE, FOXFIRE-Global) have reported their results with clinical outcome measures [25–27].

The first randomized phase III trial in 74 patients with colorectal liver metastases compared RMT (2–3 GBq of Y-90 activity) plus hepatic artery chemotherapy (HAC) with FUDR 0.3 mg/kg/day for 12 days and repeated every 4 weeks for 18 months, versus HAC alone (FUDR 0.3 mg/kg/day for 12 days and repeated every 4 weeks for 18 months). The outcome analysis showed significant improvement resulting from the addition of RMT to systemic chemotherapy. Toxicity data showed no difference in any of the grade 3 or 4 toxicity between the two treatment arms. There was a significant increase in the complete and partial response rate (17.6% to 44%, $p = 0.01$) and prolongation of time-to-disease progression (9.7 months to 15.9 months,

$p = 0.001$) in the liver for patients receiving the combination treatment. Although the trial design was not of sufficient statistical power to detect a survival difference, there was a trend observed toward improved survival for the combination treatment arm [20].

The second study combining RMT with systemic chemotherapy was designed as a randomized phase II/III trial in which RMT was used in combination with systemic chemotherapy using 5-FU and LV. This trial accrued 21 patients and closed prematurely due to the paradigm shift in the systemic therapy of metastatic CRC which involved new-generation chemotherapy agents. The toxicity profile was higher in patients receiving the combination treatment, although a dose modification of RMT decreased the toxicity profile to an acceptable level. Furthermore, the objective response rate in this small phase II trial for patients treated with the combination of RMT plus 5-FU/LV was high. Progression-free survival in the combination therapy arm was 18.6 months compared to 3.4 months in the chemotherapy-alone arm ($p < 0.0005$). Overall median survival was 29.4 months in the combination therapy arm, compared to 12.8 months in the chemotherapy-alone arm ($p = 0.02$) [21].

A phase I/II dose escalation trial of systemic chemotherapy using FOLFOX 4 + RMT was recently completed. Twenty patients were entered from Australia and the UK. The study population comprised patients with nonresectable liver-dominant metastatic colorectal adenocarcinoma, who had not previously been treated with chemotherapy. This trial was successfully escalated up to the standard FOLFOX 4 oxaliplatin dose (85 mg/m^2) and demonstrated a safety profile very similar to that observed in other phase III trials of FOLFOX 4 alone. The overall RECIST response rate for the trial was 90% (PR + CR), with the remaining patients (10%) having stable disease. Of significance is the fact that 2 of the 20 patients in this study had their disease downstaged to the extent that the liver disease was subsequently surgically resected [22].

A second phase I/II dose escalation trial of systemic chemotherapy was with using irinotecan + RMT. Twenty-five patients, who had failed previous chemotherapy, participated in the study. Irinotecan was given weekly twice every 3 weeks, starting the day before RMT, for a maximum of nine cycles. Irinotecan dose was escalated from 50 to 100 mg/m^2, and this was well tolerated. Partial responses were seen in 9 of 17 patients, median time to liver progression was 7.5 months, and median survival was 12 months [23].

A phase II study combining RMT with FOLFOX-6 or FOLFIRI in a front-line setting enrolled 20 patients. The patients received RMT in one of the two liver lobes 24 hours after starting chemotherapy. This study was implemented to demonstrate the relative efficacies of chemotherapy and chemotherapy combined with Y-90 radiomicrosphere therapy. By virtue of its design, comparing right and left liver lobes receiving different treatments in individual patients, the study provided clear data in terms of objective responses (Fig. 3.3). The evaluation of objective treatment response in this study included accurate measurements of functional and anatomic tumor volume changes. Eighteen patients were treated in the first-line setting with FOLFOX6 chemotherapy, and two patients were treated in the second-line setting with FOLFIRI chemotherapy. A decrease in functional tumor volume on FDG-PET/CT imaging was seen in all except one patient. The mean decreases in functional tumor values in the tumors receiving chemo-SIRT and chemo-only treatment were 80.47% ± 25.67% and 41.32% ± 58.46% ($p < 0.01$), 90.67% ± 17.01% and 46.67% ± 60.59% ($p < 0.01$), and 82.22% ± 38.85% and 56.00% ± 28.93% ($p < 0.08$) at 4 weeks, 2–4 months, and 6–8 months posttreatment, respectively. The study demonstrated that, under near identical conditions in terms of patient and tumor characteristics, the chemo-RMT combination produced superior objective responses compared to chemo-only treatment in a front-line treatment setting in patients with CRCLM [24] (Fig. 3.4).

FOXFIRE, SIRFLOX, and FOXFIRE-Global were randomized, phase III trials done in hospitals and specialist liver centers in 14 countries worldwide (Australia, Belgium, France, Germany,

Israel, Italy, New Zealand, Portugal, South Korea, Singapore, Spain, Taiwan, the UK, and the USA). Chemotherapy-naive patients with metastatic colorectal cancer (WHO performance status 0 or 1) with liver metastases not suitable for curative resection or ablation were randomly assigned (1:1) to either oxaliplatin-based chemotherapy (FOLFOX: leucovorin, fluorouracil, and oxaliplatin) or FOLFOX plus single-treatment SIRT concurrent with cycle 1 or 2 of chemotherapy. In FOXFIRE (registered with the ISRCTN registry number, ISRCTN83867919), FOLFOX chemotherapy was OxMdG (oxaliplatin modified de Gramont chemotherapy; 85 mg/m^2 oxaliplatin

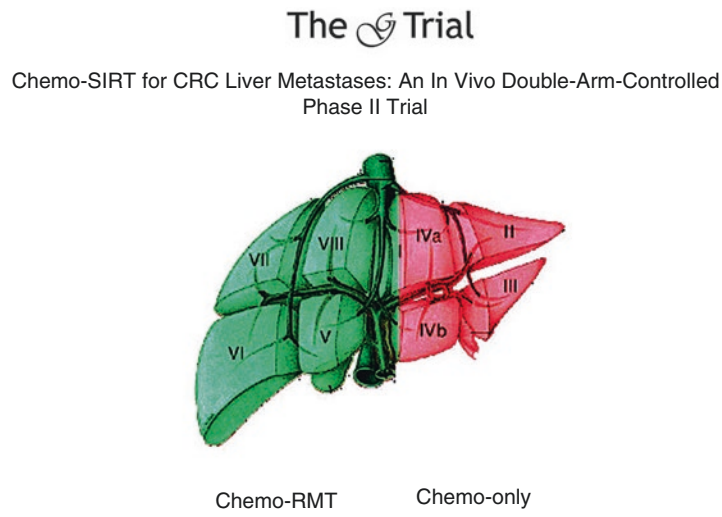

Fig. 3.3 The design of phase II in vivo lobar randomization trial (the G trial) for chemo-RMT vs chemo-alone

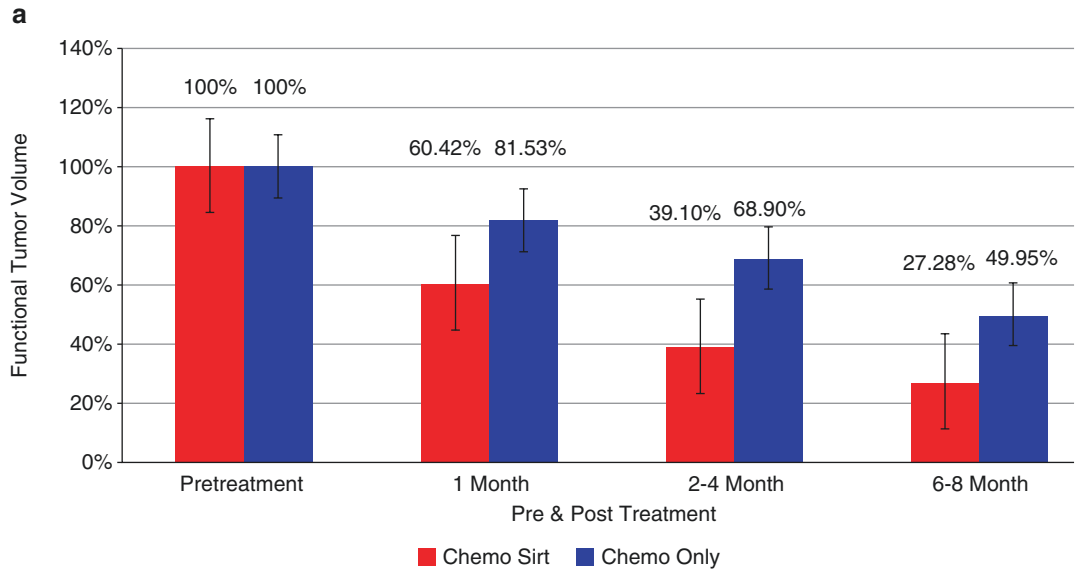

Fig. 3.4 (**a**) Functional tumor volume (%): Pretreatment and posttreatment at 4 weeks, 2–4 months, and 6–8 months. (**b**) Total lesion glycolysis (%): pretreatment and posttreatment at 4 weeks, 2–4 months, and 6–8 months. (**c**) Differential visual response in chemo-SIRT-treated lobe vs chemo-only lobe. The line delineates right and lobe border. There is a good response in the right lobe treated with combination protocol

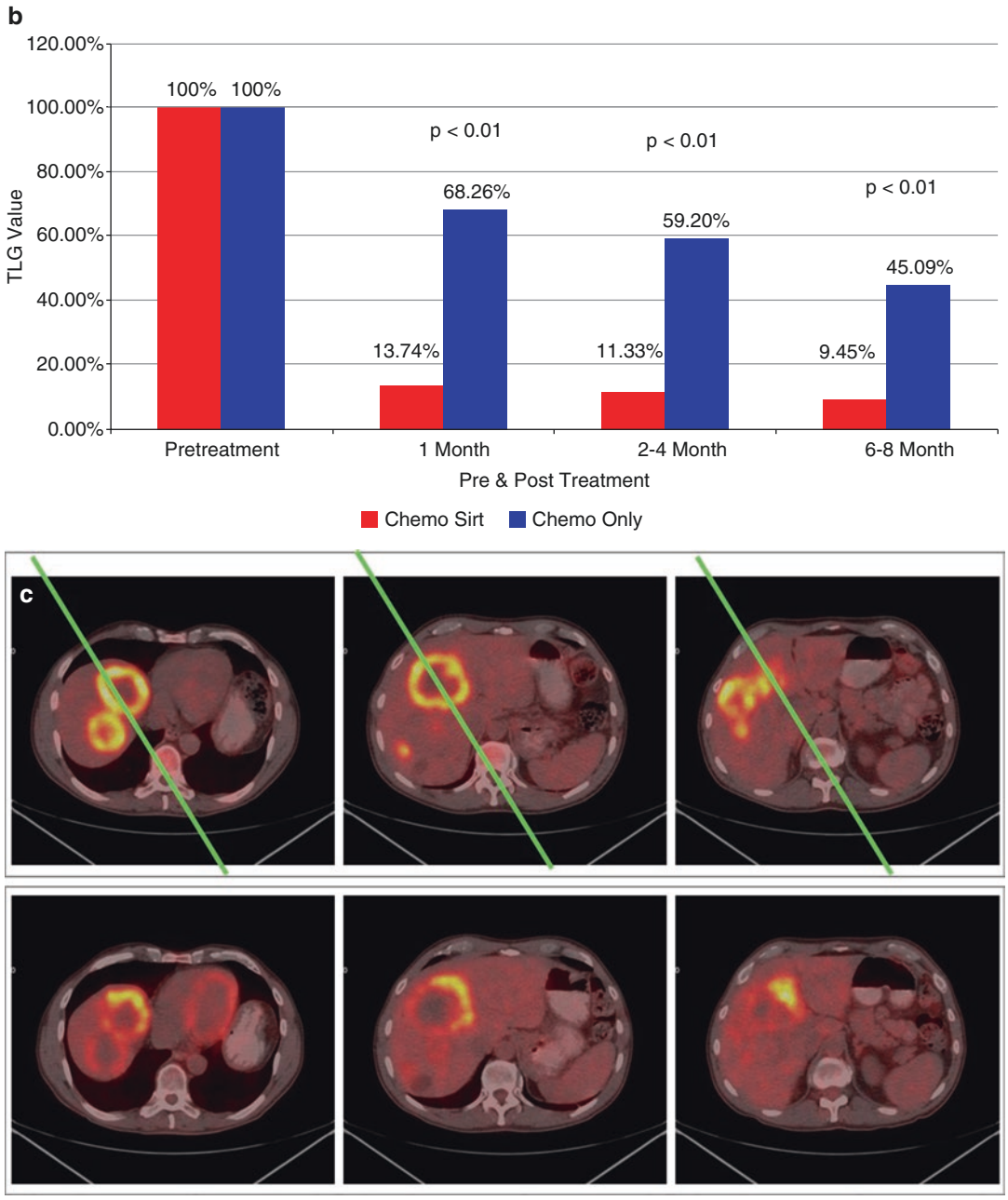

Fig. 3.4 (continued)

infusion over 2 h, L-leucovorin 175 mg or D,L-leucovorin 350 mg infusion over 2 h, and 400 mg/m^2 bolus fluorouracil followed by a 2400 mg/m^2 continuous fluorouracil infusion over 46 h). In SIRFLOX (registered with the ClinicalTrials.gov, number, NCT00724503) and FOXFIRE-Global (registered with the ClinicalTrials.gov, number, NCT01721954), FOLFOX chemotherapy was modified FOLFOX6 (85 mg/m^2 oxaliplatin infusion over 2 h, 200 mg leucovorin, and 400 mg/m^2 bolus fluorouracil followed by a 2400 mg/m^2 continuous fluorouracil infusion over 46 h).

Randomization was done by central minimization with four factors: presence of extrahepatic metastases, tumor involvement of the liver, planned use of a biological agent, and investigational center. Participants and investigators were not masked to treatment. The primary endpoint was overall survival, analyzed in the intention-to-treat population, using a two-stage meta-analysis of pooled individual patient data (Fig. 3.5). All three trials have completed 2 years of follow-up.

Between October 11, 2006, and December 23, 2014, 549 patients were randomly assigned to FOLFOX alone and 554 patients were assigned to FOLFOX plus SIRT. Median follow-up was 43.3 months (IQR 31.6–58.4). There were 411 (75%) deaths in 549 patients in the FOLFOX-alone group and 433 (78%) deaths in 554 patients in the FOLFOX plus SIRT group. There was no difference in overall survival (hazard ratio [HR] 1.04, 95% CI 0.90–1.19; $p = 0.61$). The median survival time in the FOLFOX plus SIRT group was 22.6 months (95% CI 21.0–24.5) compared with 23.3 months (21.8–24.7) in the FOLFOX-alone group. In the safety population containing patients who received at least one dose of study treatment, as treated, the most common grade 3–4 adverse event was neutropenia (137 [24%] of 571 patients receiving FOLFOX alone vs 186 (37%) of 507 patients receiving FOLFOX plus SIRT). Serious adverse events of any grade occurred in 244 (43%) of 571 patients receiving FOLFOX alone and 274 (54%) of 507 patients receiving FOLFOX plus SIRT. Ten patients in the FOLFOX plus SIRT group and 11 patients in the FOLFOX-alone group died due to an adverse event, 8 treatment-related deaths occurred in the FOLFOX plus SIRT group, and 3 treatment-related deaths occurred in the FOLFOX-alone group.

It was concluded that the addition of SIRT to first-line FOLFOX chemotherapy for patients with liver-only and liver-dominant metastatic colorectal cancer did not improve overall survival compared with that for FOLFOX alone [25–27].

Concurrent Capecitabine Treatment with RMT

Capecitabine is a prodrug that is enzymatically converted to 5-fluorouracil (5-FU) in the body

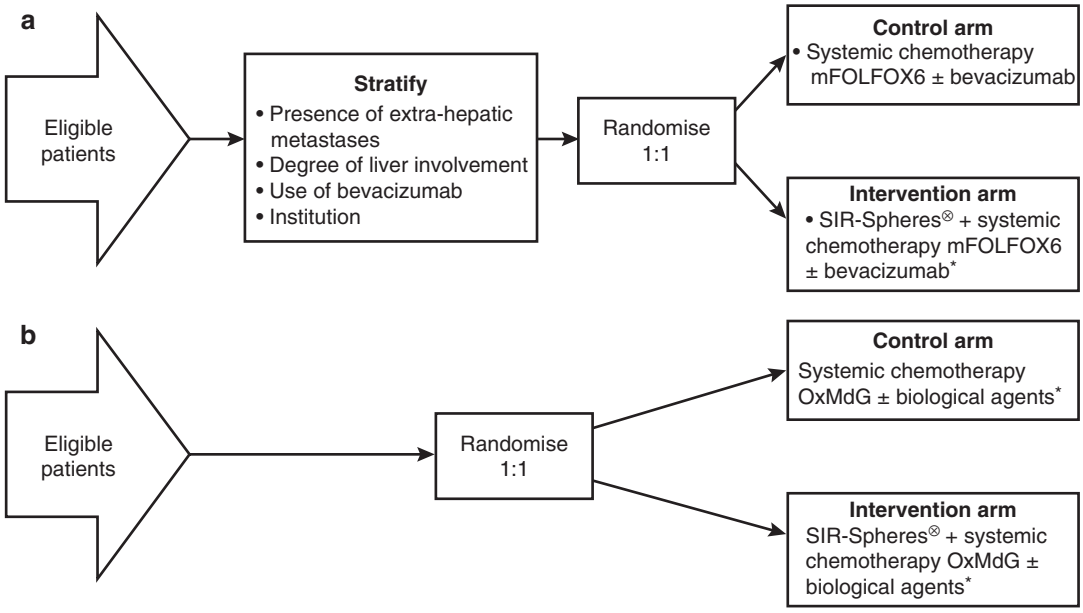

Fig. 3.5 (**a**) Basic clinical trial schema for SIRFLOX clinical trial. (**b**) Basic clinical trial schema for FOXFIRE clinical trial

and is commonly used in the treatment of patients with CRCLM. Currently, concomitant capecitabine treatment is contraindicated with RMT due to an anecdotal early report of toxicity with this combination. In Australia in the 1990s, a single patient treated with radioembolization and concurrent capecitabine developed liver failure and death. Although no other cases of liver toxicity and death with the combination have been reported, concurrent capecitabine has remained a contraindication to RMT. However, given the importance of capecitabine in the current management of patients with GI cancers and its potential role as a radiosensitizer, a formal phase I trial of capecitabine and radioembolization was conducted to document the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of the combination and to define the recommended phase II dose for further study.

In this prospective single-center, phase I study, patients with advanced unresectable liver-dominant cancer were enrolled in a 3 + 3 design with escalating doses of capecitabine (375–1000 mg/m^2 b.i.d.) for 14 days every 21 days. RMT with 90Y-resin microspheres was administered using a sequential lobar approach with two cycles of capecitabine. Twenty-four patients (17 colorectal) were enrolled. The MTD was not reached. Hematologic events were generally mild. Common grade 1/2 hepatic toxicities included transient transaminitis/alkaline phosphatase elevation (9 (37.5%) patients). The study concluded that this combined modality treatment was generally well tolerated with encouraging clinical activity. Capecitabine 1000 mg/m^2 b.i.d. was recommended for phase II study with sequential lobar radioembolization. A very important consideration in interpreting this particular safety data is that the patients with bilobar disease received sequential lobar therapy rather than whole-liver therapy. The safety of combining capecitabine with whole-liver radioembolization was not addressed in this study [28].

RMT Alone

RMT alone is usually administered in the salvage setting in chemorefractory patients. In a large multicenter retrospective review involving 208 patients with unresectable disease, majority of which had received at least 3 lines of prior chemotherapy and had also failed local-regional therapy, RMT resulted objective responses by CT in 35.5% of patients and disease stabilization in a further 55% of patients at 3-month follow-up. Response by positron emission tomography scan was observed in 85% of patients. The treatment response after RMT was highly predictive of prolonged survival, with a median survival of 10.5 months among responders versus 4.5 months for nonresponders or historical controls ($P < 0.0001$) [29].

In a prospective phase II multicenter collaborative-group trial in 50 highly chemorefractory patients who had failed prior oxaliplatin- and irinotecan-based chemotherapy regimens, the ORR after a single administration of RMT was 24% (range, 12.2–35.8%) with stable disease (SD) reported in a further 24% of patients. Two patients were sufficiently downsized to a subsequent surgical resection. The Kaplan-Meier median OS was 13 (range, 7–18) months with a 2-year survival of 19.6%. Similar to the first study, the treatment response with RMT was highly predictive of prolonged survival, with a median survival of 16 (range, 13–19) months among responders compared with 8 (range, 4–12) months among nonresponders ($P < 0.0006$) [30].

A retrospective study of 41 patients with chemotherapy-refractory CRCLM also reported similar outcomes, with an objective response rate of 17% measured by RECIST and a median OS of 10.5 months after RMT [31].

RMT for Preoperative Tumor Downsizing and Future Liver Remnant Recruitment

The extent of resection of liver metastases is restricted by the volume of the future liver remnant (FLR). Among different strategies, portal vein embolization (PVE) has gained wider acceptance to achieve the goal of increasing the volume of the FLR. Induction of hyperplasia of the nondiseased portion of the liver reduces the risk of hepatic insufficiency and associated complica-

tions after resection. Clinically adequate compensatory hyperplasia occurs approximately 2–3 weeks post-induction. An FLR of >20% in patients with an otherwise normal liver, >30% for those who have received extensive chemotherapy, and >40% in patients with hepatic fibrosis/cirrhosis is recommended for a safe major hepatic resection. A meta-analysis concluded that PVE is a safe and effective procedure for inducing liver hyperplasia to prevent post-resection liver failure due to insufficient liver remnant. The controversy over the possibility of tumor progression in non-embolized (and also in embolized) segments during the induction period, however, remains unresolved. RMT was proposed as an alternative novel approach to effectively control the tumor growth, and with appropriate scaling of radiation-absorbed dose to the lobar portal microvascular bed, to induce contralateral lobe hyperplasia. The simultaneous accomplishment of tumor control and FLR recruitment might offer a better therapeutic profile compared with that of PVE [32]. A PET/CT follow-up evaluation following application of this strategy and intraoperative exploration demonstrating significantly downsized tumor with scarring and major left lobe

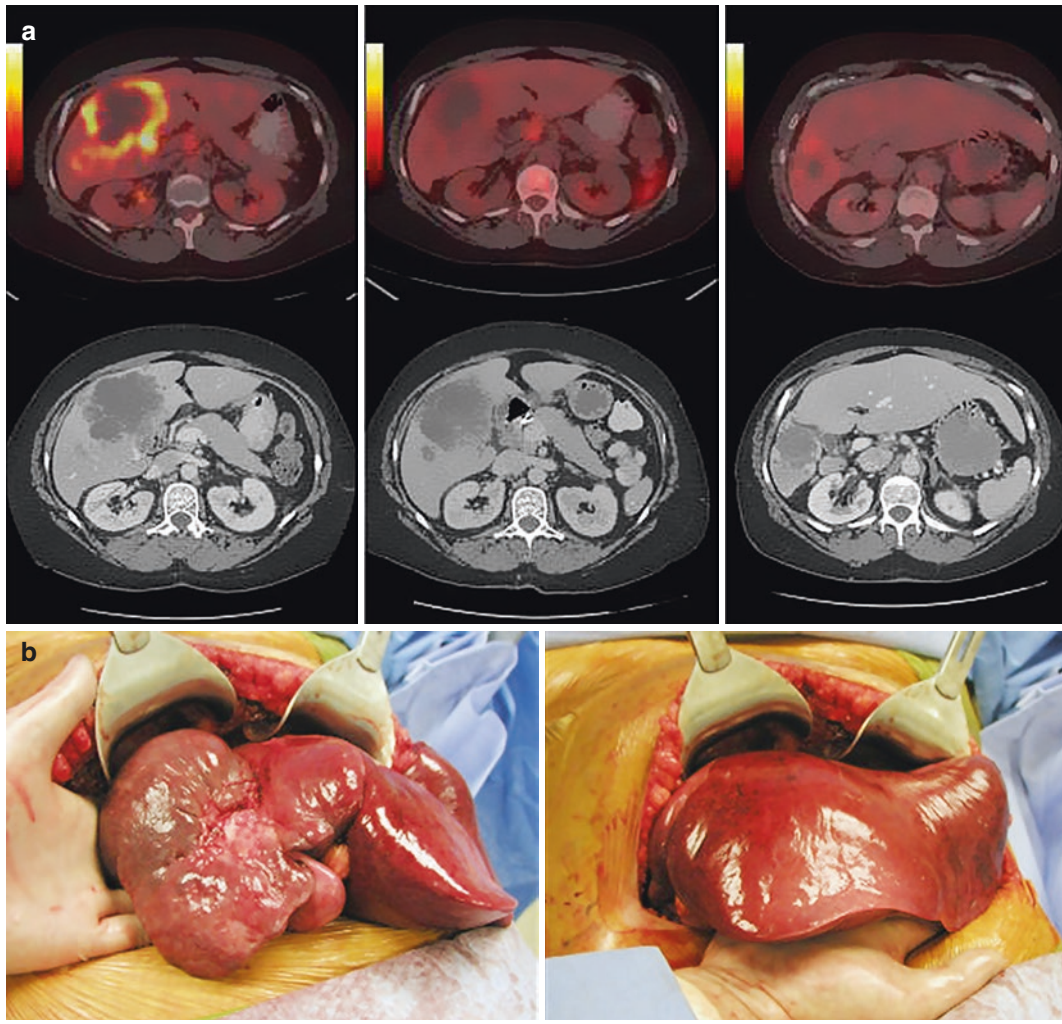

Fig. 3.6 (**a**) FDG-PET/CT image sets demonstrating progressive decrease in the functional and anatomic volume of the tumor with concurrent left lobe hypertrophy. Left: Pretreatment. Middle: 4 weeks after first SIRT treatment. Right: At the completion of the full course of the treatment. (**b**) Intraoperative pictures demonstrating significantly downsized tumor with scarring (left) and major left lobe hypertrophy (right)

hyperplasia are shown in Fig. 3.6. Clinical indications, patient selection criteria, and dosimetry for this therapeutic intervention need to be further refined.

Current Status (2019) and Future Directions

The multicenter randomized phase III trials, FOXFIRE, SIRFLOX, and FOXFIRE-Global showed no survival benefit when combining 90Y RMT with first-line chemotherapy. Currently, patients are referred for RMT at the late stages of their disease, especially when they progress in the liver while receiving second, third, or subsequent chemotherapy regimens. RMT is recommended in the chemorefractory or salvage setting. It is therefore important to identify and describe predictive factors in these settings. The MSKCC group has reviewed the factors affecting oncologic outcomes of 90Y RMT of heavily pretreated patients with colon cancer liver metastases. The median LPFS was 4 months. Six-month and 1-year LPFS were 27% and 9%, respectively. All increased metabolic tumor uptake parameters of most metabolically active tumor (SUVmax, SUVpeak, SUVmean, FTV, TLG) within the intended-to-treat region were significantly associated with decreased OS. 18F-FDG-PET/CT has proven useful to evaluate treatment response, and it is an established prognostic tool in patients with CLM undergoing RMT, with semiquantitative metabolic measures (such as FTV and TLG) correlating with survival better than RECIST criteria. It is, therefore, recommended that FDG-PET/CT metabolic imaging to be always performed before RMT [33].

Another strong biologic parameter correlating with treatment response, besides the metabolic profile of the tumors, both by objective measures and OS, is the mean absorbed dose (D) calculated post-facto (post-RMT) using 90Y-PET/CT-based dosimetry. The mean radiation-absorbed dose (D-mean) correlates with the metabolic response assessed by TLG decrease. Two tumor mean absorbed dose cutoffs of 39 and 60 Gy were defined for predicting, respectively, the nonmetabolic response (less than 15% TLG decrease) and a high metabolic response (more than 50% TLG decrease). Patients who had a D-mean above 39 Gy had improved OS. The overall survival rates for patients in which all the lesions had a D-mean above and below 39 Gy were 13 vs 5 months, respectively [34].

An assessment of SIRFLOX images by hepatobiliary surgeons, who were blinded to the study arm, time point, and clinical characteristics, concluded that the addition of SIRT led to more patients having resectable disease. Thus, potentially with a more aggressive approach to hepatic resection, a greater effect on survival could be achieved with the addition of RMT for RSP patients. The low rates of resection in SIRFLOX might also reflect the high proportion of patients (40%) with extrahepatic metastases and the requirement for all patients to be reviewed by a multidisciplinary panel for resectability [35].

The clinical value, in terms of survival benefit, of RMT is still being investigated using institutional and national registry data sets. A large, prospective, registry-based study to examine the survival of patients with unresectable, chemotherapy-refractory mCRC treated with RMT is underway in the UK. Although the absence of a contemporaneous comparator group and known shortcomings of a registry format limits data interpretation, the clinical conclusions derived from such registry data are still valuable in providing aiding treatment decisions reached between clinicians and patients in day-to-day practice. Important subgroups have been identified under this registry. Patients with no extrahepatic metastases, fewer than six tumors, and a tumor-to-liver volume percentage of less than 25% suggested better outcomes with RMT. The data has confirmed that RMT is safe and well tolerated in patients who have previously received multiple lines of chemotherapy, and it has shown that RMT in this population results in overall survival, PFS, and LPFS that are consistently favorable [36].

Radiomicrosphere therapy refers to hepatic arterial administration of radioactive microspheres. In common use in the USA, it implies Y-90 micro-

spheres, as the current products with FDA approval or supervision are Y-90 constructs. In a broader sense, many different products can be/have been/are being/will be designed and developed. Holmium-166 (Ho-166) polylactic acid (PLA) microspheres with a diameter of 30 ± 5 μm (QuiremSpheres®) received the European CE mark for quality and safety in 2015 and have reported promising results in a phase I trial (HEPAR trial) in patients with unresectable and chemorefractory liver metastases [37]. Ho-166 emits 80 keV Gamma photons and 666 keV beta particles with a 26.8-hour half-life. It has paramagnetic properties which allows dosimetric evaluation using single-photon emission computed tomography (SPECT) and magnetic resonance (MR) images. Ho-166 RMT was reported to be a feasible and safe treatment option with no significant hepatotoxicity for treatment of HCC [38]. Further clinical studies are required to place Ho-166 PLA in an appropriate context for RMT in CRCLM.

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4 Principles of Percutaneous Ablation in the Liver

Juan C. Camacho and Anne M. Covey

Introduction

Image-guided ablation is an accepted treatment for select benign and malignant tumors in multiple organs. Numerous ablation modalities are available, including but not limited to radiofrequency ablation, microwave ablation, cryoablation, laser ablation, irreversible electroporation, and chemical ablation. This chapter focuses on the principles behind commonly used ablation modalities. The number of available ablation modalities and the rapid changes in technology requires the user to understand the mechanisms behind each device, as that will allow the operators to choose the appropriate modality for a specific situation.

This chapter will summarize the mechanisms of action of the common ablation modalities with attention to the advantages, disadvantages, and limitations encountered in clinical practice. A basic understanding of the underlying physical processes is imperative to determining the modality to be used in any given clinical scenario. A summary of the clinical efficacy of the liver ablation is also included.

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Chemical Ablation

Intratumoral administration of chemicals is the oldest available percutaneous ablation technique, particularly in the treatment of hepatocellular carcinoma (HCC) [1–4]. Advantages over other techniques include its low cost and relatively simple equipment. The challenge remains in achieving a homogenous distribution of the substance throughout the tumor and the ability to treat a margin of tissue surrounding the lesion. Therefore, chemical ablation has largely been replaced by energy-based techniques and is now reserved for tumors that are difficult to treat with other therapies (i.e., close proximity to critical structures) or just as a single technique when treating smaller lesions [5].

The principle behind ethanol injection relies on two mechanisms: (1) immediate dehydration of the cell cytoplasm and subsequent protein denaturation followed by coagulation necrosis and (2) ischemic necrosis while circulating in the tumoral blood vessels due to disruption of the vascular endothelium leading to platelet aggregation, thrombosis, and ischemia [6]. Ethanol is typically reserved for HCC because it is a soft tumor that usually occurs in the setting of cirrhosis. The cirrhotic liver act as a tumor pseudocapsule limiting the diffusion of the chemical out of the tumor into the parenchyma. Liver metastases, on the other hand, tend to be fibrotic and occur in

Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_4

relatively "soft" liver allowing for diffusion of an injectate such as ethanol in the normal tissue [7]. This is the main reason why other alternatives such as acetic acid have been used for chemical ablation. The necrosis mechanisms are essentially the same; however, acetic acid has better diffusion in fibrotic tissue, which theoretically brings advantages when treating metastatic disease [6, 7].

Energy-Based Thermal Ablation

Cryoablation (Hypothermic Ablation)

The Joule-Thomson effect is the principle behind cryoablation. This describes the change in temperature of a gas that occurs as a result of compression or expansion. Argon, the most common gas used in clinically available cryoablation systems, is a gas that cools during expansion in a chamber at the tip of the cryoprobe. With intermittent freezing and thawing (which may be passive or active using helium) to below 20 C, cell death is caused by formation of intracellular ice crystals that results in damage to plasma membranes and organelles [8]. The ice crystals continue to grow during thawing, maximizing cell death [9]. Tumor response depends on the rate of cooling, depth of hypothermia, rate of thawing, the number of freeze-thaw cycles, and delayed effects of post-thaw ischemia. Repeated freeze-thaw cycles can improve the efficacy.

Cryoablation is not commonly used in the liver because of the large diameter of currently available probes, frequent need to use multiple probes, and the risk of cryoshock, a clinical syndrome characterized by renal failure, disseminated intravascular coagulation, and adult respiratory distress syndrome [10].

Hyperthermic Ablation

It has been well described that irreversible cellular injury occurs when cells are heated to 46 °C for 60 minutes, and there is direct correlation between increasing temperature and cell death [11]. High temperatures can generate immediate damage by inducing coagulation of the cytosol, mitochondrial enzymes, and nucleic acid-histone protein complexes [12–14]. This reaction triggers cell death over the course of time. That is the main reason why histopathologic studies [12–15] have demonstrated that tissues treated with thermal ablation may still have viable morphology in the immediate postoperative period and that coagulative necrosis develops as a delayed consequence.

Radiofrequency Ablation

Radiofrequency utilizes an electrical current from a generator that oscillates between electrodes through the ion channels present in most biologic tissues. Tissues act as the resistive element leading to ionic friction and subsequent heat generation (Joule effect). Heating occurs rapidly in the areas closest to the electrode, and the more peripheral areas are heated passively from thermal conduction [16, 17].

Most RF ablation systems operate in a monopolar mode by using one electrode in the probe and dispersive electrodes on the skin surface (i.e., grounding pads). That way, the probe electrode delivers the energy generating heat and the grounding pad closes the electrical circuit decreasing the possibility of skin injury.

Internally cooled electrodes were developed to minimize char formation in tissue adjacent to the electrode. In these devices, fluid is circulated inside the electrode probe, to decrease temperatures at the electrode-tissue interface. This minimizes tissue charring and allows more power deposition thereby increasing the size of the ablation zone [18, 19]. Other designs included a probe with multiple tines in an attempt to distribute energy spatially [20] in order to generate a larger ablation zone [17–19].

Bipolar systems have also been developed, which allowed the current to oscillate between two probes eliminating the need of grounding pads [21, 22]. The bipolar approach restricts current flow to the area between the electrodes, decreasing cooling mediated by the perfusion of

the area (heat-sink effect), resulting in faster and more focal heating between the electrodes. Therefore, in bipolar systems, the placement of the electrodes becomes critical to create a confluent zone of necrosis [22].

Microwave Ablation

Microwave ablation refers to electromagnetic energy operated at either 915 MHz or 2.45 GHz. The heating of tissues is produced as a result of the "dielectric hysteresis" phenomenon, which implies that when electromagnetic energy is applied to the tissue, it forces water molecules that have an intrinsic dipole moment to continuously rotate and realign. This continuous rotation of molecules increases kinetic energy and results in temperature rise [23, 24]. Microwaves can penetrate through biologic materials including tissues with low conductivity and are not affected by dehydration or charring producing extremely high temperatures (>150 °C) improving conduction into the surrounding tissue [25]. This makes microwave energy more efficient at heat generation. Microwave also does not require grounding pads and at the same time, multiple probes can be operated simultaneously [26] increasing the volume of tissue that can be ablated.

Modern microwave systems also contain a cooling jacket in order to prevent potential skin burns since the heat can be transmitted to the shaft of the probe and even the connections of the antenna [27]. The presence of cooling jackets also increases the amount of power that can safely be delivered to the tumor [25].

Laser Ablation

Laser sources emit approximately 600–1000 nm wavelength light energy [28] that induce electromagnetic heating. One of the primary advantages of using laser energy is its compatibility with magnetic resonance (MR) imaging. In addition, the relative lack of metal throughout the system and the small diameter of most applicators effectively eliminate imaging artifacts on CT and MR, allowing real-time monitoring of temperature maps [29].

Also, laser light can be a very precise energy for tissue heating. Since any tissue absorbs light very quickly, smaller ablation zones can be created (1–2-cm diameter) which make laser the perfect platform for delicate or small organs (brain, thyroid, prostate) [30]. Light does not penetrate through charred or desiccated tissues. Therefore, diffusers are used to improve the heating profiles, but when higher powers are used, the fiber needs to be cooled to avoid skin burns or probe failure [31]. Cooling mechanisms increase the diameter of the applicator, and when larger ablation zones are pursued, multiple can be used and operated independently or simultaneously [28].

Energy-Based Nonthermal Ablation

Irreversible Electroporation

Irreversible electroporation (IRE) uses pulsed electric fields to induce cell death. At a specific electric potential threshold, the cell membrane lipid bilayer becomes inundated with pores, a change that is reversible at low current but becomes permanent and results in cell death as the electric field strength is increased [32]. IRE devices can deliver up to 3000 V and 50 A through either unipolar or bipolar needle electrodes. Ablation zone size can be influenced by the number of electrodes, the length of the electrode tip, distance between electrodes, pulse number, duration of pulses, and voltage applied [33]. Electric fields are strongly influenced by the conductivity of the local environment, which depends on tissue heterogeneity and the presence of metal such as biliary stents. Since IRE does not depend on heating or cooling of target tissues, the technique is not limited by the heat-sink effect when performing ablation of tumors close to major blood vessels [34] and does not appear to have deleterious effects on adjacent normal tissues including nerves and bile ducts [35, 36].

Current IRE devices do have disadvantages, including generation of potentially dangerous electrical harmonics that can stimulate muscle contraction or cardiac arrhythmias. Therefore, the technique requires general anesthesia and para-

lytic induction. There is also a requirement for accurate placement of several needles to achieve even moderate-sized ablations. The lack of coagulation around the needle entry points can theoretically increase bleeding complication risks.

Clinical Applications in the Liver

When compared to surgical resection and radiation therapy, percutaneous ablation is a relatively new technology. As such, the indications are in evolution and vary from practice to practice. An appropriate tumor can be treated with ablation in a single outpatient session with fewer major complications than hepatic resection. Other advantages include the ability to perform additional ablations when needed to treat local recurrence or new lesions, that it is a parenchymal sparing technique, and finally that it typically does not require prolonged interruption of concurrent therapies. However, there are limitations based on size, geometry and location of the lesion in the liver (Fig. 4.1). It also requires, in most cases, sedation or anesthesia, and is more invasive than radiation therapy. Percutaneous ablation techniques can be used in many organs, from bone to thyroid, but the majority of data is for ablation of tumors in the liver.

Primary Liver Tumors

The majority of patients that develop hepatocellular carcinoma (HCC) do so in the setting of a known risk factor, commonly viral hepatitis, and

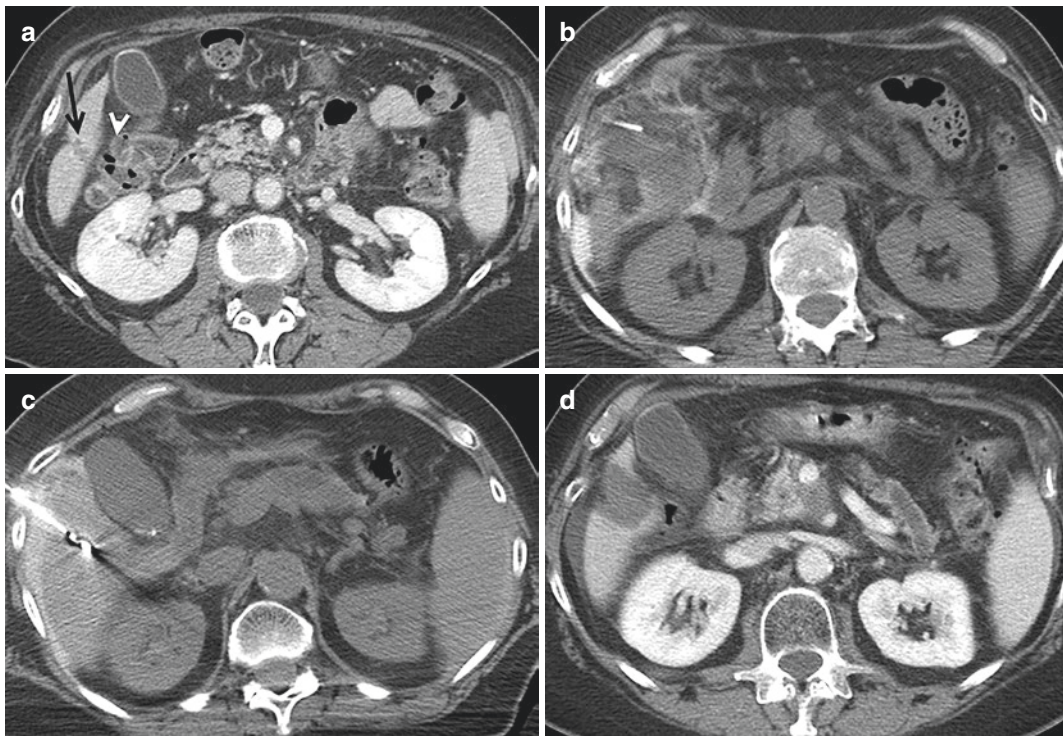

Fig. 4.1 Hydrodissection to facilitate microwave ablation of solitary liver metastasis in a 69-year-old female with pancreatic cancer. (**a**) Portal venous phase CT shows a solitary metastasis in segment 6 (arrow). The ascending colon is immediately adjacent to the lesion (arrowhead). This was the only known site of metastatic disease for over 1 year. (**b**) A 20-gauge needle was advanced between the liver and colon, and dilute contrast was injected to "hydrodissect" the colon away from the liver to prevent thermal injury to the colon during ablation. (**c**) The lesion was then targeted with a microwave probe. (**d**) Follow-up CT performed 1 month later shows the ablation zone surrounding the treated tumor. There was no clinical or radiographic suggestion of injury to the colon

increasingly nonalcoholic fatty liver disease. Despite early projections, the incidence of HCC continues to increase in the United States and HCC is a leading cause of cancer-related deaths worldwide [37, 38]. To improve early detection, medical societies including the AASLD and the NCCN to name but a few have endorsed routine screening for at-risk patients to identify small tumors amenable to curative therapies [38].

Before thermal ablative techniques were widely available, chemical ablation was commonly used to treat small HCC. Most patients with HCC have cirrhosis, and HCC is a relatively soft tumor. Injection of a chemical directly into the tumor is therefore largely contained by the surrounding fibrotic parenchyma. Chemical ablation achieved by advancing a straight or multi-pronged needle into the tumor, and incrementally injecting small aliquots of ethanol or acetic acid under imaging guidance. Ethanol is of similar density to fat, and therefore CT is particularly useful if larger doses of injectate are planned because its distribution within the tumor (and not in other structures such as vascular structures) can be easily seen (Fig. 4.2). When ultrasound guidance is used, this is typically performed as a staged procedure using smaller doses of ethanol.

Radiofrequency ablation (RFA) was introduced in the early 1990s, and in 1999 Livrhagi et al. published a prospective trial of HCC <= 3 cm that randomized to treatment with ethanol injection (PEIT) or RFA [39]. RFA was found to have a higher rate of complete necrosis and require fewer sessions than PEIT. A few years later, Lencioni et al. reported a prospective randomized comparison of RFA with PEIT in HCC patients within Milan criteria [40]. With a mean follow-up of nearly 2 years, the overall survival in the RFA group was 100% and 98% and complete necrosis was seen in 91% of tumors. This was significantly better than PEIT, and moreover, comparable to results seen after hepatic resection (HR). This made a compelling case for prospective randomized studies to directly compare outcomes of RFA and HR.

Between 2006 and 2017, there were four prospective randomized trials performed in China comparing RFA and HR for small HCC [41–44]. The inclusion criteria of each study are somewhat different, but all include lesions <= 5 cm in size. The data from these three trials are well summarized in a meta-analysis published in PlusOne in which the compiled data from prospective studies showed no difference in survival between patients undergoing RFA or HR at up to 4 years [45]. In the retrospective studies evaluated, however, there was a significant survival benefit of HR compared to RFA, likely reflecting selection bias with poor surgical candidates preferentially undergoing RFA.

Ablation for HCC may be performed in combination with arterially directed therapy. Elnekave et al. reported a retrospective case-controlled study of patients who underwent HR and combination embolization/ablation for solitary HCC <= 7 cm [46]. With a median follow-up of over 11 years, patients matched for Okuda stage who underwent HR or RFA had no significant difference in overall survival. Peng et al. randomized patients with recurrent HCC <= 5 cm to undergo RFA alone or in combination with chemoembolization (TACE) [47]. Overall survival at 5 years was better for patients who underwent combination treatment, but only for those with tumors that were 3.1–5 cm. Patients with tumors <= 3 cm did not benefit from the addition of TACE.

Three centimeters has been somewhat of a magic number for ablation, with tumors larger than 3 cm proving difficult to treat completely with ablation alone. This has long been thought to be related to the size of ablation that can be achieved with a single probe, with larger tumors requiring overlapping zones of ablation in order to achieve an adequate margin. Ideal positioning of multiple simultaneous or sequential probes is simple in theory but challenging to perform in practice.

Treating a margin of surrounding parenchyma is critical to ensure adequate treatment of microscopic tumor. In a study of 100 resected solitary HCC, Sasaki et al. found that of 100 resected tumors, 46—*or almost half*—had microsatellite of viable tumor detected by light microscopy [48]. When tumors less than 3 cm in size were found to have microsatellites, they were almost

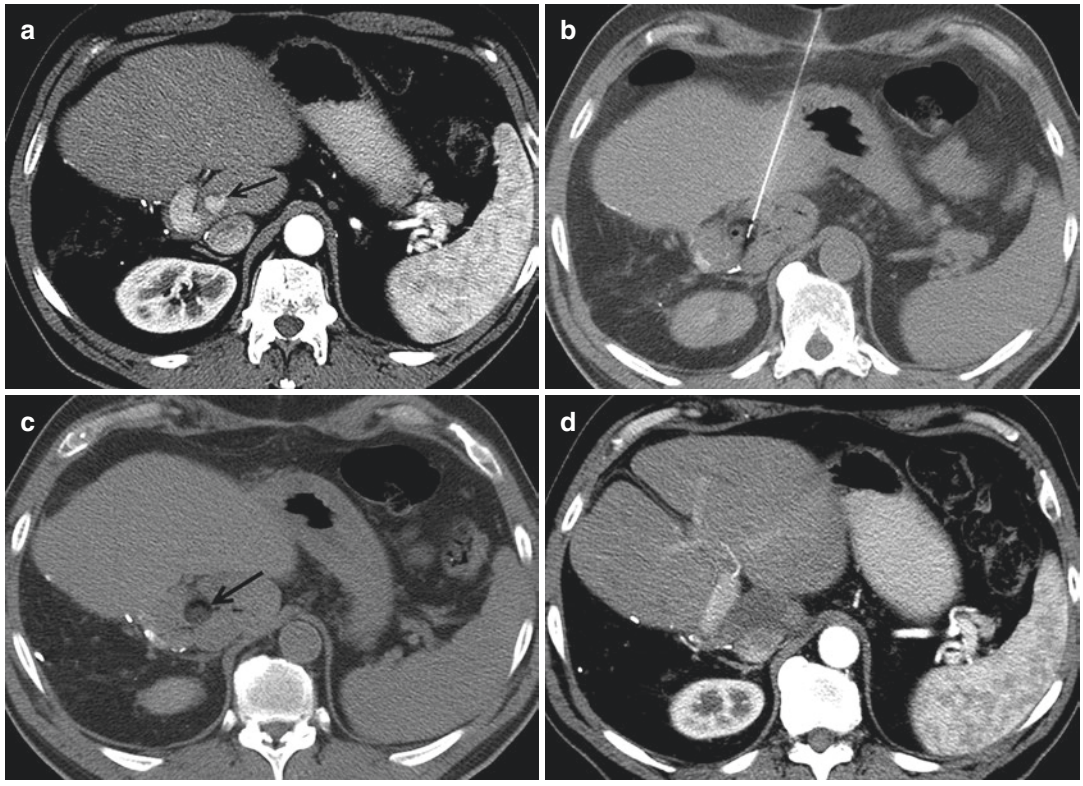

Fig. 4.2 Ethanol ablation of a focus of recurrent hepatocellular carcinoma in a 62-year-old man. (**a**) Arterial phase CT shows a solitary 1.6 cm HCC (arrow) in the caudate lobe adjacent to the portal vein and bile duct. (**b**) A 20-gauge needle was advanced into the tumor and 5 cc ethanol injected. (**c**) After a total of 14 cc ethanol injected, the low-density ethanol is seen conforming to the tumor geometry. (**d**) Arterial phase CT 3 months later shows no residual hypervascular tumor and low density in the caudate consistent with complete tumor necrosis

exclusively within a few mm of the index tumor. Tumors larger than 3 cm, however, had a significantly higher frequency and distance of microsatellites from the index tumor, with tumor cells found up to 3 cm away. Based on this data, one can easily see that ablation of a 3.5 cm tumor with the possibility of microsatellites up to 3 cm away tumor would be expected to have a high incidence of "local" recurrence.

The majority of prospective clinical trials studying percutaneous thermal ablation for HCC to date have looked at RFA. With new technologies, including microwave (MV) and irreversible electroporation (IRE), it is possible that larger tumors (MW) and tumors adjacent to structures susceptible to thermal damage (IRE) will increase the pool of candidates suitable for ablation.

Liver Metastases

The data for ablation of liver metastases is less robust than that for HCC.

Colon Cancer

Colon cancer is unusual among solid tumors in that when it metastasizes to liver, the liver is the only site of disease approximately half of the time. Although

there are no prospective randomized trials to support metastasectomy, early surgical series suggested improved survival following resection of Colorectal liver metastasis (CRLM) [49, 50]. When ablative treatments became available, it stood to reason that if ablation were able to completely eradicate viable tumor, that this would also be an acceptable technique to treat eligible patients, particularly those with lesions in difficult locations for resection.

A systematic review of 75 retrospective studies found local recurrence rates of 12–39% with 1-, 3-, and 5-year survival of 84%, 37%, and 17%, better than that typically reported for systemic chemotherapy alone even though it included studies with high local recurrence rates [51]. It is likely that the high local recurrence rates in the early studies were largely due to undertreatment. As experience with ablation has matured, it has been demonstrated that achieving a margin of at least 5 mm and ideally 10 mm circumferentially around a CRLM tumor is critical to ensuring long-term treatment success [52] (Figs. 4.3 and 4.4).

One of few prospective studies of ablation for CRLM was a phase II study that randomized patients with unresectable CRLM to systemic treatment with or without RFA [53]. At a median follow-up of 9.7 years, there was a significant benefit seen in the combination therapy arm with 35.9% alive at 8 years compared to 8.9% in patients who received systemic chemotherapy alone.

Unfortunately, our ability to predict which patients with metastatic CRLM are likely to benefit from local therapy is imperfect. A modified clinical risk score for ablation was described by Shady et al., based on the Fong Score used for surgical resection [54]. Based on a study of 162 patients, they describe 5 factors that were associated with poor survival: node-positive primary tumor, disease-free interval <12 months, multiple tumors, largest tumor >3 cm, and CEA > 30 ng/mL.

Another approach to determine to identify patients with good biology of disease is the "test of time approach" described by Livrhagi et al. [55]. This study followed 88 patients with resectable CRLM with RFA for a median follow-up of 28 months after ablation. Twenty-three (26%) patients remained disease-free and another 44 (50%) developed new lesions making them unsuitable for resection. In other words, 67 of 88 patients (76%) avoided surgery from which they were unlikely to benefit. The authors concluded ablation could reduce the number of resections without negatively impacting the clinical outcome.

Breast Cancer

Metastatic breast cancer is a systemic disease, but a subset of patients may have only oligometastatic disease for years, and these patients are good candidates for regional therapies including ablation, resection, and radiation therapy. Unfortunately, oligometastatic breast cancer has a heterogenous phenotype, and it is difficult to predict prospectively which subpopulation(s) will benefit from these treatments.

As with CRLM, the interest in local therapy of breast cancer liver metastases is based on reports in the surgical literature describing a survival advantage following hepatic metastasectomy [56, 57].

There are no prospective trials evaluating outcomes of ablation for Breast cancer liver metastasis (BCLM), and the systemic therapy options have changed dramatically in the time that ablation has been clinically available making measurable outcomes a moving target. The Mammary Cancer Microtherapy and Interventional Approaches (MAMMA MIA) study out of Germany retrospectively looked at 59 patients with breast cancer who underwent RFA, brachytherapy or radioembolization of BCLM to define characteristics of patients who benefited from local therapy [58]. Not surprisingly, they found that maximum tumor diameter <4 cm and history of <3 prior lines of systemic therapy were independent predictors of improved survival. This is supported by a retrospective study of Barral et al. who found that ablation provided effective local control and improved disease-free survival in patients with <4 cm lesions of oligometastatic breast cancer in lung and bone as well as BCLM [59].

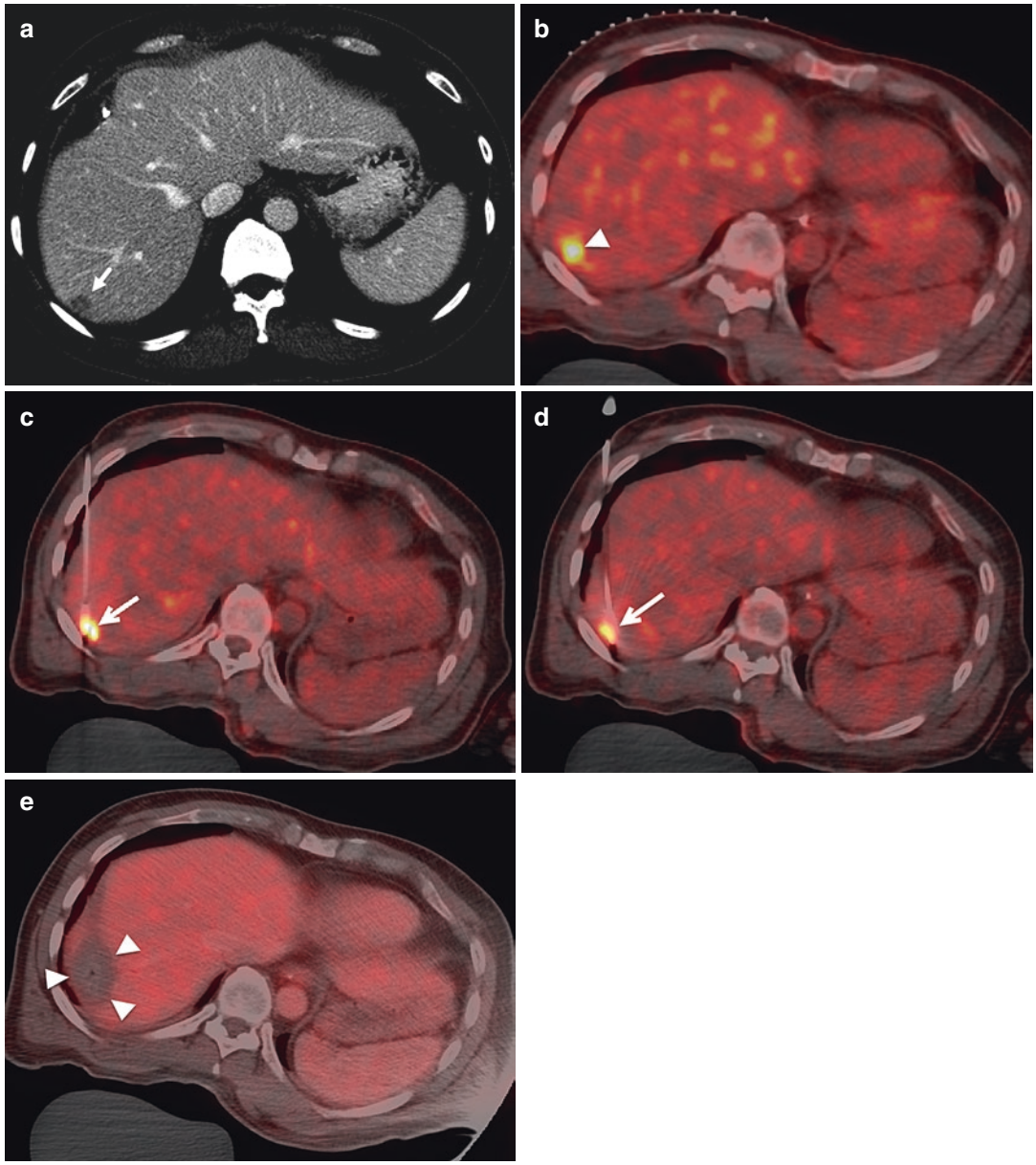

Fig. 4.3 Positron emission tomography (PET)-guided microwave ablation in a 54-year-old man with oligometastatic colorectal cancer to the liver. (**a**) Portal venous phase CT image demonstrates a solitary segment VII metastasis (arrow). (**b**) Intraprocedural planning PET/CT remonstrates solitary segment VII lesion, Fluorodeoxyglucose (FDG) avid (arrowhead). (**c**) Intraprocedural PET/CT shows microwave antenna positioned in the superior and lateral margin of the lesion (arrow). (**d**) Intraprocedural PET shows microwave antenna positioned in the inferior and medial margin of the lesion (arrow). (**d**) Immediate post-therapy PET/CT image demonstrates adequate margin and lack of metabolic activity within the ablation cavity (arrowheads). (**e**) CT abdomen with contrast in portal venous phase 1-month post-therapy shows complete response to therapy with adequate margins and no residual/recurrent disease (arrowheads)

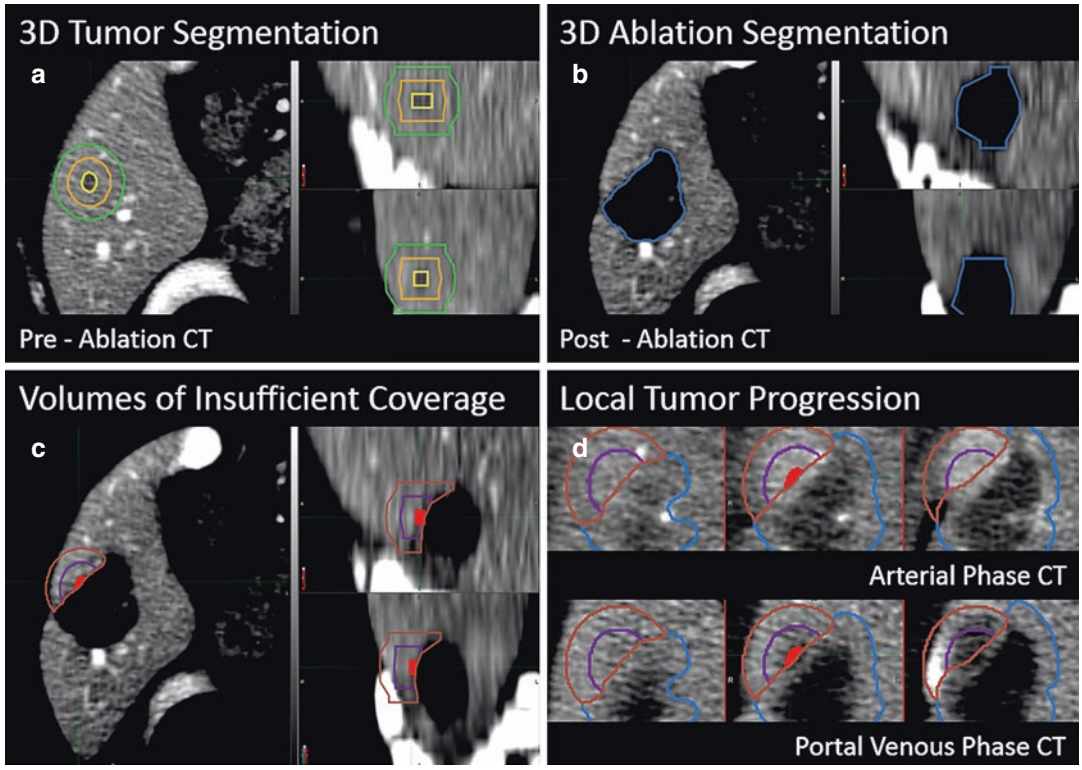

Fig. 4.4 Example of 3D assessment of ablation margins. (**a**) CT images with overlay of segmented tumor (yellow) and theoretical 5 mm and 10 mm margins shown in axial plane and sagittal and coronal reformats. (**b**) CT immediately after ablation shows segmented ablation zone. (**c**) Comparison with the initial segmentation shows insufficient treatment (residual tumor in red, 5 mm margin shown in purple contour and 10 mm margin in brown. (**d**) Axial images of follow-up CT obtained in arterial (top) and portal venous (bottom) phases show local tumor progression as hyperintense area on arterial phase and hypointense area on venous phase. Contours of ablation zone, and insufficiently covered volumes are overlaid showing spatial agreement between the location of progression and insufficiently covered regions of tumor. (Courtesy of Elena Kaye)

Conclusion

Percutaneous ablation techniques are well recognized as a primary local control tool in the treatment of focal malignancies. In the last two decades, multiple studies have characterized the basic principles underlying ablative therapies. Understanding these basic principles allows the physician understanding patient/lesion selection as well as how to improve outcomes based on the advantage and disadvantages of each technique. It is also clear that the evidence is more robust for ablation of primary liver malignancies; however, in the metastatic disease scenario and taking into account lesion size, ablation has comparable performance when compared to metastasectomy. Combination therapies continue to be an evolving field, and it is very possible that ablation may have an expanded role outside the traditional size criteria.

Key Points

- In general, we favor the use of high-powered microwave ablation for the treatment of tumors in the liver, and the operator must pursue tract cautery and avoid direct puncture of peripheral tumors.
- RF and laser ablation have substantial physical limitations compared with microwave ablation for tissue heating and thus reserved for short/precise ablation zones.

- Cryoablation should be used with caution in the liver, although it may be useful in the treatment of lesion close to critical structures.
- IRE may have a role in the treatment of central tumors or in those near critical structures.

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Regional Gene Therapy for Cancer

5

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Introduction to Cancer Gene Therapy

Gene therapy is a powerful technology that holds significant promise for cancer treatment. Many strategies have been explored for gene therapy, including correction of mutant genes, immune stimulation, prodrug activation, interference of oncogene expression, cellular therapy, and the use of oncolytic viruses. One of the main obstacles limiting these therapies has been inefficient gene transfer, with subsequently poor expression. Achieving potent gene expression with the use of viral technology has been integral to the successes recently documented for chimeric antigen receptor (CAR) T-cell and oncolytic virus therapy.

The following sections will address each therapy in detail, beginning with CAR T cells and moving on to oncolytic viruses. We will highlight the principles and controversies related to these therapies, paying special attention to how each therapy is uniquely capable of optimizing key advantages of a regional delivery approach: *enhanced delivery of therapeutics to the site of the tumor*; *enhanced targeting of cancer cells, thereby limiting normal-tissue toxicity*; *and generation of both a local and a systemic immune response that can target metastatic disease and potentially prevent tumor recurrence*. Findings from investigational basic science literature will demonstrate the robust potential of these cancer-targeted gene therapies. For each therapeutic strategy, we will discuss the clinical trials that have used a regional delivery approach.

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CAR T-Cell Therapy

Principles and Application to Solid Tumors

Genetic engineering technology can be used to redirect T cells toward cancer antigens. The T cell is an ideal host cell: it divides rapidly, facilitating viral integration, has transcriptional machinery that promotes high-level transgene expression from viral promoters, and it can establish memory for long-lasting transgene expression. And it is also a robust antitumor effector cell: the signaling elements activated upon tumor antigen recognition trigger tumor lysis, as well as T-cell proliferation and cytokine secretion.

Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_5

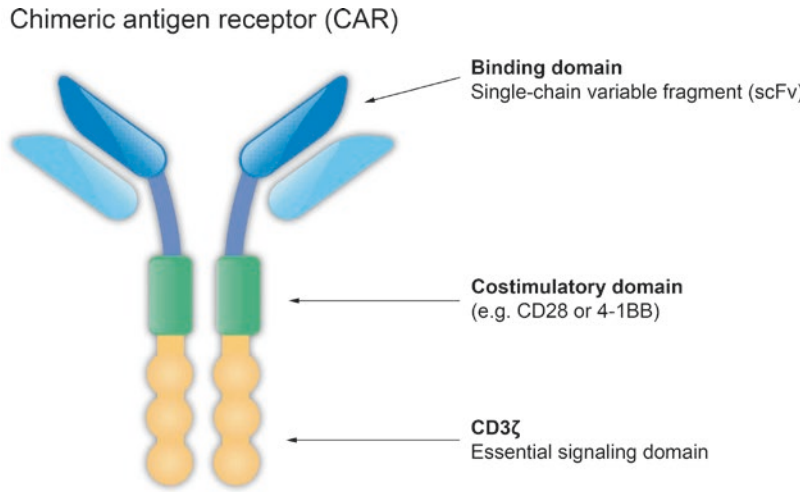

Fig. 5.1 Chimeric antigen receptors link an antibody-derived antigen-recognition domain to intracellular signaling domains that serve to activate and optimize T-cell function

CAR T cells are tumor-specific T cells generated by the transfer of genes encoding cancer-targeting receptors (Fig. 5.1) [1–4]. Retroviruses encode for these CARs and other cellular enhancements, serving as the delivery system for genome integration and subsequent expression. The "chimeric" namesake refers to the fusion of two separate protein domains; CARs link a high-avidity tumor antigen–binding element derived from a monoclonal antibody (which provides cancer cell recognition) to the CD3ζ intracellular signaling domain (to signal T-cell activation). This tandem fusion results in a high-avidity effective binding which then leads to phosphorylation of the intracellular signaling portion of the receptor, leading to T-cell activation [5–10]. Further genetic modification is then superimposed to optimize function. To provide both signals necessary to optimize T-cell proliferation and survival, signaling elements include costimulatory domains, such as CD28 and 4–1BB. Multiple studies have established that providing costimulation genetically encoded within the CAR is critical for the antitumoral activity of adoptively transferred T cells—enhancing both T-cell persistence and function [5–10]. The advent of so-called second-generation CARs, which combine activating and costimulatory signaling domains, has led to the successful use and subsequent FDA approval of two CD19-targeted CAR T-cell immunotherapies [11–13].

However, treating *solid tumors* requires overcoming multiple obstacles—achieving effective T-cell infiltration of a solid tumor mass that is highly immunosuppressive requires genetic modifications and delivery strategies that go beyond those of the original CAR design. The treatment of solid tumors is the focus of this chapter. We will highlight how regional delivery, which has the potential to efficiently deliver T cells to the primary tumor site and overcome tumor-mediated immune inhibition, is poised to become the optimal approach for CAR T-cell therapy. Furthermore, as with oncolytic virus therapy, the therapeutic benefit of regional delivery of CAR T cells extends beyond the local site of delivery. The generation of a local immune response can result in systemic immunosurveillance, with the potential to eliminate metastasis and prevent tumor recurrence.

Optimizing CAR T-Cell Therapy Using Regional Delivery

Solid malignancies pose unique obstacles to T-cell therapy. Unlike hematologic malignancies, which reside within the same peripheral compartment into which intravenously administered cells are delivered, solid tumor masses are sequestered within an immunosuppressive compartment that can be difficult to penetrate. Regional therapy can overcome the limitations

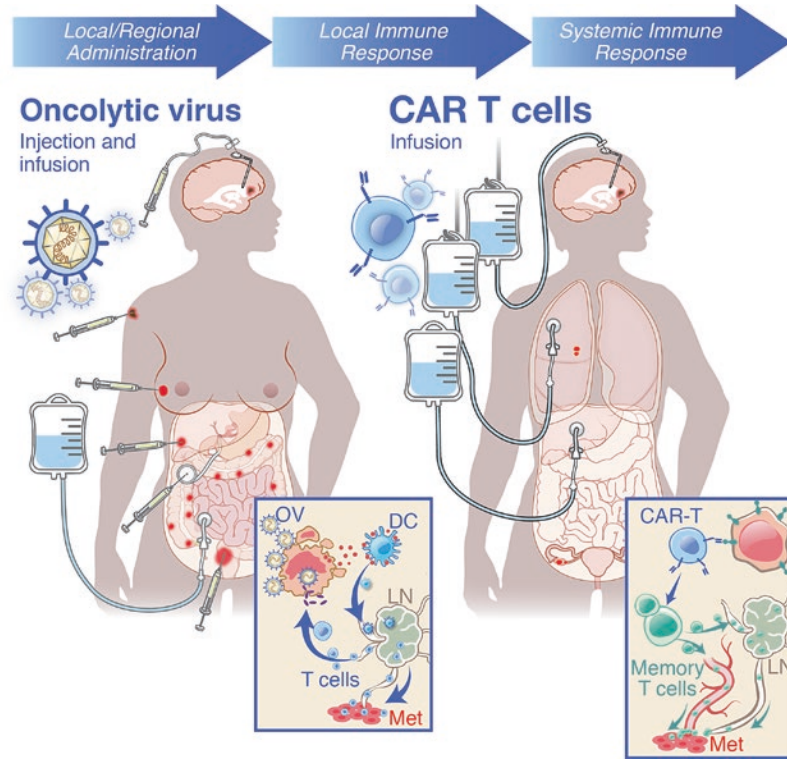

Fig. 5.2 [Left] Regional delivery of oncolytic virus (OV) is performed as either infusion or intralesional injection. Inset demonstrates viral infection of tumor cells leading to the two mechanisms of action of oncolytic viral therapy: (1) cancer cell death and (2) generation of a local and systemic antitumor immune response. Tumor cell death leads to release of damage-associated and pathogen-associated molecular patterns (DAMPs and PAMPs), triggering dendritic cell (DC) activation and migration to lymph nodes (LN), the anatomic location where T-cell priming occurs. Dendritic cells activate T cells by presenting tumor antigen and expressing activating cytokines and costimulatory ligands, leading to T-cell activation and differentiation. Effector T cells can now circulate to primary tumor, as well as to metastatic sites (MET), and effect immune-mediated tumor cell death. [Right] Regional therapy with chimeric antigen receptor (CAR) T cells employs either indwelling catheters or transient access to the delivery site to infuse cancer antigen targeted T-cell therapy. CAR T cells recognize cancer antigen, are triggered to activate, and induce regression of primary tumor. Activated T cells also generate T-cell memory that establishes a systemic immunosurveillance capable of inducing regression of metastases and preventing tumor recurrence

of systemic administration, enhancing tumor infiltration and overcoming immune suppression (Fig. 5.2). We recently demonstrated the merits of regional administration of mesothelin-specific CAR T cells in a clinically relevant model of pleural mesothelioma. Regionally administered—as compared with systemically delivered—CAR T cells displayed rapid and robust T-cell expansion and activation, with elimination of primary tumor [14]. Regional administration established circulation of CAR T cells that retained their functional activity, establishing T-cell memory and long-term systemic immunosurveillance capable of eradicating disseminated tumor sites. A single dose of regional CAR T-cell therapy provided effective protection against tumor rechallenge up to 200 days after the initial T-cell dosing; such persistence has been correlated with treatment efficacy and prevention of tumor relapse in several preclinical models and clinical trials. Based on these results, intrapleural administration of CAR T cells has now been translated to a phase I clinical trial of pleural mesothelioma and breast and lung primary tumors metastatic to the pleura (NCT02414269 and NCT02792114).

These results demonstrate that regional administration has benefits beyond treatment of the primary tumor. The ability of intrapleurally administered T cells to circulate and persist within the periphery opens new avenues of treatment for other metastatic cancers with accessible tumor sites, which may serve as a "regional charging and distribution centers" for CAR T-cell therapy—in effect, treating the most accessible tumor site can translate into sustained responses in more-inaccessible tumors. Examples of cancers that could benefit from this treatment strategy include those that metastasize to the pleural cavity (such as lung and breast cancers), those that metastasize to the peritoneal cavity (colorectal and ovarian cancers), and liver metastases (colorectal, gastric, and pancreatic).

Preclinical Data Supporting Regional CAR T-Delivery

Promising results using these approaches have been seen in preclinical studies of intracranial, intraperitoneal, and intrahepatic delivery of CAR T-cell therapy.

Our group at Memorial Sloan Kettering has shown that intrapleurally administered CAR T cells show enhanced antitumor efficacy in an orthotopic mesothelioma mouse model even at a reduced dose compared to systemically administered CAR T cells, and this enhanced efficacy is facilitated by CD4-dependent CD8 T-cell proliferation [15]. A group at Roger Williams Medical Center demonstrated that intraperitoneal administration of carcinoembryonic antigen (CEA)–targeting CARs, in an animal model of colorectal primary tumor with peritoneal carcinomatosis, was superior to intravenous administration and was able to mediate regression of extraperitoneal tumor sites [16]. Other groups have similarly shown robust antitumor activity following intraperitoneal administration of CAR T cells [17]. A group from Sloan Kettering Institute showed that intraperitoneal administration of IL-12–secreting CAR T cells was efficacious in a model of MUC16-expressing ovarian peritoneal carcinomatosis. IL-12 secretion was genetically encoded in the same viral vector used for CAR transduction, simplifying gene delivery and optimizing CD8+ T-cell function [18]. Hepatic vascular infusion is another promising avenue of regional administration, as demonstrated by the group at Roger Williams. The researchers infused CAR T cells into the portal circulation in a model of CEA-expressing colorectal liver metastases [19].

Despite these preclinical successes, obstacles remain in the treatment of solid tumors. The absence of T cells 2 weeks after initial administration in a clinical trial targeting glioblastoma suggested that, even with the robust T-cell infiltration achieved by regional delivery, CAR T cells may not be able to overcome all of the challenges that solid tumors present [20]. An increasing amount of preclinical and clinical experience has demonstrated the importance of overcoming tumor-mediated immune inhibition, which is the focus of the next section.

Gene Engineering to Enhance Efficacy: Engineering the T Cell Beyond the Car, with a Focus on Overcoming Immune Suppression

The immunosuppressive obstacles encountered by CAR T cells led to the realization that large, established solid tumors require CAR T cells with enhancements that go beyond CAR recognition and signaling. Although regionally delivered T cells may infiltrate the tumor mass more efficiently than systemically delivered T cells, they are still subdued by a formidable immunosuppressive tumor environment upon arrival. Various groups have taken advantage of the flexibility afforded by viral vectors to further enhance CAR T-cell function, creating T cells that optimize T-cell metabolism [6, 9], program a stem cell–like pattern of expression that enhances survival and self-renewal [20, 21], and express cytokines and cytokine receptors that optimize function [1, 22].

One of the more compelling strategies is engineering T cells to overcome tumor-mediated immune inhibition. To eliminate tumor cells, T cells must not only persist but must sustain function in an environment rich with inhibitory

signaling. The success of antibodies targeting immune checkpoints such as programmed death 1 (PD-1) and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) supports the therapeutic potential of counteracting immune inhibition [23–25]. Since adoptively transferred T cells are susceptible to inhibition, strategies combining adoptive T-cell therapy with checkpoint blockade have been investigated [26–28]. In "adaptive immune resistance" [29], tumor cells generate anti-immune protection by expressing coinhibitory ligands, such as PD-1 ligand, following exposure to T-cell–secreted Th1 cytokines [30–32].

Our own preclinical data established that human CAR T cells—even when combined with costimulatory signaling with either 4–1BB or CD28—are subject to inhibition. Using a model of pleural mesothelioma, we demonstrated that T-cell exhaustion can be reversed by interfering with the PD-1 pathway, either by antibody blockade or by genetically engineering CAR T cells to overexpress a PD-1 dominant negative receptor (which serves as a decoy receptor to prevent signaling through the native PD-1 receptor) or an shRNA-targeting PD-1 receptor (which downregulates PD-1). Whereas both avenues of checkpoint blockade are effective, the genetically engineered strategy might be preferred for its efficacy and simplicity, as it nullifies the need for repeated antibody administration. Other groups have also developed strategies to overcome CAR T-cell inhibition in solid tumors [32, 33]; examples include the use of IL-12–secreting CAR T cells to overcome PD-1–mediated inhibition [34], a PD1CD28 "switch receptor" that translates inhibitory ligand binding into costimulatory signaling [35], CRISPR/Cas9 gene editing to generate PD-1–deficient CAR T cells [36], and the construction of T cells that secrete PD-1 antibody [37].

Safety Engineering for CAR T-Cell Therapy

Retroviruses have been primarily used in CAR T-cell therapy to deliver the genetic sequence encoding the CAR. The payload is delivered as RNA that is then reverse-transcribed into DNA for permanent integration into the genome of patient cells. Although integration provides high fidelity and long-lasting expression, it also carries the potential for insertional mutagenesis and malignant transformation. Lentiviral vectors have a safer integration site profile than gammaretroviral vectors [38]; however, both have been safely used at major US institutions that are pioneering CAR technology [39, 40].

Although CD19 CAR T cells have shown impressive efficacy in treating leukemia, this success has come with significant and at times life-threatening side effects due to T-cell cytokine release leading to a systemic inflammatory response that manifests as fever, hypotension, and neurologic dysfunction. Most cases of *cytokine release syndrome* can be treated with corticosteroids and IL-6–targeting antibodies, with the occasional need for end-organ support in the intensive care unit. For increased safety, "suicide genes" such as iCaspase-9 [41], EGFR (epidermal growth factor receptor) mutation [42], and herpes simplex virus (HSV) thymidine kinase [43] can be used to mediate rapid T-cell elimination after administration of a prodrug or antibody, should side effects persist.

Most CARs targeting solid tumors are aimed at antigens shared by normal tissues and, therefore, carry the risk of "on-target off-tumor toxicity" [44, 45]. Judicious selection of the target antigen can offset this. The optimal target is one whose expression is restricted to expendable cells or, better yet, to tumor cells only. Examples of suitable targets include mesothelin (we have not experienced any on-target off-tumor toxicities in our ongoing phase I clinical trial), the mutated form of EGFR that is expressed on glioblastoma multiforme tumors [46, 47], and a glycosylated form of MUC1 that is unique to tumor cells [48, 49]. Genetic strategies to limit normal-tissue toxicity are also active areas of investigation [50, 51].

Clinical Trials of T Cells Using Regional Delivery Strategies

Early phase clinical trials employing regional delivery have now emerged. Hepatic arterial

infusion, achieved through percutaneous access of the arterial system using angiographic catheters, has been investigated as a method of delivery of CEA-targeting CAR T cells for the treatment of colorectal liver metastases. Hepatic arterial infusion was well-tolerated (NCT01373047) [52]; intravenous delivery, on the other hand, was associated with dose-limiting colitis (NCT00923806) [53]. All but 1 patient in the HAI study had more abundant CAR T cells in liver metastasis tissue compared to healthy liver tissue, including 1 patient who had a durable presence of CAR T cells 12 weeks after initial administration. Furthermore, CAR T cells were detected in peripheral blood samples from only 2 of 8 patients. Although hepatic arterial infusion may result in decreased toxicity, the limited systemic immunity generated may ultimately limit efficacy, especially for extrahepatic disease. As we and others have demonstrated in preclinical studies, systemic T-cell immunity focused on a safer target than CEA may be the more optimal approach, achieving both efficacy and safety [15]. The authors of the HAI study assessed response to treatment by monitoring CEA levels, as imaging studies often do not adequately reflect response to immunotherapy. Although seven of eight patients in this trial had some decrease in CEA level, all but one had died at the time of study publication, with a median overall survival of 15 weeks.

In a trial from City of Hope (NCT00730613) [54], IL13Rα[alpha]2-targeting CARs were infused directly into 3 patients with brain tumors, using a catheter/reservoir system. Treatment was well-tolerated and displayed some antitumor activity: 1 patient had decreased target antigen expression, and another had an increase in necrosis as measured by MRI. A second publication from this group [55] describes a patient with multifocal glioblastoma recurrence including multiple brain and spinal metastases who was initially treated with CAR T cells infused directly at a resected brain tumor site via catheter infusion. Although there was no relapse at the infused resection cavity, other lesions progressed. A remarkable response came when T cells were infused into the cerebrospinal fluid by accessing the lateral ventricle, a delivery method associated with complete radiographic elimination of spinal metastases and a good response in brain metastases. This response was durable to 7.5 months, and measurable T cells were present along with cytokines in the cerebrospinal fluid for at least 7 days after each ventricular infusion.

An ongoing trial from our group at the Memorial Sloan Kettering has demonstrated safety and promising antitumor activity of intrapleurally administered CAR T cells targeting mesothelin expressed on cancer cells. Although we have clearly seen indications of the potential for efficacy of regional delivery of CAR T cells, clinical trials exploring this approach have thus far been conducted with limited numbers of patients (Table 5.1). We therefore await more-mature results to further clarify the efficacy of regional delivery of CAR T-cell therapy.

Oncolytic Virus Therapy

Background, Viral Technologies, and Regional Delivery to Solid Tumors

Oncolytic viruses are versatile, capable of direct lysis of the tumor, and able to deliver transgenes to enhance efficacy and decrease toxicity. As one of the mechanisms of oncolytic efficacy is tumor cell lysis, replication-competent viruses are specifically chosen for their ability to self-replicate and reinfect. The experience of using oncolytic viruses to treat cancer has shown they not only induce tumor cell lysis but also generate antitumor immunity, both of which contribute to treatment effect. Furthermore, as with CAR T cells, oncolytic viruses can be genetically engineered to express therapeutic transgenes that further enhance antitumor activity.

The benefits of regional delivery of oncolytic viruses are similar to those for CAR T cells (Fig. 5.2). Researchers at Massachusetts General Hospital demonstrated that intraperitoneal administration of an oncolytic HSV for peritoneal metastases (colorectal primary) achieved better tumor lysis than systemic delivery. An added benefit of regional delivery was decreased

Table 5.1 Completed CAR T trials with regional delivery strategy

	NCT Year launched Phase Center Number of patients	CAR target Costimulation Other features	Cancer diagnosis	Administration	Notable study feature or finding
1	NCT00730613 [54] 2008 Phase 1 City of Hope medical center 3 patients	IL13Rα[alpha]2 NKG2D+/-CD28 costimulation Hy/TK selection/suicide fusion protein	Glioblastoma	Tumor resection cavity via catheter/ reservoir system	All patients had increased FLAIR MRI inflammatory signal after treatment, and 1 patient with re-resection had decreased tumor IL13Rα[alpha]2 expression. Both observations suggest an efficacy signal which correlated with level of IL13Rα[alpha]2 antigen expression. Due to 3 grade 3 AEs, dose escalation terminated. No ≥ grade 4 AEs
2	NCT01082926 [95] 2010 Phase 1 City of Hope medical center 6 patients	IL13Rα[alpha]2 CD28 costimulation Hy/TK selection/suicide fusion protein	Glioblastoma	Intratumoral infusion	CAR T cells were detected at the site of recurrence near corpus callosum in one patient, suggesting that CAR T cells can traffic to other sites of disease
3	NCT01373047 [52] 2011 Phase 1 Roger Williams medical center 8 patients	CEA CD28 costimulation	Colorectal and Periampullary adenocarcinoma with liver metastases	Hepatic arterial infusion using percutaneous access	CEA levels were used to monitor efficacy to overcome limitations of imaging studies in assessing response to immunotherapy No ≥ grade 3 AEs related to the CAR T-hepatic arterial infusions
4	NCT01837602 [96] 2013 Phase 0 University of Pennsylvania 6 patients	c-met 4–1BB costimulation	Breast	Intratumoral injection	Extensive necrosis at injection site and loss of c-met expression both suggest efficacy 6 ≥ grade 3 AEs
5	NCT02208362 [55] 2015 Phase 1 City of Hope medical center Ongoing patient recruitment	IL13Rα[alpha]2 4–1BB costimulation	Glioblastoma	Intratumoral, intracavitary, intraventricular	Ongoing study with case report of patient who received dual intracavitary and intraventricular therapy and had transient complete response for 7.5 months No ≥ grade 3 AEs

toxicity to normal tissues [56], enabling higher doses. Other examples of regional delivery of oncolytic viruses in the preclinical setting include portal infusion of HSV in a model of colorectal liver metastases [57], carotid infusion of HSV to treat head and neck squamous cell carcinoma [58], intrapleural administration of HSV to treat pleural-based lung cancer [59, 60], and intraperitoneal administration of a vaccinia virus to treat malignant peritoneal mesothelioma [61].

Oncolytic Viruses Generate Both a Local and a Systemic Immune Response

Although classified as a local intervention, treatment with oncolytic virus can elicit a systemic antitumor immune response, serving as an in vivo vaccine that generates a local innate and adaptive immune response with the potential of establishing systemic immunity.

The progression from a local immune response to systemic immune surveillance follows the typical immunologic sequence of triggering innate immunity followed by activation of adaptive immunity. Oncolytic viruses induce highly immunogenic cell death whereby tumor cell lysis leads to local efflux of tumor antigens and danger signals that trigger antigen-specific immunity: dendritic cells are recruited for antigen uptake (and activated by cell breakdown products) and migrate to lymph nodes to activate the adaptive immune system. The end effector is the potent T cell, which mediates antitumor effect via tumor lysis and cytokine secretion. The response induced by T cells can be particularly robust if tumor antigens that are especially immunogenic are made available; the availability of these antigens (termed "neoantigens") depends on the mutation frequency found within the tumor. The importance of these neoantigens has been highlighted by studies demonstrating that unique mutations identified by tumor sequencing identify patients likely to respond to immunotherapy [62, 63]. In effect, oncolytic viruses are in vivo vaccinations that generate systemic immunity capable of inducing regression of distant, uninjected/uninfected tumors [64]. In other preclinical studies, mice previously cleared of tumor by the use of an oncolytic virus remained tumor-free after rechallenge with tumor cells, which is consistent with the establishment of immunologic memory and suggests that oncolytic viruses can play a role in preventing recurrence [65, 66]. Such findings are consistent with our observations that regional delivery of CAR T-cell therapy generates a systemic response by establishing circulating T-cell memory.

The ability of oncolytic viruses to generate a de novo endogenous immune response supports the use of rational combinations of oncolytic viruses and immune checkpoint blockade (ICB) agents. As the efficacy of ICB depends on the activation of a preexisting immune response [23, 67–69], delivery of oncolytic virus can be used to turn a "cold" tumor into a "hot" tumor with a pro-inflammatory/immunogenic environment, which can be followed by ICB to release the "brakes" on the antitumor T-cell immune response [70, 71]. Preclinical studies have demonstrated that intralesional injection of oncolytic virus can induce T-cell infiltration and increase the efficacy of CTLA-4 blockade in melanoma tumors; the combination of intralesionally administered oncolytic virus and CTLA-4 blockade enhanced regression of both injected and distant metastases [64, 72].

Safety Engineering for Oncolytic Viruses: Enhancing Tumor Tropism for Selective Replication in Tumor Cells

As we have demonstrated for CAR T cells, the clinical promise of oncolytic virus therapeutics relies on safety as much as efficacy. Safety is of particular concern in the case of oncolytic viruses, as these viruses are infectious pathogens that can cause disease. By regulating the viral life cycle of oncolytic viruses—manipulating attachment, cell cycle entry, and viral replication—they can be optimized to selectively target tumor cells.

Genetic modification can alter the viral capsid to enhance binding to cell-entry receptors preferentially expressed on tumor cells [73] and even exchange the typical capsid epitopes for single-

chain variable fragments that target virus to a tumor cell surface receptor of choice [74]. Another way to preferentially lyse tumor cells is to preferentially spare normal tissue; the deletion of virulence genes such as thymidine kinase can result in selective replication within only rapidly dividing tumor cells that have sufficient transcriptional machinery to support viral replication [75]. The only FDA-approved oncolytic virus therapy—T-VEC—is a modified HSV-1 with ICP34.5 inactivation, which halts replication and leads to apoptosis of infected normal cells [65, 76]. Another deletion strategy is to place virulence genes under the control of tumor tissue–specific promoters [77–79].

Genetic Engineering to Express Therapeutic Genes

Oncolytic viruses are extremely versatile therapeutics, as they can be genetically engineered with elements that enhance their two primary mechanisms of action: lytic function and stimulation of antitumor immunity. Serving as a vector for the delivery of therapeutic genes, T-VEC secretes granulocyte macrophage colony-stimulating factor (GM-CSF), which recruits and activates dendritic cells for optimal antigen presentation to T cells. Other strategies aimed at bolstering the immune response include delivery of cytokines (IL-2, IL-12, TNF) [80, 81], expression of tumor-associated antigens [74], and the addition of costimulatory signaling [72, 82]. To enhance tumor lysis, transgenes have been incorporated (1) to activate chemotherapy prodrugs [83–85], and (2) to express thymidine kinase (which converts administered ganciclovir into the toxic ganciclovir monophosphate) [86].

Clinical Trials of Oncolytic Viruses Using Regional Delivery Strategies

To date, only one oncolytic virus—T-VEC, an attenuated HSV-1 engineered to express GM-CSF—has been approved by the FDA for the treatment of cancer, specifically for advanced melanoma. Promising early clinical results led to the first randomized controlled trial: OPTIM (Oncovex$^{GM\text{-}CSF}$ Pivotal Trial in Melanoma) [87–89]. In patients with stage IIIb, IIIc, or IV melanoma with unresectable but accessible lesions, treatment with T-VEC resulted in an enhanced durable objective response (16.3% vs. 2.1%; $p < 0.001$) and overall response (26.4% vs. 5.7%; $p < 0.001$) rate, compared with recombinant GM-CSF. Regression was observed in injected and uninjected lesions, which supports the role of oncolytic viruses to generate systemic immunity [90]. Following these results, the FDA-approved T-VEC for the treatment of unresectable, injectable cutaneous, subcutaneous, and nodal melanoma with limited visceral disease. Locally delivered intralesional T-VEC generated an antitumor immune response; injected lesions accumulated MART-1–specific $CD8^+$ T cells, with an associated decrease in $CD4^+FoxP3^+$ regulatory T cells and myeloid-derived suppressor cells [90, 91].

Many of the preclinical studies supporting combination therapy with an oncolytic virus and an ICB agent have now been translated into clinical trials (Table 5.2). The use of intralesional T-VEC followed by the anti–CTLA-4 antibody ipilimumab in patients with advanced melanoma [92] resulted in an objective response rate of 50%, with 44% of the patients exhibiting durable responses lasting >6 months. A subsequent randomized controlled trial (comprising 198 patients with unresectable stage IIIB-IV melanoma) compared T-VEC with and without ipilimumab and found a significant difference in the response rate (39% vs. 18%; $p = 0.002$); correlative studies found increased levels of T cells in patients receiving T-VEC with ipilimumab [93]. The use of the anti–PD-1 antibody pembrolizumab may be even more effective—in a phase I study of 21 patients with melanoma, pembrolizumab resulted in a 62% objective response rate and an impressive 33% complete response rate (NCT02263508) [94].

Preclinical and clinical studies have explored other methods of delivery for oncolytic virus therapy, including pleural and peritoneal delivery and hepatic arterial infusion. These methods have been combined with systemic therapy, including chemotherapy and ICB. Intraperitoneal delivery

Table 5.2 Selected oncolytic trials with Regional Delivery Strategy with published results and novel study findings or features

	NCT Year launched Phase Center Number of patients	Virus design	Cancer diagnosis	Notable study feature or finding
Intrahepatic				
1	NCT00012155 [97] 2003 Phase 1 MSK 12 patients	NV 1020	Colorectal	A majority of virus cleared by the liver and not found in systemic circulation, proving advantage of regional delivery 1 SAE attributed to viral therapy
Intraperitoneal				
1	NCT00002960 [98, 99] 1997 Phase 1 Multicenter 36 patients	Recombinant adenovirus-p53 SCH-58500	Fallopian tube, ovarian, primary peritoneal	50% of women who completed 3 cycles of treatment had a CA-125 response, used to monitor responses 8 ≥ grade 3 AEs
2	NCT00408590 [100] 2004 Phase 1 Mayo Clinic, NCI 37 patients	CEA-expressing measles virus with thyroidal sodium iodide symporter	Ovarian	Dose-dependent CEA elevation was observed in peritoneal fluid and serum, supporting dose- dependent activity 5 patients had significant decreases in CA-125 levels, used to monitor responses 3 SAEs in cohort 1, 2 SAEs in cohort 2
Intrapleural				
1	NCT01212367 [101] 2009 Phase 1 UPenn, NCI 9 patients	Ad.hIFN-α[alpha] (Scheme 721015, adenoviral-mediated interferon alpha)	Mesothelioma	No increase in humoral immune response to the virus antigen or mesothelin, however there was response to the mesothelioma cells. Two patients subsequently underwent radical pleurectomy Dose escalation terminated due to severe "flu-like" symptoms. Two patients had catheter infections
2	NCT01119664 [102] 2010 Phase 1,2 UPenn 40 patients	Ad.hIFN-α[alpha] (Scheme 721015, adenoviral-mediated interferon alpha)	Mesothelioma	Median overall survival for all patients with epithelial histology was 21 months versus 7 months for patients with non-epithelial histology. For both cohorts combined, there was stable disease in 62.5% of patients and partial responses in 25% of patients, however, no complete responses were observed 6 SAEs, none attributable to drug instillation
Intratumoral				
1	NCT00289016 [103] 2005 Phase 2 Multicenter 50 patients	HSV with GM-CSF (Talimogene laherparepvec)	Melanoma	26% of patients on study got to NED (3 able to have surgery after T-VEC). 1-year survival was achieved for all patients who had partial response, complete response, or surgical complete response No SAEs related to treatment

Table 5.2 (continued)

	NCT Year launched Phase Center Number of patients	Virus design	Cancer diagnosis	Notable study feature or finding
2	NCT00769704 [104] 2009 Phase 3 Multicenter 436 patients	HSV with GM-CSF (Talimogene laherparepvec)	Melanoma	26% of patients treated with T-VEC had OR, vs. 6% of patients treated with GM-CSF No ≥ grade 3 AE occurred in ≥3% of pts. in either arm
3	NCT01740297 [88] 2013 Phase 1,2 Multicenter 217 patients	HSV with GM-CSF (Talimogene laherparepvec)	Melanoma	The ORR of the combination therapy group was 38.8% vs. 18% with ipilimumab alone. 13.3% of patients in the combination group achieved complete response (vs. 7%) Combination therapy group had a higher rate of response in uninjected lesions (35.5% vs. 13.6%) 28% of combination therapy patients and 18% of ipilimumab patients had ≥ grade 3 AE
4	NCT02263508 [105] 2014 Phase 1b Multicenter 21 patients	HSV with GM-CSF (Talimogene laherparepvec)	Melanoma	Circulating CD8+ T cells, including those expressing Tim3 and BTLA became elevated during treatment with T-VEC initially but decreased after pembrolizumab began 33% of patients had grade 3 or 4 AEs
5	NCT00554372 [106] 2008 Phase 2 Multicenter 30 patients	JX-594: Recombinant vaccinia virus (TK-deletion plus GM-CSF)	Hepatocellular	Assessed induction of humoral antitumor immunity through antibody—Mediated complement dependent toxicity (CDC). 11/16 patients in the high-dose cohort developed CDC. Also assessed cellular immunity and found that cytotoxic T cells were induced to vaccinia peptides and the JX-594 transgene product β-gal 4/14 patients in low dose and 4/16 patients in high dose had SAEs
6	NCT01227551 [107] 2011 Phase 2 Multicenter 57 patients	Coxsackievirus A21 (CVA21)	Melanoma	Both injected and uninjected lesions responded. 14/40 evaluable patients (35%) achieved irPFS at 6 months No ≥ grade 3 or 4 product related AEs
7	NCT02272855 [108] 2014 Phase 2 Multicenter 46 patients	HF10	Melanoma	Responding tumors showed increased total TILs and CD8+ T cells 3 ≥ grade 3 AEs

AE, adverse event; *BTLA,* B and T lymphocyte associated; *CEA*, carcinoembryonic antigen; *GM-CSF*, granulocyte macrophage–colony stimulating factor; *HSV*, herpes simplex virus; *NED*, no evidence of disease; *SAE*, severe adverse event; *T-VEC*, talimogene laherparepvec; *TK*, thymidine kinase

can be used for primary tumors presenting as carcinomatosis. Early studies have demonstrated the safety and feasibility of intraperitoneal delivery. Patients with ovarian or primary peritoneal cavity cancers have received intraperitoneal delivery of an adenovirus (NCT00002960) via Hickman, Tenckhoff, or PortaCath catheters. The authors observed manageable toxicity and found transgene expression in both ascitic fluid and tumor biopsy specimens. Similar to the difficulties faced when attempting to estimate the peritoneal surface disease during preoperative evaluation, CT scan did not reliably identify an effect on disease, and measured CA-125 levels may be a better way to gauge treatment response in this context. Combination treatment with chemotherapy performed the best, and a dose-dependent effect was observed. Regional therapy has also shown promise for malignant pleural mesothelioma. Intrapleural delivery (via pleural catheter) of adenovirus with IFN-γ (NCT01119664) and adenovirus with IFN-α[alpha] (NCT01212367) have been safely applied in early phase clinical trials. One patient from the latter study had a significant response at both intra- and extrathoracic disease sites, suggesting that systemic immunity was generated. Hepatic arterial infusion is a potential regional delivery method for primary and metastatic lesions to the liver. In NCT00012155, patients received an intraarterial injection of NV1020 (HSV) into the hepatic artery for the treatment of colorectal liver metastases.

Conclusion

As our understanding of solid tumor immunology deepens, and as genetic engineering technology continues to advance, regional gene therapies are poised to become effective options in cancer treatment. Regional gene therapy may be an essential first step to achieving durable responses in solid tumors. The ability to generate both local and systemic antitumor immunity is an especially promising attribute of these treatments. Solutions to avoiding normal-tissue toxicity have been addressed in preclinical studies and have already been translated to the clinic. Combination treatment strategies, incorporating chemotherapy, radiation therapy, and immunotherapies, will serve to enhance efficacy.

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Part II

Peritoneal Regional Therapy for Cancer

6 Historical Perspective for Regional Peritoneal Therapy: HIPEC, EPIC, and Port-Based Therapy

Paul H. Sugarbaker

Introduction

From the beginning of the clinical and pharmacologic exploration of the utility of chemotherapy administration into the peritoneal space, the prospect for profound dose intensity was recognized. Dedrick and Flessner showed that the exposure of peritoneal surface cancer nodules could be increased logarithmically by chemotherapy instillation directly into the peritoneal space as compared to intravenous drug delivery [1]. Drugs with a large molecular weight will remain in the peritoneal space for a prolonged time period causing the ratio of intraperitoneal drug concentration times time to be much greater than the plasma drug concentration times time. This area under the curve (AUC) ratio of intraperitoneal to intravenous exposure of peritoneal surfaces has long been used to select agents for intraperitoneal administration. Speyer and colleagues demonstrated the marked differences in the activity of 5-fluorouracil when the drug is delivered by continuous infusion, by bolus intravenous injection [2], or by intraperitoneal administration. The metabolism of drug within the body compartment is always more rapid than its clearance from the peritoneal space. This causes large differences in intraperitoneal as compared to intravenous drug concentration over long time periods. This phenomenon is demonstrated in Fig. 6.1.

Dose Intensity of Chemotherapy for Peritoneal Metastases by Intraperitoneal Administration

Sugarbaker and colleagues tabulated the chemotherapy agents that may be used for intraperitoneal instillation. A maximal AUC ratio was shown to be approximately 1000 for paclitaxel and pegylated liposomal doxorubicin. Several drugs show an AUC ratio between 100 and 200 including doxorubicin, 5-fluorouracil, gemcitabine, and mitoxantrone. Pertioneal exposure with AUC ratio under 100 occurs with floxuridine, melphalan, and pemetrexed. Mitomycin, often used for intraperitoneal administration, has an AUC ratio of 27. Some drugs leave the peritoneal space in 20 minutes or less. These drugs include carboplatin, cisplatin, and oxaliplatin. Clearly, the dose intensity of intraperitoneal drug administration will depend greatly on the choice of chemotherapy agent [3].

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Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_6

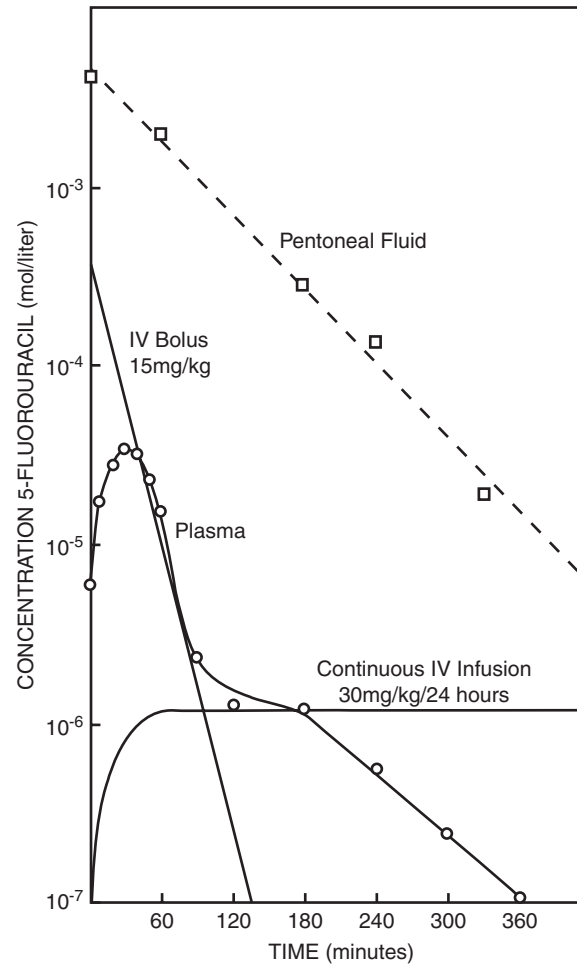

Fig. 6.1 Diagram of three methods of 5-fluorouracil delivery. □ peritoneal fluid, ○ plasma. (From Speyer et al. [2]; used with permission)

Limited Intraperitoneal Drug Penetration into Abdominal and Pelvic Tissues

Chemotherapy agents that are administered via the intravenous route are rapidly distributed to all tissues of the body exclusive of the brain and spinal cord as a result of the "blood–brain barrier." In sharp contrast, drugs instilled directly into the peritoneal space have very limited access to the tissues within the abdomen and pelvis. Drug penetration is by simple diffusion only. The rate of diffusion into tissues is largely dependent upon the concentration of the intraperitoneal drug [4]. Ozols and colleagues studied the drug penetration of the peritoneal surface by doxorubicin. They estimated 6–8 cell layers were exposed to increased concentrations of the intraperitoneal drug [5]. Los and colleagues studied intraperitoneal cisplatin and carboplatin. The cisplatin penetrated significantly better than carboplatin. The distance of the penetration was measured in micromillimeters [6].

Not only is the drug penetration limited by diffusion, the drug that reaches the rich subperitoneal lymphatic and capillary network is rapidly removed into the body compartment. Chemotherapy that does enter the tissues is rapidly distributed by the rich vascular and lymphatic network that underlies the peritoneum. As a result of these observations, the early clinical studies with intraperitoneal chemotherapy involved the prevention of peritoneal metastases.

Sugarbaker and coworkers explored this in patients with colorectal cancer [7]. Koga and colleagues explored the prevention of peritoneal metastases from gastric cancer [8].

Advantages and Disadvantages of Hyperthermic Intraperitoneal Chemotherapy Administration

There is no doubt that the inventor of HIPEC is John Spratt [9]. In 1990, at the University of Louisville, he treated a single patient with hyperthermic intraperitoneal thiotepa and repeated the treatment with hyperthermic intraperitoneal methotrexate. He called his HIPEC machine the "thermal infusion filtration system." He credited Robert Dedrick with the pharmacologic rationale for his treatments. Shiu and Fortner had previously published on the benefits of intraperitoneal hyperthermic perfusion in a rat model [10]. The invention was not appreciated in the USA, but Koga at Tottori University in Yonago, Japan, went to work in the laboratory confirming the concept of combined hyperthermia and intraperitoneal chemotherapy [11]. In 1984, he published laboratory work showing that optimal control of peritoneal metastases was achieved not by heat alone, not by mitomycin C alone, but by a combination of hyperthermia and mitomycin C chemotherapy. Fujimoto in Chiba, Japan [12] and Yonemura in Kanazawa [13] were two other Japanese investigators publishing their results of this new treatment option for prevention of gastric cancer peritoneal metastases and treatment of established disease.

The global application of HIPEC in patients with peritoneal metastases of a wide variety of primary sites has occurred within the last decade. The combination of intraperitoneal cancer chemotherapy with heat has a strong rationale in that the cytotoxicity of the cancer chemotherapy is increased by heat, the drug penetration into tissues is increased by heat, and prolonged moderate heat that can be tolerated within this peritoneal space can, in and of itself, destroy tumor nodules [14].

HIPEC has most successfully evolved for its use in the operating theater. It is employed after a maximal surgical removal of peritoneal metastases has occurred. The large benefits in terms of improved survival with cytoreductive surgery and HIPEC occur only in those patients who have complete visible removal of cancer cells on peritoneal surfaces. Also, the problem with drug distribution is eliminated through HIPEC. Surgical separation of all of the peritoneal surfaces that may be held together by scar tissue takes place prior to HIPEC being initiated. Uniform distribution of the heat and chemotherapy solution is possible with this intraoperative application of intracavitary chemotherapy.

These treatments occur in the operating room and the time devoted to the HIPEC procedures is limited. The heated chemotherapy dwell time within the peritoneal space varies between 30 minutes and 3 hours [3]. The time devoted to HIPEC will depend on the rate at which the chemotherapy is cleared from the peritoneal space. Only those chemotherapy agents which are active over a short time period should be utilized. Appropriate drugs for HIPEC are doxorubicin, melphalan, mitomycin C, cisplatin, and oxaliplatin. Drugs that require metabolism for their activity, such as 5-fluorouracil and paclitaxel, would not be appropriate for short-term peritoneal exposure [3]. Of course, another requirement for drugs used for HIPEC would be their augmentation by heat. Doxorubicin, melphalan, mitomycin C, and cisplatin are all heat-augmented.

A disadvantage of HIPEC is the requirement for a heat pump in the operating room to recirculate the chemotherapy solution. The expense, expertise, and unavailability of the apparatus limit the use of HIPEC to centers devoted to the management of peritoneal metastases.

Advantages and Disadvantages of Early Postoperative Intraperitoneal Chemotherapy

The first reported series of patients treated by EPIC was in 1995. Sugarbaker and Jablonski treated 51 colorectal and 130 appendiceal cancer patients with peritoneal metastases [15]. Their treatments were mitomycin C used on the first postoperative day and then 5-fluorouracil used on

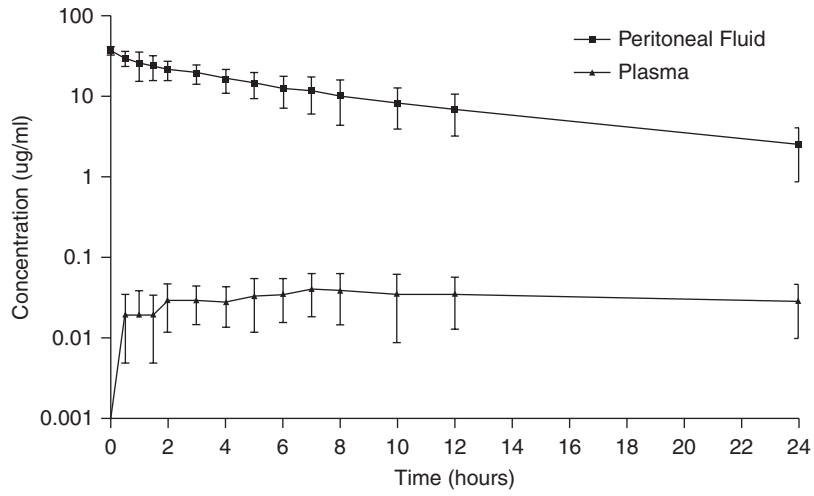

Fig. 6.2 Plasma and peritoneal fluid concentration versus time following a single early postoperative intraperitoneal administration of paclitaxel (20 mg/m^2) in eight patients. (From Mohamed and Sugarbaker [19]; used with permission)

postoperative days 2–6. The EPIC, when combined with complete cytoreduction, showed that appendiceal malignancy always did better than colorectal cancer. The histopathology was important in determining prognosis as was the completeness of cytoreduction, lymph node-positive versus lymph node-negative patients, and the volume of peritoneal metastases as measured by the peritoneal cancer index [16]. When the peritoneal metastases treatments were started at the Institut Gustave Roussy by Elias, EPIC was used [17]. To this day, EPIC is used at the peritoneal metastases unit in Basingstoke, UK [18].

Early postoperative intraperitoneal chemotherapy is instilled into the peritoneal space, either immediately after the completion of a surgical procedure or in the first 1–5 postoperative days. EPIC has the advantage over HIPEC in that is does not require a heat pump for administration. Also, EPIC can utilize those drugs which require metabolism for their activity. This involves paclitaxel and 5-fluorouracil and floxuridine. All three of these drugs are large molecules with a high AUC ratio. A third drug currently being developed for EPIC is pegylated liposomal doxorubicin (Doxil). If the cancer causing peritoneal metastases has responses to paclitaxel, this may be an ideal drug for instillation in the early postoperative period. The AUC of paclitaxel is 1000 or more. Its dwell time within the peritoneal cavity is up to 24 hours (Fig. 6.2). Also, its penetration into peritoneal surfaces may be greater than other chemotherapy agents. Paclitaxel has been used for EPIC in ovarian cancer and in gastric cancer [19, 20]. Of recent interest is the use of intraperitoneal nanoparticles. Because of the large size of this chemotherapy preparation, it has a prolonged dwell time within the peritoneal space. Very similar and sometimes even more prolonged than paclitaxel. Figure 6.3 shows the concentrations over time with a 24-hour dwell of this drug instilled in the operating room after the closure of the abdomen. It is instilled in 2 liters of fluid as the patient is being taken to the surgical intensive care unit following the cytoreductive surgery. The drug has activity for approximately 24 hours. Somewhere between 70–90% of the drug is utilized and stored in the peritoneal surfaces over the 24 hours.

EPIC has been suggested to be associated with a greater incidence of adverse events if it is applied along with HIPEC after cytoreductive surgery. Perhaps, this was true in the early experience with HIPEC and EPIC reported in the multi-institutional study by Glehen [21]. More recently, EPIC using 5-fluorouracil for gastrointestinal cancer, especially primary colorectal cancer, can create a FOLFOX-type perioperative chemotherapy regimen. In the operating room, the high-dose oxaliplatin by HIPEC is used with 5-fluorouracil administered intravenously (Elias regimen). This is followed by 2 days of intraperitoneal 5-fluorouracil (by EPIC) to maximize the effects of the periopera-

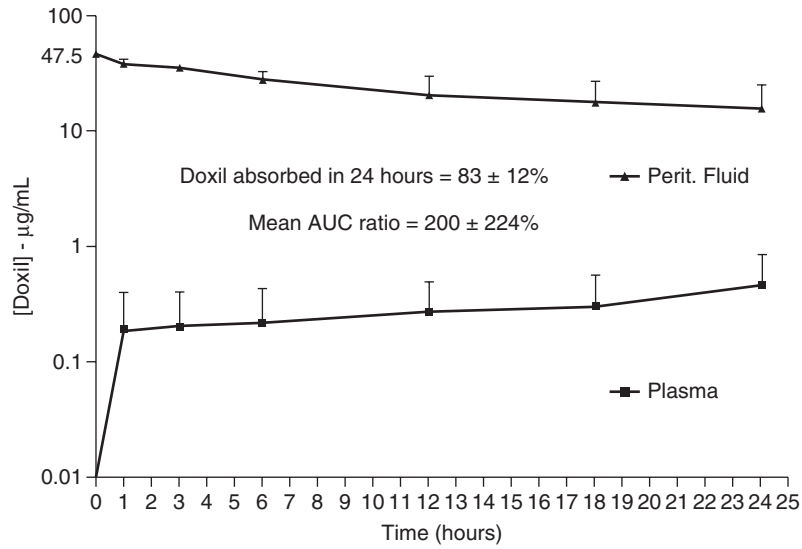

Fig. 6.3 Twenty-four hour dwell of pegylated liposomal doxorubicin. A majority of drug has entered abdominal and pelvic tissues

tive treatments. A single dose of intravenous 5-fluorouracil with the heated oxaliplatin is insufficient 5-fluorouracil dose for maximal augmentation of the oxaliplatin activity.

Advantages and Disadvantages of Normothermic Intraperitoneal Chemotherapy Administered Through an Intraperitoneal Port

The original studies with NIPEC were conducted at the Surgery Branch, National Institutes of Health. Sugarbaker and colleagues performed a randomized controlled study which compared intravenous 5-fluorouracil versus intraperitoneal 5-fluorouracil as an adjuvant treatment for poor prognosis colon or rectal cancer patients who had had a successful resection of their primary disease. Although survival in the two groups was not statistically significant, the incidence of peritoneal metastases in the two groups was markedly different with 10 of 11 intravenous 5-fluorouracil patients having peritoneal seeding and 2 of 10 of the intraperitoneal treated patients developing peritoneal seeding. These data were gathered at the time of second-look surgery [22].

The other important NIPEC studies involved ovarian cancer. The groundbreaking work of Alberts, who compared intravenous to intraperitoneal cisplatin in ovarian cancer patients must be mentioned [23]. Also, Markman and Armstrong showed positive results with intraperitoneal chemotherapy within a randomized controlled trial [24, 25]. More recently, Sugarbaker and colleagues showed that NIPEC pemetrexed gave superior long-term survival as compared to historical controls treated with intravenous pemetrexed in patients with malignant peritoneal mesothelioma [26].

The major disadvantage and lack of efficacy of HIPEC and EPIC may be the inability to administer repeated doses of cancer chemotherapy. A single large dose of chemotherapy may help control the malignant process on peritoneal surfaces but its eradication by a single treatment would require an extremely small cancer target, perhaps only single cells. A great advantage of port-based therapy is the possibility for repeated doses of the cancer chemotherapy. Also, the intraperitoneal drug can be combined with intravenous chemotherapy as a "bidirectional" treatment plan. Chemotherapy regimens that combine two drugs can definitely be simultaneously administered by intravenous and intraperitoneal routes to achieve a maximal response. Intraperitoneal taxol and systemic cisplatin may be recommended for the management of peritoneal metastases from ovarian cancer [27]. Also, intraperitoneal pemetrexed and systemic

cisplatin have been suggested to be of benefit for malignant peritoneal mesothelioma. The data from randomized controlled trials in ovarian cancer strongly recommend intraperitoneal chemotherapy using taxol as an optimal management plan for optimally cytoreduced ovarian cancer [25].

NIPEC through an intraperitoneal port does have some logistical and technological disadvantages. Perhaps, the best way to install the port is at the time of a cytoreductive surgery. If not placed in the operating room it can be implanted by an interventional radiologist with great safety. Some have proposed port placement with a laparoscopy. However, many of the patients requiring NIPEC have had extensive prior surgery and laparoscopy may not be without adverse events. Perhaps, the most important aspect of port therapy is the selection of a chemotherapy agent which does not have sclerotic effects within the peritoneal space. Drugs such as doxorubicin and mitomycin C that cause fibrosis should not be used for repeated intraperitoneal instillation through a port. However, it does not mean that these drugs cannot be used for a single intraperitoneal instillation such as for HIPEC or EPIC. Drugs that would be strongly recommended for NIPEC involve 5-fluorouracil, pemetrexed, paclitaxel, or docetaxel. These drugs have no sclerotic effects and show high AUC ratio within the peritoneal space. Also, these drugs ideal for prolonged intraperitoneal drug treatments may have systemic chemotherapy agents that will markedly augment the control of peritoneal metastatic disease. A recent randomized trial using NIPEC 5-fluorouracil for peritoneal metastases for colon cancer should be mentioned [28].

Effective management of peritoneal metastases is a new and challenging part of oncology. It requires the combined efforts of surgeon to remove all visible evidence of the peritoneal metastases and the medical oncologist to supervise the combined intraperitoneal and systemic chemotherapy that may eradicate this component of cancer progression. The profound dose intensity which is possible with intraperitoneal treatment suggests large benefit from this route of chemotherapy administration. The limited penetration of intraperitoneal chemotherapy into tissues demands careful selection of patients for treatment who have small volume of peritoneal surface disease. There are advantages and disadvantages of HIPEC, EPIC, and NIPEC. These treatment modalities should not be regarded competitive in their use for control of peritoneal metastases but should be considered complimentary. HIPEC can be used with EPIC in the same patient following adequate cytoreduction. An intraperitoneal port can be placed after the completion of the cytoreductive surgery preparing the patient for NIPEC long-term. Technical and logistical problems with all three of these potential treatments continue to exist but are, with the passage of time and with increasing experience, becoming less problematic. The proper selection of chemotherapy agents appropriate for HIPEC, EPIC, and NIPEC is an important part of their potential benefit.

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7 Rationale Behind HIPEC/Molecular and Genetic Considerations in HIPEC

Jula Veerapong and Andrew M. Lowy

Introduction

Intraperitoneal (IP) chemotherapy combined with hyperthermia is a well-recognized adjunct to cytoreductive surgery (CRS) when used to treat certain types of peritoneal surface malignancies (PSM), either originating from or spreading to the lining of the abdominopelvic cavity. Hyperthermia has long been utilized as a means to improve efficacy in tumor killing as it is selectively cytotoxic to malignant cells in the range of 41–43 °C due to inhibition of oxidative metabolism, producing a lower microenvironment pH in the malignant cell and increased activity of lysosomes [1]. It has been used alone, in combination with systemic chemotherapy, or in combination with radiotherapy. When hyperthermia is used with IP chemotherapy, the result is an improved therapeutic index and efficacy of the agent [2]. Over the past few decades, hyperthermic intraperitoneal chemotherapy (HIPEC) has emerged as a modality commonly employed at the time of CRS for PSM. Though achieving clearance of all gross visible disease at the time of surgery is the mainstay of therapy, the rationale for direct instillation of HIPEC is based on the theoretical benefit that its addition will provide an additive or synergistic anticancer effect on the microscopic or cellular level while avoiding systemic toxicity. The multimodal approach of utilizing CRS and HIPEC in combination has been clinically demonstrated to impact progression-free and overall survival in several disease processes, such as appendiceal and ovarian cancer [3, 4]. However, it is difficult to parse out the individual contributions of the individual components, as most clinical studies examine CRS and HIPEC as a complete package. Moreover, there is great heterogeneity in the application of CRS/HIPEC, as there is no uniform consensus on technique of HIPEC delivery, duration of IP chemotherapy, temperature of hyperthermia, or chemotherapeutic agent utilized. The scientific basis for use of intraoperative HIPEC is anchored mostly in pharmacologic studies, with data generally supporting improved drug penetration/permeability or increased cytotoxicity [5, 6]. The pharmacokinetics and drug profiles of the chemotherapeutic agents are discussed elsewhere in this book. This chapter explores the molecular and genetic rationale of employing HIPEC.

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Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_7

Carcinomatosis

Molecular Biology of the Peritoneal Metastatic Cascade

Complete comprehension of the biologic nature of peritoneal tumor seeding has been elusive. Understanding the molecular events of carcinomatosis is important in designing a therapy that is both effective and devoid of unnecessary toxicity. Carcinomatosis may be regarded as a continuous and interdependent series of events forming a peritoneal metastatic cascade [7]. It is a multistep process that requires adaptation of the primary tumor as well as mechanisms enabling tumor adhesion and growth [8]. Lemoine et al. have described a set of well-defined steps in the peritoneal metastatic cascade of colorectal cancer, conditional upon communication between tumor cells and the microenvironment on a molecular level. First, an individual cell or clump of cells detach from the primary tumor. Then, the exfoliated cells are subjected to the forces of peritoneal transport, which tends to occur in a clockwise fashion as a result of bowel peristalsis, changes in intra-abdominal pressure with respiratory variation, and gravity. These cells attach to peritoneal surfaces distant from the primary site. Once attached, cells invade the subperitoneal space, and then finally, angiogenesis with resultant proliferation occurs. The molecular events and pathways are summarized in Table 7.1 [9].

Tumor Microenvironment in Carcinomatosis

The peritoneum, consisting of a monolayer of mesothelial cells supported by a basement membrane on connective tissue, is often regarded as the first line of defense in carcinomatosis [10]. The impact of the tumor microenvironment on tumorigenesis in colorectal cancer carcinomatosis was studied by Seebauer et al. by characterizing proliferation, senescence, and neovascularization in primary tumor cells and metastatic cells. Interestingly, metastatic cancer cells demonstrated lower proliferation (Ki-67, PCNA, Cyclin D1) and higher senescence (H3K9me3, $p21^{Cip1}$, CDKN2A) rates than primary cancer cells. This may partially explain the greater resistance of metastatic cancer cells to systemic chemotherapy. The tumor microenvironment of peritoneal carcinomatosis was found to be abundant in natural killer cells, which play a role in tumor growth, dissemination, and recurrence. In addition, the microenvironment was shown to be rich in angiogenic mediators, such as vascular endothelial growth factor A (VEGF-A) [11].

Gene Expression in Peritoneal Metastases

Gene expression in metastatic colorectal cancer has been studied utilizing DNA microarray. Kleivi et al. found that gains of chromosome arm 5p are common in peritoneal carcinomatosis and several candidate genes (PTGER4, SKP2, and ZNF662) mapping to this region were overexpressed [12]. While histopathologic subtype and grade may provide prognostic information in patients with carcinomatosis, the biologic signature of PSM as it relates to prognosis is poorly understood. Genomic analysis of peritoneal metastases from low-grade appendiceal and colorectal cancer was performed by Levine et al., demonstrating three phenotypic clusters with distinct signatures for low-risk appendiceal cancer, high-risk appendiceal cancer, and high-risk colorectal cancer. The signatures not only predicted survival but also highlighted the unique biology of appendiceal cancer compared to colorectal cancer [13]. The same group more recently reported on a 139-gene expression panel that distinguished two molecular subtypes of disseminated mucinous appendiceal neoplasms with statistically significant survival differences. In a validation cohort, the 139-gene panel reproducibly partitioned tumors treated with CRS/HIPEC into subtypes with significant survival differences. These data are exciting and require further independent validation but suggest the potential for genomics to be incorporated into patient selection for CRS/HIPEC in the future [14].

Table 7.1 The peritoneal metastatic cascade

Step in peritoneal metastasis cascade	Molecule or molecular pathway
Detachment from the primary tumor	Spontaneous tumor shedding: E-cadherin ↓ N-cadherin ↑ EMT PC1 and PC2 ↑ Interstitial fluid pressure ↑ Perioperative tumor seeding during surgery
Peritoneal transport	Mucinous ascites Actin microfilament system Lamellipodia, filopodia
Attachment to distant peritoneum	Transmesothelial dissemination: ICAM-1 ↑, PECAM-1, VCAM-1 ↑ TNF-α, IL-1β, IL-6, IFN-γ β1 integrin subunit CD43, CD44 Hyaluronan Translymphatic dissemination: Lymphatic stomata Milky spots
Invasion into the subperitoneal space	Rounding of mesothelial cells: HGF/SF ↑ c-met ↑ Tumor-induced apoptosis Fas ligand/Fas Adherence to the basement membrane: Integrins Invasion of the peritoneal-blood barrier: MMP-1, MMP-2, MMP-7, MMP-9, MMP-13, MMP-14 ↑ TIMP-1, TIMP-2, TIMP-3, TIMP-4 uPA/uPAR Plasminogen activator inhibitor-1 and -2
Proliferation and angiogenesis	Proliferation: EGFR, EGF, TGFα IGF-1, IGF-binding Protein-3 Angiogenesis: HIF-1α, HIF-1β VEGF/VEGFR

Adapted from Lemoine et al. [9]; used with permission
E-cadherin epithelial-cadherin, *N-cadherin* neural-cadherin, *EMT* epithelial to mesenchyme transition, *PC* polycystin, *ICAM* intercellular adhesion molecule-1, *PECAM* platelet-endothelial cell adhesion molecule-1, *VCAM-1* vascular adhesion molecule-1, *TNF-α* tumor necrosis factor-α, *IL-1β* interleukin-1β, *IL-6* interleukin-6, *IFN-γ* interferon-γ, *CD43* Sialophorin, *HGF* hepatocyte growth factor, *SF* scatter factor, *MMP* matrix metalloproteinases, *TIMP* tissue inhibitor metalloproteinases, *uPA* Urokinase plasminogen activator, *uPAR* Urokinase plasminogen activator receptor, *EGFR* epidermal growth factor receptor, *EGF* epidermal growth factor, *TGFα* tumor growth factor α, *IGF-1* insulin like growth factor-1, *HIF* hypoxia inducible factor, *VEGF* vascular endothelial growth factor, *VEGFR* vascular endothelial growth factor receptor

Molecular and Genetic Considerations in HIPEC

It is generally acknowledged that the synergism of hyperthermia and IP chemotherapy may be in part due to increased cell permeability and improved membrane transport [1]. However, surprisingly little is known about the impact of HIPEC on the molecular and genetic level. Such information could serve highly valuable to developing targeted treatment strategies. The putative effect of HIPEC is often extrapolated from the

Table 7.2 Cellular effects of hyperthermia

Destabilization of the cell membrane
Changes in cell shape
Impaired transmembrane transport
Changes in membrane potential
Modulation of transmembrane efflux pumps
Induction of apoptosis
Impairment of protein synthesis
Protein denaturation
Aggregation of proteins at the nuclear matrix
Induction of heat sensitive protein synthesis
Impairment of DNA and RNA synthesis
Inhibition of enzyme repair
Altered DNA conformation
Alteration of gene expression and signal transduction
Inhibition of oxidative metabolism

Adapted from Goodman et al. [16]; used with permission

effect of hyperthermia in inhibiting angiogenesis, inducing apoptosis, denaturing cell membrane protein denaturation, and interfering with DNA repair [15]. Table 7.2 summarizes some of the cellular effects of hyperthermia [16]. This portion of the chapter will focus on data derived from combined hyperthermia and IP chemotherapy.

Histologic Alterations

The Pittsburgh group examined histologic alterations in peritoneal tumor and nonneoplastic peritoneal tissue samples from patients undergoing CRS/HIPEC for carcinomatosis due to appendiceal or colorectal cancer. Conventional histologic analysis demonstrated extensive subendothelial inflammatory infiltrate, endothelial activation, mesothelial karyolysis, and fibrin surface deposition following HIPEC. Immunohistochemical markers for early DNA damage (mesothelial nuclear γH2AX) and early necrosis (high-mobility group box 1 (HMGB1)) were found to be increased in CRS and HIPEC. H2AX is a component of histone octamer in nucleosomes; it is phosphorylated in response to breaks in double-stranded DNA, as an early step in recruiting DNA repair proteins. High-mobility group box 1 is a DNA-binding nuclear protein that may stimulate downstream inflammatory effects when released in the extracellular environment, and its presence may be an indicator of early necrosis [17]. Pelz et al. studied the effects of HIPEC with Mitomycin C in a rat model of colon carcinomatosis. Tumor cells demonstrated clear shrinkage and partial loss of contact, presence of thromboses of larger adjacent vessel on the tumor-muscle border, and macrophage infiltration. All of these findings were considered indicators of irreversible cell damage [18].

Assessment of Tumor Burden after HIPEC

Intraperitoneal free cells (IFCC) may result from spontaneous exfoliation of cancer cells from the primary tumor or from iatrogenic dissemination during CRS. Ji et al. studied the effect of HIPEC on IFCCs by examining carcinoembryonic antigen (CEA) and cytokeratin-20 (CK20) mRNA with conventional and real-time quantitative RT-PCR in the peritoneal fluid of 50 patients undergoing CRS/HIPEC for gastric, colorectal, epithelial ovarian, or appendiceal cancer. Positive cytology rate was 22% post-HIPEC, compared to 100% pre-HIPEC. The pre- and post-HIPEC rates of CEA and CK20 mRNA detection by conventional RT-PCR were 100% vs 86% (p-value = 0.012) and 100% vs 96% (p-value = 0.495), respectively. However, by quantitative RT-PCR, relative expression of CEA (36% of patients) and CK20 mRNA (34% of patients) was both significantly decreased post-HIPEC. In this study, the authors concluded that not only can HIPEC eradicate IFCCs, but it may also result in partial cytologic cure [19]. Though the mechanisms of action of HIPEC are unclear, they may include tumor microvessel embolization at the tissue level, perturbations of cell homeostasis and energy metabolism, and disruption in cell membrane integrity [20]. Baratti et al. investigated the prognostic value of tumor markers in patients with pseudomyxoma peritonei (PMP). Baseline and serial CEA, CA 19–9, CA-125, and CA 15.3 were obtained in CRS/HIPEC patients. Normal CA-125 correlated with the likelihood to achieve a complete cytoreduc-

tion, which in turn is a prognostic factor in PMP. Baseline elevated CA 19–9 was an independent factor of worse progression-free survival after CRS/HIPEC [21]. The Pittsburgh group obtained baseline CEA, CA 19–9, and CA-125 prior to CRS/HIPEC. At least one tumor marker was elevated in 70% of patients prior to CRS/HIPEC, allowing for surveillance. CA 19–9 was found to be a marker for progression, and CA-125 was associated with shorter survival [22].

Gene Expression

MicroRNAs (miRNAs) are small noncoding RNA sequences containing about 22 nucleotides that function in RNA silencing and posttranslational regulation of gene expression. Up- or downregulation of specific miRNAs has been associated with cancer development. Zhang et al. demonstrated that microRNA-218 (miR-218) was upregulated by greater than eightfold in the serum of patients with advanced gastric cancer after undergoing CRS/HIPEC. In addition, miR-218 increased chemosensitivity to cisplatin in vitro and in vivo by inducing apoptosis [23]. Long noncoding RNAs (lncRNAs), defined as transcripts longer than 200 nucleotides, have also been shown to be involved in the cancer development and progression. Zeng et al. identified two important lncRNAs, BC031243 and RP11–356I2.2, in the serum of patients with gastric cancer that were differentially expressed before and after CRS/HIPEC [24]. Further investigation is required to understand the biologic significance of these small molecules and the utility of targeting them to prevent cancer progression.

DNA Damage Response to HIPEC

There is a large body of literature suggesting that hyperthermia increases cell sensitivity to DNA damaging agents (such as cytotoxic chemotherapeutic agents) as well as a number of studies indicating a direct effect of hyperthermia on DNA damage. The latter is more difficult to unravel as there are profound differences in studies examining mild hyperthermia (41–43 °C), as utilized during HIPEC, versus more severe hyperthermia (>43 °C). The most sophisticated recent studies reveal that hyperthermia appears to act to inhibit mechanisms of DNA repair, and in this manner may act synergistically with cytotoxic agents. For instance, several studies have demonstrated that mild hyperthermia inhibits DNA repair of homologous recombination occurring after double strand breaks induced upon DNA damage. Repair occurs during the S-phase and G2-phase of the cell cycle via a cascade requiring the RPA, RAD51, and the BRCA2 proteins. Hyperthermia above 40 °C was found to inhibit the accumulation of RAD51 at sites of DNA damage by targeting BRCA2 for proteasomal degradation. Schaaf et al. studied the effects of hyperthermia in combination with chemotherapy and noted that hyperthermia delayed the repair of DNA damage caused by cisplatin or doxorubicin, by acting upstream of multiple repair pathways to block histone polyADP-ribosylation. This histone modification which is required for DNA repair is similarly targeted by PARP inhibitors. Not surprisingly, the investigators found that hyperthermia and PARP inhibitors had similar effects on cell cytotoxicity and impact on DNA repair function in models of ovarian and colon cancer. Importantly, these studies were performed in BRCA-competent cells, which comprise the majority of cancers that give rise to peritoneal metastases treated by CRS/HIPEC [25]. Finally, a recent study demonstrated that 42 °C of hyperthermia induced degradation of BRCA2 in cell lines and in human tumors treated ex vivo, also suggesting the potential for therapeutic synergism of hyperthermia and PARP inhibition [26]. These studies raise provocative questions regarding both the potential for enhancing the efficacy of CRS/HIPEC via selection of specific chemotherapeutic agents and for their combination with DNA damage repair inhibitors.

Heat Shock Protein Expression

Heat shock proteins (HSP) act as molecular chaperones inside cells and are protective against

cellular stressors, such as ischemia, heat stress, and oxidative stress. A study by Pelz et al. established an in vitro model of hyperthermia utilizing the HT-29 colon carcinoma cell line treated with HIPEC between 39 °C and 43 °C. Upregulation of HSP27, HSP72, and HSP90 mRNA was found at 41 °C and 43 °C. Increased protein expression of HSP70/72 by Western blot analysis was demonstrated at 30 minutes after exposure to HIPEC, while increased protein expression of HSP27 and HSP70/72 was seen at 12 hours. Tumor samples from patients undergoing CRS/HIPEC for a variety of histopathologic subtypes (appendiceal cancer, diffuse malignant mesothelioma, gastric cancer, ovarian cancer, pancreas cancer, and appendiceal carcinoid) were analyzed for HSP gene expression. Upregulation of HSP70/72 and HSP90 mRNA was found at varying levels on quantitative RT-PCR. This study postulates that targeting HSP in HIPEC procedures may be a promising therapeutic strategy [27]. Tu et al. subjected SGC7901 gastric cancer cells to HIPEC and found mRNA and protein expression of the HSP70 and HSP90 to be elevated. Serum levels of HSP70 and HSP90 were collected from patients undergoing CRS/HIPEC for gastric cancer. The serum concentration peaked at 12 hours and 18 hours post-HIPEC, respectively, and returned to normal levels at 24 hours. The authors advocated a second round of HIPEC at least 24 hours following the initial treatment in order to minimize any potential thermoresistance or chemoresistance of tumor cells [28]. As several HSP inhibitors are now reaching early Phase clinical trials, it will be of great interest to study their activity in the context of CRS/HIPEC.

Danger-Associated Molecular Patterns

Danger-associated molecular pattern (DAMP) molecules are endogenous molecules that are released upon tissue damage. They may elicit a systemic inflammatory response and induce an immunosuppressive state, leading to increased susceptibility to nosocomial infection. A study by Leitje et al. collected blood samples of 20 patients undergoing CRS/HIPEC at various time-points. Circulating levels of DAMP (Table 7.3) and cytokines [TNF-α, IL-6, IL-8, IL-10, macrophage inflammatory protein (MIP)-1α, MIP-1β, MCP-1] were measured and were all found to be increased significantly following CRS/HIPEC. Increase in HMGB-1 correlated with a decrease in HLA-DR expression, which may increase vulnerability to sepsis due to the impairment of optimal presentation of microbial antigens to T-cells [29]. Peak HMGB-1 concentrations were found to be significantly higher in the subset of five patients who went on to develop wound infections [30]. The implications are that release of DAMPs post-HIPEC could impair immune responses that result in clearing of tumor cells. Studies exploring this hypothesis and the potential therapeutic value of targeting DAMPs are clearly of interest.

Table 7.3 Danger-associated molecular pattern (DAMPs) [30]

Danger-associated molecular pattern (DAMPs)
Heat-shock proteins (HSP70)
HMGB-1
S100 proteins (S100A12, S100A8/S100A9)
Nuclear DNA
Mitochondrial DNA
Lactate dehydrogenase

Somatic Mutations as Prognostic Factors Post-CRS/HIPEC

As next generation sequencing has become widely available, several studies have characterized somatic mutations within rare peritoneal surface malignancies as a means to understand their biology, and in the hopes of revealing actionable alterations. Several studies have examined this data in the context of patient prognosis. Singhi et al. analyzed the prognostic implications of mutations in 86 patients with malignant peritoneal mesothelioma. They noted that loss of expression of the tumor suppressors CDKN2A and NF2 were each prognostic of poor survival. Furthermore, loss of function of both genes (by mutation or epigenetic silencing) resulted in a hazard ratio for death of 4.4, which was more potent than even the peritoneal cancer index or the extent of cytoreduction [31]. The most com-

mon mutational event in peritoneal mesothelioma is in the BAP1 gene. Germline mutation in BAP1 is associated with increased risk for both pleural and peritoneal mesothelioma. Interestingly, a study by Baumann et al. demonstrated that 23 mesothelioma patients with inherited BAP1 mutations had a favorable prognosis compared to mesothelioma patient survival as recorded in the Surveillance, Epidemiology, and End Results (SEER) database [32].

Loss of expression of the tumor suppressor SMAD4 was shown by Davison et al. to be associated with high tumor grade and a poor prognosis in mucinous neoplasms of the appendix, the majority of which were treated with CRS/HIPEC [33]. Mutations in the GNAS gene are among the most common in mucinous appendiceal tumors. The effect of GNAS mutations on prognosis remains unclear as studies have demonstrated somewhat conflicting findings. Alakus et al. characterized mutations in peritoneal metastases from low- and high-grade mucinous appendiceal neoplasms and found GNAS to be more common in low-grade tumors [34]. In contrast, Singhi et al. found GNAS mutations to be prevalent in both low- and high-grade tumors but to hold no prognostic significance [31]. A more recent study of patients with recurrent pseudomyxoma peritonei treated with capecitabine and bevacizumab found that GNAS mutations were predictive of poorer survival. Finally, Ang et al., in a study of appendiceal tumor subtypes, noted that low-grade tumors were enriched for GNAS mutations, whereas high-grade tumors were enriched for p53 mutations. Interestingly, the coexistence of GNAS and p53 mutations conferred a more favorable prognosis than p53 mutation alone [35]. Clearly, additional studies are required to further our understanding of the prognostic impact of gene mutations in peritoneal surface malignancies and how they may interact with response to CRS/HIPEC and systemic therapies.

Summary

Combined hyperthermia and intraperitoneal chemotherapy have been demonstrated in many in vivo and in vitro studies to produce a synergistic antitumor effect. Some of this effect has been attributed to the direct cytotoxic effects of the chemotherapeutic agent, which is essentially governed by pharmacokinetics. However, HIPEC has been shown to produce histologic alterations and cellular stress on the molecular level. Selective gene expression may occur in response to cellular stress, which may provide potential targets for therapy or may provide prognostic information about morbidity or survival. The molecular and genetic effects of HIPEC are extremely complex and require further study to fully elucidate their impact.

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Data for HIPEC for Pseudomyxoma Peritonei/Tumors of the Appendix

8

Joel M. Baumgartner and Kaitlyn J. Kelly

Introduction

Pseudomyxoma peritonei (PMP) is a condition of mucinous ascites and peritoneal nodules, typically originating from a mucinous appendiceal tumor. PMP has historically had various evolving definitions and variants; however, a consensus is emerging for standardized classification with defined pathologic criteria [1]. Under this classification, PMP can include low-grade mucinous peritoneal metastases, often known as diffuse peritoneal adenomucinosis (DPAM) or low-grade mucinous carcinoma peritonei (LGMCP), which arise from low-grade appendiceal mucinous neoplasms (LAMN) (Fig. 8.1). However, PMP can also include neoplastic cells with high-grade features, known as peritoneal mucinous carcinomatosis (PMCA) or high-grade mucinous carcinoma peritonei (HGMCP), typically arising from a high-grade appendiceal mucinous neoplasm (HAMN). Other PMP variants include acellular mucin from low-grade or high-grade appendiceal tumors, mucinous peritoneal tumors with signet ring cells, and mucinous adenocarcinoma.

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Carcinomatosis from non-mucinous tumors of the appendix is not considered PMP. These tumors are characterized by firm, invasive peritoneal implants that often appear as areas of peritoneal thickening and enhancement on imaging and are associated with serous ascites (Fig. 8.2). Non-mucinous adenocarcinoma of the appendix can arise de novo or in goblet cell neuroendocrine tumors of the appendix with mixed neuroendocrine/adenocarcinoma components. When carcinomatosis develops from these tumors, it is typically the adenocarcinoma component that gives rise to peritoneal disease. The aim of this chapter is to summarize existing data on CRS with HIPEC for appendiceal neoplasms with peritoneal dissemination, including both PMP from mucinous neoplasms and carcinomatosis from appendiceal adenocarcinoma.

Preclinical Data for Hipec

Hyperthermia has long been known to have greater cytotoxicity in tumor cells than in non-neoplastic cells [2, 3]. The mechanism of this cytotoxicity may include impaired damaged DNA repair, potentially sensitizing tumor cells to alkylating agents [4]. Intraperitoneal administration allows exposure of a higher dose of chemotherapy with theoretically less systemic effects than with systemic chemotherapy. A canine animal model has been used to demonstrate the

Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_8

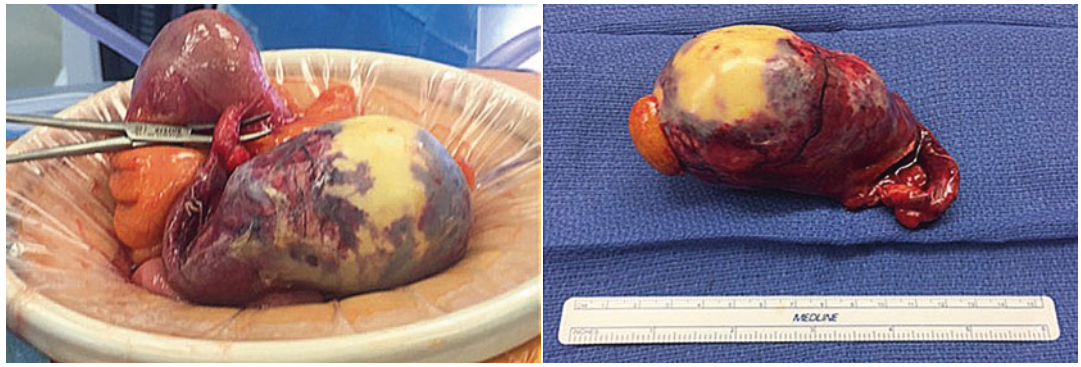

Fig. 8.1 Intact low-grade mucinous neoplasm of the appendix. This lesion is cured with appendectomy to negative margins with no need for HIPEC. When these lesions rupture, they can lead to the development of PMP

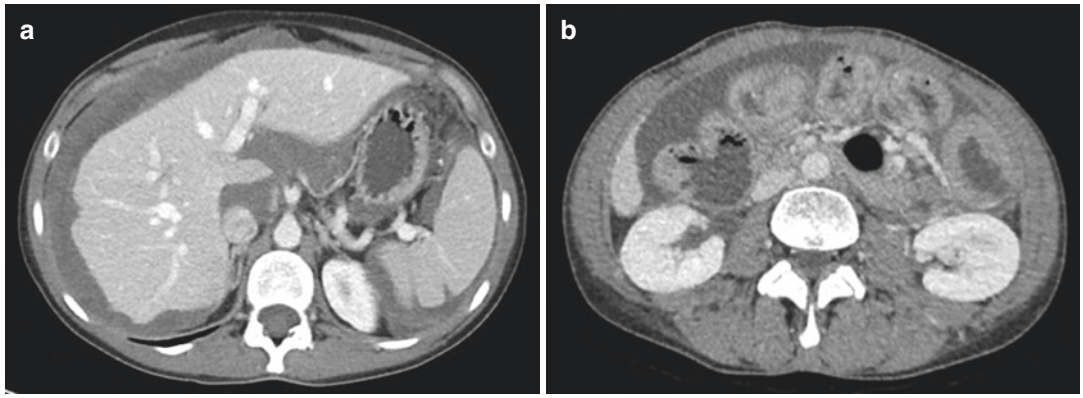

Fig. 8.2 Computed tomography scans of patients with (**a**) PMP with mucinous ascites showing characteristic scalloping of the liver edge and (**b**) carcinomatosis from non-mucinous appendiceal adenocarcinoma demonstrating thin, serous ascites and diffuse peritoneal thickening and enhancement

technical feasibility and safety of performing hyperthermic intraperitoneal chemotherapy administration [5].

Clinical Data for CRS/Hipec for PMP

Phase I Data

There have been three phase I studies of standard HIPEC agents in patients with appendiceal tumors. The first examined escalating doses of cisplatin with tumor necrosis factor under hyperthermia over 90 minutes after tumor debulking and identified a maximum tolerated cisplatin dose of 250 mg/m^2 [6]. The second examined escalating doses of oxaliplatin under hyperthermia over 120 minutes and found a maximum tolerated dose of 200 mg/m^2 [7]. This study included both patients with colorectal and appendiceal cancer, but the majority of patients (12 of 15) had the latter. The most recent study evaluated the use of intraperitoneal irinotecan, or CPT-11, in combination with a fixed dose of mitomycin C, delivered with a closed perfusion technique. The maximum tolerated dose of intraperitoneal irinotecan was found to be 100 mg/m^2 [8].

Case Reports and Small Clinical Series

PMP has been treated with extensive resection of gross peritoneal tumors (cytoreductive surgery,

CRS) since the 1970s when it was recognized that PMP had a low propensity for extraperitoneal spread. A single-institution series of 38 patients with PMP who underwent surgical resection with or without abdominal radiation and systemic chemotherapy reported a 54% actuarial 5-year survival [9]. Another series of CRS without HIPEC from Memorial Sloan Kettering Cancer Center included 97 patients, 52% of whom had low-grade disease, who underwent a mean of 2.2 cytoreductions (only 55% of which being complete gross cytoreductions) with a median overall survival of 9.8 years [10]. A case report describes the first human to receive hyperthermic intraperitoneal chemotherapy (HIPEC). This was a 35-year-old man with PMP of appendiceal origin. He was treated in 1979 and received intraperitoneal thiotepa [11].

Over subsequent years, HIPEC protocols and perfusion systems were optimized in patients with ovarian, appendiceal, colorectal, and gastric cancers. Sugarbaker et al. spearheaded the use of CRS with HIPEC for PMP in North America. Multiple studies from the late 1980s and early 1990s demonstrated favorable technical results and early disease control rates [12, 13]. In 2008, the Fifth International Workshop on Peritoneal Surface Malignancy took place in Milan, Italy. This workshop resulted in several consensus statements establishing CRS with HIPEC as the standard of care for appendiceal neoplasms. The HIPEC agents deemed appropriate for routine clinical use without need for further clinical trials for this disease included mitomycin C and cisplatin [14–16].

A study by Sardi and colleagues investigated the use of melphalan as an alternative agent for HIPEC in patients with peritoneal carcinomatosis from aggressive primary tumors. There were 25 total patients who underwent 31 CRS with HIPEC procedures, 19 of which were repeat procedures. Seventeen patients had primary appendiceal adenocarcinoma. In this study, the majority of patients had a peritoneal carcinomatosis index (PCI) >20. The rate of complete CRS was 88%. For those patients with appendiceal primary cancer, the 5-year overall survival (OS) following the melphalan HIPEC was 32.1%. The treatment was relatively well tolerated with a rate of postoperative grade III/IV morbidity of 22%. Myelosuppression was the most common complication. The authors concluded that melphalan is an efficacious agent for intraperitoneal therapy for patients with aggressive and recurrent peritoneal disease [17].

Another recent study evaluated the role of CRS with HIPEC for patients with high-grade appendix cancer and minimal peritoneal disease. Patients who were diagnosed incidentally by pathology after appendectomy were identified [18]. There were 62 total patients and 35 (57%) had gross peritoneal disease at the time of subsequent exploration for CRS with HIPEC. The mean peritoneal carcinomatosis index (PCI) for these patients was 5. All patients underwent right hemicolectomy as part of the CRS procedure and HIPEC was performed. Five-year disease-free and overall survival for these patients were excellent, at 83.2 and 76.0%, respectively. Additionally more recent small series have focused on CRS with HIPEC in unique patient populations, such as elderly patients, and those with particular comorbidities like obesity and cirrhosis [19]. These studies have shown that CRS with HIPEC is feasible and can be performed safely in selected patients with these conditions.

Large Retrospective Series

The strongest data on CRS with HIPEC for appendiceal neoplasms come from large retrospective studies. Table 8.1 summarizes the largest (each with greater than 200 patients) published series of CRS with HIPEC for appendiceal tumors. Each of these series included a combination of patients with low-grade and high-grade histologies, and concordance with the modern consensus pathologic classification is variable. The postoperative mortality ranges from 0 to 3%, and the postoperative major morbidity ranges from 15 to 34%. The 5-year overall survival is 53–87% and is variable by grade, with low-grade patients having an 81–83% 5-year survival and high-grade patients having a significantly lower 5-year survival at 41–59%.

Table 8.1 Largest published series of CRS with HIPEC for appendiceal neoplasms

Series	*n*	% LG	% CC-0/1	% 30d major morbidity[a]	% 30d mortality	Median PFS (yrs)	Median OS (yrs)	% 5 yr OS
Chua et al. [22]	2054[b]	62	83	22	2	Overall: 8.2 LG: NA HG: NA	Overall: 16.3 LG: NA HG: NA	Overall: 78[2] LG: 81 HG: 59
Votanopoulos et al. [23]	481	77.3	72.4[c]	27.8	2.7	NA	Overall: 14.6 (R0/1) HG: NA LG: NA	NA
Austin et al. [24]	282	64	82	23.7	1.1[d]	NA	Overall: 6.7 LG: NA HG: NA	Overall: 53 LG: NA HG: NA
Jimenez et al. [25]	202	38	85	15.8	0	Overall: 3.3 LG: NR HG: 2.2	Overall: 7.5 LG: NR HG: 3.9	Overall: 56 LG: 83 HG: 41
Ansari et al. [26]	738	80	100	15.2	0.8	Overall: 7.5 (mean) LG: NA HG: NA	Overall: 8.6 (mean) LG: NA HG: NA	Overall: 87.4 LG: NA HG: NA
Gonzalez-Moreno et al. [27]	501	NA	NA	NA	NA	NA	Overall: 13 LG: NA HG: NA	Overall: 72 LG: NA HG: NA
Kuijpers et al. [28]	300	47	80 (CC-0)[e]	34[e]	3[e]	Overall: 4.4 LG: NA HG: NA	Overall: 10.8 LG: NA HG: NA	Overall: 65 LG: NA HG: NA

LG low grade, *HG* high grade, *PFS* progression-free survival, *OS* overall survival, *NA* not available

[a]Clavien-Dindo Grade III–IV

[b]Those who received HIPEC, of 2298 total patients

[c]Included residual disease <5 mm

[d]60-day mortality

[e]Among all 960 CRS/HIPEC

Table 8.2 Summary of studies evaluating predictors of progression and death following CRS with HIPEC for appendiceal neoplasms

Study	Predictors of progression	Predictors of death
Low-grade disease		
Chua et al. [22]	–	Age > 53 CC-score > 1 Postoperative complications Preoperative systemic therapy
Votanopoulos et al. [23]	–	Positive lymph nodes CC-score > 0 Preoperative systemic therapy
Austin et al. [24]	–	Increasing age Preoperative systemic therapy High PCI
Jimenez et al. [29]	–	CC-score > 1
Reghunathan et al. [30]	Preoperative CEA ≥10 CC-score > 1	–
High-grade disease		
Halabi et al. [31]	–	Positive lymph nodes CC-score > 1 Increasing PCI
Jimenez et al. [29]	–	CC-score > 1 PCI ≥ 20 Positive lymph nodes
Votanopoulos et al. [23]	–	CC-score > 0 Preoperative systemic therapy
Baumgartner et al. 2015 [32]	Positive lymph nodes	–
Grotz et al. 2017 [33]	Non-mucinous histology Increasing PCI	Non-mucinous histology Gross peritoneal disease[a] Signet ring cells Increasing PCI

CEA carcinoembryonic antigen, *CC-Score* completeness of cytoreduction score, *PCI* peritoneal carcinomatosis index
[a]As opposed to positive peritoneal fluid cytology only

In addition to reporting survival data, these retrospective studies have also identified factors associated with recurrence and death after CRS with HIPEC for appendiceal neoplasms. Table 8.2 summarizes studies that have specifically reported independent predictors of progression and/or death following CRS with HIPEC for low- and high-grade appendiceal neoplasms. Consistently identified predictors of progression after CRS with HIPEC for low-grade disease include incomplete cytoreduction and elevated preoperative serum carcinoembryonic antigen (CEA) level. Predictors of progression in high-grade disease include positive lymph nodes, non-mucinous histology, and increasing PCI. Identified predictors of death or more variable across different studies, but those consistently identified in both low- and high-grade diseases include incomplete cytoreduction, advanced age, increasing PCI, incomplete cytoreduction, and receipt of systemic therapy prior to surgery.

Prospective Trials

There is a lack of prospective data available for CRS with HIPEC for appendiceal neoplasms. This is likely due to their overall low incidence, a problem compounded by the biologic heterogeneity of the different histologic subtypes. There are no randomized controlled trials comparing CRS alone versus CRS with HIPEC for appendiceal neoplasms. There has been one randomized controlled trial of CRS with HIPEC using mitomycin C versus systemic therapy with or without

palliative debulking. The majority of patients in this trial had colorectal primary tumors but 21% (n = 11) had appendiceal primary adenocarcinoma [20]. This study compared CRS with HIPEC with mitomycin C to systemic therapy with 5-fluorouracil (5-FU) and showed a survival benefit for CRS with HIPEC. The median OS for the CRS with HIPEC arm was 22.3 months compared to 12.6 months for the systemic therapy arm.

There has been one randomized controlled trial of CRS with HIPEC using mitomycin C versus oxaliplatin in 126 patients with mucinous appendiceal neoplasms with peritoneal dissemination [21]. This multicenter trial examined the hematologic toxicity of the two agents and found that mitomycin C resulted in lower white blood cell count from postoperative day 5 to 10, and oxaliplatin use led to slightly lower platelet count on postoperative day 5–6, with no differences in Clavien-Dindo complications between the two groups. There is an ongoing randomized phase II trial comparing complete CRS with HIPEC using mitomycin C to CRS with early postoperative intraperitoneal chemotherapy (EPIC) with floxuridine (FUDR) and leucovorin, which includes patients with appendiceal adenocarcinoma. This is a multicenter trial that is actively recruiting (https://clinicaltrials.gov/ct2/show/NCT01815359).

Conclusions

There are abundant retrospective data supporting the use of CRS with HIPEC for the treatment of appendiceal neoplasms with peritoneal dissemination showing favorable results in over 4500 patients. There have been no prospective trials comparing CRS versus CRS with HIPEC in this disease, in part because of the low incidence and due to the histologic and biologic heterogeneity, making prospective study difficult. CRS with HIPEC is currently the standard-of-care, with mitomycin C and cisplatin the most broadly applied and investigated agents for intraperitoneal perfusion.

Patient selection is critical for favorable outcomes. For patients with low-grade disease, complete cytoreduction can result in 5-year survival rates >80%. For patients with high-grade disease, long-term outcomes are poorer with 5-year survival on the order of 40%–60% for those with gross peritoneal disease. For those high-grade patients diagnosed early with minimal or no gross peritoneal disease, data suggest that long-term outcomes may be better. The rationale for current commonly used HIPEC agents is based on favorable pharmacokinetic profiles for intraperitoneal delivery, not on factors specific to appendiceal tumors. There is a need for a better understanding of the pathogenesis and molecular aberrations in this heterogenous disease, as well as development of more effective and potentially targeted intraperitoneal agents.

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9 Data for HIPEC in Colorectal Cancer (T4 Lesions and Metastases)

Victoria Aveson and Garrett M. Nash

Introduction

Peritoneal carcinomatosis (PC) is a common progression in the natural history of colorectal cancer (CRC). PC is present in 4–7% of patients at the time of initial diagnosis [1]. However, in patients who develop metachronous metastases, 20% will develop PC, and of these patients 25% of them will have metastases confined to the peritoneal cavity [2]. Historically, PC from colorectal cancer was associated with a dismal prognosis, 5.2–7 months median survival in the era of fluorouracil-only treatment with significant morbidity during that time [3].

Even in the era of modern chemotherapy, PC in patients with advanced colon cancer is associated with shorter overall survival. A 2016 pooled analysis of 10,533 pts. enrolled in phase III trials of systemic chemotherapy for metastatic colorectal cancer found isolated peritoneal carcinomatosis was associated with a worse median survival than isolated metastases to any other site (16.3 versus 20 months) and approximately the same median survival as multifocal nonperitoneal metastases (16.3 versus 15.7 months) [4]. Similar findings were reported in a second pooled analysis of patients in two phase III trials of systemic chemotherapy for patients with metastatic CRC. Overall survival was worse for patients with PC as compared to other metastatic disease, 12.7 months versus 17.6 months, and that peritoneal carcinomatosis was associated with also worse survival when stratified by chemotherapeutic regimen [5].

Data for Survival Benefit with HIPEC

When regional therapy with cytoreductive surgery (CRS) and intraperitoneal chemotherapy (IPC) for peritoneal carcinomatosis from colorectal cancer was first proposed in the 1990s, multiple small case series suggested prolonged survival with CRS and IPC or hyperthermic intraperitoneal chemotherapy (HIPEC) [6]. However, due to the novelty and complexity of the procedure, it was only performed at a small number of expert centers and recruitment of patients for controlled studies was challenging. In the past decade, as more centers have begun performing regional therapy, studies with internal controls and large-scale multi-institution studies have suggested improved outcomes with this approach.

To date, only two randomized controlled trials comparing systemic chemotherapy to CRS and IPC have been completed. Between 1998 and 2001, Verwaal et al. randomized 105 patients to

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Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_9

either to receive cytoreductive therapy and mitomycin C HIPEC or to receive standard of care systemic chemotherapy (fluorouracil with leucovorin) with palliative surgery for bowel obstruction as indicated. Overall survival for the experimental arm was 22.3 months versus 12.6 months in the standard arm. Moreover, in patients without evidence of residual disease after surgery, median survival was 48 months [7].

One major criticism of the study is that the patients in the control arm received fluorouracil (5-FU) and leucovorin, standard of care at the time, but now no longer first-line chemotherapy. Advances in modern systemic chemotherapy have significantly improved the overall survival of patients with advanced CRC. A recent randomized controlled trial comparing surgery and IPC to modern systemic chemo alone recapitulated the findings of Verwaal et al., demonstrating better survival with surgery and IPC than systemic chemotherapy.

Forty-eight patients with confirmed CRC or appendiceal cancer and spread to two or more peritoneal sites without extra-abdominal metastases were randomized to receive resection and CRS followed by early postoperative intraperitoneal chemotherapy (EPIC) with 5-FU and leucovorin 3 hours postoperatively and then every 4–5 weeks for a total of six treatments over 6 months or to receive systemic chemotherapy with the FOLFOX (folinic acid, fluorouracil, and oxaliplatin) regimen for 6 months. The study ended prematurely due to slow accrual, but was sufficiently powered to draw significant conclusions. Survival was better in the surgery arm than in the systemic chemotherapy arm, 54% versus 38% 2-year survival, and 33% versus 4% 5-year survival. On multivariate analysis, it was found that surgical resectability was the only factor affecting survival, and the 5-year survival among patients with resectable disease median survival was 40 months with 5-year survival of 40% [8].

Two more recent nonrandomized studies compared outcomes in patients receiving CRS and HIPEC with those in patients receiving modern systemic chemotherapy alone and demonstrated a significant survival difference in patients who received CRS and HIPEC.

Elias et al. compared 48 prospectively evaluated patients with PC from CRC undergoing CRS and HIPEC with 48 retrospective matched controls who received only systemic chemotherapy. The experimental arm received induction therapy, complete resection (CCR0 or CCR1), and HIPEC with oxaliplatin with intravenous (IV) 5-FU potentiation. Both groups received a mean of 2.3 lines of modern chemotherapy. Median survival for the HIPEC group was significantly longer than for the group receiving systemic therapy alone, 62.7 versus 23.9 months. It is notable that these median survivals are quite long in comparison with other studies, and the patients in both groups were highly selected for age < 65, low tumor burden, and lack of symptoms [9].

In 2010, Franko et al. published a case-control study of 105 patients at University of Pittsburgh Medical Center. Sixty-seven patients in the experimental arm underwent CRS and HIPEC with mitomycin C at two closely associated facilities with the same physician team. These patients were matched with 38 controls with confirmed CRC peritoneal carcinomatosis who either refused CRS and HIPEC or were unable to receive it for logistical reasons. Patients in both arms received 5-FU and irinotecan. Median survival was longer for patients who underwent surgery and HIPEC, 34.7 months versus 16.8 months for those who received systemic chemotherapy only. Again, the groups were not analyzed based on completeness of resection, but six patients included in the analysis of the experimental arm were noted to have R2 resections [10].

Two large multi-institution prospective studies from France were performed in the mid-2000s. These large-scale multicenter studies represent wide range of techniques, intraperitoneal and systemic chemotherapeutic regimens, and institutional expertise.

In 2004, Glehen et al. published a “world tour” retrospective cohort study evaluating outcomes in 506 patients with PC from CRC and no extra-abdominal metastases in patients who underwent CRS and HIPEC or EPIC from 28 institutions on 4 continents between 1987 and 2002. The institutions represented a range of volume and experience, with over half contributing

25 or fewer cases to the study. Median overall survival was 19.2 months, and survival of patients with complete resection was 32.4 months, while that for patients in whom complete resection was not possible was 8.4 months [11]. Five years later, Elias et al. published another retrospective multi-institution cohort study of 523 patients with the same selection criteria as those who underwent CRS and perioperative intraperitoneal chemotherapy between 1990 and 2007. In this study, median overall survival was 30.1 months, and median survival for complete resection was 33 months versus 7 months in those patients for whom complete resection was not possible [12].

Morbidity and Mortality

Cytoreductive surgery with HIPEC is traditionally associated with a high morbidity and perioperative mortality. The extensive nature of the surgical cytoreduction and exposure of fresh surgical sites, including bowel anastomoses, to concentrated chemotherapeutic agents may make this a challenging procedure with high risk of complication. The most common complications include gastrointestinal fistula, anastomotic leak, and hematologic toxicity.

A 2006 systematic review of morbidity and mortality from 10 studies across nearly two decades with patient numbers ranging from 18 to 506 reported morbidity ranging from 23% to 44% and mortality from 0% to 12% [13]. A meta-analysis of 76 studies on HIPEC for CRC published between 1993 and 2016 found a mean morbidity of 25–34% and mean mortality of 2.8% [14].

In the two recent large multicenter studies out of France, mortality and morbidity were 3–4% and 23–31%, respectively. Elias et al. also found that high volume of treated patients had a lower rate of morbidity and mortality [11, 12].

It has been established that in some complex surgical procedures for advanced cancers, institution volume correlates strongly with morbidity and survival [15]; this may also be true for CRS and IPC for PC for CRC. Several single institution analyses of outcomes following CRS and HIPEC for peritoneal carcinomatosis of gastrointestinal (GI) origin have demonstrated lower complication rate and better survival with increasing experience. One study estimated the plateau of the learning curve at around 130 cases [16, 17].

Overall, while CRS and HIPEC have a high morbidity and mortality, it is comparable to other similarly extensive oncologic surgeries. Furthermore, complication rate and perioperative mortality appear to correlate with institutional experience, suggesting that as physicians and staff are more widely trained in cytoreductive therapy and intraperitoneal chemotherapy techniques, overall complication rates may further decline.

Data for Hyperthermia

The advantage of hyperthermia in intraperitoneal chemotherapy for colorectal cancer remains uncertain even in animal studies. Hyperthermia was added to intraperitoneal chemotherapy regimens based on animal studies suggesting improved tumor penetration of chemotherapeutic agents and adjuvant thermotoxicity [18–20]. More recent animal studies, however, have demonstrated no survival benefit from hyperthermia in addition to CRS or IPC [21].

No clinical studies directly examining the effect of hyperthermia have been completed. Several studies comparing HIPEC with other forms of intraperitoneal chemotherapy have been performed, which suggest no effect or minor advantage to hyperthermia; however, the differences in chemotherapeutic agent and technique between the hyperthermic and normothermic groups make strong conclusions difficult to draw (Table 9.1).

A retrospective cohort study by Cashin et al. examined 126 patients who were identified to have peritoneal disease from colorectal cancer. Of those, 69 underwent CRS and HIPEC with mitomycin C, oxaliplatin, or oxaliplatin and irinotecan, and 57 underwent CRS and sequential intraperitoneal chemotherapy with 5-FU. Ninety-day mortality was identical between groups. The

Table 9.1 Hyperthermia trials

Study	Years of recruitment	Comparison	Study size	Study type	Results
Cashin et al.	1996–2010	HIPEC versus IPC HIPEC: Mitomycin C 30 mg/m^2 in peritoneal dialysis solution 90 min at 41–42 ° C or Oxaliplatin 460 mg/m^2 in 50 mg/ml glucose 30 min at 41–42 °C with concurrent IV 5-FU 400 mg/m^2 and leucovorin 60 mg/m^2 or Oxaliplatin 360 mg/m^2 and irinotecan 360 mg/m^2 in 50 mg/ml glucose 30 min at 41–42 °C with concurrent IV 5-FU 400 mg/m^2 and leucovorin 60 mg/m^2 IPC: 5-FU 500–600 mg/m^2 with IV leucovorin 60 mg/m^2 once a day for 6 days. Eight cycles with 4–6 week intervals.	126	Retrospective cohort Single center	On multivariate analysis, HIPEC was associated with longer overall survival With CC0 resection, there was no difference in overall survival No difference in 90-day mortality
Elias et al.	1999–2002	HIPEC versus EPIC HIPEC: Oxaliplatin 460 mg/m^2 in dextrose 30 min at 43 °C EPIC: Mitomycin C 10 mg/m^2 in lactated Ringer's day 0 and 5-FU 650 mg/m^2 from days 1 to 4	46	Retrospective case-control Single center	No difference in overall survival or rate of extraperitoneal disease recurrence Rate of peritoneal recurrence was lower in the HIPEC group
Elias et al.	1990–2007	HIPEC versus EPIC HIPEC: Mitomycin 30–50 mg/m^2 ± cisplatin 50–100 mg/m^2 60–120 min at 41 °C or Oxaliplatin 360–460 mg/m^2 ± irinotecan 200 mg/m^2 30 min at 43 °C with IV 5-FU and leucovorin EPIC: Mitomycin (10 mg/m^2) day 0 and 5-FU (600 mg/m^2) from day 1 to 4	523	Retrospective cohort 23 centers	No difference in survival
Gremonprez et al.	1999–2016	HIPEC versus EPIC HIPEC Oxaliplatin 200 mg/m2 in 5% dextrose 90 min at 41 ° C or Oxaliplatin 460 mg/m2 in 5% dextrose 30 min at 41 ° C EPIC: Same regimens at 37 ° C	146	Retrospective Propensity-matched Single center	No difference found in mortality or major morbidity

HIPEC group demonstrated higher median overall survival and 5-year survival (34 months and 40%) compared to the sequential IPC group (25 months and 18%). Multivariate analysis revealed the type of IPC was an independent prognostic factor, with better outcomes in patients who received HIPEC. In patients with CC0 resections, however, no significant difference in median survival was noted between HIPEC and sequential IPC groups (39 months versus 32 months $p = 0.3$) [22].

Retrospective case-control study of 46 patients by Elias et al. matched 23 patients with CRC who underwent CRS and HIPEC with oxaliplatin and IV 5-FU with 23 CRC patients who underwent CRS with normothermic intraperitoneal (IP) mitomycin C and 5-FU EPIC on postoperative day 4. No statistically significant difference in mortality or survival was identified between the groups.

Peritoneal recurrence was significantly lower in the HIPEC group (26% versus 57% $p = 0.03$) [23]. In a follow-up multicenter study of 523 patients by Elias et al., no difference in survival was noted between patients who underwent HIPEC and those who underwent normothermic EPIC [12].

To evaluate concerns that hyperthermia may increase perioperative complications, Gremonprez et al. performed a recently published propensity-matched study comparing CRS followed by intraperitoneal oxaliplatin at either normothermia (38°) or hyperthermia (40°) in 146 patients and found no significant different in mortality, major morbidity, or anastomotic leakage [24].

Data for Selection of Intraperitoneal Chemotherapeutic Agent

To date, it is unknown which agent or combination of agents is optimal for intraperitoneal chemotherapy for CRC. Centers of expertise have published studies using mitomycin C, irinotecan, oxaliplatin, and doxorubicin with apparent efficacy. Choice of agent is directed by physician preference, cost, availability, and prior patient exposure but no randomized trials comparing regimens for CRC have been conducted.

Four nonrandomized studies have been performed comparing IPC with oxaliplatin and mitomycin C in patients with PC from CRC receiving CRS and HIPEC, without a clear consensus (Table 9.2). Two studies found no significant difference in disease-free or overall survival between groups, one study found better outcomes with mitomycin C in patients with low disease burden and favorable histology, and the final study found better survival with oxaliplatin [25–27].

The largest study was performed by the American Society of Peritoneal Surface Malignancies which evaluated outcomes of HIPEC with mitomycin C versus oxaliplatin in 539 patients who underwent complete cytoreduction for PC from CRC. Median survival was the same between both groups, but when stratified based on Peritoneal Surface Disease Severity Score (PSDSS), an evaluation of symptoms burden of disease and histology, patients with low severity scores (PSDSS I/II) were found to have better overall survival with mitomycin C versus oxaliplatin (54.3 versus 28.2 months $p = 0.012$) [28].

Two nonrandomized studies have been performed comparing oxaliplatin and irinotecan. Quenet et al. performed a prospective study on 146 patients undergoing CRS and HIPEC for CRC. Forty-three patients received oxaliplatin alone and 103 received oxaliplatin and irinotecan; treatment was otherwise the same. No difference was found in in-hospital mortality, disease-free survival, or overall survival; a significant difference in morbidity was noted in the group that received irinotecan as compared to oxaliplatin alone (52.4% versus 34.9% $p = 0.05$) [29]. Glockzin et al. compared outcomes between oxaliplatin and irinotecan in 32 patients with colorectal or appendiceal cancer who underwent CRS and HIPEC with CCR0/1 resections. There was no perioperative mortality and morbidity, and 3-year survival was not significantly different between groups [30]. These limited studies suggest that intensification of oxaliplatin HIPEC may increase complications without added

Table 9.2 Chemotherapeutic agent trials

Study	Years of recruitment	Comparison	Study size	Study type	Results
Hompes et al.	2004–2006	Oxaliplatin versus mitomycin C Mitomycin: Mitomycin 35 mg/m^2 90 min 41–42 °C Oxaliplatin: Oxaliplatin 460 mg/m^2 30 min 41–42 °C. IV folinic acid 20 mg/m^2. 5-FU 400 mg/m2 and leucovorin 20 mg/m2 IV given 1 hour prior to HIPEC	95	Retrospective	Corrected for extent of PC: Higher postoperative complication rate in the mitomycin group No difference found in intra-abdominal complication rate, recurrence-free survival, or overall survival
Leung Et al.	1996–2015	Oxaliplatin versus mitomycin C Oxaliplatin: Oxaliplatin 350 mg/m^2 in dextrose 30 min at 42 °C Mitomycin: Mitomycin 12.5 mg/m^2 90 min at 42 °C	201	Retrospective	Median survival was longer with oxaliplatin
Van Eden et al.	2010–2016	Oxaliplatin versus mitomycin C Mitomycin C: Mitomycin 35 mg/m^2 in Dianeal 90 min at 42 °C Oxaliplatin: Oxaliplatin 460 mg/m^2 in Dianeal 30 min at 42 °C. 5-FU 400 mg/m2 and Leucovorin 20 mg/m2 IV given 30 minutes prior to HIPEC	177	Retrospective	No difference found in rate of postoperative complications, disease-free survival, or overall survival
Prada-Villaverde et al.	2000–2012	Oxaliplatin versus Mitomycin C Details of therapy not included	539	Retrospective	With complete cytoreduction, no difference was found in overall survival
Quenet et al.	1998–2007	Oxaliplatin versus oxaliplatin and irinotecan Oxaliplatin + irinotecan: Oxaliplatin 300 mg/m^2 and irinotecan 200 mg/m^2 dextrose at 43 °C. 5-FU 400 mg/m^2 and leucovorin 20 mg/m^2 IV given 1 hour prior to HIPEC Oxaliplatin: Oxaliplatin 460 mg/m^2 in dextrose at 43 °C. 5-FU 400 mg/m^2 and leucovorin 20 mg/m^2 IV given 1 hour prior to HIPEC	146	Retrospective	No difference found in overall survival or recurrence-free survival Lower overall morbidity rate in the oxaliplatin alone group
Glockzin et al.	2007–2010	Oxaliplatin versus irinotecan Oxaliplatin: Oxaliplatin 300 mg/m^2 30 min at 41–43 °C. 5-FU 400 mg/m^2 and leucovorin 20 mg/m^2 IV given 30 minutes prior to HIPEC Irinotecan: Irinotecan 300 mg/m^2 30 min at 41–43 °C. 5-FU 400 mg/m^2 and leucovorin 20 mg/m^2 IV given 30 minutes prior to HIPEC	32	Retrospective	Overall survival was better in the oxaliplatin group No difference found in grade 3–4 complications and 3-year survival

benefit, but show little to recommend one agent over another.

Data for IPC in Addition to CRS in CRC

The rationale for IPC following resection of gross disease is that chemotherapy will address residual microscopic disease, reducing recurrence and improving survival. Most studies have demonstrated improved outcomes associated with the completeness of cytoreduction, without demonstrating an added benefit from intraperitoneal chemotherapy. A randomized study in rats has shown improved outcomes with IPC plus CRS versus CRS alone [21]. Two randomized controlled trials in humans have been performed, one ended prematurely due to poor accrual, and the other found the addition of HIPEC to CRS increased late postoperative complications without providing a survival benefit.

A randomized trial started by Elias et al. was stopped prematurely due to poor accrual and subject rejection of randomization into the non-IPC arm. Thirty-five of 90 patients were recruited, of whom 16 were randomized to receive CRS with immediate IP mitomycin C and postoperative IP 5-FU and 19 were randomized to receive CRS with systemic chemotherapy alone. Two-year survival was 60% in both groups; however, the EPIC group was notable for three postoperative deaths, more extensive peritoneal disease, and higher incidence of concomitant hepatectomy. In light of the limited size and premature conclusion, no definitive conclusions can be drawn from this study [31].

The PRODIGE 7 trial recruited patients who had CRC and PC with metastases limited to the abdomen. All recruited patients underwent CRS, and of the patients with resection with residual tumor $\leq$1 mm, 133 were randomized to receive HIPEC with oxaliplatin potentiated with 5-FU and 132 were randomized to receive no IPC. Postoperative mortality and 30-day morbidity were the same between groups, but 60-day morbidity was higher in the arm that received HIPEC compared to those undergoing CRS alone, 24.1 versus 13.6%. Overall survival and relapse-free survival were identical between groups [32] indicating that HIPEC with oxaliplatin is not an effective therapy for colorectal carcinomatosis; however, the median overall survival of almost 4 years in both arms suggests that surgical outcomes in selected patients are favorable.

Future Directions: Proactive HIPEC, Second-Look Surgery, and PIPAC

Even in patients with colorectal cancer who do not present with advanced disease, peritoneal carcinomatosis has been reported in 2–19% of patients following curative surgery and on autopsy in 36–40% of patients who received curative surgery and succumbed to their disease [33]. In patients who do have recurrence after curative surgery, peritoneal carcinomatosis is the only site of disease in up to 25% [34].

Many investigators hypothesize that CRS and HIPEC are most efficacious in patients with limited disease where complete resection is possible [35]. Limited peritoneal disease, as defined by PCI (peritoneal cancer index) score, is also associated with lower perioperative morbidity and mortality [12]. Therefore, early diagnosis and intervention for patients with peritoneal carcinomatosis may improve long-term outcomes, and novel locoregional therapies are needed for patients with advanced and unresectable disease. This has led investigators to consider adjuvant HIPEC at the time of surgery or planned "second-look" surgery with or without HIPEC for selected patients at high risk of peritoneal recurrences and to investigate pressurized intraperitoneal aerosolized chemotherapy (PIPAC) for patients with unresectable PC.

Identification of patients at high risk of developing PC after curative resection has been based on retrospective analysis of outcomes. In a retrospective analysis of 8044 patients who underwent resection of colorectal tumors, Segelmen found emergency surgery, non-R0 resection, and pT4 and pN2 with lymphadenectomy to be associated with increased risk of recurrence with PC [36]. A systematic review of recurrent PC after

CRC resection was performed in 2013. All studies available had low-quality evidence, but 16 informative nonrandomized clinical studies consisting of a total of 598 patients were identified. Synchronous PC, synchronous isolated ovarian metastases, and perforated primary tumor were identified as probable risk factors for the development of PC, but no other significant conclusions were able to be drawn [37].

To assess the utility of adjuvant IPC, Noura et al. reported on a nonrandomized comparative study of 52 patients with positive cytology on peritoneal lavage but no macroscopic evidence of PC. Thirty-one of the 52 patients were administered intraperitoneal mitomycin C at the time of resection. Subjects receiving IPC had significantly better 5-year survival as compared to those who received conventional treatment (54.3% versus 9.5%) and significantly lower rates of peritoneal recurrence (12% versus 59.9%) [38].

Sammartino et al. also performed a nonrandomized study comparing outcomes in 25 patients with T3/T4 colon cancer without macroscopic evidence of PC who received adjuvant HIPEC with oxaliplatin during their initial resection with 50 well-matched controls who received only conventional therapy. They again found better overall survival and disease-free survival, and locoregional recurrence was significantly reduced (4% versus 28%) [39].

Based on the preliminary data from these limited comparative studies, two randomized clinical trials are currently underway to evaluate adjuvant HIPEC in patients at elevated risk of peritoneal recurrence. HIPECT4 has been registered in Spain, intending to recruit 200 patients with cT4NxM0 tumors of colorectal origin for intraoperative randomization to adjuvant HIPEC with mitomycin C or conventional therapy with systemic chemotherapy only. The primary outcome is locoregional control after 3 years of follow-up [40]. COLOPEC is a Dutch study planning to randomize 176 patients with T4 or intra-abdominally perforated colorectal cancer to receive adjuvant HIPEC with oxaliplatin and systemic chemotherapy or systemic chemotherapy alone. Patients will be followed for 18 months, at which point diagnostic laparoscopy will be performed to assess disease-free survival in each group [41].

An alternative adjuvant approach pairs HIPEC with planned second-look surgery in patients with risk factors for recurrence with peritoneal carcinomatosis on their initial operation. Preoperative computed tomography (CT) scans have shown poor detection of PC with large interobserver variation, particularly in PC with small tumor deposits [42], an observation which has been borne out in preliminary second-look surgery studies which have consistently found PC in >50% of high-risk patients without radiographic evidence of PC. This alternative opens the option for a prospective randomized trial of HIPEC for patients with high-risk features noted during resection not performed at a regional therapy center and may limit morbidity associated with HIPEC in patients who would not otherwise go on to develop PC.

Between 2007 and 2011, Delhorme et al. performed planned second-look surgery on 14 patients who had undergone a complete initial oncological resection of CRC with synchronous PC and/or ovarian metastasis with PC. Seventy-one percent of the patients were found to have PC on second look, with a median PCI of 10. All patients with PC received HIPEC with mitomycin C or oxaliplatin. Postoperative mortality was 0%, and Clavien-Dindo grade II–IV complications occurred in 7% of patients, much lower then in other reports of HIPEC for PC from CRC. The 2-year overall survival and disease-free survival rates were 91% and 38%, respectively. Radiographic peritoneal recurrence occurred in only 8% of patients who had undergone HIPEC at a second-look operation [43].

In 2011, Elias et al. performed a prospective study of “second-look” surgery on patients with resected CRC with risk factors for recurrence with PC. Forty-one patients who had undergone R0 resections for CRC and had no symptoms or radiographic findings consistent with PC but were considered high risk because of minimal synchronous PC, ovarian metastases, or perforation of the primary tumor during the initial surgery underwent “second-look” laparotomy approximately 1 year after surgery. Macroscopic

PC was found in 56% of subjects; all subjects underwent HIPEC. Mortality was 2% and > grade II morbidity was 9.7%, again demonstrating lower complication rates than in CRS and HIPEC for patients with established PC. The 5-year overall survival was 90% [44].

This same group is continuing their work with a phase III study, ProphyloCHIP. In this study, 130 patients with resected CRC with high risk of peritoneal recurrence (limited peritoneal implants, ovarian metastases, or perforated tumor) will be randomized to either undergo laparotomy with HIPEC (intraperitoneal oxaliplatin and intravenous 5-FU) within 12 months of surgery or conventional follow-up, both groups receiving systemic adjuvant therapy. Recruitment and data collection are completed, and analysis was scheduled to be completed in June 2019 [45].

For patients with advanced or unresectable peritoneal carcinomatosis who would not be candidates for CRS and HIPEC, pressurized intraperitoneal aerosolized chemotherapy (PIPAC) has been suggested as an alternative treatment. Preclinical and animal studies of PIPAC, in which chemotherapeutic agents are applied as a pressurized aerosol to the peritoneal cavity, have suggested tissue penetration in PIPAC may be superior to HIPEC, allowing for the treatment or downstaging of bulky disease [46].

While many centers, primarily in Europe, have started offering PIPAC, evidence for the efficacy of the technique in CRC is limited. Several small studies in mixed tumor types including CRC have demonstrated the safety of PIPAC with histologic response ranging from 71% to 100% [47]. One study by Demtroder et al. in 2016 focused on PIPAC for PC from CRC exclusively. In this small retrospective study, 17 patients with PC from CRC ineligible for CRS and HIPEC underwent PIPAC with oxaliplatin. Median survival was 15.7 months and 71% of patients showed histologic tumor response [48]. While early trials have used low doses of oxaliplatin, a number of studies have begun testing escalating doses of oxaliplatin in PC from digestive cancers. One such study, the PIPOX trial, recently reported complete response in 3 of 10 patients during the phase I portion of the trial [49].

To further establish the role for PIPAC in treating PC, a number of phase II trials are underway. Public registries report 10 international clinical trials of PIPAC in gynecological and gastrointestinal malignancies [50].

Conclusion

As CRS and IPC for CRC with PC have become more widely practiced, data have accumulated to demonstrate its utility in selected patients. Ongoing research to optimize this technique may further improve outcomes. An abundance of case studies has demonstrated that survival with CRS and HIPEC appears better than historical controls treated with systemic chemotherapy. Two randomized controlled trials also demonstrated longer survival with CRS and IPC compared to systemic chemotherapy alone. More recent reports have demonstrated lower morbidity and perioperative mortality compared to initial studies. The incremental benefit of adding HIPEC to CRS remains unknown. Recent data demonstrated that HIPEC with oxaliplatin has no survival benefit over CRS alone. Nevertheless, there are ongoing investigations into the efficacy of adjuvant HIPEC with or without second-look surgery in patients at high risk of peritoneal recurrence from CRC. These trials may identify a new role for IPC in the coming years.

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10

Role of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in the Treatment of Peritoneal Metastasis of Gastric Cancer

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Introduction

Gastric cancer (GC) is the fourth most common cancer in the world and accounts for 9% of all cancer deaths [1, 2]. Among causes of GC deaths, peritoneal metastasis (PM) is more frequent than hematogenous metastasis, and 53–60% of GC patients have died of PM. In the early 1990s, PM from GC (GC-PM) had been considered as terminal stage, and the traditional therapies for GC-PM were systemic chemotherapy, palliative surgery, and best supportive care. Accordingly, the prognosis of GC-PM was approximately half a year [3].

However, an innovated therapy for PM, named as "comprehensive treatment," was proposed by Peritoneal Surface Oncology Group International (PSOGI) in 1998 in London [4]. Comprehensive treatment consists of cytoreductive surgery (CRS) for PM and hyperthermic intraperitoneal chemotherapy (HIPEC), which is aimed to eradicate residual micrometastasis left behind after complete macroscopic removal of PM by CRS [5].

At present, the comprehensive treatment (CRS + HIPEC) is considered safe and effective treatment for pseudomyxoma peritonei [6], ovarian cancer [7], colorectal cancer [8], and mesothelioma [9].

Currently, more than 430 centers are performing CRS + HIPEC around the world, and a majority of experts consider CRS + HIPEC to be a treatment with curative intent. Additionally, the treatment is acknowledged as standard of care in national guidelines of ten countries, and the guidelines now accept treatment for selected colorectal cancer (CRC) patients with PM or CRC patients at high risk of developing metachronous PM (e.g., T4, perforated colorectal cancer, mucinous type).

However, CRS + HIPEC is not still acknowledged as a standard of care for GC-PM. The purpose of this study was to verify the evidence of the efficacy of CRS + HIPEC in GC-PM.

Natural Course of GC-PM

PM is an important cause of mortality in GC patients. Thomassen et al. reported the reliable population-based data on the prognosis of 491

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Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_10

GC-PM, and the median survival was 4 months [3]. Sadeghi B et al. studied the natural course of 125 GC patients with PM, and the mean and median overall survival (OS) periods were 6.0 and 3.1 months [10].

Systemic Chemotherapy for GM-PM

Table 10.1 [11–21] shows the treatment results of systemic chemotherapy on survival in GC patients with PM.

Median survival time (MST) ranged from 5.0 to 13.0 months, and the 1- and 5-year survival rates after systemic chemotherapy alone range from 20% to 54.3% and 0% to 3.4%, respectively. Hong et al. reported that overall survival (OS) was associated with the extent of PM, and OS of patients with no measurable disease was significantly longer than that of patients with measurable disease [14].

MST after systemic chemotherapy alone was significantly longer than median survival period of best supportive care. Although a small number of patients survived longer than 5 years after systemic chemotherapy, all patients died of PC within 8 years after chemotherapy [14]. Accordingly, the effect of systemic chemotherapy on survival improvement is limited, and systemic chemotherapy alone cannot cure patients with PM. The reasons include the existence of the plasma-peritoneal barrier [22] and

Table 10.1 Outcomes of gastric cancer patients with peritoneal metastasis treated by systemic chemotherapy

First author	Treatment	No. of patients	MST	Response rate (%)	1-year survival rate (%)	5-year survival rate	Disease-free survivors after 5 years	Side effects Grade 3, 4, 5 (Grade 5)
Nishina T [12]	5-FU+(MTX)	49	7.7 m	ND	27.10	0%	0	0–28.6% (0%)
	Paclitaxel	51	7.7 m	ND	31.40	0%	0	0–17.6% (0%)
Koizumi W [11]	S-1 + CDDP	51	13.0 m	54	54.10	NR	0	0–11% (0%)
	S-1	36	11.0 m	31.00	46.70	NR	0	0–40% (0%)
Imamoto H [13]	Paclitaxel	64	5.0 m	31.30	20	0%	0	7.9–22.2% (0%)
Hong SH [14]	5-FU/CDDP, TaxanCDDP, etc.	61	12.5 m	ND	54.30	3.40%	0	0
Wilke H [15]	Ramucirumab	163	9.6 m	17	42	NR	NR	81% (12%)
	Ramucirumab+paclitaxel	152	7.4 m	28	30	NR	NR	63% (16%)
Pernot S [16]	Docetaxel, 5FU, oxaliplatin	51[a]	12.1 m	66	51	0%	0	30% (0%)
Lee HH [17]	FOLFOX-6	82[a]	13.0 m	40.20	37	NR	NR	34.1% (0%)
Kim BG [18], Kaya AO [19]	FOLFIRI	44, 97[a]	10.3, 10.5 m	38.4, 26.8	50	NR	NR	13.6% (0%)
Park SR [20]	SOX	59[a]	10.5 m	ND	82	NR	NR	28.8% (0%)
Kim ST [21]	CapeOX+pazopanib	66[a]	6.5 m	62.40	36	NR	NR	22.7% (0%)

NR not reached, *ND* not described

[a]peritoneal metastasis and/or other stage IV factor

cancer stem cells [23]. Plasma-peritoneal barrier (PPB) consists of perivascular basement membrane, submesothelial stromal tissue, basement membrane of mesothelial cells, and mesothelial cells. Having a width of about 100 μm, the PPB hinders the diffusion of anticancer drugs from submesothelial blood capillaries to the peritoneal cavity [24]. Accordingly, systemically administered drugs hardly penetrate into the peritoneal cavity, resulting in the low efficacy on PM.

Cancer stem cells are strongly resistant to anticancer drugs because these cells are in the resting phase of the cell cycle [25]. Even if the chemotherapy is very effective, cancer stem cells survive and proliferate, resulting in the failure of the systemic chemotherapy [25].

To overcome the limits of systemic chemotherapy, comprehensive treatment was developed.

Treatment Options in Comprehensive Treatment for Intent of Cure

Figure 10.1 shows the time schedule of comprehensive treatment for GC-PM. The treatment consists of nine treatment options: (1) laparoscopic diagnosis of peritoneal cancer index (PCI) and laparoscopic HIPEC (LHIPEC), (2) neoadjuvant intraperitoneal/systemic chemotherapy (NIPS), (3) patients' selection for CRS using laparoscopy after NIPS, (4) laparotomy and extensive intraperitoneal lavage (EIPL) by 10 L of saline to remove peritoneal free cancer cells, (5) CRS combined with gastrectomy plus D2 lymph node dissection using peritonectomy technique, (6) EIPL to remove cancer cells spilled from torn blood and lymphatic vessels during surgical procedures, (7) HIPEC, (8) early postoperative intraperitoneal

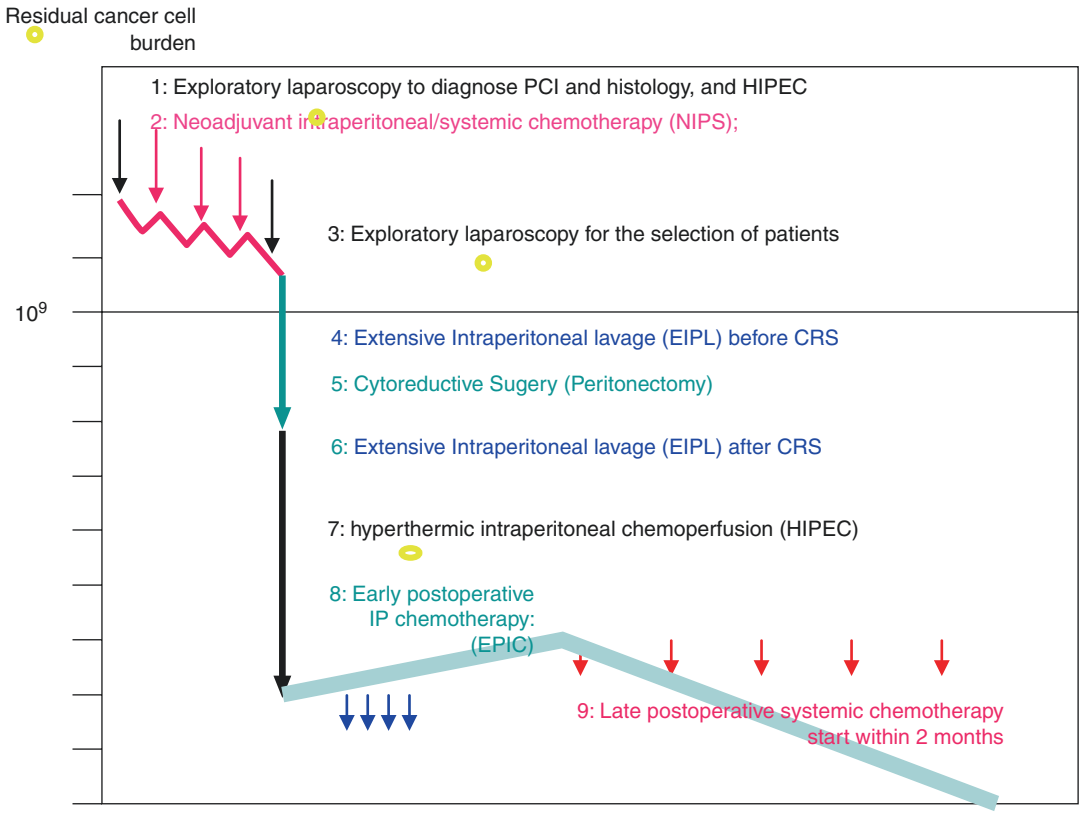

Fig. 10.1 Schedule of a comprehensive treatment for patients with PC from peritoneal malignancies [9]

chemotherapy (EPIC), and (9) late postoperative systemic or IP chemotherapy. Sensitivity for the diagnosis of GC-PM by image diagnostic modalities such as contrast enhancement computed tomography (ceCT) and magnetic resonance tomography is low [26]. Koh et al. reported that the sensitivity of ceCT for PM with diameter less than 1 cm was 10% [27]. Accordingly, accurate evaluation of PCI is recommended to be performed by laparoscopy because sensitivity of the diagnosis of small PM by laparoscopy is very high [28, 29]. At the time of exploratory laparoscopy, determination of PCI and cytological status and histologic diagnosis for peritoneal nodules by biopsy should be performed. LHIPEC is then performed and a peritoneal port is placed. Two weeks after LHIPEC, NIPS is started. After several cycles (3–5 courses) of NIPS, a second laparoscopy is performed to select the patients for CRS + HIPEC. If the PCI at second laparoscopy is less than cutoff level (PCI $\leq$ 12) and small bowel PCI $\leq$ 3, these patients are selected for CRS [30]. Because PCI higher than cutoff value means the significantly poor prognosis and no survival benefit from patients treated with chemotherapy alone, these patients should be treated with chemotherapy again [31].

Three to 4 weeks after the last NIPS, laparotomy is performed. At laparotomy, PCI, cytology, and lymph node status are evaluated, and then EIPL is performed to wash out peritoneal free cancer cells [32]. In EIPL, 1 L of saline, introduced in the peritoneal cavity, is vigorously stirred by hand and is completely aspirated. The procedures are repeated 10 times. Radical gastrectomy is then performed, and all the macroscopic peritoneal nodules are removed by peritonectomy technique [31]. After complete removal of intraperitoneal tumors, EIPL is performed again to remove cancer cells spilled during CRS.

HIPEC is performed with 4 L of heated saline at 40~43°C with chemotherapeutic drugs for 30–120 min. Temperature and HIPEC time vary from institute to institute (Table 10.2).

From postoperative day 1 to 4, EPIC is performed using 5-fluorouracil (5FU) with 500 ml of saline. The aim of EPIC is to kill residual micrometastasis as early as possible [33]. Postoperative systemic or intraperitoneal chemotherapy is started before postoperative month 2.

Aims of LHIPEC and NIPS are to reduce PCI to less than cutoff value, to kill peritoneal free cancer cells, and to eradicate micrometastasis in the subperitoneal tissue.

Valle et al. reported that complete cytoreduction can be performed in only 30% of patients without neoadjuvant chemotherapy [28]. Yonemura et al. reported that the incidence of patients with PCI less than cutoff level (PCI $\leq$ 11) after NIPS was significantly higher (67.3%, 35/52) than that before NIPS and that PCI values were decreased in 67.3% (35/52) of patients after NIPS [34]. Additionally, complete cytoreduction was achieved in 57.6% of the 52 patients after NLHIPEC+NIPS [34]. Cytologic status at CRS is an independent prognostic factor, and positive cytology is an independent sign of poor prognosis even after complete cytoreduction [35]. After NLHIPEC+NIPS, positive cytology became negative in 71% (22/31) of patients. Additionally, complete disappearance of PM was found in 11.5% (6/52) of patients [34]. These results indicate that NLHIPEC+NIPS plays a crucial role to reduce PCI and disappearance of peritoneal free cancer cells, resulting in downstage of PM and increase in the incidence of complete cytoreduction.

Residual intraperitoneal cancer cell burden is least just after CRS, and HIPEC and EPIC may have a potential to achieve complete eradication of residual micrometastasis. Hyperthermia is known to enhance cytotoxicity when combined with chemotherapeutic drugs [36, 37], and HIPEC just after CRS is considered as the best timing to achieve total cell kill of small number of residual intraperitoneal micrometastases. Meta-analysis and randomized controlled trial revealed that HIPEC significantly improved the survival after CRS for GC-PM [38, 39]. However, at present, power of HIPEC is not enough to achieve total cell kill in the majority of GC patients with PM because peritoneal recurrence was found in around 70% of patients who received complete cytoreduction and HIPEC [40–43].

Table 10.2 Studies of CRS+HIPEC for peritoneal metastasis from gastric cancer

First author	No. of patients	Treatment	Method	Drugs	Temperature (°C)	Duration (minutes)	Median OS (months)	5-year OS (%)
Yang XJ [39]	68	CRS + HIPEC	Open	CDDP 120 mg + MMC 30 mg	43	60–90	11	NR
Wu HT [45]	50	CRS + HIPEC	Open	LOB 50 mg/m2 + DOC 60 mg/m2	43	60	14.3	NR
Tu Y [46]	231	CRS + HIPEC	Closed	5-FU 1500 mg + CDDPP100mg	43	60	37	NR
Boerner T [47]	102	CRS + HIPEC	Closed	CDDP 75 mg/m2 + DOX 15 mg/m2	42–43	60	17.2	6.40
Passot G [48]	127	CRS + HIPEC	Closed	CDDP, MMC, OHP, DOX CPT-11	40–43	30–90	13	14.00
Canby E [49]	194	NIPS+CRS + HIPEC	Open	DOC 30 mg/m2 + CDDP 40 mg/m2	43–43.5	40	15.8	10.70
Glehen O [42]	159	CRS + HIPE/EPIC	Open/closed	CDDP, MMC, OHP, CPT-11	40–43	60–120	9.2	13.00
Hall JJ [40]	74	CRS + HIPEC	Closed	MMC 40 mg	40–41	120	8	6.00
Yonemura Y [43]	367 (CC0–3)	NIPS+CRS + HIPEC	Open	CDDP+MMC or DOC+CDDP	42–43.5	40–60	10.9	8.20
	197 (CC-0)	NIPS+CRS + HIPEC	Open	CDDP+MMC or DOC+CDDP	42–43.5	40–60	16.8	16.60
	170 (CC1–3)	NIPS+CRS + HIPEC	Open	CDDP+MMC or DOC+CDDP	42–43.5	40–60	6	0.70

CDDP cisplatin, *MMC* mitomycin C, *LOB* lobaplatin, *5-FU* 5-fluorouracil, *DOX* doxorubicin, *OHP* oxaliplatin, *CPT-11* irinotecan, *DOC* docetaxel

Methods of HIPEC for Gastric Cancer

Hyperthermia enhances the cytotoxicity on cancer cells when combined with certain chemotherapeutic agents such as mitomycin C (MMC), cisplatin (CDDP), doxorubicin (DOX), and docetaxel (DOC). Accordingly, these drugs have been used in combination with hyperthermia (Table 10.2) [40, 42, 44–49]. The concept of thermal dose determined by temperature and exposure time during hyperthermic treatments has been proposed [36]. An exponential relationship between temperature and exposure time is found for cytotoxicity. When the treatment temperature is higher than 43°C, cells are killed due to irreversible changes of cellular protein according to the time-dependent and exponential relationship [36]. If the cells are treated below 43°C, cells survive by thermo-tolerance, which is induced by the production of heat-shock protein [36].

This relationship can be stated as 1-degree increase in temperature above 43°C requires a twofold decrease in time for the same effect at 43°C. In contrast, 1-degree decrease below 43°C needs three- to fourfold increase in time for the same effects at 43°C. This relation is expressed as the following equation: If the treatment is performed at higher than 43°C, time for HIPEC is calculated as $2^{43\text{-}T1}$. If the treatment temperature is lower than 43°C, time for HIPEC is expressed as 4 to $6^{43\text{-}T1}$, where t1 = treatment temperature.

Accordingly, a thermal dose that is clinically relevant to the cytotoxic effect is needed for the standardization of HIPEC. In HIPEC, one thermal dose is equivalent to treatment for 30 min at 43°C [37]. At a treatment temperature of 42°C, the treatment time should be prolonged from 90 to 120 min to obtain the cytotoxic effect equivalent to 43°C for 30 min. In contrast, 15 min is sufficient when the temperature is 44°C. However, temperature higher than 44°C may result in development of intestinal necrosis or anastomotic insufficiency. In a report of Shimizu et al., intraperitoneal hyperthermia in rats up to 44.0°C for 30 min. Had no adverse effects on the healing of intestinal anastomosis [50]. However, intraperitoneal hyperthermia of 45°C for 30 min in the rats resulted in 90% mortality [50].

From these results, HIPEC under temperature of 43–43.5°C and treatment time of 40 min is considered as a standard thermal dose for clinical application. During HIPEC, even temperatures of 43–43.5°C over all the peritoneal surfaces should be maintained by stirring the heated saline by hand to achieve even distribution of heated saline on the peritoneal surface.

Many clinical trials for HIPEC have been reported, but there is a wide variety among the HIPEC methods (open or closed method), differences in choice of chemotherapeutic drugs, and different inflow temperatures [39, 42, 51] (Table 10.2). The temperatures used varied from 40°C to 43°C, and the duration of treatment and the chemotherapeutic drugs have also varied (Table 10.2). Hyperthermia significantly potentiated the chemotherapeutic effects only at temperatures above 40°C in vitro and enhanced the drug penetration into the tumor tissues [52]. Additionally, Schaaf L et al. reported that that this temperature threshold was also critical for overall survival and progression-free survival of patients with PM [52]. As mentioned above, if the temperature of HIPEC is 42°C, the treatment time should be longer than 120 min. to obtain the cytotoxic effects equivalent to when treated at 43–43.5°C. HIPEC treatments at temperatures lower than 43°C (mild hyperthermia) require long treatment time [36].

The heterogeneity in chemotherapeutic drugs, temperature, and techniques reflects the confusion regarding the treatment strategies. Accordingly, prospective randomized studies should be performed to develop an effective HIPEC method as the standard of care for GC-PM.

Direct Effects of HIPEC on Peritoneal Metastasis of Gastric Cancer

Yonemura et al. first reported the direct effect of HIPEC by comparing PCI levels before and 1 month after laparoscopic HIPEC (LHIPEC) [34]. LHIPEC was performed two times sepa-

rated by a 1-month rest interval in 53 patients with GC-PM. Changes in PCI score were compared at the time of first and second laparoscopy. PCI at the second session (11.8 ± 11.0) was significantly lower than that at the first session (14.2 ± 10.7). At the time of the first LHIPEC, 26 (49%) of 53 patients had PCI levels ≤11, but at the second laparoscopy, 31 (59%) patients showed PCI levels ≤11. Additionally, 8 (15%) patients showed complete disappearance of PM, and 24 (45.3%) patients showed a decrease in PCI levels. Positive cytology at the first LHIPEC changed to negative in 13/19 (68%) patients [34].

These results indicate that LHIPEC is an effective method to reduce PCI levels and to eradicate peritoneal free cancer cells.

Furthermore, Yonemura et al. studied the effects of LHIPEC plus NIPS by comparing PCI levels of the LHIPEC and after LHIPEC plus 3 cycles of NIPS. Two weeks after LHIPEC, a series of 3-week cycles of NIPS with oral S1 plus intraperitoneal/systemic administration of docetaxel, and cisplatin was performed. Then, 4 weeks after NIPS, cytoreductive surgery was performed in 86 patients. Positive cytology in 38 patients changed to negative in 26 (68.4%) patients at laparotomy. PCI after LHIPEC and NIPS (6.7 ± 7.8) was significantly lower than pre-treatment-PCI (10.6 ± 10.2) ($P = 0.0001$). Thirty patients (34.9%) showed pre-treatment-PCI ≥ 12, but post-treatment-PCI of 19 (63.3%) of the 30 patients came to be ≤11. Post-treatment-PCI cut-off level (PCI ≥ 12 vs. PCI ≤ 11) and cytology after treatment emerged as independent prognostic indicators. However, pre-treatment-PCI levels and cytologic status were not independent prognostic factors. These results indicate that surgeons should select patients for CRS from the post-treatment-PCI cutoff level (PC ≥ 12 vs. PCI ≤ 11) and cytologic status (negative vs. positive).

Effects of HIPEC on Survival of the GC-PM

HIPEC without CRS did not improve the long-term survival, and the survival was not significantly better than in those treated with NIPS alone [53]. In contrast, the most promising result after CRS + HIPEC is the long-term survival. Nine studies after CRS + HIPEC treatment are summarized in Table 10.2. The median overall survival (OS) was 16.7 months (range 8–37). In contrast, the median overall survival of GC-PM patients treated with systemic chemotherapy alone was 10.7 months (Table 10.1), shorter than with CRS + HIPEC. Additionally, the median 5-year survival of patients treated with systemic chemotherapy (Table 10.1) and CRS + HIPEC were 0.7% (range 0–3.4%) and 10.3% (range 6.0–13.0%).

Ji et al. analyzed five prospective studies and reported that the median OS was 11 months (range 10.0–11.3) in the CRS + HIPEC group versus 5.4 months (range 4.3–6.5 months) in the CRS alone group [54].

Coccolini et al. studied 20 prospective RCTs including 2145 patients with GC-PM and reported that overall recurrence rates were significantly improved by CRS + HIPEC as compared with CRS alone (OR = 0.46) [55]. Additionally, they analyzed the survival of 784 GC-PM patients treated with CRS. The survival after complete cytoreduction was significantly better than that after incomplete cytoreduction (5-year risk ratio = 7.95) [56].

Passot et al. reported that the 10-year survival without recurrence was 9% [48]. Yonemura et al. similarly reported that the 5-year survival rate of 201 patients with GC-PM treated with CRS + HIPEC was 12%, and 12 patients were alive without recurrence 5 years after CRS + HIPEC [43].

Different from systemic chemotherapy, CRS + HIPEC is the only possible treatment strategy with a hope of cure.

Side Effects of HIPEC and Morbidity and Mortality after CRS + HIPEC

Yonemura et al. performed LHIPEC for 408 patients with PM from various primary sites, and Grade 1, 2, and 3 morbidities were experienced in 19 (4%), 6 (1.5%), and 4 (1%), respectively. LHIPEC was associated with no Grade

4 morbidity and no deaths [55]. In 166 patients with GC-PM, renal dysfunction of Grade 1, 2, and 3 was found in 11 (6.7%), 2 (1.2%), and 4 (2.4%) after LHIPEC. Cisplatin used in HIPEC carries a risk of renal impairment [57]. However, renal impairment after LHIPEC was completely recovered by infusion therapy [53]. HIPEC alone is a safe treatment. Mizumoto et al. reported that HIPC is not a significant risk factor associated with postoperative complications [58].

However, Grade 3, 4, and 5 morbidities and mortality after CRS + HIPEC are still high. Ji ZH reported that mortality and Grade 3 and 4 morbidities ranged from 0% to 6.3% and 6.9% to 52.2%, respectively [42, 44–49, 51]. The most frequent adverse events included pleural effusion, ileus, sepsis, wound infection, and anastomotic leakage [58]. Meta-analysis of 13 reports of RCTs showed a significant increase of intra-abdominal abscess by 137% after CRS + HIPEC, when compared with the CRS alone group [59]. CRS + HIPEC is associated with high postoperative morbidity and mortality; however, anastomosis following total or subtotal gastrectomy is safe in experienced centers [60].

Yan et al. proposed the number of patients needed in training, performing the complicated procedure safely (learning curve), was 70 by a well-trained surgeon [61]. As described in NICE Interventional Guideline 2010 (http://www.nice.org.uk/guidance/IPG331), and NCCN Guideline 2017: Colon cancer (http://www.nccn.org/patients), CRS + HIPEC can be considered in experienced centers for selected patients with limited peritoneal metastases for whom R0 resection can be achieved. To educate surgeons who want to start CRS + HIPEC, the European School of Peritoneal Surface Oncology Training Program (http://www.essoweb.org/school-of-peritoneal-surface) and Japanese/Asian School of Peritoneal Surface Malignancy Treatment (http://www.facebook.com/yutaka.yonemura.hipec.gastric) were funded from 2014 and 2016, respectively. In these schools, participants were provided high-quality, structured, basic, and advanced training in peritoneal surface oncology.

Effects of HIPEC on the Survival of Patients with Cytology-Positive (Cy1) Peritoneal Lavage Fluid and without Macroscopic Peritoneal Metastases (P0/Cy1)

Patients with positive peritoneal cytology but no macroscopic PM are grouped as P0/Cy1. The survival of P0/Cy1 group was almost the same as for patients with macroscopic (P1) [62], and the 5-year survival rate of P0Cy1 group was less than 5% [62, 63]. Accordingly, P0Cy1 group is considered an independent prognostic factor in GC patients who are supposed to undergo potentially curative resection. Yamamura et al. reported that P0Cy1 patients are unlikely to be optimal candidates for surgical removal of primary tumors and omentum [64]. Conversely, several options, such as postoperative systemic chemotherapy, HIPEC, EIPL, and NIPS, have been reported to be able to improve the postgastrectomy survival of P0Cy1 group [65]. However, there is no universal consensus on the most appropriate treatment regimen for this particular group. Cabalag et al. performed a systemic review and meta-analysis of nine articles that describe treatment for GC patients with P0Cy1. The use of S1 monotherapy was associated with a significant survival benefit [66]. Intraperitoneal chemotherapy using intraperitoneal dwelling of paclitaxel after gastrectomy showed a trend toward improvement in overall survival [67]. Kuramoto et al. reported that EIPL with intraperitoneal dwelling of CDDP showed a significant improvement in overall survival in comparison to that without EIPL group [32]. According to a meta-analysis of three reports regarding intraperitoneal chemotherapy using HIPEC, EIPL+IP chemotherapy, and IP chemotherapy, survival of 164 P0Cy1 patients was significantly improved by HIPEC [63].

Regarding the survival benefit of HIPEC on the prophylaxis of peritoneal recurrence after gastrectomy for T3- and T4-patients, two RCTs and one ongoing study were reported [54, 68, 69]. Hamazoe et al. conducted an RCT to evaluate the efficacy of HIPEC as a prophylactic treatment for the prevention of peritoneal recurrence in GC patients with serosal invasion.

However, the 5-year survival rate after gastrectomy+HIPEC was not significantly better than that after gastrectomy alone [68]. Yonemura et al. reported that HIPEC had an efficacy for the prophylaxis of peritoneal recurrence after curative resection of advanced gastric cancer with high risk of peritoneal recurrence [69]. The GASTRICHIP study is an ongoing French trial comparing CRS + HIPEC vs. CRS alone in advanced GC patients with a high risk for PM, and it was still recruiting participants at the time of this writing [54].

Conclusion

The comprehensive treatment combining CRS and perioperative chemotherapy is a promising treatment for GC-PM that brings cure in selected patients with PCI less than cutoff level who received complete cytoreduction and HIPEC. Because there is still no standard protocol for HIPEC, as urgent further evaluation, HIPEC methods were confirmed by RCTs.

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11 Regional Therapy for the Treatment of Ovarian Cancer: HIPEC and Intraperitoneal Chemotherapy

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Introduction

Peritoneal surface malignancies of gynecologic origin, including ovarian, fallopian tube, and primary peritoneal and uterine cancers, are the deadliest of gynecologic cancers. This is attributed largely to a paucity of effective screening tools for these cancers and the absence of early symptoms. Most patients with these malignancies therefore present at an advanced disease stage when tumors have spread to the pelvis, omentum, and upper abdomen. In the United States, the current standard of care is primary maximal effort cytoreductive surgery, where optimal results are achieved with no gross residual disease at surgery completion, followed by a platinum and taxane-based chemotherapy regimen for six to eight cycles. Patients suspected with disease that is not optimally resectable are considered for preoperative neoadjuvant chemotherapy followed by maximal effort cytoreductive surgery after a documented response to treatment [1]. Several chemotherapy regimens for treatment of primary ovarian cancer exist, including intravenous (IV) only, intraperitoneal (IP), and IV combinations.

There has been significant interest in using regional-based therapies for gynecologic malignancies, especially epithelial ovarian cancers. Despite the fact that patients with epithelial ovarian cancers often have evidence of metastatic disease at the time of diagnosis, these cancers are found primarily in the abdominal/pelvic cavity on the peritoneal surfaces and not in the parenchyma of various organs. Therefore, clinicians/scientists have leveraged the biology of this cancer to develop a strategy of directly exposing chemotherapy to the areas of cancer involvement. This chapter will focus on therapies that are being delivered directly to the abdominal and pelvic cavity for patients with epithelial ovarian cancer. Although the discussion in this chapter is focused on epithelial ovarian cancers, the therapies discussed also apply to fallopian tube cancers and primary peritoneal cancers, which are normally treated the same as epithelial ovarian cancers. These three cancers are often grouped together in clinical trials. In addition, this chapter does not generally apply to non-epithelial ovarian cancers.

Rationale for Cytoreduction with Regional Therapies

Gynecologic cancers are generally confined to the peritoneal cavity, both at initial diagnosis and at recurrence. The tumors in this cavity often affect

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Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_11

freestanding organs within the peritoneal cavity, allowing for sloughed cancer cells to disperse widely. These cells seed the peritoneal cavity by traveling in the circulation of the peritoneal fluid. These concepts suggest that the IP administration of chemotherapy should result in a pharmacologic advantage in exposure to and penetration of primary and recurrent tumors. The peritoneal cavity provides a potential space for chemotherapy instillation, thus allowing the drug to come into direct contact with deposits of malignant cells. This direct contact with tumor deposits, particularly those <0.5–1 cm in maximum diameter, has been reported to result in better penetration of individual tumors. In addition, the potential for systemic toxicity may be reduced with IP chemotherapy, as high ratios of IP to serum concentrations of drug should be achievable. The infusion of chemotherapy into the peritoneal cavity provides distinct pharmacokinetic advantages. The addition of hyperthermia potentiates the effect of IP chemotherapy through anti-tumor synergism, without systemic drug absorption. Hyperthermic perfusion of tumor sites is based on the principle that heat is directly cytotoxic to the tumor by disrupting the microtubule system, inducing primary protein damage, and promoting vascular stasis in synergy with chemotherapy [2, 3]. Proposed mechanisms of synergy between heat and cisplatin include increased platinum DNA-adduct formation, enhanced transcellular transport especially in optimally resected tumors, increased membrane permeability, and deeper tumor penetration. It is the combination of direct cytotoxicity to the peritoneal surface and synergy between heat and cisplatin, as well as the advantage of dose-dense regional delivery of cytotoxic agents with relatively little systemic toxicity, which position HIPEC as an attractive regional therapy in ovarian cancer.

Although HIPEC permits the delivery of high local drug concentrations to exposed peritoneal surface tumors, one important limiting factor is the narrow depth of tissue penetration by the delivered cytostatic agent [4]. Depth of drug peritoneal penetration is limited to ≤3 mm from the parietal peritoneal surface [5, 6]. Hence, the efficacy of HIPEC is inversely proportional to the volume of residual disease; therefore, therapeutic benefit is maximized when all grossly apparent disease is resected (complete cytoreduction). Optimal therapeutic synergy is achieved when HIPEC is administered immediately after maximal cytoreduction, thereby minimizing trapping of viable peritoneal tumor cells in fibrin and postoperative adhesions and maximizing the killing of tumor cells shed during resection [7]. Adhesions are lysed during cytoreduction to facilitate uniform distribution of perfusate, maximize direct contact of drug with residual peritoneal tumor cells, and harness the advantage of "thermo-chemotherapeutic" anti-tumor synergism [8–11].

Intraperitoneal-Based Chemotherapy for Treatment of Ovarian Cancers

Intravenous-based chemotherapy has been predominantly the gold standard front-line treatment for ovarian cancer [12] (Table 11.1). Intravenous carboplatin and paclitaxel have emerged as the standard by which new treatments are compared. Studies that added cytotoxic chemotherapies concurrently or sequentially to this standard regimen failed to improve survival in a large phase III trial [13] indicating that adding more chemotherapy did not improve survival. Newer approaches to therapy were needed. Intraperitoneal chemotherapy had gradually emerged as an approach to improve survival. Intraperitoneal chemotherapy has been extensively investigated in patients with newly diagnosed ovarian cancer who have undergone tumor-debulking surgery. Intraperitoneal therapy in ovarian cancer is associated with improved survival based on randomized, controlled, phase III trials of first-line IP chemotherapy in conjunction with surgical cytoreduction [14–17]. The first trial randomly assigned patients who had undergone optimal cytoreductive surgery to receive cisplatin at a dose of 100 mg/m^2 administered either IP or intravenously (IV) and cyclophosphamide IV at a dose of 600 mg/m^2. Overall, survival (OS) was 41 months for the IV group and 49 months for the IP group; and grade 3 and 4 toxicities were lower in the IP group [14].

Table 11.1 Phase III trials of platinum−/taxane-based upfront chemotherapy for treatment of epithelial ovarian cancer

Study	Patient characteristics	Regimen	Median PFS	Median OS
Ozols [12] 2003 (GOG 158)	FIGO Stage III optimal <1 cm	(A) IV cis 75 mg/m^2 + IV P 135 mg/m^2 (over 24 h), d1 (B) IV Carbo AUC 7.5 + IV P 175 mg/m^2 (over 3 h), d1	(A) 19.4 m (B) 20.7 m	(A) 48.7 m (B) 57.4 m
Armstrong [16] 2006 (GOG 172)	FIGO Stage III optimal <1 cm	(A) IV P 135 mg/m^2 (over 24 h), d1 + IV cis 75 mg/m^2, d2 (B) IV P 135 mg/m^2 (over 24 h), d1 + IP cis 100 mg/m^2, d2 + IP P 60 mg/m^2, d8	(A) 18.3 m (B) 23.8 m	(A) 49.7 m (B) 65.6 m
Katsumata [19] 2009 (JGOG 3016)	FIGO Stage II–IV, Optimal debulking ≤1 cm (46% dose-dense vs 45% control); 89% underwent primary debulking	(A) IV Carbo AUC 6 + IV P 180 mg/m^2, d1 (B) IV Carbo AUC 6 d1 + IV P 80 mg/m^2 d1, 8, 15	(A) 17.2 m (B) 28 m	
Pignata [28] 2014 (MITO-7)	FIGO Stage IC–IV, Optimal debulking ≤1 cm (53% control and experimental arms)	(A) IV Carbo AUC 6 + IV P 175 mg/m^2, d1. (B) IV Carbo AUC 2 + IV P 60 mg/m^2, d1, 8, 15	(A) 17.3 m (B) 18.3 m	
Burger [21] 2011 (GOG 218)	FIGO Stage III–IV, Optimal debulking ≤1 cm (34.9% control, 34.7% arm B, 32.8% arm C)	(A) IV Carbo AUC 6 + IV P 175 mg/m^2, cycles 1–6 + placebo (B) IV Carbo AUC 6 + IV P 175 mg/m^2, cycles 1–6 + Bev 15 mg/kg, cycles 2–6 (C) IV Carbo AUC 6 + IV P 175 mg/m^2, cycles 1–6 + Bev 15 mg/kg, cycles 2–22	(A) 10.3 m (B) 11.2 m (C) 14.1 m	
Perren [22] 2011 (ICON7)	FIGO Stage IIB–IV, FIGO Stage I or IIA, high risk (9% of patients), Optimal debulking ≤1 cm in 74% exp. and control arms	(A) IV Carbo AUC 5–6 + IV P 175 mg/m^2, cycles 1–6 (B) IV Carbo AUC 6 + IV P 175 mg/m^2, cycles 1–6 + Bev 7.5 mg/kg, cycles 1–18	(A) 20.3 m (B) 21.8 m	(A) 44.6 m (B) 45.5 m
Du Bois [28] 2016 (AGO-OVAR 12)	FIGO Stage IIB–IV, Optimal debulking to no macroscopic residual disease (51% exp. and control arms).	(A) IV Carbo AUC 5 + IV P 175 mg/m^2, d1 + placebo d2–21 of every 3-w cycle for up to 120 w (B) IV Carbo AUC 5 + IV P 175 mg/m^2, d1 + nintedanib, d2–21 of every 3-w cycle for up to 120 w	(A) 16.6 m (B) 17.2 m	
Vergote [29] 2019 (TRINOVA-3/ ENGOT-ov2/ GOG-3001)	FIGO Stage III–IV, Optimal debulking ≤1 cm (57% exp. arm vs 56% control); 63% underwent primary debulking	(A) IV Carbo AUC 5–6 + IV P 175 mg/m^2, d1 + placebo. (B) IV Carbo AUC 5–6 + IV P 175 mg/m^2, d1 + trebananib × 6 cycles, then maintenance trebananib	(A) 15 m (B) 15.9 m	
Armstrong [20] 2019 (GOG 252)	FIGO Stage II–IV, Optimal debulking ≤1 cm (91.9% control vs 93.8% Arm B, 93.6% Arm C	(A) IV P 80 mg/m^2 d1, 8, 15 + IV carbo AUC 6. (B) IV P 80 mg/m^2 d1, 8, 15 + IP carbo AUC 6 (C) IV P 135 mg/m^2 (over 3 h), d1 + IP cis 75 mg/m^2, d2 + IP P 60 mg/m^2, d8 All arms received bev 15 mg/kg, d1, cycles 2–22	(A) 24.9 m (B) 27.4 m (C) 26.2 m	(A) 75.5 m (B) 78.9 m (C) 72.9 m

Note: For all chemotherapies, six cycles were given with a cycle consisting of 3-week schedule, unless otherwise stated *FIGO* International Federation of Gynecology and Obstetrics, *exp* experimental, *Cis* cisplatin, *carbo* carboplatin, *P* paclitaxel, *bev* bevacizumab, *AUC* area under curve, *IV* intravenous, *h* hour, *d* day, *m* month, *PFS* progression-free survival, *OS* overall survival, *GOG* Gynecologic Oncology Group, *JGOG* Japanese Gynecologic Oncology Group, *ICON* International Collaboration on Ovarian Neoplasms, *MITO* Multicenter Italian, Trials in Ovarian Cancer, *AGO-OVAR* Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom, *ENGOT* European Network of Gynaecological Oncological Trial

In the second trial, patients were randomly assigned to receive standard IV chemotherapy with paclitaxel 135 mg/m^2 IV over 24 h on day 1 followed by cisplatin 75 mg/m^2 IV on day 2, administered every 3 weeks for six cycles. The experimental arm consisted of carboplatin (AUC = 9) IV every 4 weeks for two courses, followed by paclitaxel 135 mg/m^2 IV over 24 hours on day 1 and cisplatin 100 mg/m^2 IP on day 2 for six cycles. The experimental arm showed improvement in progression-free survival (PFS) (27.9 versus 22.2 months) and OS (63.2 versus 52.2 months). Grade 3 and 4 toxicities, including leukopenia and gastrointestinal disturbances, were higher in the experimental arm and were thought to be caused by the high doses of carboplatin and the increased number of total cycles [15]. The third and most compelling trial randomly assigned optimally debulked patients to receive either IV paclitaxel 135 mg/m^2 over 24 h plus IV cisplatin 100 mg/m^2 or IV paclitaxel 135 mg/m^2 plus IP cisplatin 100 mg/m^2 and IP paclitaxel 60 mg/m^2. The IP arm showed favorable outcomes in PFS (23.8 versus 18.3 months) and OS (66.9 versus 49.5 months), but the IP arm had more toxicities including leukopenia, neurotoxicity, and gastrointestinal disturbances. Significantly, only 42% of patients were able to complete the full six cycles of IP chemotherapy. However, despite a follow-up report noting that quality of life was initially worse in patients undergoing IP treatment, quality of life did recover to baseline after 12 months in all areas except neurotoxicity [16, 17]. Based on these results, the National Cancer Institute (NCI) released a clinical announcement in January 2006, recommending that clinicians make patients aware of the IP regimen described in this study as primary chemotherapy option after optimal cytoreductive surgery [18]. Nonetheless, incorporation of IP/IV chemotherapy into routine clinical practice to treat primary ovarian cancer has been limited due to the above named toxicities and the complexities of IP administration. Moreover, critics have cited that the survival benefit of IP chemotherapy may be primarily due to the nearly dose-dense administration of paclitaxel, rather than the intraperitoneal administration effect. In fact, a phase III trial of dose-dense administration of paclitaxel was reported by the Japanese Gynecologic Oncology Group (JGOG) [19]. When paclitaxel was given in a dose-dense fashion with IV carboplatin as compared to standard IV treatment every 3 weeks, there was a significant improvement in the primary endpoint of PFS (28 months vs 17.2 months; HR 0.71, CI 0.58–0.88, $p = 0.0015$) (Table 11.1)) [19].

Given that the last IP trial demonstrated one of the largest benefits in overall survival ever seen in any clinical trial for ovarian cancer despite the significant toxicities seen, another large randomized phase III trial was performed to further address and clarify the benefits of intraperitoneal therapy compared to a more current intravenous control arm that contained a dose-dense regimen (GOG 252, [20]). This was a three-arm trial that enrolled 1560 patients and included a control arm with dose-dense paclitaxel (80 mg/m^2 IV weekly) with IV carboplatin (AUC 6 IV every 3 weeks). The experimental arms involved two different IP regimens. One involved a modification of the experimental arm used in the 2006 Armstrong trial [16]. This involved day 1 IV paclitaxel (135 mg/m^2 over 3 hours), day 2 IP cisplatin (75 mg/m^2), and day 8 IP paclitaxel (60 mg/m^2). This regimen was given every 3 weeks. It is important to note that the intravenous regimen on day 1 involved an outpatient-based regimen with paclitaxel given over 3 h as opposed to 24 h in the original Armstrong trial. In addition, the dose of IP cisplatin was lowered from 100 to 75 mg/m^2. The intent was to try to minimize side effects from IP therapy and to further facilitate delivery of IV therapy as well. A third arm also involved a regimen to reduce potential side effects and included dose-dense IV paclitaxel (80 mg/m^2 once per week) with IP carboplatin (AUC 6). All participants also received bevacizumab IV (15 mg/kg) every 3 weeks and cycles 2 to 22. Bevacizumab was added to all regimens because of two phase III trials demonstrated statistically significant improvements in PFS when bevacizumab was added to IV front-line chemotherapy followed by maintenance bevacizumab [21, 22]. The results from GOG 252 were somewhat surprising. The primary endpoint, median PFS, was found to be

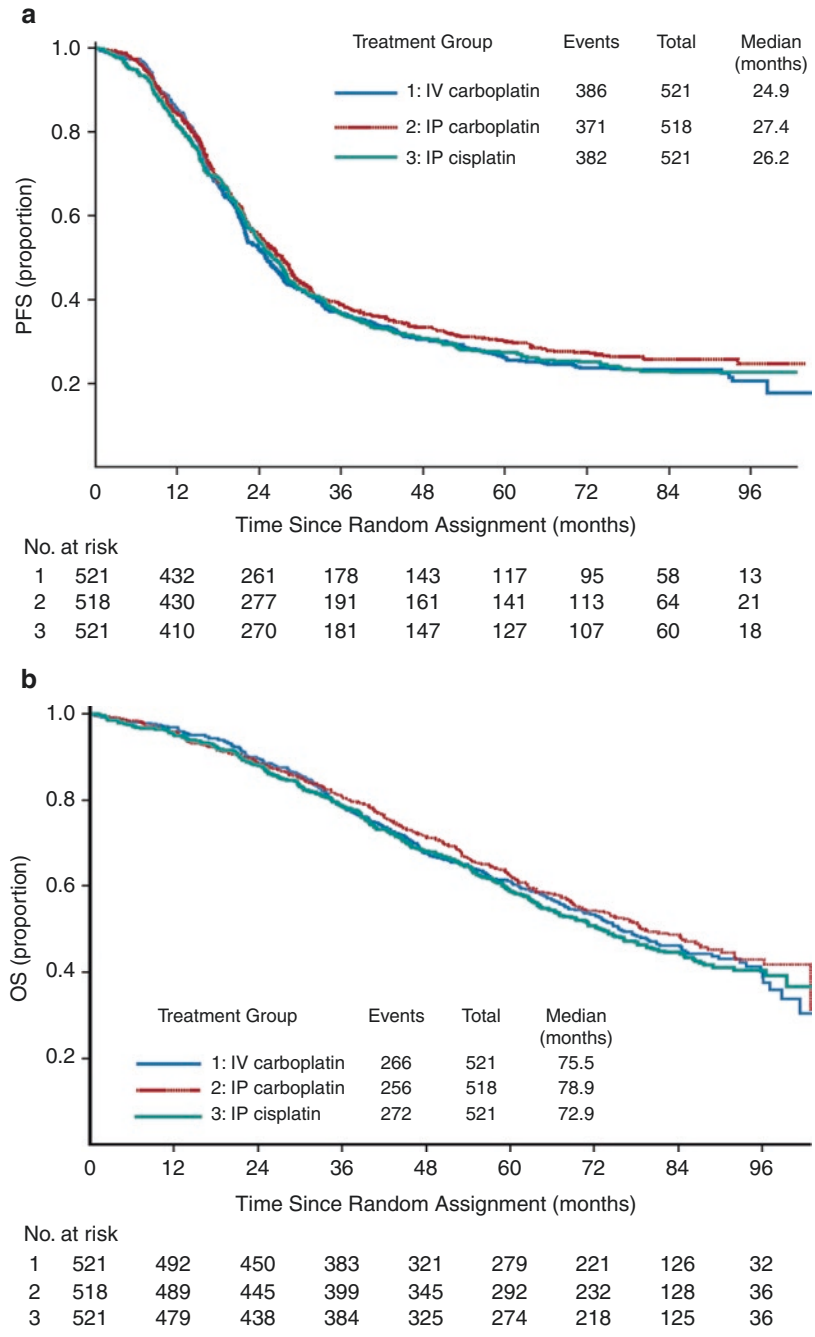

Fig. 11.1 Progression-free survival (**a**) and overall survival (**b**) curves for recent phase III trial (GOG 252) of two intraperitoneal chemotherapy regimens vs dose-dense intravenous chemotherapy in patients with newly diagnosed ovarian, fallopian tube, and primary peritoneal cancers [20]. There was no statistical difference in PFS or OS between the various regimens. (From Walker et al. [20]; used with permission)

similar in all three arms (24.9 months IV carboplatin, 27.4 months IP carboplatin, 26.2 months IP cisplatin; Fig. 11.1a) [20]. In addition, median overall survival was similar as well (75.5, 78.9, 72.9 months, respectively) (Fig. 11.1b). Thus, despite evidence of a clinical survival benefit using IP chemotherapy in older clinical trials, the current IP trial (i.e., GOG252) failed to demonstrate a clinical advantage with IP therapy.

Although the results from the recent phase III GOG 252 IP trial may have dampened enthusiasm for IP therapy, there are more questions that

now arise with regard to the role of IP therapy in ovarian cancer. Based on the results of GOG 252, there is still controversy on whether IP chemotherapy should be utilized in the management of ovarian cancer patients. Some authors have suggested that significant modifications to the IP regimen may have led to alterations of efficacy [23]. For example, there was lowering of the IP chemotherapy dose of IP cisplatin from 100 to 75 mg/m^2. In addition, IV paclitaxel was changed from 24 h to 3 h infusion. However, the rationale for these changes was to make IP therapy more tolerable and easier to administer. In addition, bevacizumab was added to all arms, and some have argued that bevacizumab might affect response to therapy [23]. This was based on a phase III trial (GOG262) of IV dose-dense chemotherapy vs standard 3-week dosing with or without bevacizumab, where bevacizumab appeared to negate the effects of dose-dense chemotherapy compared to standard 3-week dosing [24].

Beyond such issues, it may be important to determine whether IP therapy may benefit a specific population of ovarian cancer patients. A long-term follow-up and examination of prognostic factors indicative of survival advantage was performed for patients on GOG 172 trial. This study showed that factors associated with poorer survival involved clear cell/mucinous histology (vs serous histology), gross residual disease (vs no visible disease), and fewer cycles of IP chemo [25]. When BRCA1 tumor expression was examined in patients enrolled to the GOG 172 trial, patients who had aberrant BRCA1 expression and underwent IP therapy had a statistically better median OS (84 months; $P = 0.0002$) compared to those had IV chemotherapy (47 months) [26]. Patients with normal BRCA1 expression demonstrated similar median OS irrespective of chemotherapy treatment (58 months for IP group, 50 months for IV group). In a retrospective analysis of patients undergoing IP chemotherapy, patients who had pathogenic mutations in the BRCA gene had better PFS and OS compared to BRCA negative patients (BRCA+: median PFS not reached, median OS 110 months; BRCA-: median PFS 17.3 months; median OS 67.1 months) [27]. These studies suggest that patients with BRCA mutations may significantly benefit from IP-based therapies compared to those without BRCA mutations. Additional studies are needed to better define the patients that would potentially best benefit from IP-based therapies in the treatment of ovarian cancer.

Table 11.1 summarizes recent phase III trials of various chemotherapy approaches used in the upfront setting. The gold standard therapy of a platinum/taxane combination has remained the primary backbone of therapy for ovarian cancer. In order to improve survival, recent large phase III trials have focused on dose-dense therapy [19, 28] and adding novel biologics that target vascular endothelial growth factor (bevacizumab [21, 22]), multiple receptor tyrosine kinases (nintedanib [29]), and angiopoietin (trebananib [30]). There is no clear indication that one particular approach is superior to another, although it is interesting to note that the IP trials have demonstrated some of the largest PFS and OS benefits seen in any upfront ovarian cancer clinical trial.

HIPEC Clinical Trials in Newly Diagnosed Ovarian Cancer

The theoretical rationale for HIPEC for the treatment of advanced gynecologic cancers is to combine the demonstrated pharmacological activity of IP chemotherapy in this disease with the advantage of intraoperative hyperthermia that exerts an enhancement of cytotoxicity following cytoreductive surgery (CRS). A recent phase III randomized prospective study reported a significant survival benefit for ovarian cancer patients undergoing interval CRS and HIPEC. A total of 245 newly diagnosed, advanced-stage ovarian cancer patients were randomized following neoadjuvant chemotherapy, to interval CRS with or without HIPEC, with cisplatin (100 mg per square meter over 90 minutes) [31]. The median PFS, which was the primary endpoint of this study, was 10.7 months in the CRS group, versus 14.2 months in the CRS + HIPEC group (Fig. 11.2a). The median overall survival was longer in the CRS + HIPEC group by nearly a year,

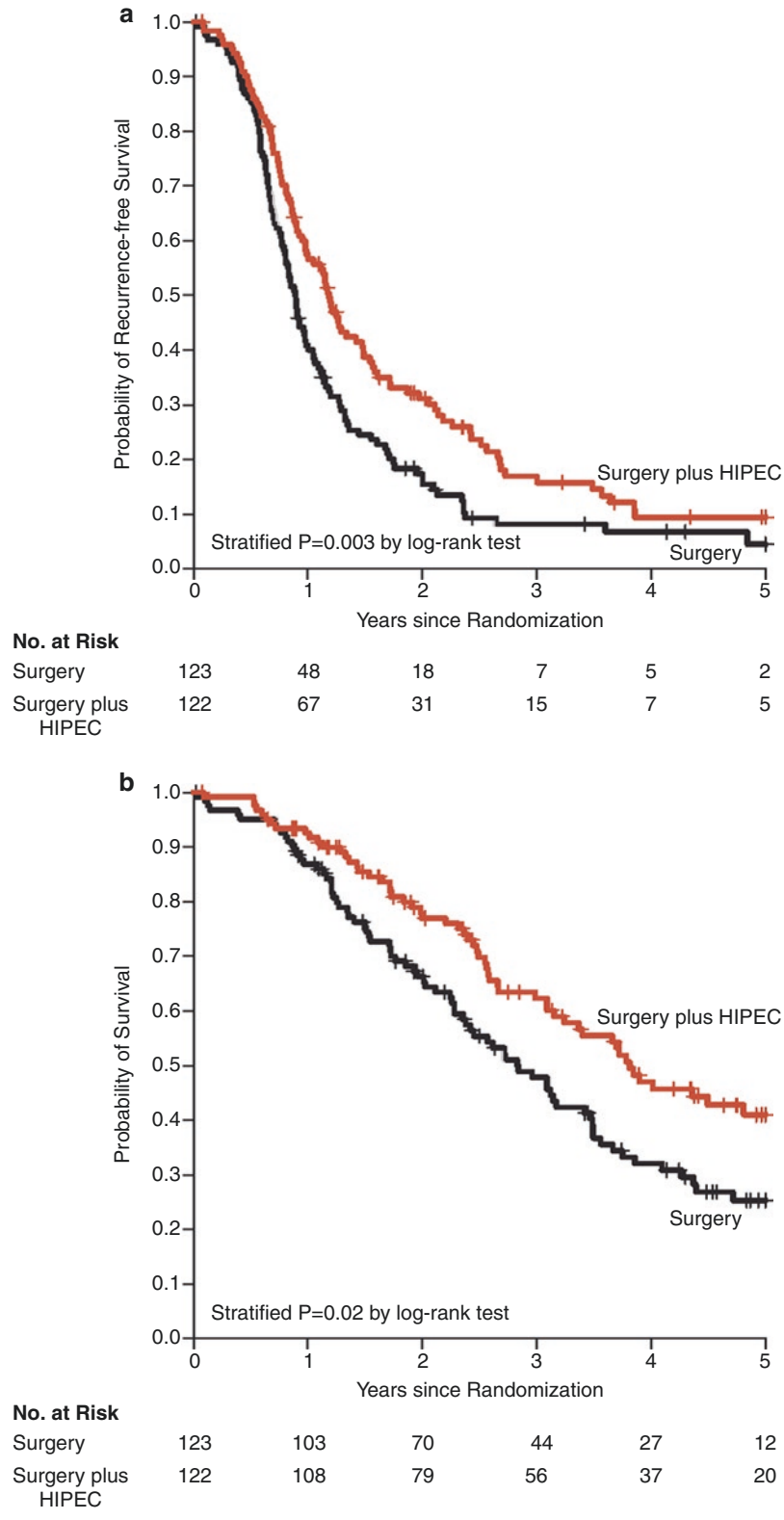

Fig. 11.2 Kaplan-Meier estimates of progression-free survival (**a**) and overall survival (**b**) in a phase III trial of hyperthermic intraperitoneal chemotherapy with surgery vs surgery alone in patients with ovarian, fallopian tube, and primary peritoneal cancers who have undergone neoadjuvant chemotherapy with IV carboplatin and paclitaxel [31]. There was a statistically significant difference noted in both PFS and OS between the HIPEC arm vs surgery only arm. (From van Driel et al. [31]; used with permission)

45.7 versus 33.9 months (Fig. 11.2b). Criticisms of this study include the exclusion of Stage IV patients in this trial, which represents a large portion of ovarian cancer patients undergoing neoadjuvant chemotherapy. Another concern expressed was that the median PFS achieved in this trial by the CRS + HIPEC group did not reach the PFS of approximately 2 years, for advanced-stage ovarian cancer undergoing optimal CRS alone, as reported in other studies [16, 32]. However, when compared to trials examining ovarian cancer cohorts undergoing neoadjuvant chemotherapy, these trial results approximate both the PFS and the OS [1]. Several randomized controlled trials are ongoing in Europe and Asia, which will shed further light onto these concerns [33]. Interestingly, one yet unpublished Korean phase III trial which randomized 184 women with Stage III or IV disease to CRS with or without HIPEC, did not report a difference in PFS or OS between the two arms [34]. Among retrospective data, the largest study included 91 primary EOC patients who underwent cisplatin +/− doxorubicin HIPEC, where PFS was 11.8 months, and OS was 42 months, with a 5-year overall survival of 17% [35].

Despite persistent concerns and criticisms regarding the use of HIPEC in ovarian cancer, current evidence suggests that there is a role for cytoreductive surgery with HIPEC and that further studies are needed to identify subpopulations who best benefit from this treatment while continuing to optimize both delivery and toxicities of HIPEC.

HIPEC Clinical Trials in Recurrent Ovarian Cancer

A large pool of evidence supporting the role of HIPEC in recurrent ovarian cancer exists, primarily in the form of retrospective studies and phase II trials. A single prospective, randomized trial has been published [36], which randomized 120 women with recurrent ovarian cancer to secondary cytoreductive surgery with or without HIPEC. This study reported a significant OS benefit in the HIPEC arm (26.7 vs 13.4 months). This study however was criticized for the lack of PFS reporting, postoperative complication rate, and adjuvant chemotherapies. As expected, this study reported higher OS with complete cytoreduction and HIPEC. Peritoneal carcinomatosis index was an independent prognostic factor, with worse survival associated with a high PCI (>15). Interestingly, there was no difference in survival between platinum-sensitive and platinum-resistant patients.

Several retrospective studies have suggested a survival benefit associated with HIPEC and secondary cytoreductive surgery (CRS) in patients with recurrent EOC [37, 38]. The largest retrospective multicenter study to date was conducted by Bakrin et al., reporting on 474 recurrent EOC patients who underwent CRS and HIPEC for recurrent ovarian cancer, with an associated median OS of 45.7 months [35]. Seventy-five percent of patients were completely cytoreduced patients, with a median OS of 52 months, while incompletely cytoreduced patients had a median OS of 33 months. Moreover, there was no difference in OS between chemosensitive and chemoresistant patients, suggesting that HIPEC may especially be attractive for chemoresistant patients. In a subanalysis of this retrospective study limited to EOC patients with a first recurrence, published by the same group, 314 patients were included, with a reported median follow-up of 50 months, and five-year overall survival of 38.0%, with no difference between platinum-sensitive or -resistant patients [39].

Another retrospective case-control study from Italy examined 30 platinum-sensitive recurrent EOC patients who underwent CRS- and platinum-based HIPEC and compared this

to a 37 matched platinum-sensitive recurrent group that underwent CRS [40]. In this study, significantly fewer patients relapsed in the HIPEC cohort (66%) than in the control group, where all patients suffered a recurrence within 2 years. The duration of secondary response was 26 months in the HIPEC cohort and 15 months in the control group. In an update to this study, this group reported on a total of 70 platinum-sensitive recurrent EOC patients who went on to have a PFS of 27 months, with a median follow-up of 73 months [41].

While several large retrospective studies exist to support the role of HIPEC in recurrent ovarian cancer, large, well-designed phase III trials demonstrating clinical benefit are still lacking. Nonetheless, evidence to date suggests a potential role for HIPEC in both platinum-resistant and platinum-sensitive recurrent patients, and several ongoing clinical trials examining HIPEC in recurrent EOC patients will inform us in the coming years regarding its indication in this setting.

Safety of HIPEC for Ovarian Cancer

While the toxicity of HIPEC is higher than that of surgical cytoreduction alone, studies in recent years have reported lower morbidity and mortality rates from these procedures, likely due to improved supportive care measures and the expanding surgical skills of gynecologic oncologic surgeons [38, 42, 43]. Current evidence thus suggests that complete cytoreductive surgery and HIPEC are a feasible option for patients with EOC with potential benefits that may exceed the survival outcomes of current standard of care treatment options. Morbidity and mortality rates appear to be comparable to current cytoreduction procedures for EOC, and the literature supports a mortality rate of 0–4% and a morbidity rate of up to 31% of grade 3 or 4 Clavien-Dindo complication rate. The largest retrospective data by Bakrin et al., reporting on 566 ovarian cancer patients in two French centers who underwent HIPEC, reported an overall morbidity of 31%, with a mortality of 0.8% [35]. A meta-analysis in 2018 reported a perioperative mortality of 1.4% for primary OC, and 3.9% for recurrent OC, which is similar to that reported with optimal debulking without HIPEC [38, 44]. In the randomized phase III trial led by Van Driel, toxicity profiles in both arms were similar, with 25% versus 27% of grade 3 or 4 adverse events in the CRS versus CRS + HIPEC group, respectively.

Acute renal failure has been a common toxicity in patients undergoing HIPEC with cisplatin, which is the most commonly used chemotherapy agent in ovarian cancer patients undergoing HIPEC. In a study by Sin et al. [45], 47 OC patients underwent HIPEC with cisplatin at a median dose 90 mg/m^2, with a reported 40% overall incidence of acute kidney injury, of which 9% were grade 3–4, and 4% requiring long-term dialysis. In a dose-finding multicenter phase I trial, the optimal cisplatin dose delivered at HIPEC following neoadjuvant chemotherapy (with six cycles) was determined to be 70 mg/m^2. Patients who were administered the top dose of 80 mg/m^2 suffered four DLTs, including two due to renal failure, one due to hemorrhage, and one due to peritonitis [46]. In the Dutch randomized phase III trial, similar grade 3–4 renal toxicities were noted in both arms, with administration of sodium thiosulfate as nephroprotectant, with 0% ($n = 0$) in the non-HIPEC arm, and 1% ($n = 1$) in the HIPEC arm (supplemental data [31]). In this study, sodium thiosulfate was administered at the start of perfusion as an intravenous bolus (9 g per square meter in 200 ml), followed by a continuous infusion (12 g per square meter in 1000 ml) over 6 h. More recently, a French study evaluated renal toxicities in patients undergoing HIPEC with cisplatin, with or without sodium thiosulfate [47]. Patients were treated with sodium thiosul-

fate perfusion at 9 mg/m^2 prior to HIPEC, and renal impairment (RI) was defined by postoperative creatinemia >1.6 (WHO grade I toxicity). The impact of sodium thiosulfate treatment was evaluated by comparison of the RI rates between two successive periods at a single institution: without introduction of sodium thiosulfate (Period nST: November 2016 to September 2017) and with sodium thiosulfate utilization period (Period ST: October 2017 to March 2018). During Period ST, 0 of 31 patients (0%) developed RI versus 11 of 35 patients (43%) during Period nST ($p < 0.05$). Two of them required definitive hemodialysis. Baseline characteristics, background circumstances, indications, and laboratory parameters before HIPEC were comparable between the two groups, as well as cisplatin dose use during HIPEC.

Heavily pre-treated OC patients are at risk for renal toxicity with surgical debulking and hyperthermic infusion of the abdominal cavity with cisplatin. Cisplatin-related renal toxicity appears to be preventable by administration of nephroprotective drugs such as sodium thiosulfate to protect renal function, though larger studies are required to determine the optimal dose of cisplatin and selection and dosing of nephroprotectants and other supportive agents.

Future Directions

A large pool of evidence exists to support the use of HIPEC in ovarian cancer, suggesting continued incorporation of hyperthermic and other novel intraperitoneal chemotherapies into novel clinical trial designs in ovarian cancer. While critics of HIPEC point toward the availability of alternate therapies in the upfront setting, such as maintenance therapy or the addition of bevacizumab to IP chemotherapy, to reach similar progression-free survival improvements, more data is required to compare these treatment modalities and to determine ideal patient subpopulations for HIPEC as well as ideal drug selection and administration. The variability of HIPEC administration remains a key issue, as there is no standard chemotherapy agent, procedure duration, or temperature currently considered optimal or required. Furthermore, the ideal tumor histology or disease indication for HIPEC is also not well established. This is particularly important in recurrent EOC patients who are a heterogeneous patient cohort, and factors such as type of cytoreduction (such as secondary or tertiary), platinum-sensitive status, and prior and subsequent chemotherapies may have a significant prognostic impact. Several phase III clinical trials in recurrent and primary ovarian cancer are underway in Europe and Asia (Table 11.2), and their results are eagerly awaited. Additionally, other novel IP delivery methods are explored, including PIPAC (pressurized intraperitoneal aerosolized chemotherapy), an emerging, novel method to deliver pressurized, aerosol chemotherapy into the intraperitoneal cavity of ovarian cancer patients at time of laparoscopic surgery. This novel IP delivery method has garnered promising preliminary data in ovarian cancer, allowing for reduced chemotherapy dosage and improved tissue absorption and intraabdominal dissemination [48]. Lastly, the mechanism of how HIPEC exerts clinical benefit has not been sufficiently explored, including the question of whether heat in itself, the intraperitoneal delivery, and the timing of the chemotherapy administration are the key contributors to improved clinical outcomes. Studies exploring the effect of HIPEC on the immune microenvironment are lacking. Future HIPEC studies which include the molecular characterization of tumors will likely improve patient selection for this promising therapy.

Table 11.2 Ongoing phase II or III randomized clinical trials evaluating HIPEC in ovarian cancer

NCT number	Study acronym	Study title	Phase	Indication	Study description	HIPEC drug	n	Primary outcome	Country	Study duration	Status
NCT03842982	CHIPPI	Hyperthermic intraperitoneal chemotherapy (HIPEC) in ovarian cancer	III	Primary EOC	Arm 1: 1'CRS or IDS with HIPEC Arm 2: 1'CRS or IDS without HIPEC	Cisplatin 100 mg/ $m^2 \times 90$ min	432	DFS	France	4/2019–6/2024	Recruiting
NCT02681432	HIPEC-OVA	Hyperthermic intraperitoneal chemotherapy with paclitaxel in advanced ovarian cancer	III	Primary EOC	HIPEC arm: 1'CRS with HIPEC No HIPEC arm: 1'CRS without HIPEC	Paclitaxel 175 mg/ $m^2 \times 60$ min	60	OS	Spain	1/2012–12/2019	Recruiting
NCT03772028	OVHIPEC-2	Primary cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy (HIPEC)	III	Primary EOC	Arm 1: 1' CRS with HIPEC Arm 2: 1'CRS without HIPEC	Cisplatin	538	OS	The Netherlands	11/2019–4/2025	Not yet recruiting
NCT03373058	HIPEC-04	Efficacy of HIPEC in the treatment of advanced-stage epithelial ovarian cancer after cytoreductive surgery	III	Primary EOC	Arm 1: 1'CRS followed by successive post-op HIPEC 24 h, 48 h after 1'CRS	Paclitaxel 175 mg/m^2 (24-h post-op) Cisplatin 75 mg/m^2 (48-h post-op)	214	DFS	China	3/2018–7/2021	Not yet recruiting

(continued)

Table 11.2 (continued)

NCT number	Study acronym	Study title	Phase	Indication	Study description	HIPEC drug	n	Primary outcome	Country	Study duration	Status
NCT03180177	HIPEC-03	Efficacy of HIPEC as NACT and postoperative chemotherapy in the treatment of advanced-stage epithelial ovarian cancer	III	Primary EOC	Arm 1: NACT followed by IDS followed by successive post-op HIPEC 24 h, 48 h after IDS Arm 2: NACT followed by IDS without HIPEC	Paclitaxel 175 mg/m^2 (24-h post-op) Cisplatin 75 mg/m^2 (48h post-op)	263	DFS PR/SD rate	China	3/2018–7/2022	Recruiting
NCT01628380	CHORINE	Phase III trial evaluating hyperthermic intraperitoneal chemotherapy in upfront treatment of Stage IIIC epithelial ovarian cancer	III	Primary EOC	Arm 1: NACT - > IDS + HIPEC Arm 2: NACT- > IDS without HIPEC	Cisplatin 100 mg/ m^2 + paclitaxel 175 mg/m^2 × 90’	94	DFS	Germany	6/2012–6/2018	No longer recruiting
NCT03371693	HIPECOV	Cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) with lobaplatin in advanced and recurrent epithelial ovarian cancer	III	Primary and recurrent EOC	Arm 1: 1’CRS with HIPEC Arm2: 1’CRS without HIPEC	Lobaplatin 30 mg/m^2 × 60’	222	OS	China	9/2017–12/2020	No longer recruiting

NCT03220932	HIPOVA-01	Cytoreductive surgery and HIPEC in first or secondary platinum-resistant recurrent ovarian epithelial cancer	III	Recurrent (platinum-refractory)	Arm 1: Carbo/taxol/bev × 3 followed by IDS with HIPEC followed by Carbo/taxol/bev × 3 Arm 2: Carbo/taxol/bev without CRS/HIPEC	Cisplatin 70 mg/m^2	220	PFS	France	9/2019–9/2022	Not yet recruiting
NCT01376752	CHIPOR	Hyperthermic intraperitoneal chemotherapy (HIPEC) in relapse ovarian cancer treatment.	III	Recurrent (platinum-sensitive)	Arm 1: Platinum-based NACT × 6 cycles, followed by 2'CRS with HIPEC Arm2: Platinum-based NACT × 6 cycles, followed by 2'CRS without HIPEC	n/a	444	OS	Belgium/France	4/2011–4/2025	Recruiting

(continued)

Table 11.2 (continued)

NCT number	Study acronym	Study title	Phase	Indication	Study description	HIPEC drug	n	Primary outcome	Country	Study duration	Status
NCT01767675	N/a	Outcomes after secondary cytoreductive surgery with or without carboplatin hyperthermic intraperitoneal chemotherapy (HIPEC) followed by systemic combination chemotherapy for recurrent platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer	II	Recurrent (platinum-sensitive)	Arm 1: 2'CRS with or without HIPEC followed by platinum-based chemo × 5 cycles Arm 2: 2'CRS without HIPEC followed by platinum-based chemo × 6 cycles	Carboplatin	98	Proportion of patients without disease progression	United States	1/2013–2/2020	Recruiting

Studies selected: Phase III with $n > 50$

1'CRS Primary cytoreductive surgery, *IDS* Interval debulking surgery, *DFS* Disease-free interval, *OS* Overall survival, *PR* Partial remission, *SD* Stable disease, *n/a* Not available, *NACT* Neoadjuvant chemotherapy, *Bev* Bevacizumab

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12 Mesothelioma and Miscellaneous Disease Processes

Laura M. Enomoto, Perry Shen, Konstantinos I. Votanopoulos, and Edward A. Levine

Introduction

Peritoneal surface disease (PSD) disseminates from a wide range of tumors, most commonly including colorectal, appendiceal, ovarian, gastric, and neuroendocrine neoplasms. Mesothelioma, however, is an unusual malignancy of the serosal membrane itself, with potential involvement including the pleura, peritoneum, pericardium, and tunica vaginalis testes. First described over a century ago by Miller and Wynn [1], malignant peritoneal mesothelioma (MPM) is a rare cancer, with an estimated incidence of approximately 400 new cases per year in the United States [2]. MPM typically presents with diffuse peritoneal studding and/or ascites with uncommon spread beyond the abdomen. Unlike its more common pleural counterpart, most research on MPM includes single-institution case series or multi-institutional cohort studies, with no randomized controlled trials.

Another rare form of PSD includes carcinomatosis from a urachal origin. Although challenging to differentiate from other intra-abdominal mucinous tumors, evolving pathologic methods used to classify tumor origin and multiinstitution collaborations have helped elucidate the pathophysiologic characteristics and prognosis of urachal PSD. This chapter reviews the diagnosis, treatment options, and prognosis of MPM and urachal sources of PSD.

Epidemiology

Mesothelioma is a relatively uncommon disease, with an incidence in the United States of 1.94 and 0.41 cases per 100,000 for men and women, respectively [3, 4]. The vast majority of mesothelioma arises from the pleura, with only 7–30% of cases arising from the peritoneum [3–6]. There is an equal distribution of MPM among men and women, in contrast to pleural mesothelioma, where there is a significant predominance of men diagnosed with disease [3, 4]. Mesothelioma has been linked to radiation [7], infection with simian virus 40 [8], and mineral exposure, specifically erionite [9], but the most common and well-known carcinogen remains asbestos exposure [10, 11]. However, unlike pleural mesothelioma where asbestos exposure accounts for approximately 80% of cases [10, 12], MPM is less associated with asbestos (if at all), and patients present at a younger age [13–15]. In patients with MPM, only 33–50% report any prior asbestos exposure [10, 11], and time and duration of exposure do not correlate with the development of disease [16]. Due to the rarity of MPM, risk of developing MPM due to exposure to other minerals or

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Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_12

pollutants has not been well quantified. It is noteworthy that ferruginous (asbestos) bodies have not been found in any pathologic specimens from resections of MPM at our institution.

Presentation and Diagnosis

MPM is typically diagnosed between 40 and 65 years of age [17] and often presents with vague, nonspecific symptoms that can be quite variable depending on the extent and distribution of disease throughout the peritoneum. Patients most commonly complain of increasing abdominal distension and abdominal pain, and in the majority of patients, the increase in abdominal girth is due to ascites [18, 19]. Abdominal pain is generally diffuse and nonspecific, although occasionally a palpable mass or malignant bowel obstruction can be found [19, 20]. Early satiety, weight loss, and nausea are also common complaints. Occasionally, MPM is discovered incidentally during laparoscopy for other indications [21]. Because of the nonspecific presentation of MPM, diagnosis is often significantly delayed. Average time from onset of symptoms to diagnosis is 4–6 months [22]. Not surprisingly, most patients have diffuse disease throughout the abdomen by the time of diagnosis; however, hematogenous and nodal metastases are rare occurrences [23].

Diagnosis of MPM first begins with a thorough history and physical examination, with careful attention to asbestos and chemical exposures. Potential physical examination findings may include a protuberant abdomen with a fluid wave or palpable mass. Serum chemistry and tumor makers have a limited role. CA-125 may be elevated, but this is nonspecific for diagnosis and best used as a marker for disease recurrence or progression [24, 25].

The most common modality used in detecting MPM is contrast-enhanced CT scan. MPM appears as a contrast-enhancing, heterogeneous, solid, soft-tissue mass in the peritoneum or omentum [26, 27]. It often lacks a distinct primary site as well as lymph node involvement or extra-abdominal metastasis, which may help to differentiate it from other malignancies [28]. Peritoneal thickening, omental caking, and scalloping of solid organs indicative of tumor infiltration are often discovered [27], and ascites is present in over 60% of patients (Fig. 12.1) [29, 30]. If the disease infiltrates the small bowel mesentery, the mesentery may have a pleated appearance while the mesenteric vessels have an uncharacteristically straight course [31]. Late findings of MPM include small bowel obstruction and replacement of mesenteric fat by solid tumor (Fig. 12.2) [32].

Recent studies suggest that compared to CT imaging, diffusion-weighted and dynamic contrast-enhanced MRI more accurately assesses the extent of disease or peritoneal cancer index

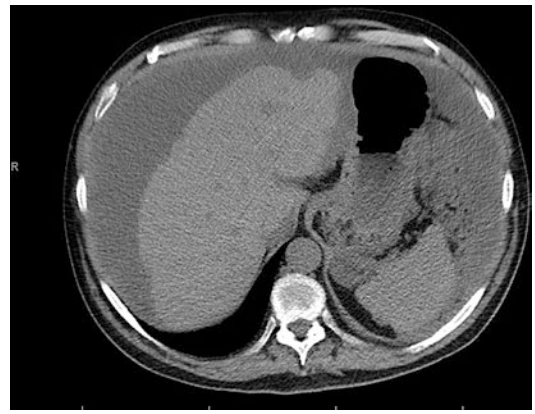

Fig. 12.1 CT scan

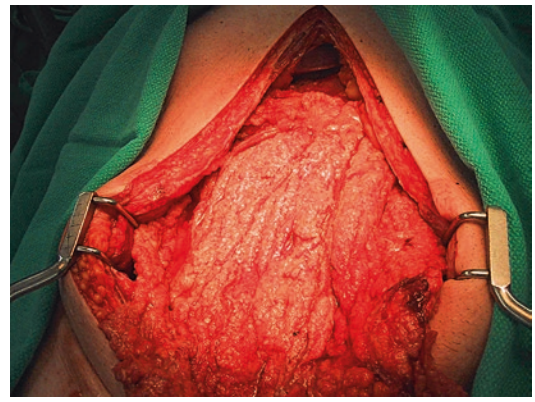

Fig. 12.2 Extensive epithelioid malignant peritoneal mesothelioma involving the omentum

(PCI) in patients with PSD [33]. In patients undergoing CRS, the PCI was correctly predicted by MRI in 88% of patients [33]; however, only one of these patients had MPM. Likewise, CT-PET has an evolving role in cancer staging, but its value in imaging MPM is limited in our experience and remains unclear [28].

To definitively diagnose MPM, pathologic evaluation is required. As the majority of patients present with ascites, it is tempting to send this fluid for cytologic examination. However, due to the low number of malignant cells in ascites, analysis of ascitic fluid has a low diagnostic yield and is often inconclusive [10, 19, 34]. Even if diagnostic paracentesis is suggestive of MPM, a pathologic specimen is still required for immunohistochemical staining to confirm a diagnosis. Fine-needle aspiration of peritoneal implants can confirm a diagnosis, but for improved accuracy, the preferred diagnostic modality is core-needle biopsy or direct tissue sampling by diagnostic laparoscopy [35]. Diagnostic laparoscopy also offers the advantage of direct visualization of the abdominal cavity with improved assessment of tumor burden, as CT scans often underestimate the volume of disease [28]. If undertaken, it is incumbent upon the surgeon to define the extent of disease as well as to obtain tissue sufficient for accurate pathologic analysis.

MPM is divided into three histopathological subtypes: epithelioid, sarcomatoid, and biphasic. Approximately 75% of MPM is epithelioid, 25% is biphasic, and sarcomatoid is rare and associated with very poor outcomes [36]. Histologically, epithelioid MPM cells resemble normal mesothelial cells in a tubulopapillary or trabecular pattern with rare mitotic figures [31, 37]. Because of occasional signet ring cells and desmoplastic response, it can be difficult to distinguish from adenocarcinoma [38]. In contrast, sarcomatoid MPM has tightly packed spindle cells with malignant osteoid, chondroid, or muscular elements. As the name suggests, the biphasic subtype contains both epithelioid and sarcomatoid cellular components, with each contributing to at least 10% of the overall histology [31, 37].

Because cellular histology is often similar to other tumors, immunohistochemical staining plays an important role in the diagnosis of MPM. No single marker is specific for MPM, but panels of antibodies are used to differentiate MPM from other tumors with similar cellular features, such as papillary serous carcinoma of the peritoneum, serous ovarian carcinoma, colorectal adenocarcinoma of the peritoneum, and borderline serous tumors [16]. MPM stains positive for cytokeratin 5/6 (CK 5/6), calretinin, vimentin, epithelial membrane antigen (EMA), Wilms tumor 1 (WT-1), mesothelin, and antimesothelial cell antibody-1 [39–41]. Negative staining for CEA, Ber-EP4, thyroid transcription factor 1 (TTF-1), PAX-2, LeuM1, Bg8, and B72.3 supports the diagnosis of MPM. Current histopathologic recommendations include using two mesothelioma markers and two carcinoma markers for diagnosis [39–41].

Pathologic characteristics of MPM are also prognostic even within the epithelioid group. We have found that histomorphologic features of the epithelioid subtype of MPM convey strong prognostic information [38]. Specifically, using nuclear features and mitotic rate, the epithelioid MPM cases can be divided into low- and high-risk groups with significantly different 5-year survival rates after CRS/HIPEC of 57% versus 21% survival at 5 years. The utility of expert pathologic review of these cases cannot be understated.

Staging

Due to its unusual natural history with diffuse spread throughout the abdomen and rare nodal or extra-abdominal metastatic spread, MPM does not logically fit into typical Tumor-Node-Metastasis (TNM) staging systems. The 8th edition of the AJCC staging manual has a staging system for pleural mesothelioma, but it does not have a staging system for MPM [42]. To address this issue, a novel TNM staging system was proposed by Yan and colleagues [43]. In this system, T was assigned based on the extent of disease burden quantified by intraoperative PCI and divided into four subgroups: T1 (PCI 1–10),

T2 (PCI 11–20), T3 (PCI 21–30), and T4 (PCI 31–39). Node status (N) was assigned based on the presence (N1) or absence (N0) of positive lymph nodes on histopathology of surgical specimens. Any extra-abdominal metastasis discovered on preoperative imaging was assigned M1. Stage I disease included T1N0M0, stage II included T2–3N0M0, and stage III included T4N0M0 and N1 or M1 disease [43]. Using this staging system, 5-year survival for stages I, II, and III disease was 87%, 53%, and 29%, respectively [43].

Treatment

MPM is an aggressive disease, and without treatment, it is uniformly fatal, with an estimated survival of 6–16 months from time of diagnosis [22, 44]. Due to its rarity, there are no randomized controlled trials evaluating the best treatment strategies. Recommendations for therapy are based on single-institutional cohort studies and retrospective data from multiinstitutional registries and include systemic chemotherapy, immunotherapy, and surgical resection.

Systemic Chemotherapy

Most of the data on systemic therapy for MPM is extrapolated from experience with pleural mesothelioma. Early trials of systemic chemotherapy for MPM used a doxorubicin-based regimen and demonstrated a measurable response in only 43% of patients [45]. Of those who responded, median overall survival (OS) was 22 months; median OS for those with stable or progressive disease was 5 months [45]. Since that time, a randomized clinical trial demonstrating longer median OS, longer disease-free progression, and higher rate of clinical response using pemetrexed plus cisplatin in treatment of pleural mesothelioma has prompted further study in MPM [46].

Efficacy of pemetrexed alone or in combination with cisplatin on surgically unresectable MPM was reported by Janne et al. [47] They found a median survival of 13.1 months for patients who received combination pemetrexed and cisplatin, compared to 8.7 months for those who received pemetrexed alone. Additionally, they showed the response rate by RECIST criteria for patients who received the combination was greater than for patients who received pemetrexed alone (30% versus 19%, respectively), and all patients with a complete response received the combined treatment. Pemetrexed was well tolerated, with low rates of grade 3 or 4 toxicities. These results established pemetrexed in combination with cisplatin as first-line systemic chemotherapy for MPM.

Other chemotherapeutic drug combinations have also been investigated. Campbell and colleagues studied carboplatin instead of cisplatin in combination with pemetrexed and demonstrated a similar efficacy, with a 24% objective response rate and 76% disease control rate [48]. As carboplatin is often better tolerated than cisplatin, they proposed the use of carboplatin in older patients and for palliation. Gemcitabine in combination with pemetrexed was investigated as part of a larger study for pleural mesothelioma, but results were dismal [49]. Due to toxicity, only 75% of patients completed the planned treatment, and response rate and disease control rate were inferior to that of platinum-based regimens. As a result, pemetrexed in combination with a platinum agent remains first-line systemic treatment.

A trial reported at the European Society of Medical Oncology meeting from the Francophone trials group evaluated the utility of adding bevacizumab to pemetrexed and platinum for pleural mesothelioma [50]. That study found that adding bevacizumab increased the median OS from 2.7 months to nearly 19 months. As a result, this three-drug regimen has become the current standard for MPM at our, and many other, centers.

Immunotherapy

Similar to other malignancies, immunotherapeutic approaches are being considered in MPM. Tremelimumab, an anti-CTLA-4 agent, was studied as a second-line agent in patients with MPM who progressed on a platinum-

based regimen [51]. A modest benefit was shown, with a median OS of 10.7 months and median progression-free survival of 6.2 months. Investigations targeting epidermal growth factor receptor (EGFR) and phosphatidylinositol-3-kinase/mammalian target of rapamycin (PI3K/mTOR) pathways are underway [52–55].

Surgical Resection

Operative therapy provides the mainstay for treatment of MPM. A study of patients treated in the USA and recorded in the National Cancer Database (NCDB) found that only 50% of MPM patients underwent CRS, and CRS/HIPEC offered the best survival [56]. Other studies have shown prolonged survival in well-selected patients, with studies demonstrating a median survival of 34–92 months and 5-year survivals of 29–59% [17, 19, 21, 56–64]. There is a wide range of surgeon variability and CRS/HIPEC technique, although the overall goal of resecting all intra-abdominal disease is the same. Our techniques have been published in detail elsewhere, but are briefly outlined below [65].

At our institution, prior to CRS/HIPEC, we first confirm a histologic diagnosis of MPM with a pathologic second opinion. Patients with the sarcomatoid variant are not candidates for the procedure; however, the biphasic and epithelioid cases are [36]. Exclusion criteria for resection include comorbid conditions that significantly decrease functional status, extra-abdominal metastasis, poor performance status (ECOG >2), or a tumor burden so extensive on preoperative imaging or diagnostic laparoscopy as to preclude an R2a resection or better [58, 65]. Although laparoscopic resection is possible with a PCI less than 10 in some cases, this is not commonly encountered with MPM. Anesthesia is secured with arterial line monitoring, and nasogastric and urinary catheters are routinely placed. If the patient has significant pelvic disease volume or a complex history of prior surgery, we arrange for temporary external ureteral stents to be placed at the outset of the case to facilitate retroperitoneal dissection. A wide prep including the lower chest is performed, and antibiotics and venous thrombosis prophylaxis are routine. We start with a midline laparotomy incision to thoroughly explore the abdomen and proceed to quantify the PCI. We perform a routine supracolic omentectomy and resection of all gross disease. Peritoneal stripping and resection of intra-abdominal organs are performed only as indicated by the presence of visible disease. Small tumor implants on the small bowel or mesentery are treated with electrofulguration or ultrasonic surgical aspiration if they are too numerous or diffuse to be removed with small bowel resection.

Following CRS, we use a closed abdomen HIPEC technique and perfuse with cisplatin according to the National Cancer Institute (NCI) described protocol with sodium thiosulfate given intravenously [59]. Due to a paucity of trials and comparison studies, there is no standardized HIPEC technique, and a variety of chemoperfusion regimens are currently used. Brigand et al. in France report using cisplatin and mitomycin as a combined chemoperfusion, with overall 1-, 3-, and 5-year survivals of 69, 43, and 29%, respectively [60]. At the National Cancer Institute in Milan, Deraco et al. reported a combined chemoperfusion regimen of cisplatin plus mitomycin, or cisplatin plus doxorubicin with a 5-year survival of 57% [61]. Other large cancer centers report HIPEC combined with early postoperative intraperitoneal chemotherapy (EPIC). At the NCI, Feldman et al. report cisplatin-based HIPEC with 5-fluorouracil and paclitaxel EPIC between postoperative days 7 and 10 [59], and the Washington Cancer Institute reports combined cisplatin and doxorubicin HIPEC, with the same regimen plus paclitaxel for EPIC on postoperative days 1–5 [2].

The large variability in treatment regimens for MPM is due to the paucity of comparative studies examining outcomes of the various chemoperfusion regimens [58, 61]. In their series, Deraco et al. found no statistically significant difference between cisplatin plus mitomycin versus cisplatin plus doxorubicin on OS or progression-free survival (PFS) [61]. In a study conducted at our institution, Blackham et al. compared DFS, PFS,

event-free survival (EFS), and OS in patients who underwent HIPEC with mitomycin versus cisplatin [58]. Prior to 2004, we perfused with 30–40 mg/m^2 of mitomycin; however, based on data from the NCI, we began using cisplatin in 2004. When comparing survival with cisplatin or mitomycin perfusion, we demonstrated a statistically significant OS benefit at 1, 2, and 3 years in patients perfused with cisplatin (80% vs. 47%, 80% vs. 47%, and 80% vs. 42%, respectively) [58]. Median OS survival for cisplatin and mitomycin was 40.8 months and 10.8 months respectively, although this difference did not reach statistical significance. DFS, PFS, and EFS showed a trend of better outcomes for those perfused with cisplatin, but likely due to the small number of patients in the study and shorter follow-up period of the cisplatin cohort, these differences were not significant.

Precision Medicine

Using tumor DNA to identify actionable genetic mutations for use in adjuvant treatment is an emerging strategy in precision oncology. At our institution, work is underway to develop microengineered 3D tumor organoids from fresh-tissue specimens to provide patient-specific models with which treatment optimization can be performed in vitro prior to initiation of adjuvant therapy. Specifically, Mazzocchi and colleagues have demonstrated the viability of this organoid platform in tumor specimens resected from two patients with MPM [66]. They showed the results of in vitro chemotherapy on the organoids mimicked the response to chemotherapy observed in the patients themselves. Moreover, they identified a specific genetic mutation in one patient which conferred susceptibility to a nonstandard treatment, and further confirmed its effectiveness in tumor regression [66]. Although a limited study, the results are promising for a personalized treatment strategy in MPM, and potentially other diseases.

Prognosis

Due to the rarity of the disease, the best data on MPM following CRS/HIPEC stem from large single-institution studies, multiinstitutional registries, and national databases, which are summarized in Table 12.1. The largest multiinstitutional registry of patients with MPM treated with CRS/HIPEC included 8 international institutions during a 10-year period and accrued 405 patients [23]. The median OS was 53 months, and 1-, 3-, and 5-year survival rates were 81%, 60%, and 47%, respectively. Epithelioid subtype, absence of lymph node metastasis, CC0/CC1 resection, and HIPEC itself were independently associated with improved survival. The overall complication rate was 46%, of which 31% were grade 3 or 4 complications, and perioperative mortality was 2%. Another multiinstitutional study with patients from three US institutions included 211 patients and demonstrated a median OS of 38.4 months with a 5-year survival rate of 41% [62]. Independent predictors of survival included age, sex, histology, resection status, and chemoperfusate. A similar perioperative mortality rate (2.3%) and complication profile were found.

More recently, a meta-analysis that included 20 studies and 1047 patients found a median OS ranging from 19 to 92 months, median PFS of 11–28 months, and median DFS from 7.2 to 40 months [63]. OS at 1 and 5 years was 84% and 42%, respectively. There was a wide range of morbidity (8.3–90%) and mortality (0–20%), however, likely related to the steep learning curve in some reporting institutions. A recent study of national trends using the NCDB identified 1514 patients with MPM, 216 (14%) of which underwent CRS/HIPEC [56]. Their median OS was 61 months, compared to those who underwent CRS with systemic chemotherapy (52 months), CRS alone (21 months), systemic chemotherapy alone (17 months), and observation (6 months). Independent predictors of survival included age, gender, insurance status, histology, and CRS/HIPEC. Due to limitations of the database, resection status and stage were not included in

Table 12.1 Reported survival outcomes of patients with peritoneal mesothelioma

Author (year of publication)	Study type	*N*	Subtype	PCI	CC score	Perfusion technique	Agent	Median OS, months	5-Year OS
Brigand et al. [60] (2006)	Single institution	15	Epithelial/ biphasic		0–3	HIPEC	Cisplatin, mitomycin	35.6	28.9%
Deraco et al. [61] (2006)	Single institution	49	Epithelial/ biphasic	22 (mean)	0–3	HIPEC	Cisplatin and mitomycin/ doxorubicin		57%
Feldman et al. [59] (2003)	Single institution	49	Multiple			HIPEC and EPIC (POD 7 and 10)	Cisplatin (HIPEC); 5-FU and paclitaxel (EPIC)	92	59%
Yan et al. [2] (2007)	Single institution	100	Epithelial/ biphasic		0–3	HIPEC and EPIC (POD 1–5)	Cisplatin and doxorubicin (HIPEC); cisplatin, doxorubicin, paclitaxel (EPIC)	79	50%
Blackham et al. [58] (2010)	Single institution	34	Epithelial/ biphasic		R0-R2a (22), R2b-c (12)	HIPEC	Mitomycin (30–40 mg)	10.8	
							Cisplatin (250 mg/m^2)	40.8	
Yan et al. [23] (2009)	Multiinstitutional data registry	405	Epithelioid/ biphasic/ sarcomatoid	20 (mean)		Variable	Variable	53	47%
Helm et al. [63] (2012)	Review	1047	Multiple	19 (median)	0–3	Variable	Variable	19–92	42%
Verma et al. [56] (2018)	Retrospective database	216	Multiple					61	52%
Magge et al. [66] (2014)	Single institution	65	Epithelial/ biphasic	12 (mean)	CC 0/1 in 86%	HIPEC	Mitomycin (93.8%) or cisplatin (6.2%)	46.2	39%
Votanopoulos et al. [36] (2018)	Multiinstitutional data registry	34	Biphasic	18 (median)	0			6.8 years	50.2%
					1			2.8 years	41.6%
Alexander et al. [62] (2013)	Multiinstitutional data registry	211			CC 0/1 in 52.6%	Variable	Variable	38.4	41%

the analysis. However, it seems clear that CRS combined with chemotherapy either via HIPEC or systemically is associated with the best outcomes [56].

Histologic subtype of MPM has remained one of the most consistent factors in predicting survival. Multiple studies have demonstrated that the epithelioid subtype confers a more favorable OS (51.5 months) [67] compared to sarcomatoid and biphasic subtypes (10.5 months) [23, 67–69]. The sarcomatoid subtype carries such a dismal prognosis that most centers, including ours, consider it a contraindication to CRS/HIPEC, as there is no proven survival benefit [67]. Recent work by Votanopoulos et al., however, has demonstrated that for the biphasic subtype, long-term survival can be achieved in patients with a complete cytoreduction (CC-0) and HIPEC [36]. The previously nihilistic view of the biphasic subtype likely stemmed from its rarity and traditional practice to group it with the sarcomatoid subtype. Median OS for biphasic subtypes with a CC-0 resection was 6.8 years, but dropped off steeply with an incomplete resection (2.8 years for CC-1 resection). This study demonstrated that the biphasic subtype should not be considered an absolute contraindication to CRS/HIPEC as long-term survival can be attained with a complete cytoreduction.

The completeness of cytoreduction or resection status has also been well established as an independent predictor of survival in patients with MPM who undergo CRS/HIPC. In the largest analysis by Yan et al., the CC score had a statistically significant impact on survival, with a median OS of 94, 67, 40, and 12 months for CC 0, 1, 2, and 3, respectively [23]. Alexander and colleagues had similar findings, showing that patients with a CC of 2 or 3 had nearly twice the risk of death compared to those with a CC of 0 or 1 (HR 1.81, $p = 0.02$) [62]. In biphasic cohorts, survival depends so greatly on resection status that even a CC 1 resection has a shorter survival by 4 years [36]. Thus, at many institutions, if a complete or near complete cytoreduction cannot be obtained, CRS/HIPEC is considered contraindicated. However, there is potential value in controlling malignant ascites with HIPEC even if complete CRS is not achievable [70, 71].

Both age and gender have been shown to affect survival in patients with MPM. Although the age division varies between studies, multiple institutions report improved outcomes in patients less than 65, 60, 54, and 50 and decreasing survival with advanced age [23, 56, 59, 62, 67, 72]. Magge et al. demonstrated a median OS of 17 months in patients over 65 years of age, compared to 85.6 months in patients less than 65 [67]. Male sex is also an indicator of poor survival in some studies [23, 62]. A median OS of 119 months has been shown in women, as compared to a 36-month median OS in men [23]. The improved survival outcomes in women are found in pleural mesothelioma as well, causing speculation that men generally present with more disease spread and less favorable histology [16].

Staging systems, by definition, should include factors prognostic for survival. With the creation of a novel TNM staging system for MPM, Yan and colleagues identified seven prognostic factors previously shown to impact survival: age, gender, histologic subtype, CC score, PCI, and lymph node metastasis [43]. As age, gender, and histologic subtype were intrinsic and not affected by disease progression, and CC score could only be determined postoperatively; only PCI, nodal status, and extra-abdominal metastasis were included in the staging system. Previous studies demonstrated a median OS of 119 months for patients with a PCI less than or equal to 20, but an only 39-month survival if the PCI was greater than 20 [23]. Likewise, Magge et al. demonstrated that preoperative PCI was predictive of OS [67]. Although a rare finding, patients with nodal metastasis had an OS of 20 months, as compared to 56 months in patients without nodal metastasis. The poor prognosis of involved lymph nodes was also confirmed by Baratti and colleagues, who found that pathologically negative nodes were independently correlated with increased OS [73]. The presence of extra-abdominal metastases as a poor prognostic indicator is not surprising, as this is true of all intra-abdominal malignancy. In their study, Yan et al. included 12 patients with disease that penetrated the tendinous portion of the diaphragm. Despite resection of extra-abdominal disease in all cases, the median OS of 20 months

was poor and significantly less than patients with no metastatic disease [23].

In order to provide an assessment tool for clinicians, Schaub and colleagues developed a nomogram for MPM that predicts survival [69]. Their nomogram uses histologic subtype, estimated preoperative PCI, and serum CA-125 levels to determine estimates of 3- and 5-year survival. In this model, patients with epithelioid subtype, preoperative PCI less than or equal to 10, and serum CA-125 of less than or equal to 16 have the best 3- and 5-year OS, approaching nearly 100%, while patients with sarcomatoid or biphasic subtype, PCI of greater than 19, or CA-125 of greater than 71 have a poor estimated 3- and 5-year OS. Intermediate survival is estimated for patients with combinations of subtype, PCI, and CA-125 in between these extremes. The authors intended for clinicians to use the nomogram in the office as a quick reference, so they may better evaluate patients with MPM who are potential candidates for CRS/HIPEC.

Miscellaneous Diseases

The urachus is tubular structure that extends medially to connect the bladder to the allantois during embryonic development. The lumen gradually degenerates throughout fetal development and ultimately becomes the median umbilical ligament in adults. If the lumen of the urachus fails to close completely, this may lead to various disease processes, including malignant transformation [74]. Urachal carcinoma is an overall rare disease, as is pseudomyxoma peritonei (PMP), a clinical condition involving extensive spread of intraperitoneal mucin. Not surprisingly, urachal-derived PMP is, thus, exceedingly rare, with only 20 case reports in the English literature [75–77]. Not all peritoneal metastases from urachal carcinoma result in PMP [78, 79].

Diagnosing urachal carcinoma-derived peritoneal metastases can be challenging not only due to the rarity of the disease but also due to the difficulties in differentiating it from other more common primaries. Clinical presentation and histologic grade are variable, but most authors agree that urachal-derived PMP more closely resembles the pathophysiology of PMP of appendiceal origin, rather than that typical for urachal carcinoma [75]. In contrast to urachal adenocarcinoma, urachal-derived PMP rarely causes nodal metastasis or hematogenous-derived distant metastases, and local recurrence is more likely [75]. Currently, three criteria are used for diagnosis: midline mass on preoperative CT scan, mucosuria from the persistent connection between the urachal remnant and bladder, and elevated serum CA 19–9 [77].

Because of its similarities to PMP of appendiceal origin, CRS/HIPEC has emerged as the optimal treatment strategy for urachal-derived PMP. In the largest published series of urachal-derived PMP, a prospectively maintained, multicenter international registry identified 36 patients who underwent CRS/HIPEC over a 23-year period at 14 specialized centers [77]. There was a male predominance (66.7%) with a median age of 43 years. Half received preoperative chemotherapy, and the median PCI was 8.5 (range 1–33). An open HIPEC technique was used in 63.9% of patients, with various chemoperfusion agents and combinations. A macroscopic complete resection (CC-0/CC-1), including resection of the urachus and typically partial cystectomy, was achieved in 86.1% of patients, and 11.5% had lymph node involvement. There was a 37.9% rate of major complications, but no perioperative deaths.

Liu et al. had similar findings in their series of nine patients treated at one specialty hospital in Japan [76]. The median age of their cohort was 48 years, but they found a female predominance (55.6%). The median PCI was 10 (range 2–33), and all patients underwent HIPEC with an open technique with mitomycin and cisplatin chemoperfusion. All patients had a complete cytoreduction, and there was no lymph node involvement in any patients. No grade 3 or 4 complications were reported, but one patient had a urinary leak and another had a pancreatic fistula postoperatively, both of which resolved with nonoperative management.

Mercier and colleagues reported a median OS of 58.5 months, with a median DFS survival of 60.5 months [77]. Liu et al. found a median DFS of 27.5 months [76]. Mercier and colleagues found

that resection status was the only significant predictor of survival, with a 53.9% 5-year survival for patients with a CC-0/CC-1 resection, and no 3- or 5-year survivors with a CC-2 or CC-3 resection [77]. Although patients with a PCI greater than 14 trended toward worse OS compared to those with a PCI less than or equal to 14, this difference was not significant. Higher PCI did significantly affect DFS, however, with those with a higher PCI being 15 times more likely to recur. Lymph node involvement was also not associated with poor OS, but it was a significant factor in DFS.

Conclusions

MPM and urachal carcinoma with peritoneal metastases or PMP are both rare diseases typically localized only to the abdominal cavity with low potential for lymphatic or extra-abdominal metastases. CRS/HIPEC has provided the mainstay of treatment for both diseases, demonstrating long-term survival especially in patients with favorable subtypes, low PCIs, and complete cytoreductions. Treatment strategies will continue to be refined as more data emerge regarding intraperitoneal perfusion options and adjuvant systemic therapies. As targeted molecular therapies continue to evolve, a multimodal strategy is likely to involve both a surgical and systemic approach.

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Part III

Perioperative Considerations for HIPEC

13 Anesthetic Considerations for Regional Therapies

Lawrence B. Marr and Shiv K. Goel

Introduction

The basic principles and goals governing the anesthetic management for regional therapies have remained remarkably consistent, although the means by which they are achieved have been changing, to coincide with the improvements in the specialty of anesthesia.

The traditional goal of anesthetic management—to support the surgical mission in terms of keeping the patient anesthetized, oxygenated, and hemodynamically stable throughout the surgery—remains our starting point. However, with recognition of the short- and long-term impacts of our care, it has become far more deliberate, patient-centered, and evidence-based. Postoperative considerations include short-term outcomes (minimizing nausea, pain, and delirium; promoting early mobilization, recovery of bowel motility, optimal pulmonary function, and reduced hospital length of stay), as well as long-term outcomes (prolonging cancer survival). Over the last few years, our model of delivery has gone from a mixed type of anesthesia to complete total intravenous anesthesia, eliminating the use of inhalational anesthetics and narcotics. This is consistent with the ERAS program, aimed at reducing complications and shortening the length of stay.

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Anesthetic Management

Preoperative Evaluation

There should be a complete evaluation of the patient with special emphasis on the airway, the cardiopulmonary systems, and renal function. A knowledge of the medications they are taking and the chemotherapeutic agenets they have received is important in deciding what testing is to be done. They include decisions regarding chest x-ray, complete blood work, pulmonary function studies, and transthoracic echocardiogram.

Preinduction

The acute management team will place neural blockade catheters (either paravertebral or quadratus lumborum blocks) while the patient is still in the preoperative holding area. Though only a small sedative dose is given for block placement, the dexmedetomidine additive used to enhance the block may increase the patient's level of sedation prior to arrival in the operating

Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_13

room. Its sympatholysis may also cause bradycardia, which, if present, should be treated. The neural blockade that is established is an important component of the intraoperative anesthetic as well as the postoperative care. The catheters can be redosed intraoperatively. This will be dealt with in more detail in the section on pain management.

Lines and Monitors

In the absence of specific cardiopulmonary comorbidities, there is no need for invasive monitoring lines prior to induction of anesthesia.

The routine monitors, consisting of an EKG, SaO_2, BIS, and neuromuscular blockade, are placed prior to induction, and an NG tube, urinary catheter, $ETCO_2$, and forced air warming blanket are placed after induction. Invasive monitors including an arterial line, a central line (two lumen #8 French placed in an internal jugular vein) for access, and the use of vasopressors a second large bore IV are placed postinduction. There is a trend beginning that in some patients with large bore peripheral access, to forgo the central line in patients undergoing tumor debulking patents. In the isolated liver perfusion patients, we place a MAC catheter in the left internal jugular for our use and a #8 French 2 lumen catheter in the right internal jugular which can be prepped in the field and rewired to a perfusion catheter if the procedure proceeds to veno-veno bypass.

Anesthesia

Substantial evidence points to an adverse effect of volatile anesthetics, sympathetic stimulation, inflammation, and opiates on cancer recurrence after oncologic surgery. The total intravenous anesthesia (TIVA) used for these cases is designed around these principles, and indeed recurrence-free survival after cancer surgery has been shown to be prolonged by the use of TIVA. Our TIVA protocol avoids both volatile agents and opiates using a three-drug combination of propofol, ketamine, and dexmedetomidine. Propofol has no adverse effect on immune cell function, has no enhancement of cancer cell survival or invasiveness, and has an anti-inflammatory action through COX inhibition. Low-dose ketamine supplements the TIVA, significantly enhances postoperative analgesia, and has an anti-inflammatory action seen in the cytokine response to surgery and in preservation of lymphocyte function. Dexmedetomidine also supplements the TIVA, provides sympatholysis, may decrease postoperative dementia, and substantially enhances the intraoperative and postoperative nociceptive blockade of the nerve block, thereby reducing the need for postoperative opioids.

The use of a BIS monitor is necessary with TIVA as there is no end-tidal agent concentration to provide an alternative guide to anesthetic depth. Though higher doses of ketamine will falsely elevate BIS, the low dose and constant infusion allow for its continued usefulness. Maintaining a target BIS of 40–50 is suggested.

Suggested infusion rates following induction:

- Propofol—120 mcg/kg/min titrate down over time and with BIS, up if needed.
- Dexmedetomidine—initial load 1 mcg/kg/h over 15 min, then 0.6 mcg/kg/h and titrating as clinically indicated.
- Ketamine—0.2 mg/kg/h.

As the conclusion of surgery approaches, one needs be attentive to reducing infusion rates, even stopping dexmedetomidine and ketamine infusions approximately one-half to one hour prior. Target BIS to 60 at this stage. Expect a different and slower emergence than you are used to with inhalational agents/opioids. Patients may be quite sedated but breathing well and can be safely extubated at a level of sedation different from a conventional anesthetic. Whereas sedation and respiratory depression are correlated with opioids, this is not the case with dexmedetomidine and ketamine.

Ventilation Management

Protective lung ventilation is geared toward avoiding volutrauma, barotrauma, atelectrauma, and oxidative injury. Atelectasis begins with induction and is worsened by the use of 100% oxygen. Therefore, preoxygenation with less than 100% oxygen is advised and ventilation maintained with air/oxygen (60% FiO_2 or less). Tidal volumes recommended are 6 mL/kg according to ideal weight in addition to a modest level of PEEP. Periodic lung recruitment will counter development of atelectasis. Several stepwise increases in PEEP at 20–30 sec increments or switching to manual ventilation with pop-off valve set to 30 mm Hg for 30–60 seconds (avoid the temptation to squeeze the bag) are alternative methods to accomplish this.

Intraoperative Fluid Management

The goal of fluid management is to preserve intravascular volume, to optimize tissue perfusion and oxygen delivery, and to restore normal acid base physiology. At the present time, we do not have a noninvasive monitor that will provide us with information about tissue perfusion. So, the search for the delivery of the correct type and amount of fluid has been evolving. Two issues are of interest here, the discussion about the use of balanced electrolyte versus saline-based fluids, and the best way to determine the amount of fluid to give. Intravenous fluids should be considered a pharmacotherapeutic agent, and they can be both beneficial and harmful. We now know there is a greater understanding of the harm of excessive liberal fluid management and fluid overload in the surgical patient. The risk of abdominal compartment syndrome and generalized edema are greater than previously realized. We reviewed our anesthesia record from 2006 to 2014 and extrapolated data including total intraoperative fluids, broke it down into three cohorts, and looked at complications. Initially, we used a very liberal fluid regime, and in the period of 2006–2008, the average fluid amount intraoperatively was 24 liters of crystalloid. In 2008, we adopted a more restrictive regime, and in the period from 2010 to 2012, the average amount was 16 liters, and in the 2013 and 2014, it was 11 liters. This amounted to about 10–12 ml/kg/hr. In the very liberal group, we found marked generalized edema, including the head and neck, anastomotic leaks, ARDS, and kidney and respiratory issues. Extubation was difficult and often delayed until the following day because of the amount of facial swelling and fluid overload, not to mention the effect of edema on wound healing. Since 2014, we also eliminated saline, and the only crystalloids given are LR and plasmalyte. Since the restricted (meaning optimizing fluid delivery and not zero balance) use of fluids there is little visible edema in most cases, most patients are extubated in the operating room, except for those drowsy from our TIVA delivery, and are usually extubated in the PACU. Rarely are they admitted to ICU intubated. Many of our patients are now admitted from the PACU directly to the ward if they are uncomplicated. We see many less respiratory problems, and fewer bring backs for anastomotic leaks [1]. This is an ongoing exercise, and it will be interesting to review the results as we proceed with a more liberal use of the ERAS program. We know what does not help with the delivery of optimum fluids. There is no meaningful correlation between MAP and DO_2. CVP shows no correlation with blood volume [2], and urine output does not predict postoperative renal function [3].

We started using the Vigileo (Edwards Labs.) noninvasive fluid monitor in 2008 and now using the ED1000 (Edwards Labs). We find the best use of this monitor is to track responsiveness of SV and cardiac output to fluid administration. Ultimately, we are trying to optimize cardiac output by measuring increase in stroke volume and cardiac output on the Starling curve after fluid cahllenges. When there are no further increases, we feel optimum flow has been achieved. Advanced monitoring allows you to comfortably adopt a fluid restrictive strategy with a margin of safety. There are other goal-directed devices such

as the esophageal Doppler or pulse wave analyzer to accomplish this.

There has been much written on the negative effects of 0.9% saline administration. It is well documented that large volume 0.9% saline administration causes a non-anion gap hyperchloremic metabolic acidosis (HCMA), a phenomenon described by Stewart in the early 1980s [3–5]. The criticism of normal saline is not new. George H. Evans wrote in *JAMA* in 1911, "One cannot fail to be impressed with the danger . . . (of) the utter recklessness with which salt solution is frequently prescribed, particularly in the postoperative period . . ." " . . . the disastrous role played by the salt solution is often lost in light of the serious conditions that call forth its use" [6]. Hyperchloremia causes renal artery vasoconstriction in an animal model, suggesting a possible role in kidney function [7]. It was first shown in humans by Choudhury et al. using MRI scanning that 0.9% saline infusion results in a reduction in renal blood flow velocity and renal cortical perfusion [8]. This study also showed retention of fluid in the extravascular space; the patients gained more weight; with the balanced solution, they produced higher urine volumes; and in the normal saline trials, serum chloride was significantly higher from the first hour on. Saline-induced HCMA is associated with decreased gut perfusion. The risk of HCMA is no longer being considered innocuous, and there has been a paradigm shift in fluid management with respect to saline-based volume therapy.

Intra-abdominal Compartment Syndrome

We have a better understanding that the risk of abdominal compartment syndrome is greater than previously recognized. Elevation of abdominal pressures leads to a reduction in perfusion gradients of the gut and kidney.

Hyperthermia Associated with HIPEC

We do see a rise in core temperature with the introduction of HIPEC. Stop the forced air-warming device prior to initiating HIPEC and follow. It usually does not go above 39 °C, but if it does, you can introduce other cooling measures. The hyperthermia will cause increase in heart rate, cardiac index, and oxygen consumption, as well as decrease in systemic vascular resistance [9]. Plasma norepinephrine levels were found to increase linearly parallel to the core body temperature [9]. This temperature rise is temporary, so if there were a need to treat the tachycardia, I would do so with a short-acting beta-blocker.

Pain Management

Regional therapy surgeries like tumor debulking and HIPEC etc. remain one of the most painful abdominal surgical procedures. It is not only because of the extent of the surgical resection but also due to the extreme inflammation caused by the dose intense hyperthermic chemotherapeutic drug.

The most effective and efficient method of pain control in these patients is a combination of multimodal analgesic strategy coupled with a regional analgesic technique.

Multimodal Analgesia

Multimodal pain management [10] should be incorporated in the intraoperative anesthetic management plan, as part of the opioid-sparing ERAS anesthetic strategy. Continuous infusions of dexmedetomidine and ketamine should be used as an adjunct to propofol as part of the TIVA. This should be further augmented with intravenous acetaminophen administration every 6 hours as well as use of other components of the multimodal analgesic strategy like magnesium and decadron. Additionally, if regional nerve blocks with local anesthetic are not being used, then intravenous lidocaine infusion can be added as part of the analgesic strategy.

Intraoperative multimodal strategy should be continued postoperatively. Continuous ketamine infusion and lidocaine infusions (if no regional nerve blocks with local anesthetics are present)

can be continued for 48–72 hours postoperatively, thereby greatly decreasing the need to opioids postoperatively.

Regional Anesthesia

Regional anesthetics or nerve blocks remain the mainstay of any analgesic strategy for major abdominal procedures. The techniques which are the most effective and are being used widely are:

Thoracic Epidural [11] The oldest and one of the most effective analgesic techniques. A well-placed lower thoracic epidural (around T 8 level) provides excellent analgesia. However, the risk of bleeding complications; the need for anticoagulation postoperatively, either prophylactic or sometimes therapeutic; and the hemodynamic effects (hypotension) in a patient with significant fluid shifts coupled with possible risk of impaired ambulation have all contributed to thoracic epidural not being the favored technique anymore.

Thoracic Paravertebral Nerve Blocks [12] Thoracic paravertebral blocks have largely replaced thoracic epidurals as the technique of choice for all major abdominal procedures. Well-placed bilateral thoracic paravertebral around T8 level provides excellent analgesia without the usual risks associated with thoracic epidurals. Paravertebral continuous catheters have minimal risk of hypotension and no risk of lower extremity weakness hampering ambulation. However, a large learning curve for placement, risk of pneumothorax, and some concern for bleeding complications around the neural axis in patients with altered coagulation or on therapeutic anticoagulation remain some of the drawbacks of this technique.

Quadratus Lumborum Blocks First described by Blanco in 2007 [13] as a modification of the well-known and existing transverse abdominis plane (TAP) block. This technique of interfascial infiltration of local anesthetic along the posterolateral border of the quadratus lumborum muscle in the lumbar interfascial triangle [14] provides a prolonged and effective abdominal analgesia, which is at least equianalgesic to the paravertebral block. It can be a single injection of local anesthetic injected bilaterally (often mixed with additives like dexmedetomidine and decadron) providing analgesia for up to 36 hours or preferably, in large abdominal cases like the tumor debulking and HIPECs, continuous catheter placement. The learning curve for these blocks is smaller, they are easier to perform, patients tolerate the procedure better, and these blocks are done away from the neural axis, so concerns of bleeding around the spinal cord in anticoagulated patients are not present. Because of the above-mentioned advantages, and, in spite of being relatively new, these blocks are fast replacing the traditional blocks as the regional anesthetic of choice for major abdominal surgeries around the world and being incorporated into the ERAS protocols for abdominal surgeries [15].

Besides the combination of the above-mentioned techniques, IV narcotics should always remain available to these patients, either as bolus doses or as a PCA. This is due to the severe nature of pain as well as the prolonged ileus these surgeries often invoke, making PO medications less reliable in their absorption. Additionally, intravenous anti-inflammatory medications like ketorolac should be added in the postoperative period once renal function has stabilized and the coagulation profile and platelets have returned toward normal.

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14

Postoperative Management of Patients Undergoing Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

Mustafa Raoof

Introduction

Cytoreductive surgery and heated intra-peritoneal chemotherapy (CRS/HIPEC) were popularized in the 90s for management of carcinomatosis of ovarian, gastrointestinal, and primary peritoneal origin in patients without extra-abdominal disease. Over the course of the past three decades, a significant body of work has established the general safety of this approach. The initial studies reported high morbidity and mortality. The procedure has been routinely described as "aggressive cytoreduction" and "mother of all surgeries." However, increasing experience, better patient selection, advances in perioperative management, and improved ability to recognize and manage complications have resulted in significantly improved outcomes.

A recent report utilized data from the American College of Surgeons National Surgical Quality Improvement Program to benchmark postoperative recovery of CRS/HIPEC in comparison to other complex oncologic procedures [1]. Surprisingly, the risk-adjusted morbidity and mortality of CRS/HIPEC were significantly lower than hepatectomy, esophagectomy, and pancreatico-duodenectomy.

Unlike other complex oncologic operation of the gastrointestinal tract, the CRS/HIPEC patient population consists of individuals with widely varying burden of disease. In addition, complex cytoreduction is utilized for many different cancer types. Therefore, the postoperative recovery in each patient with carcinomatosis is fraught with unique challenges commensurate with the extent of cytoreduction and baseline patient-disease characteristics. This heterogeneity in disease and operative characteristics accounts for the majority of variation in postoperative recovery. Despite this variation, the complex management of these patients can be distilled to essential principles which will be discussed in this chapter.

Fluid Resuscitation

Patients undergoing cytoreduction are subject to major fluid shits in the perioperative period. Major determinants of fluid shift include: preoperative fasting and mechanical bowel preparation; evacuation of large volume intraabdominal ascites; losses from surgical dissection surfaces; enhanced vascular permeability due to inflammatory response to surgery; blood loss; and insensible losses through open abdomen accentuated by hyperthermia. Malnourished patients have more significant fluid shifts from decreased intravascular oncotic pressure which is a direct result of hypoalbuminemia.

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Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_14

There are limited studies guiding administration of fluids in the postoperative period specifically for patients undergoing cytoreduction. These data are extrapolated from patients undergoing elective abdominal surgery. However, these data need to be generalized with caution as many patients who undergo cytoreductive surgery have much longer operations with many more organs resected in comparison to those undergoing elective single organ directed cancer operation. In addition, peritonectomy increases the raw surface area that contributes to fluid losses and hypovolemia. However, it is established that majority of fluid losses and hence the need for replacement is most important during the surgery and the first 24 hours postsurgery.

Achieving postoperative fluid balance is critical for optimal outcomes of cytoreductive surgery. After major abdominal surgery volume overload can be detrimental. These patients develop pulmonary complications that include hypoxia; pleural effusions; pneumonia; and need for ventilator support. In addition, hypervolemia cause bowel wall edema which prolongs ileus, and is thought to be a contributing factor in anastomotic leaks. Hypervolemia leads to increased preload that not only compromises cardiac function, it also leads to arrhythmias. On the other hand, hypovolemia can lead to acute kidney injury due to renal hypoperfusion. Wound and anastomotic hypoperfusion can also enhance anastomotic leaks, organ-space, and surgical site infections.

There are two main strategies to postoperative fluid resuscitation: restrictive and liberal. In restrictive strategy, fluid is administered to obtain a zero balance during surgery and the immediate 24-hour postoperative period. This is primarily guided by close monitoring of all intake and output with replacement or restriction as necessary. Fluid administration with a restrictive strategy is typically at an average of 0.8 ml/ kg/ hour. Liberal strategies employ standardized weight-based fluid administration at a prespecified rate that is only titrated if there is evidence of fluid overload. Liberal fluids are typically administered at a rate of 1.5 ml/ kg/ hr. In a recent international trial, 3000 patients were randomized to liberal or restrictive fluid management groups [2–4]. Restrictive fluid group received a median intravenous fluid intake of 3.7 liters (interquartile range, 2.9 to 4.9), as compared with 6.1 liters (interquartile range, 5.0–7.4) in the liberal fluid group ($P < 0.001$). Primary outcome was disability-free survival as measured by persistent impairment in health status (lasting ≥6 months). Secondary outcome was rate of acute kidney injury, rate of septic complications or death, surgical site infections, and need for renal replacement therapy. The rate of disability-free survival was not different between the two groups. Similarly, the rate of septic complications and death were similar. However, liberal fluid group had a lower incidence of surgical site infections (16.5% vs. 13.6%, $P = 0.02$), acute kidney injury (8.6% vs. 5.0%, $P < 0.001$), and need for renal replacement therapy (0.9% vs. 0.3%, $P = 0.048$). These findings demonstrate that among patients undergoing major abdominal surgery, modestly liberal rather than restrictive fluid strategy is more beneficial. Randomized studies evaluating more liberal fluid regimens than those in the above trial have clear shown detrimental outcomes with aggressive fluid administration [5–15]. Taken together, the data support modestly liberal fluid administration (1.5 ml/ kg/ hour) with isotonic fluids in the first 24-hour period after major cytoreduction.

Because of several levels of heterogeneity in patients undergoing cytoreduction, a one-size-fits-all strategy of modestly liberal fluid administration leaves room for improvement. An emerging and burgeoning area of goal-directed hemodynamic therapy (GDT) is likely to replace current paradigms. It is now possible to anticipate and individualize fluid administration to each patient's specific need. This represents the beginning of personalized postoperative care. Simply put, goal-directed hemodynamic therapy allows titration of fluids and inotropic drugs to physiological flow-related end points rather than surrogates for end-organ perfusion, e.g., urine output. While the goal of resuscitation is to prevent cellular hypoxia, a strategy that

monitors this end point is likely to fail because by the time cellular hypoxia is manifested, tissues have exhausted their autoregulatory mechanisms leading to irreversible damage. In contrast, flow-related end points allow guidance of fluid therapy before end-organ hypoperfusion occurs. A randomized trial that compared 160 patients undergoing major abdominal surgery randomized to standard fluid management vs GDT guided by invasive radial artery pulse monitoring, demonstrated significant reduction overall complication rate [16]. In particular, infectious complications were reduced. These results were amplified in patients undergoing intestinal surgery. However, return of bowel function and length of hospital stay were similar. This trial demonstrated the utility of GDT for fluid management during and after major abdominal surgery.

The cornerstone of GDT is estimation of preload and cardiac index using arterial pulse waveform over time. The pulse pressure variation (PPV) with breathing can be deconvoluted to estimate preload. Cardiac output is estimated using flow. As an initial step patient is resuscitated with fluids to achieve a PPV of <10% during surgery (Fig. 14.1a). Once this has been achieved (full-tank), cardiac index (body surface adjusted cardiac output) is optimized with inotropes. Finally, vasopressors are used to optimize MAP. Following initial set-up, patients are evaluated periodically (every 15 min or so) and the fluids are administered per algorithm (Fig. 14.1b).

To overcome the limitation of invasive monitoring of flow-related end points, several noninvasive devices have been evaluated. The list of these devices continues to grow and these devices are anticipated to become commonplace within the next few years [17]. A meta-analysis [18] of studies that evaluated patients undergoing major abdominal surgery using uncalibrated noninvasive pulse contour methods demonstrated that the total fluid volume and fluid volume variability is not decreased with these methods. However, postoperative morbidity is significantly reduced with GDT (OR 0.46, 95% CI 0.30–0.70, $P < 0.001$). Similarly, another meta-analysis confirmed these findings and also demonstrated a lower risk of short-term and long-term postoperative mortality [19]. A prospective observational study evaluated GDT during the first 3 postoperative days for 92 patients undergoing CRS/HIPEC [20]. This study demonstrated the feasibility of using stroke-volume variation in guiding fluid therapy. A randomized trial of GDT vs. standard fluid therapy in 80 patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy demonstrated significant reduction in postoperative complications (10% vs. 38%, $P < 0.0001$) in favor of GDT [21]. A matched study of 44 patients undergoing primary debulking with high carcinomatosis burden demonstrated the utility of GDT compared to standard therapy [22]. Taken together, these findings support the use of GDT over standard fluid resuscitation. However, more data are needed in a larger cohort of patients undergoing CRS/HIPEC.

At our institution, postoperative fluid management is individualized to the patient and the operation. We have established that excessive intra-operative fluid administration is associated with significant morbidity [23]. Therefore, patients undergo cautious/restrictive fluid therapy during the operation. Once the patients arrive in the recovery room, we usually obtain a fresh set of laboratory parameters to guide management. Most importantly, we also obtain an arterial blood gas and monitor the patient's deficit. We have recently demonstrated that failure to correct base-deficit within the first 48 hours is predictive of a complicated postoperative course [24]. Based on this analysis, we aim for a base excess of greater than +4.3 mmol/L at 48 hours. The patients are switched to maintenance fluids as soon as they are clinically euvolemic and the base-deficit is corrected. Diuretics are used on second or third postoperative day and are individualized based on the extent of third-spacing—as assessed by radiographic (Chest X-ray) or clinical exam evidence (peripheral edema, drain output).

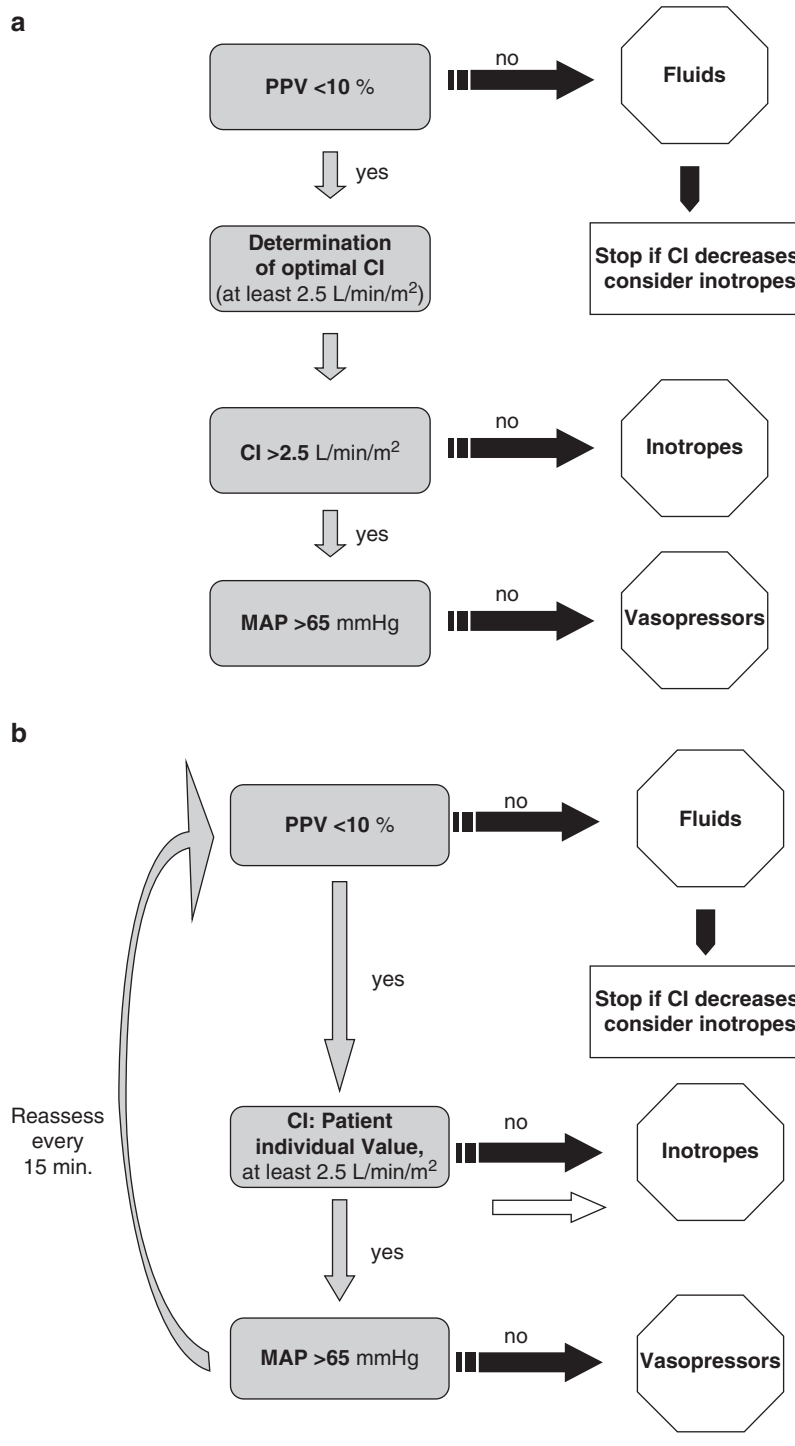

Fig. 14.1 Goal-directed hemodynamic therapy algorithm: (**a**) Initial set-up; (**b**) Maintenance. (Adapted with permission from Michard et al. [18])

Transfusion

Intra- and postoperative transfusion rates approach 70% in retrospective studies evaluating patients undergoing CRS/HIPEC. This is much higher than other elective oncologic operations and is a reflection on the extent of operation. Majority of patients are transfused for acute blood loss and receive a packed red-blood cell (pRBC) transfusion. It is recognized that patients who receive a transfusion have worse morbidity and mortality compared to those who do not. This association by confounding likely to represents the surgical extent and complexity in patients who receive a transfusion. However, even when adjusting for covariates, postoperative infections are significantly increased in patients who receive three or more units of pRBCs. More importantly, a recent study demonstrated worse long-term survival in patients who received blood transfusion in a dose-dependent manner. This is presumably due to the immunosuppressive effects of a blood transfusion. It is also speculated that pRBCs may directly support tumor progression through less understood pleiotropic effects. While these studies are not causal, they highlight the need for conservative use of blood transfusion in this patient population. Transfusion-sparing strategies include meticulous surgical technique; permissive hemodilution; and preemptive use of cryoprecipitate or tranexamic acid.

There are limited data on the threshold for postoperative transfusion in CRS/HIPEC patients. A restrictive transfusion threshold of hemoglobin <7 g/dL is superior in general critical-care patients [25], patients with non-catastrophic gastrointestinal bleeding [26–27], and patients with septic shock [28]. A threshold of hemoglobin <7.5 g/dL is optimal in patients undergoing cardiac surgery [29] and that of <8 g/dL in hip surgery [30]. A randomized trial of 198 patients who underwent major surgery for abdominal cancer (mostly gastrointestinal, pancreatic, or urogenital) in Brazil, compared a transfusion threshold of 7 g/dL (restrictive) to 9 g/dL (liberal) [31]. Only 5% of patients in this trial were CRS/ HIPEC patients. Transfusion rates were 21% (restrictive) and 42% (liberal). The primary end point (death or severe complication at 30 days) occurred significantly more often in the restrictive group than in the liberal group (36% vs. 20%). Several individual adverse outcomes also occurred significantly more frequently with the restrictive strategy: 30-day mortality (23% vs. 8%), 60-day mortality (24% vs. 11%), cardiovascular complications (14% vs. 5%), and abdominal infection (15% vs. 5%). This study stands in contrast to virtually all prior studies evaluating restrictive vs. liberal thresholds for blood transfusion. It is clear that more data are needed to confirm the results of this trial. In practice, we use a transfusion threshold of 7–8 g/dL for most patients without coronary artery disease.

Coagulopathy

Abnormal coagulation has been defined as platelet count <100,000, INR ≥ 1.5, or PTT ≥ 45 sec. Severe coagulopathy has been defined as a platelet count <50,000, INR > 2.0, or PTT > 60 sec. It is estimated that coagulopathy and severe coagulopathy occur in 38% and 4.7% of patients, respectively. Hypofibrinogenemia (Fibrinogen <1.5 μMol/L) occurs in 5.8% of patients [32–33]. Platelet count reaches a nadir on the third postoperative day and these counts are recovered by the sixth postoperative data. Similarly, Partial thromboplastin time (PTT) and International Normalized Ratio (INR) are significantly elevated in the initial three postoperative days. Two main predictors of coagulopathy include the need for pRBC transfusion and the peritoneal carcinomatosis index [32]. In a randomized study comparing heated Mitomycin C and Oxaliplatin, the choice of chemotherapy perfusion did not affect the occurrence of thrombocytopenia [33].

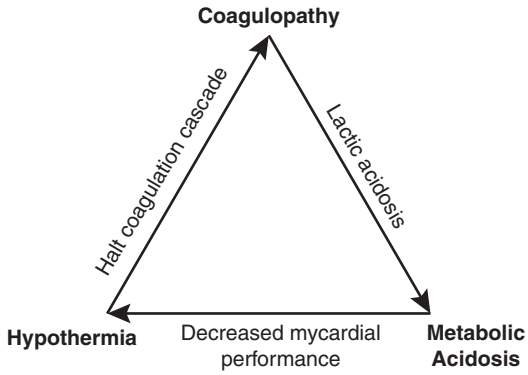

Fig. 14.2 Trauma triad of death. Uncorrected, this triad can lead to a vicious cycle of metabolic derangement and coagulopathy

The underlying cause of coagulopathy in this patient population is multifactorial. Some basic principles can be extrapolated from the "trauma triad of death" [34] as shown in Fig. 14.2. Tissue injury (such as cytoreduction) triggers coagulation cascade and restores homeostasis. However, excessive tissue injury in the setting of tissue hypoperfusion can be detrimental. For instance, tissue hypoperfusion and hypothermia can impair the coagulation cascade leading to severe coagulopathy which further leads to hypoperfusion due to ongoing blood loss. Restoring optimal perfusion to correct acidosis (hemodynamics), reversing hypothermia (central and peripheral warming strategies), and correcting coagulation parameters (supplementing clotting factors) are the key tenets of managing severe coagulopathy.

In the perioperative period, as mentioned above, we attempt to correct base deficit/ acidosis within the first 24–48 hours. We also attempt to keep intra- and postoperative core body temperature above 36 °C per the Agency of Healthcare Research and Quality Metric guidelines [35]. We recommend correcting severe coagulopathy (INR > 2) or platelet count (<50,000) in the immediate postoperative period up to 72 hours. In patients with postoperative hemorrhage, early return to the operating room to control bleeding source can mitigate the vicious cycle of coagulopathy.

Electrolyte Imbalances

Electrolyte imbalances are mainly a direct result of fluid shifts in the perioperative period. Other causes include stress hormones; transfusion; renal insufficiency; and refeeding syndrome. As a result, the magnitude of derangement mirrors the extent of cytoreduction. For patients who require significant fluid resuscitation, electrolytes (such as potassium, magnesium, calcium, and phosphate) should be measured and corrected immediately after surgery and then twice daily for the first 3 days and once daily thereafter. Because oral absorption in unreliable during this time, intravenous replacement is preferred. This can be facilitated with a peripherally inserted central venous catheter if simple peripheral venous access is exhausted. Common electrolyte imbalances after CRS/HIPEC include hyponatremia, hypernatremia, hypokalemia, hypercalcemia, hypomagnesemia, and hypophosphatemia [36]. Iatrogenic electrolyte derangement may result from errors in parenteral nutrition prescription, intravenous fluid prescription, or electrolyte replacement therapy (e.g., potassium content). The description of electrolyte abnormalities, possible causes, consequences, and treatment is summarized in Table 14.1.

Nutrition

Patients undergoing CRS/HIPEC can have a number of nutritional imbalances [37]. In a study of preoperative nutritional assessment in 214 patients undergoing CRS/HIPEC, it was found that 14 (6.5%) had a BMI $\geq$ 35 kg/m^2, 90 (42%) were sarcopenic, 19 (9%) presented albumin <35 g/L, and 2 (1%) had prealbumin <20 mg/dL [38]. It is imperative that preoperative nutritional assessment should be a major selection criterion for patients to undergo CRS/HIPEC.

Several studies have evaluated preoperative clinical, biochemical, and radiologic nutritional assessment markers. Clinical tools to assess malnutrition include Nutrition Risk Index and Subjective Global Assessment [39]. These are

Table 14.1 Electrolytes

Sodium	Hypernatremia (sodium >145 mEq/L)	Iatrogenic free-water deficit; hormonal response to surgery (i.e., antidiuretic hormone, aldosterone); evaporative, gastrointestinal, or urinary electrolyte-free water loss	Major derangements cause lethargy, weakness, and irritability, and can progress to twitching, seizures, and coma. Severe symptoms usually require an acute elevation in the serum sodium concentration to above 158 mEq/L	Minor elevations of sodium are easily corrected by decreasing the sodium content of the intravenous fluid (e.g., switch from 0.9% sodium chloride to 0.45% sodium chloride or 5% dextrose in water) or by adding free water to enteral feeds
	Hyponatremia (sodium <135 mEq/L)	Water retention (e.g., excess anti-diuretic hormone, administration of hypotonic fluids); excessive sodium loss (e.g., vomiting, nasogastric tube, diarrhea, abdominal drains, diuretics)	Nausea and malaise, which are the earliest findings, may be seen when the serum sodium concentration falls below 125–130 mEq/L. headache, lethargy, obtundation, and eventually seizures, coma, and respiratory arrest can occur if the serum sodium concentration falls below 115–120 mEq/L. noncardiogenic pulmonary edema has also been described	Mild postoperative hyponatremia generally resolves without specific intervention as the stress response decreases and does not need to be corrected. Sodium below 130 mEq/L should be corrected by changing the fluid from hypotonic to isotonic 0.9% sodium chloride. Hypertonic saline should be considered if hyponatremia is acute and associated with neurologic findings. The serum sodium should be raised by no more than 8 mEq/L in a 24-hour period to avoid osmotic demyelination syndrome (ODS)
Potassium	Hyperkalemia (potassium >5.5 mEq/L)	Iatrogrenic; ischemia-reperfusion; renal failure; hemolysis-transfusion; acid–base imbalance (e.g., acidemia)	Nausea, vomiting, diarrhea, bradycardia, cardiac arrhythmias, cardiac arrest, skeletal muscle weakness, paralysis	For mild hyperkalemia eliminate potassium in i.v. fluids. If volume overload consider nonpotassium-sparing diuretics. For moderate to severe hyperkalemia with clinical symptoms or ECG changes: Calcium gluconate; insulin with D50; albuterol; sodium bicarbonate; enteral/rectal sodium polystyrene therapy; emergency dialysis

(continued)

Table 14.1 (continued)

	Hypokalemia (potassium <3.5 mEq/L)	Potassium losses (via GI tract–Nasogastric tube, diarrhea, vomiting); inadequate intake (NPO status); diuretic therapy; acid-base imbalance (e.g., alkalosis)	Cardiac arrhythmias, muscle weakness, confusion, nausea, vomiting	Potassium chloride may be given through a peripheral intravenous catheter at a rate of 10–20 mEq/hour at a low concentration (i.e., 10 mEq per 100 mL) to minimize the caustic effects of potassium infusion on peripheral veins (i.e., chemical thrombophlebitis) and to avoid transient severe hyperkalemia that can have serious consequences. If the GI tract is working as much as 80 mEq of liquid potassium chloride can be administered into the stomach at once
Magnesium	Hypermagnesemia (magnesium >2.6 mg/dL	Renal failure, ingestion of magnesium containing antacids	Lethargy, muscle weakness, confusion, coma, cardiac arrhythmias, cardiac arrest	If renal function is normal, loop (or even thiazide) diuretics can be used to increase renal excretion of magnesium. If renal function is abnormal, cautious use of diuretics or dialysis should be considered
	Hypomagnesemia (magnesium <1.8 mg/dL)	GI losses, severe malnutrition, urinary losses (e.g., diuretics)	Tremors, skeletal irritability, seizures	Magnesium sulfate is typically used for intravenous replacement therapy; 2 g (8 mmol) is mixed in 50–100 mL of fluid and infused over 30–60 minutes through a peripheral or central venous catheter, except in emergencies. In emergencies (e.g., severe or symptomatic hypomagnesemia), 2–4 g (8–16 mmol) of magnesium sulfate diluted in 10–50 mL of sodium chloride can be given intravenously over 2–15 minutes

Table 14.1 (continued)

Calcium	Hypercalcemia (calcium >10.5 mg/dL)	Renal dysfunction; paraneoplastic	Cardiac arrhythmias, muscle weakness, confusion, nausea, vomiting	Patients with asymptomatic or mildly symptomatic hypercalcemia (calcium <12 mg/dL [3 mmol/L]) do not require immediate treatment. Patients with calcium >14 mg/dL (3.5 mmol/L) require more aggressive therapy. This includes volume expansion with isotonic fluid, calcitonin, zolendronic acid
	Hypocalcemia (calcium <9 mg/ dL)	Diarrhea; alkalosis; renal dysfunction; diuretics; vitamin D deficiency	Tingling, tremors, muscle cramps, tetany, convulsions, cardiac arrhythmias	In mild-to-moderate hypocalcemia, calcium replacement is typically given as 1 or 2 g (2.3 or 4.6 mmol) of IV calcium gluconate mixed in 50 mL of fluid and infused over 30 or 60 minutes through a peripheral or central venous catheter. The dose may be repeated as needed based on ionized serum calcium level. In severe symptomatic hypocalcemia, 1 g (6.8 mmol) of calcium chloride or 3 g (6.9 mmol) of calcium gluconate diluted in 50 mL of fluid can be infused over 10 minutes to rapidly control symptoms; this dose is repeated as necessary. Avoid rapid intravenous bolus of calcium, which can result in acute respiratory depression and asystole
Phosphate	Hyperphosphatemia (phosphate >4.5 mg/dL)	Renal failure, in particular acute on chronic renal failure; major tissue trauma; oral supplementation	Rarely symptomatic. Symptoms are due to reciprocal changes in calcium levels	Enteral phosphate binders may not be an option. However, acute hyperphosphatemia is rarely life-threatening; emergency dialysis is not usually needed

(continued)

Table 14.1 (continued)

	Hypophosphatemia (phosphate <2.5 mg/dL)	Decreased oral intake; increased urinary output (e.g., diuretics); increased utilization (e.g., refeeding syndrome)	Weakness, lethargy, respiratory insufficiency	Intravenous phosphate (in the form of sodium phosphate or potassium phosphate) is typically diluted in 250 mL of fluid and infused at a rate of 4 or 5 mmol/hour through a central or peripheral venous catheter. As an example, 30 mmol sodium phosphate may be administered intravenously over 6 hours. Slow infusion of phosphate is preferred to decrease the risk of injury due to calcium-phosphate precipitate, which can result in acute kidney failure. Oral phosphate replacement is typically given in three or four divided doses through the day. Note that oral phosphate supplements include variable amounts of sodium and potassium. One commonly available phosphate tablet preparation (K-Phos neutral) delivers 13 mEq sodium and 1.1 mEq potassium in a fixed ratio with 8 mmol of phosphate

clinical techniques that combine data from subjective and objective aspects of medical history (weight change, dietary intake change, gastrointestinal symptoms, and changes in functional capacity) and physical examination (loss of subcutaneous fat, muscle wasting, ankle or sacral edema, and ascites). A study evaluating 60 consecutive patients undergoing CRS/HIPEC measured subjective global assessment and postoperative outcomes [37]. This study demonstrated that malnourished patients had a significantly longer length of stay and worse long-term survival. The study was not powered to detect a difference in complications. Serum albumin level is an important predictor of postoperative morbidity. Low albumin levels indicate sub-optimal nutritional reserve, chronic inflammatory state, or cancer cachexia [40]. In a study of 108,898 patients undergoing colorectal procedure, modest hypoalbuminemia was associated with increased morbidity and threefold increased odds of postoperative mortality compared to those with normal albumin levels [41]. Similarly, a study on patients undergoing CRS/HIPEC, hypoalbuminemia was associated with a detriment in long-term survival [38].Radiologic parameters such as sarcopenia and visceral fat accumulation have also been evaluated. At least three studies have evaluated radiologic assessment of skeletal muscle depletion with mixed results. In a study of 206 patients undergoing CRS/HIPEC, sarcopenic patients were at higher odds of severe postoperative complications [42].. However, a similar study demonstrated that sarcopenic patients were at increased odds of chemotherapy side effects but not postoperative complications [43]. These results were

reproducible in a study by Banaste et al. [38] In this study, visceral fat reserves were evaluated as well and were not associated with short-term or long-term survival [38]. These findings suggest that preoperative albumin levels should be used to assess nutritional reserves, whereas more data are needed prior to routine use of clinical nutritional assessment tools, sarcopenia, and visceral fat reserves in patient selection.

Patients who have preoperative nutritional deficiency could theoretically be optimized for CRS/HIPEC by nutritional supplementation. In most circumstances, CRS/HIPEC is an elective procedure. There is lack of data evaluating routine use of nutritional supplementation for malnourished patients. A randomized trial comparing 395 malnourished patients undergoing noncardiac laparotomy or thoracotomy were randomly assigned to receive total parenteral nutrition vs. not for 7–15 days before surgery and 3 days afterwards [44]. In this trial, there was no major difference in complications or mortality rate between the two groups. In fact, there were more infectious complications in the Total Parenteral Nutrition (TPN) group (14% vs. 6%, $P = 0.01$). A subset analysis demonstrated that patients who were severely malnourished had significantly lower risk of non-infectious complications than controls with no concomitant increase in infectious complications (5% vs. 43%; $P = 0.03$; relative risk, 0.12). Severe malnourishment was defined as Nutritional Risk Index score of <83.5 [39]. Consistent with the evidence in this trial, our practice is to reserve TPN for patients who are severely malnourished but have otherwise preserved physical function to undergo CRS/ HIPEC. More data and newer strategies are needed to improve nutritional assessment, status, and outcomes of patients undergoing CRS/HIPEC.

There are limited data to guide postoperative nutritional plan in patients undergoing CRS/HIPEC. In clinical practice, we extrapolate data from studies evaluating related gastrointestinal procedures. An important question is to determine if patients should have early or delayed resumption of feeding. In a meta-analysis of 1240 patients (15 studies) undergoing gastrointestinal resections, early postoperative feeding was associated with a 45% reduction in the odds of postoperative complications and no detrimental effect on anastomotic healing [45]. Early feeding was defined as introduction of food (liquid or solid) within 24 hours postoperatively. Delayed feeding was defined as patients who were allowed to eat after resumption of bowel function. While majority of patients in this study had intermediate to high complexity gastrointestinal operations, none had CRS/HIPEC. Whether or not this can be extrapolated to CRS/HIPEC population is unclear at this time. A study evaluating 214 CRS/HIPEC patients compared postoperative feeding tolerance with or without gastrectomy [46]. Patients who had gastrectomy had higher peritoneal carcinomatosis index (21 vs. 13) and also had a significantly longer time to full feed tolerance (8 vs. 5 days). These findings suggest that patients undergoing gastrectomy or extensive cytoreduction are at risk for prolonged ileus. Early total parenteral nutrition should be considered especially if they have severe preoperative nutritional deficiencies. In this regard, malnourished patients undergoing gastrectomy stand to benefit from TPN in the early postoperative period. A study by Wu et al. reported that in 118 malnourished patients undergoing total ($n = 40$) or subtotal ($n = 78$) gastrectomy, patients who did not receive TPN had higher morbidity (67% vs. 16% and 44% vs. 22% for subtotal and total gastrectomy, respectively) as well as a longer hospital stay (35 vs. 21 days) [47].

At our institution, nutritionists are routinely involved in the care of patients, preoperatively for malnourished patients and immediately postoperatively for all patients. Patients anticipated to have a prolonged ileus based on extent of operation and need for gastrectomy are started early on total parenteral nutrition. Patients who have not demonstrated feeding tolerance by day 7 are also started on total parenteral nutrition. A fraction of patients is discharged on total parenteral nutrition as they improve their feeding tolerance. For logistical reasons and ease of mobility, the infusions are administered for 12–14 h during the nighttime. These patients are monitored with a full set of nutritional labs at least once a week. In addition, these patients are closely monitored by a multi-disciplinary team

of pharmacists, nutritionists, and surgeons. Total parenteral nutrition is slowly weaned as patients develop feeding tolerance. The duration of total parenteral nutrition is individualized based on the nutritional status of the patients, underlying complications (e.g., fistula, dysmotility, persistent disease), and calorie counts.

Bone Marrow Stimulants

Patients undergoing CRS/HIPEC are at risk of hematologic toxicity. This is directly related to the agent used during the perfusion and its systemic absorption [33]. An optimal agent to use for intraperitoneal chemotherapy has not been identified. In the US, Mitomycin C is commonly employed whereas in Europe, Oxaliplatin is the drug of choice. In terms of efficacy for appendiceal and colorectal cancers, there is no apparent difference in retrospective studies and one randomized trial [33]. For ovarian cancer, cisplatin has become standard of care [48]. These agents differ in their propensity to cause hematologic toxicity. For instance, when administered for 2 hours, Mitomycin C cause more leukopenia compared to Oxaliplatin [33].

Bone marrow stimulants, i.e., G-CSF (Filgrastim, Filgrastim-SNDZ, TBO- Filgrastim, or Pegfilgrastim) are used to manage neutropenia in the postoperative period. The use of these agents is highly variable among different institutions. Currently, the guidelines are extrapolated from those pertinent to systemic therapy [49]. The decision to use G-CSF is based on patient's risk for febrile neutropenia. Febrile neutropenia is defined as single temperature, ≥38.3 °C orally or ≥38.0 °C over 1 h; neutropenia, <500 neutrophils/mcL or <1000 neutrophils/mcL; and a predicted decline to ≤500 neutrophils/mcL over the next 48 h. By default, patient's undergoing cytoreduction are at an intermediate risk to develop febrile neutropenia and should be considered for prophylactic use of G-CSF [49]. In one study, 39% of the patients undergoing CRS/HIPEC developed neutropenia defined as absolute neutrophil count <1000 per mcL. [50] Female gender and MMC dose per BSA were independent predictors of neutropenia. Interestingly, in this study neutropenia did not increase the risk of morbidity or mortality. Other general factors that may aggravate the risk of febrile neutropenia include older age, poor performance status, presence of comorbidities, low baseline white blood cell counts, low BMI/BSA, and advanced disease [51]. However, currently there are no data to support prophylactic use of G-CSF in CRS/HIPEC patients. At our institution, patients with white blood cell count (WBC) <4000 per mcL are given G-CSF at 5 μg/kg daily until the WBC exceeds 10,000 per mcL.

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15 Complications of Cytoreductive Surgery and HIPEC

Andrew M. Blakely and Byrne Lee

Introduction

In the last 20 years, the survival benefit of cytoreductive surgery (CRS) and heated intraperitoneal chemotherapy (HIPEC) has been demonstrated for highly selected patients for a range of primary tumor types [1–3]. Patients are more commonly undergoing CRS and HIPEC, leading to a greater number of presentations in the emergency department or the ambulatory setting with a wide range of complications and treatment-related symptoms (Table 15.1).

Table 15.1 Major complications following CRS and HIPEC

Inpatient setting
Pneumonia, ventilator-associated or otherwise
Deep vein thrombosis, pulmonary embolism
Pneumothorax, pleural effusion
Acute kidney injury
Prolonged paralytic ileus
Anastomotic leak or perforated viscus
Ureteral injury or urine leak after reconstruction
Postoperative neutropenia
Abdominal wall hernia or dehiscence
Anesthesia-related complications
Outpatient setting
Enterocutaneous or other fistula
Bowel obstruction
Failure to thrive

Assessment of Complications

Surgical complications are most frequently graded using the Clavien–Dindo classification [4]. However, a limitation of that grading system is that it only considers the highest-grade complication experienced [5]. Therefore, its applicability to a complex surgical population such as CRS and HIPEC patients may be limited, given that one patient may experience multiple complications. A different grading system, the Comprehensive Complication Index (CCI), assesses all complications experienced within 30 days and their treatment to provide arguably a more complete assessment of postoperative recovery [6]. The CCI has recently been validated in an analysis of an institutional CRS and HIPEC population, demonstrating a higher correlation with postoperative length of stay than Clavien–Dindo [7]. Since Clavien–Dindo is still the most widely used grading system, it retains utility in comparing CRS patients with other surgical patient populations. There is arguably good rationale for using both assessments in evaluating postoperative outcomes of HIPEC.

Assessment of complications at 30 versus 90 days has received greater attention recently

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Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_15

[8, 9]. Many patients will develop new complications beyond 30 days or will ultimately die of complications that initially manifested within 30 days. Assessment at 90 days may, therefore, better capture the ultimate outcomes of complications suffered in the immediate postoperative phase. At the same time, in patients with advanced malignancy, progression of disease is an important driver of mortality as time since surgery increases [10]. Therefore, cause of death should be specifically delineated at the 90-day mark or beyond whenever possible in order to best identify postoperative versus disease-related mortality.

Inpatient Postoperative Complications

Complications that are inherent to general anesthesia and abdominal surgery but not specific to HIPEC will not be covered in great detail. However, it is worth mentioning that the extent of exploration and resection required to optimally cytoreduce peritoneal carcinomatosis may expose the patient to a wider range of overall and organ-specific complications compared to a more focused operation. Coupled with longer anesthesia times for a greater extent of surgery and for the HIPEC portion of the operation, patients will experience more physiologic stress and might partially explain the relatively higher rate of complications seen in this surgical patient population [11].

Cardiopulmonary

Cardiopulmonary complications are the most frequent type of adverse events and the greatest driver of postoperative mortality. HIPEC patients often remain intubated following completion of the operation, which increases ventilator time and associated pneumonia. Postoperative respiratory failure leading to re-intubation also occurs, which further increases pneumonia risk. Hypercoagulable states attributable to disseminated malignancy, any preexisting congenital condition, and extensive debulking are associated with higher risk for deep vein thrombosis and subsequent pulmonary embolism [12]. Unrecognized violation of the diaphragm during upper abdominal peritoneal surface stripping may manifest as a pneumothorax requiring tube thoracostomy [13]. Clinically significant pleural effusions requiring thoracentesis or thoracostomy may also be a result of extensive diaphragmatic stripping or resection [14].

Renal

Prolonged anesthesia time and significant fluid shifts during resuscitation frequently manifest as acute kidney injury and less commonly renal failure in the immediate postoperative phase. This is most often mitigated with dose adjustment according to creatinine clearance and an aggressive perioperative fluid resuscitation plan [15]. Our practice is to initiate postoperative resuscitation based on initial base deficit, by giving additional fluid boluses in the immediate phase of recovery and administering a higher maintenance rate of fluids. Base deficit is then checked on the morning of postoperative days 1 and 2, with titration of fluid resuscitation until normalization. In a review of our institutional HIPEC database, we found that correction of base deficit was associated with decreased complications [16].

Specific note should be made of the increased risk associated with platinum agent-based HIPEC given its known renal clearance and risk for nephrotoxicity [17]. The addition of bolus sodium thiosulfate at the start of the peritoneal perfusion and carried as a continuous infusion for 6 hours has been utilized to protect renal function [1].

Gastrointestinal

Significant involvement of the serosal or mesenteric peritoneal surfaces with carcinomatosis will lead to relatively more manipulation of the bowel and its mesentery, which along with the paralyzing effect of HIPEC at least partially explain the higher rates of prolonged ileus seen in this popu-

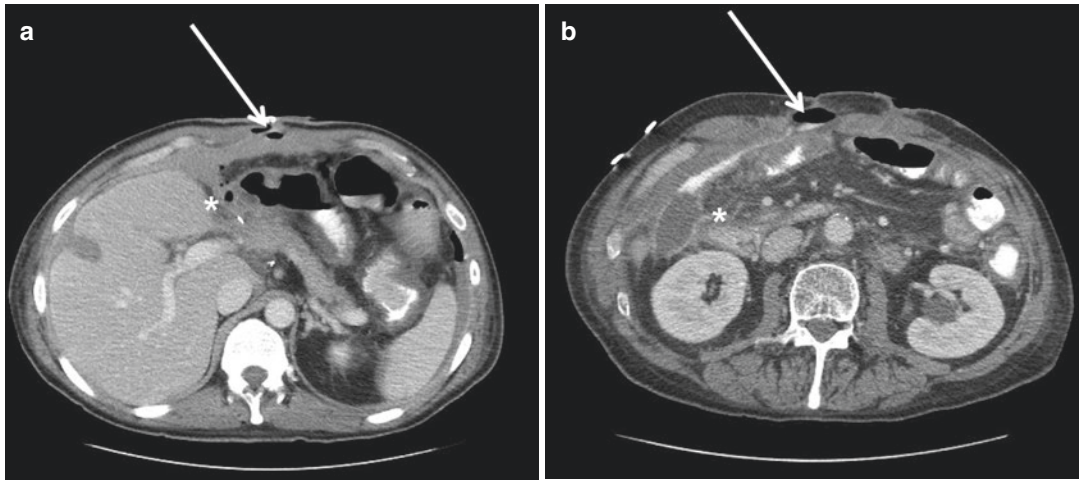

Fig. 15.1 Computed tomography images of gastrocutaneous (**a**) and enterocutaneous (**b**) fistulae. ∗ denotes origin of fistula; arrow denotes site of extravasation of fistula contents through midline incision

lation [18]. Return of bowel function may be substantially delayed, leading to longer duration of nasogastric tube decompression. In addition, there may be a need for nasogastric tube reinsertion for persistent nausea and vomiting despite partial or full return of lower gastrointestinal tract function [19]. Therefore, the rates of parenteral nutrition administration during admission are significant, with some patients requiring continuation of parenteral support beyond discharge [20].

Cytoreduction involving excision or focused superficial ablation of intestinal serosal implants may compromise the integrity of the underlying bowel. The administration of HIPEC, given both the supraphysiologic temperature of the lavage as well as cytotoxic effects of the chemotherapeutic agent, may additionally increase the risk of bowel perforation [21]. For that reason, most practitioners will defer gastrointestinal anastomoses until after HIPEC. Even so, perforated viscus and anastomotic leak represent two of the more feared and potentially morbid complications, particularly when compounded by a delay in diagnosis [22]. These clinical scenarios most often present as some combination of fever, decreased urine output, and bilious drainage from the incision or via a drain placed intraoperatively. Upright abdominal film might detect free air indicative of perforation [23]. Cross-sectional imaging may help identify the exact source of the effluent [24]. Principles of management are based on control of sepsis and are outlined in Fig. 15.1.

The adverse impact of bowel perforation is potentially profound. Reoperation following a prolonged operation and extensive tumor debulking is a significant physiologic stress, particularly when the patient has not fully recovered from the initial surgery. Laparotomy when nearing the 2-week postoperative time point may be quite hazardous given the accumulation of adhesion formation, with a higher risk of occult and obvious bowel injury during adhesiolysis leading to a proportionately higher risk of subsequent enterocutaneous fistula formation [25]. Reoperation, especially when the patient was physiologically unstable at the time of diagnosis of perforation, is associated with higher rates of admission to, length of stay in, and attendant complications of the intensive care unit [26]. Delayed recovery from the second operation will further prolong time to receipt of postoperative chemotherapy, increasing the risk of disease progression in the interim [27].

Genitourinary

Two components of cytoreduction substantially increase the potential risk for injury to the urinary collecting system, particularly when performed

in combination: (1) rectosigmoid or gynecologic organ resection and (2) pelvic peritoneal stripping with or without the need for urinary bladder repair from unintentional injury or partial cystectomy for direct tumor involvement [28]. Careful identification and preservation of the ureters and their vascular pedicles are critical to safely resect the pelvic peritoneum and adnexal structures. However, tumor encasement of one or both distal ureters may necessitate segmental resection, frequently reconstructed with psoas hitch and uretero-neocystic reimplantation [29]. Our institutional practice is two-layer urinary bladder repair, prolonged catheter decompression for 10–14 days, and performance of a cystogram prior to catheter removal. A low threshold for bladder catheter methylene blue instillation is prudent to identify leaks intraoperatively. Operatively placed drains may develop subsequent high-volume pale yellow output, which may be tested for body fluid creatinine if a urine leak is suspected. Further management of a urine leak identified postoperatively is based on the location of the leak, adequacy of drainage, and physiologic sequelae [30].

Hematologic

The reliability of white blood cell counts in guiding postoperative management of HIPEC patients may be questioned. Immunosuppressive effects of cytotoxic chemotherapy often manifest as profound neutropenia, particularly following HIPEC with mitomycin or oxaliplatin [31, 32]. This may be corrected with the administration of filgrastim or an analog in the immediate postoperative phase, with resultant elevated white blood cell counts. However, this severely limits its utility in assessing for postoperative complications. Meanwhile, white blood cell counts may be temporarily higher as a manifestation of neutrophil demargination from endothelial surfaces following splenectomy [33]. Postoperative anemia is also prevalent, with substantial rates of red blood cell transfusion, which might be a marker of worse long-term outcomes [34].

Abdominal Wall

Peritoneal carcinomatosis may erode through the anterior abdominal wall de novo or at prior surgical incisions, prompting partial abdominal wall resection as part of optimal cytoreduction [35]. In the setting of extensive resection of abdominal wall layers, reconstruction presents unique challenges. Cytoreduction patients may require temporary or permanent ostomies, which preclude ipsilateral component separation. Meanwhile, intestinal procedures make the operation at least clean contaminated by National Surgical Quality Improvement Program (NSQIP) definitions, with increased risk of infectious complications with synthetic mesh placement [36]. Although not the ideal solution, many practitioners opt to perform the best primary reconstruction possible with biologic mesh reinforcement, accepting a higher long-term risk of eventual abdominal wall hernia development over the immediate and long-term sequelae of mesh infection and more challenging subsequent reconstruction.

Enhanced Recovery After Surgery Pathways

Patient selection for CRS and HIPEC has improved, identifying those patients with lower peritoneal carcinomatosis index (PCI) scores and therefore a better chance at optimal cytoreduction. In the setting of less extensive cytoreduction, patients tend to be deemed ready for discharge sooner [18]. In addition, strategies to reduce postoperative lengths of stay without increasing readmission rates have been increasingly applied to a wide range of surgical populations, with HIPEC patients as no exception. Thus far, few studies have evaluated specific aspects of intra- and postoperative care in the CRS and HIPEC population in terms of enhanced recovery. Osseis et al. evaluated epidural analgesia paired with a structured physical therapy program, finding shorter intensive care unit lengths of stay and increased patient satisfaction among the intervention group [37]. As interest in evaluating and quantifying the relative benefits of such pathways in the HIPEC

patient population grows, we expect the number of publications on the topic to rapidly increase in the near future.

Outpatient Postdischarge Complications

With diminishing lengths of stay for selected patients, some complications that are frequently identified during the course of a longer hospital stay instead may not manifest until after discharge. As such, many of the aforementioned complications will present in the emergency department or ambulatory setting. Specific complications that are more likely to develop among outpatients warrant specific discussion.

Fistula

Anastomotic leak or delayed bowel perforation may present in delayed fashion, manifesting as a spectrum of signs and symptoms such as fever, abdominal pain, new-onset surgical incision drainage, or abdominal wall abscess with or without active feculent drainage [38]. Standard tenets of enterocutaneous and colocutaneous fistula management still hold, including *nil* per os status, minimization of oral medications, quantification of daily output volume, and consideration of octreotide analogs and parenteral nutrition. Example images of fistulae are shown in Fig. 15.2, and the approach to management is outlined in Fig. 15.3.

The detrimental effects of enterocutaneous fistulae cannot be overstated. Higher output fistulas will lead to fluid, electrolyte, and nutrient depletion, which in turn produces a catabolic state [39]. However, long-term dependence on parenteral nutrition to minimize output is associated with increased risk of bacteremia [40]. In the best circumstances, conservative measures will aid in spontaneous closure of the fistula, which may take at least a month to occur [38]. Practitioners who undertake operative takedown of the fistula frequently wait for 3–6 months to optimize nutrition and minimize systemic inflammation [41]. Enterocutaneous fistulae are potentially quite difficult to manage and can diminish the survival benefit conferred by the original cytoreductive surgery.

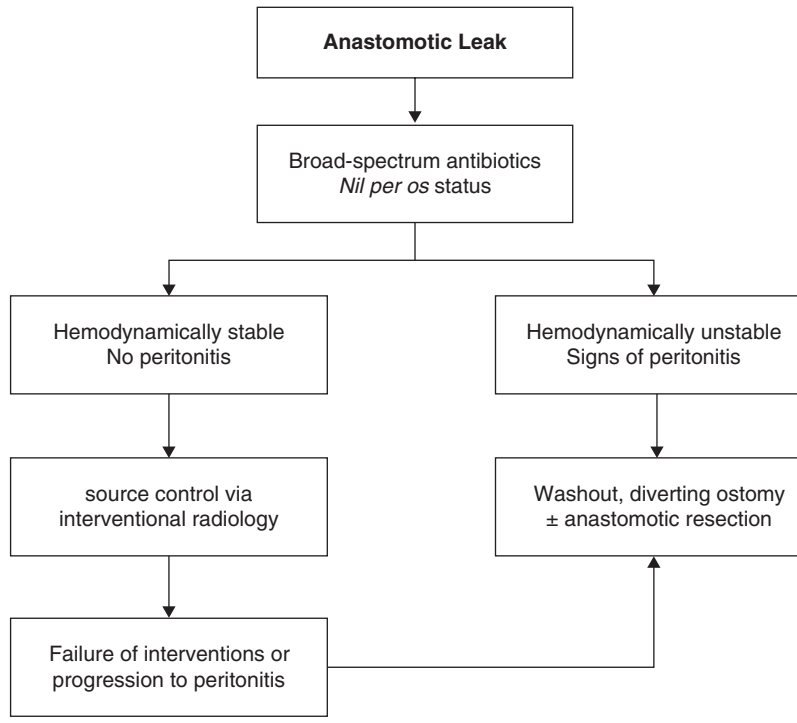

Fig. 15.2 Treatment algorithm for suspected postoperative bowel perforation or anastomotic leak

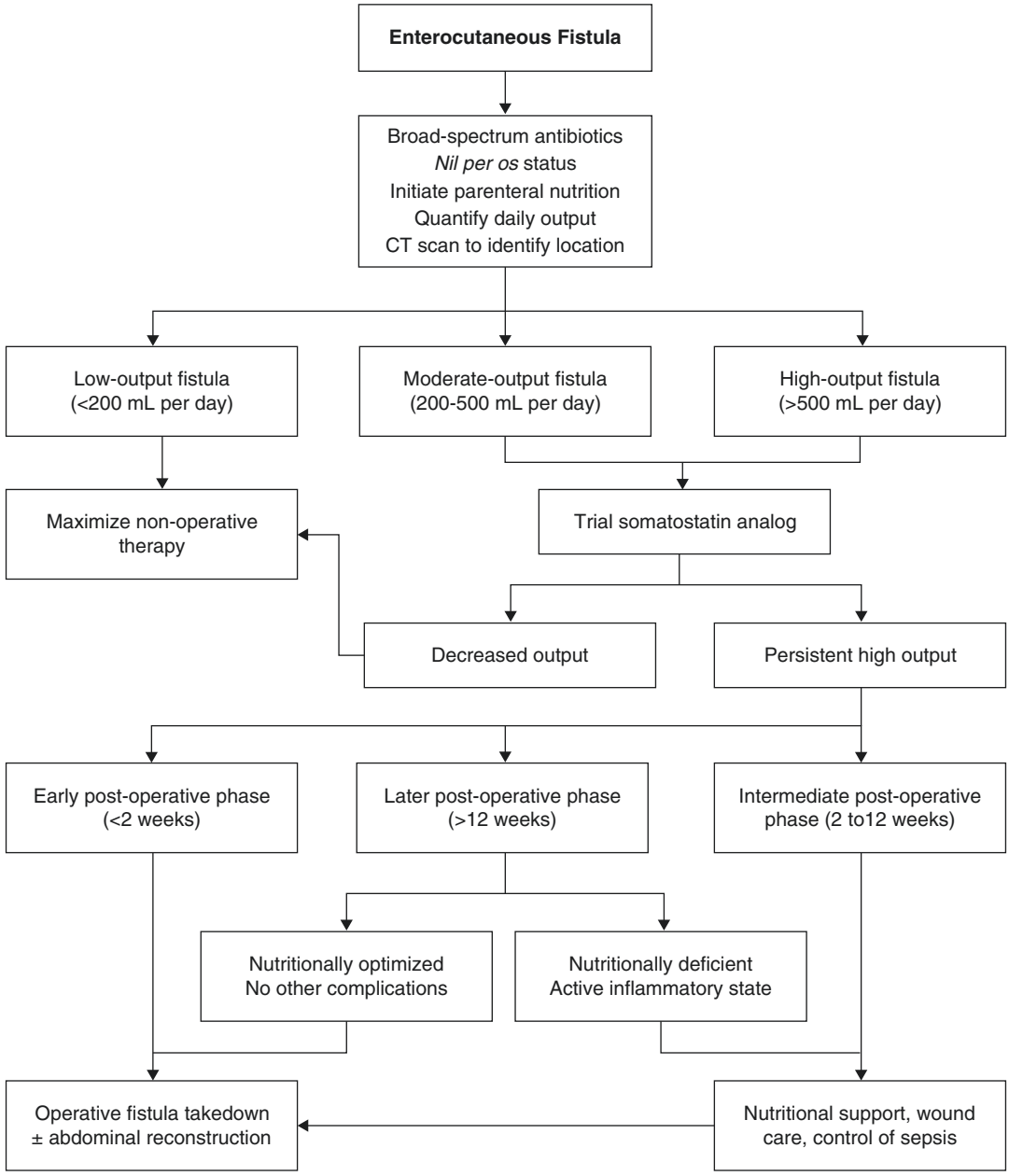

Fig. 15.3 Treatment algorithm for suspected postoperative enterocutaneous fistula

Bowel Obstruction

Part of the rationale underlying CRS and HIPEC is to debulk peritoneal carcinomatosis directly involving intestinal serosa and mesentery, which if left untreated will generally progress to recurrent malignant bowel obstruction [42, 43]. Postoperative patients presenting with clinical concern for bowel obstruction may represent adhesive and/or malignant etiologies of blockage. Based on the potential mechanical component of obstruction, initial treatment with *nil* per os, intravenous fluid resuscitation, and nasogastric tube decompression are appropriate. Evaluation with

Gastrografin enteroclysis may further characterize the extent and severity of bowel obstruction. If the clinical picture is more likely carcinomatosis related, other management involving antisecretory agents, glucocorticoids, and antiemetics is more appropriate [44]. For patients who fail to improve with such measures, the relative benefit versus the risk of re-exploration must be carefully weighed. Patients who have undergone substantial peritoneal stripping have lost the normal physiologic function of the peritoneal lining, and adhesion formation is subjectively denser around those areas, which is compounded by any prior intra-abdominal complications [45, 46]. Together, such profound adhesion formation may lead to a clinically "frozen" abdomen. Extensive adhesiolysis is often required, and even meticulous technique carries the risk of inadvertent occult weakening of friable bowel or frank enterotomy. This, in turn, may subsequently develop into a perforation or enterocutaneous fistula. Patients' tolerance of such complications may be poor, with fistula formation having been described as a negative predictor of survival.

Failure to Thrive

A common reason for readmission within 90 days of CRS and HIPEC is failure to thrive [47, 48]. Cytoreductive surgery may create one or more physical alterations to the gastrointestinal tract, including distal gastrectomy and loss of the pylorus or multiple small and/or large bowel resections leading to decreased absorption and transit time of enteric contents. Formation of a temporary loop or permanent end ileostomy may further compound ongoing fluid and electrolyte losses refractory to antimotility agents [48]. Functional alterations also may occur, with delayed gastric emptying or early satiety potentially limiting adequate oral intake. Calorie counts and demonstration of adequate oral fluid intake compared to ostomy output prior to discharge may help preempt issues that are likely to lead to poor nutritional intake and dehydration requiring readmission. Assessment of social support systems before and after CRS is crucial to identify patients who would benefit from discharge to a skilled nursing facility prior to transition home, particularly among older patients [49].

Management of Complications

Given the wide range of organ-specific resections that may comprise cytoreduction, management of complications in this patient population must take into consideration what specific procedures were performed. For unstable inpatients, as in the general surgical population, initial treatment should consist of stabilization of hemodynamic status, procurement of blood cultures and prompt initiation of antibiotics, and diagnostic workup as appropriate. For hemodynamically stable patients, diagnostic workup and treatment can be pursued more deliberately, considering the relative contribution of individual components of cytoreduction and of HIPEC in the patient's clinical picture. Optimal management of complications may be characterized by judicious use of antibiotics or blood products, careful selection of invasive operative or radiology-based procedures, partial or total nutritional supplementation, or psychosocial support [50]. Multidisciplinary approaches to care are important to involve surgical oncology, medical oncology, social work, case management, dieticians, wound care services, pain management team, and palliative care medicine in order to provide a comprehensive, tailored approach to care.

When complications develop after discharge, patients should be encouraged to re-present to the facility where CRS and HIPEC were performed. However, for some patients, whether due to long distance or unstable clinical status, returning to the original facility may not be feasible initially. Communication between the outside facility and the operative surgeon is critical in order to help guide diagnosis and management of complications, specifically by providing operative specifics of cytoreduction, details of the postoperative hospital stay, and ambulatory follow-up to that time. Clinically stable patients requiring admission should be transferred to the operative facility at the earliest opportunity for continuity of care.

Summary

Cytoreductive surgery and HIPEC patients represent a particularly complex surgical patient population. The location and extent of cytoreduction confer specific risks of morbidity that often involve multiple organ systems and are additive in nature. Furthermore, the administration of HIPEC is associated with additional risk of complications specific to its heated and cytotoxic nature. Two of the most feared and potentially morbid complications are those of anastomotic leak and enterocutaneous fistula. Specific knowledge of the patient's anatomy, tumor debulking, and HIPEC is critical to best assess and manage postoperative complications in this population. As the body of literature on complications after CRS and HIPEC grows, their diagnosis, management, and prevention will improve.

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Liver Resection and HIPEC

16

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Introduction

Synchronous intra-parenchymal hepatic involvement (HI) in patients with peritoneal disease (PD) has traditionally served as a contraindication for cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) on the basis that HI represents a systemic rather than locoregional disease. In recent years, however, multidisciplinary management of peritoneal cancers has evolved, with the addition of modern systemic chemotherapy to surgical resection resulting in improved survival in carefully selected patients with HI or PD. Several studies have also demonstrated the feasibility and safety of combined liver resection with CRS/HIPEC in well-selected patients with synchronous HI and PD. Despite growing evidence that acceptable long-term outcomes are achievable, however, concerns over the safety of synchronous hepatic resection and CRS/HIPEC have persisted due to the relative magnitude of both procedures. This chapter examines the perioperative considerations and outcomes of liver resection as a component of CRS/HIPEC.

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Preoperative Considerations

Incidence

Synchronous HI and PD are most commonly found in patients with colorectal or high-grade appendiceal (HGA) primaries, but the true incidence of combined HI and PD is unknown. Most studies demonstrate between 8% and 45% of patients with colorectal cancer have both HI and PD, but these studies investigate only patients who undergo liver resection and CRS/HIPEC, excluding patients who were not candidates for resection [1–6]. However, Franko et al. compared patients with PD from colorectal cancer who underwent CRS/HIPEC to those who received systemic chemotherapy alone [7]. In patients who underwent CRS/HIPEC, 15% had HI and PD; in those who received systemic chemotherapy alone, 35% had HI and PD, giving perhaps a better estimate of the true incidence of HI and PD.

Evaluating patients with HI and PD can be challenging due to the inability of CT imaging to detect all PD. In a study conducted by Jacquet and colleagues, sensitivity of CT scan in determining disease was 70–88%, depending on the region of the abdomen. Moreover, the false negative ranged from 20% to 28% [8]. An additional study by Denzer et al. showed PD on exploration in 100% of patients with a wide range of histologically proven malignancy in whom an earlier CT showed only 47.8% with PD. [9] Allard et al.

Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_16

examined the rate of unexpected PD at the time of liver resection for colorectal HI. Of 1340 patients with a planned liver resection, 42 (3%) had unexpected PD. [10] Thus, more HI and PD may exist than is captured, because not every patient will undergo surgical exploration and have the presence or absence of PD confirmed.

Preoperative Evaluation

When considering liver resection as part of CRS/HIPEC, like any patient with HI or peritoneal involvement, a thorough preoperative evaluation is imperative. At our institution, we perform a complete history and physical examination, measure relevant serum tumor markers, as well as obtain a CT scan of the chest, abdomen, and pelvis and a dedicated liver MRI [2]. Eligibility for CRS/HIPEC includes a histologic or cytologic diagnosis of peritoneal carcinomatosis, potentially resectable or resected primary lesion, debulkable PD based on imaging, absence of extra-abdominal disease, and complete recovery from any previous radiation or chemotherapy [2]. The biological behavior of the tumor should also be considered, such that only patients who show a response or no progression on preoperative chemotherapy are eligible for operative resection. When considering HI, whether superficial or parenchymal, disease must be considered resectable by standard definitions of colorectal liver metastases [11]. Thus, all HI must be resectable with a negative margin which allows for preservation of at least two functional liver segments with intact portal and arterial inflow, venous outflow, and biliary drainage [11].

For patients with colorectal and HGA lesions, we recommend 3 months of preoperative first-line systemic chemotherapy with FOLFOX or FOLFIRI with or without bevacizumab [2]. In our experience with 108 combined liver resections and CRS/HIPEC, all patients with HI due to colorectal or HGA adenocarcinoma received first-line chemotherapy prior to referral. In addition, 31% received second-line chemotherapy, and 13% received third-line chemotherapy prior to CRS/HIPEC [2]. In a study by Berger et al., 56.6% of patients undergoing liver resection with CRS/HIPEC for a variety of primary peritoneal involvement received at least one line of preoperative systemic chemotherapy [1].

Operative Technique and Findings

The goal of CRS/HIPEC, with or without HI, is to remove all gross disease. At our institution, we start with a midline laparotomy incision and proceed to quantify the distribution of disease using the peritoneal carcinomatosis index (PCI) [12]. We perform a routine supracolic omentectomy and resection of the primary if not previously completed. Peritoneal stripping and resection of intra-abdominal organs are performed only as indicated by presence of visible disease [13]. Liver resections range from superficial liver capsule stripping to anatomic resection based on the extent of disease. HI is defined as superficial for cases in which HI is not invading Glisson's capsule, or parenchymal for cases with parenchymal invasion. Parenchymal invasion can occur via hematogenous spread identified on preoperative CT scan or through direct invasion from intraperitoneal dissemination [2]. Hemostasis of raw liver surface is achieved with electrocautery or argon beam coagulation. Although several chemotherapeutic agents are used, most patients receive Mitomycin C using a closed abdomen technique [13]. Other chemotherapeutic agents are used based on primary tumor and previous systemic therapy.

In our series of CRS/HIPEC performed between 1991 and 2013, 108 of 1067 (10.1%) CRS/HIPEC procedures included a liver resection, and this represent one of the largest series of published combined liver resections and CRS/HIPEC [2]. The majority of HI was due to a colorectal primary (39.0%), followed by appendiceal (32.9%), mesothelioma (4.9%), ovarian (4.9%), and gastric (2.4%). Other primaries represented 15.9% of HI. Of the liver resections performed, 89.9% ($N = 97$) were subsegmental resections; more than one liver resection was performed in 28.7% of cases ($N = 31$). Parenchymal involvement was found in 22.2%

of patients (N = 24), and the mean volume of parenchyma resected was 87.3 cm^3 [2]. Patients with colorectal primaries were more likely to have parenchymal disease compared to patients with appendiceal primaries (37.5% versus 6.7%, respectively; $p < 0.001$) [2]. All of the patients with parenchymal disease with an appendiceal primary were high-grade lesions; low-grade appendiceal (LGA) lesions were only caused superficial disease confined to the liver capsule.

In a similar study by Berger et al., 269 CRS/HIPEC were performed at a single institution, with 103 procedures including a liver resection (38.3%) [1]. A similar distribution of primaries was found compared to our study, but more parenchymal resections were performed (44.7%, N = 46). In their series, they performed 31 subsegmental resections, 10 segmentectomies, 2 right hepatectomies, 2 central hepatectomies, and 1 left hepatectomy [1]. Likewise, Saxena and colleagues performed 936 CRS/HIPEC procedures, with 132 (14%) including liver resection [14]. Similar to Berger et al., 54% of liver resections had intra-parenchymal metastases with a wide variety of primaries.

Multiple other smaller series have similar resection profiles but only include patients with colorectal primaries [4, 6, 15–19], so a distinction between superficial liver capsule stripping and parenchymal resection is not drawn. Several studies include radiofrequency ablation (RFA) and cryoablation as an adjunct to or in place of liver resection [6, 17–20], so results have to be interpreted with caution, as RFA alone carries a different complication profile than liver resection.

Outcomes

Feasibility and survival from an early series of liver resection and CRS with intraperitoneal chemotherapy (IPIC) were reported by Elias et al. [21] They studied 12 patients with HI due to multiple primaries, 9 patients of which underwent major hepatectomy in addition to CRS. All patients underwent IPIC for 5 days postoperatively. There were no perioperative deaths, and morbidity was largely attributed to transient bile leaks (33%). At 14-month median follow-up, there was no recurrent disease reported, leading the authors to conclude that despite the magnitude of both procedures, the combination of liver resection and IPIC was safe in well-selected patients.

In continuation of their work, the same group compared 37 patients with synchronous HI and PD who underwent liver resection and some form of IPIC (early postoperative, intra-operative HIPEC, or combination) with colorectal cancer as the main primary to 61 patients with PD without HI who underwent some form of IPIC [16]. They demonstrated that a PCI of 12 or greater and number of liver metastases (LM) were independent risk factors for poor OS. Median OS was 76 months for patients with a PCI less than 12 and no LM, and 40 months for patients with a PCI less than 12 and 1 or 2 LM. If the PCI was 12 or more, median OS dropped to 21–29 months, regardless of the number of LM. Because the odds ratio for PCI was higher than the odds ratio for presence of LM, Maggiori et al. concluded that the presence of LM was not the most important prognostic factor for OS but rather the PCI itself [16]. They proposed that aggressive surgical resection for patients with HI and PD should be limited to patients with a PCI less than 12 and less than 3 areas of HI. Saxena and colleagues had similar findings [14]. Median OS in patients with 1, 2–3, and ≥4 areas of HI was 37.5, 46.6, and 14.5 months, respectively, and these differences were significant. Moreover, the median OS in patients undergoing liver resection had a steep drop with increasing PCI, with 92.5, 27.4, and 19.7 months OS for PCI ≤ 5, PCI 6–10, and PCI ≥ 11, respectively [14].

Multiple other studies have continued to evaluate the overall morbidity, mortality, and survival of liver resection and CRS/HIPEC. Most are small cohort studies comparing patients with colorectal primaries with HI and PD who underwent liver resection and CRS/HIPEC to patients with PD who underwent CRS/HIPEC. Major complication rates (Clavien-Dindo Grades III and IV) [22] range from 31% to 45% in patients with HI and 11% to 42% in patients without HI, with conflicting results on whether these

differences are significant [4, 6, 14, 18, 20]. Thirty-day mortality was relatively low, ranging from 0% to 7.1% in patients with HI and 0.6% to 8.3% in patients without HI, with no significant difference found in any studies [4, 6, 14, 18–20]. Median OS ranged from 13 to 36.1 months in patients with HI, and from 15.8 to 45.5 months in patients without HI when measured from time of surgery [4–6, 14, 18–20]. Berger et al. reported a median OS of 45.1 months for patients with HI, and 73.5 months without HI, when measured from date of diagnosis [1]. They also separately reported median OS with a HGA primary, demonstrating a median OS of 42.0 months with HI. In those without HI, median OS had not been reached [1]. Overall, however, these ranges can be difficult to interpret due to the wide variability in PCI, HI, type of liver resection, and single institution nature of each study.

A recent study performed by Cloyd et al. examined the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) database to evaluate liver resection and CRS/HIPEC in a nationally representative cohort [3]. Of 1168 patients who underwent CRS/HIPEC, 100 (8.6%) also underwent synchronous liver resection. The most common primary diagnosis was unspecified (65.3%), distantly followed by appendiceal and colorectal. They demonstrated a significantly higher complication rate, longer LOS, and re-operation rate in patients who underwent liver resection with CRS/HIPEC compared to CRS/HIPC alone [3]. As a result, they suggested that patients with HI and PD may therefore benefit from a staged operative approach rather than combined liver resection and CRS/HIPEC [3].

In our own institutional series, we compared 99 patients who underwent 108 liver resections as part of CRS/HIPEC to 957 patients with no HI who underwent CRS/HIPEC with primaries and liver resections as noted above [2]. We found no statistically significant difference in minor (Clavien-Dindo Grades I and II) or major complications between the two groups (Table 16.1), and no significant difference in 30-day mortality was found in patients with or without HI (6.5% vs. 2.8%, $p = 0.07$). Additionally, there were no significant differences in operative time, length of hospital stay, length of intensive care unit stay, or 30-day readmission in patients who underwent liver resection compared to those who did not. Even when stratifying by the type of HI (superficial versus parenchymal) and extent of liver resection (subsegmental versus anatomic), there were no differences in minor complications, major complications, mortality, or 30-day readmission.

Table 16.1 Morbidity and mortality after cases of CRS/HIPEC for patients with or without hepatic involvement and partial hepatectomy

	No hepatic involvement	Hepatic involvement	P-value
	($n = 957$)	($n = 108$)	
Minor morbidity, *n* (%)	342 (35.7)	30 (27.8)	0.11
Major morbidity, *n* (%)	215 (22.5)	20 (18.5)	0.39
30-day mortality, *n* (%)	27 (2.8)	7 (6.5)	0.07
30-day readmission, *n* (%)	354 (37.0)	30 (27.8)	0.07
Operation time, mean (SD) hours	8.5 (3.1)	8.8 (3.2)	0.41
Length of hospital stay, mean (SD) days	14.2 (16.2)	13.6 (16.4)	0.71
Intensive care unit stay, mean (SD) days	3.3 (9.0)	3.5 (7.6)	0.92

SD standard deviation

Median follow-up for patients with HI in our series was 49.4 months and 49.9 months without HI. For patients with LGA primaries, median OS was 42.1 months for patients with HI and 95.5 months for patients without HI ($p = 0.03$) (Fig. 16.1). Median OS for patients with LGA primaries and complete cytoreduction (R0/R1) was not reached, regardless of HI ($p = 0.55$). For patients with colorectal primaries and complete cytoreduction, median OS was 21.2 months for those with HI and 33.6 months without HI ($p = 0.03$) (Fig. 16.2). Regardless of resection status, patients with colorectal primaries with parenchymal HI had no difference in survival compared to those with superficial HI (19.2 versus 21.2 months, $p = 0.97$).

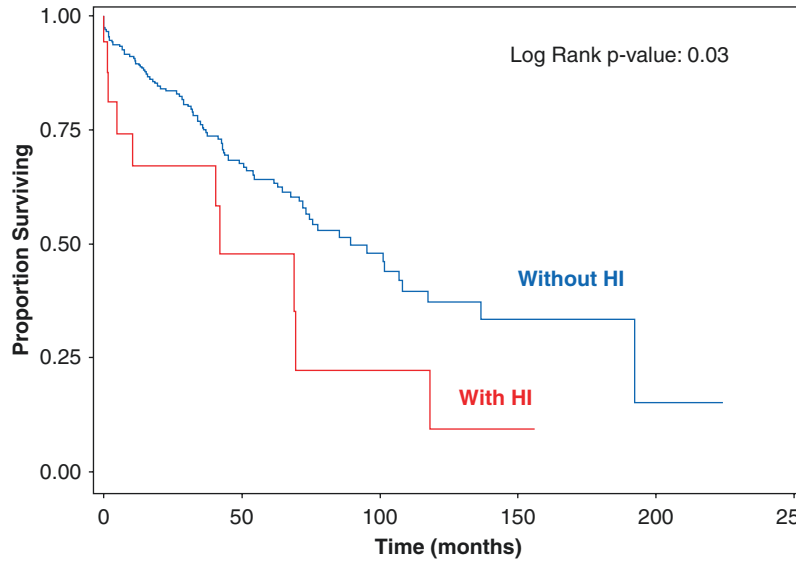

Fig. 16.1 Median overall survival after CRS/HIPEC with and without hepatic involvement (HI) for patients with low-grade appendiceal (LGA) cancer who underwent complete cytoreduction

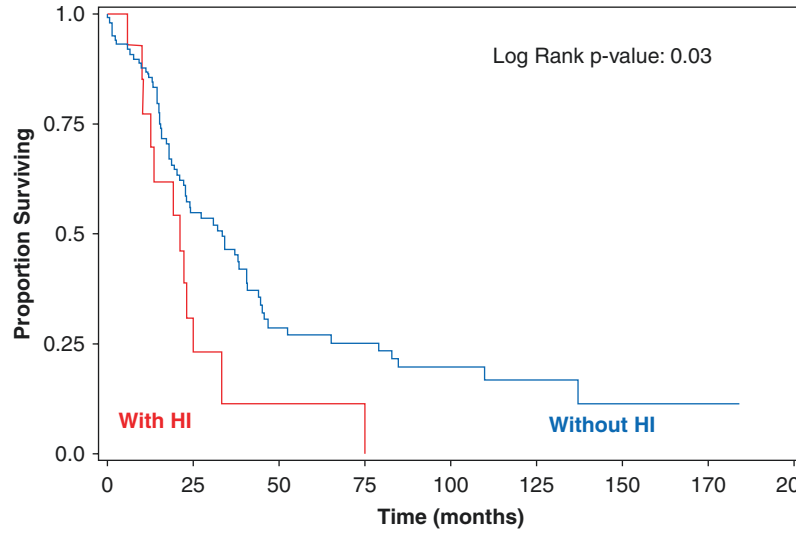

Fig. 16.2 Median overall survival after CRS/HIPEC with and without hepatic involvement (HI) for patients with colorectal cancer who underwent complete cytoreduction

When a complete cytoreduction was obtained, there was no significant difference in recurrence rates for patients with colorectal primaries or LGA primaries based on HI (Table 16.2). Despite similar recurrence rates, however, median time to recurrence was shorter in patients with HI than in those without HI (6.8 versus 12.0 months, $p = 0.001$) (Fig. 16.3). Of those with HI who recurred, only 12.5% had high-grade lesions, but 71.9% had lymph node involvement. For patients with LGA primaries, there was no difference in median time to recurrence with or without HI (118.9 versus 128.3 months, $p = 0.23$). There was no difference in site of recurrence (liver, peritoneal, or extra-abdominal) for colorectal primaries or LGA primaries regardless of HI (Table 16.2).

Discussion

Surgical management of patients with synchronous HI and PD remains controversial, with the majority of experience stemming from single institution studies [1, 2, 4–7, 14, 16, 18–20].

Table 16.2 Disease recurrence after complete CRS/HIPEC

	No hepatic involvement	Hepatic involvement	P-value
	(*n* = 433)	(*n* = 37)	
Recurrence, n/N (%)			
Colorectal	57/107 (53.3)	11/17 (64.7)	0.44
Low-grade appendix	20/118 (16.9)	2/5 (40.0)	0.22
Median time to recurrence, months			
Colorectal	12.0	6.8	0.001
Low-grade appendix	128.3	118.9	0.23
Site of recurrence, n/N (% of recurrence)			
Liver			
Colorectal	22/57 (38.6)	2/11 (18.2)	0.30
Low-grade appendix	6/20 (30.0)	1/2 (50.0)	1.00
Peritoneum			
Colorectal	21/57 (36.8)	5/11 (45.5)	0.74
Low-grade appendix	13/20 (65.0)	1/2 (50.0)	1
Extra-abdominal			
Colorectal	14/57 (24.6)	4/11 (36.4)	0.46
Low-grade appendix	1/20 (5.0)	–	1

Its study can be challenging due to the uncommon nature of the disease process, in addition to the difficulties in detecting PD on imaging. Moreover, both HI and PD can present with a diverse set of disease distribution, with small lesions that are unresectable and large burdens of disease that can be completely removed, making quantifying and comparing patients additionally complex. Most studies also include a variety of primaries with differing biologic machinery and methods of dissemination.

Based on our institutional data and work by others, we regard liver resection as part of CRS/HIPEC as another form of metastasectomy that is safe and feasible in well-selected patients. CRS/HIPEC carries a known complication rate of 25–41% [23], and our study and others found major morbidity rates equal to or less than this even with the inclusion of liver resection. No studies have demonstrated a statistically significant increase in 30-day mortality in patients undergoing liver resection with CRS/HIPEC, although OS is dependent on type of primary, PCI, and completeness of cytoreduction.

Not all HI with PD is equal. HI from LGA primaries is significantly different from that of colorectal primaries. Patients with LGA primaries often present with a large volume of disease

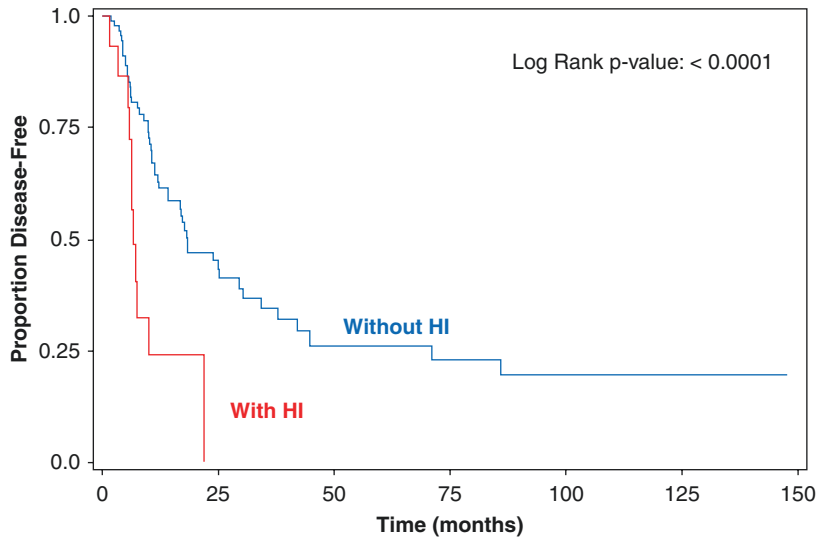

Fig. 16.3 Median disease-free survival for patients with colorectal cancer after CRS/HIPEC with complete cytoreduction. HI hepatic involvement

involving the liver capsule, but this represents true peritoneal surface disease, rarely invades the parenchyma and has no effect on DFS or OS after a complete cytoreduction. Thus, for LGA, HI may function as a marker of greater disease volume. When incomplete cytoreductions were included our analysis, the decreased survival observed likely reflected the effect of residual peritoneal surface disease on survival, and not the effect of the HI itself. In LGA primaries, superficial HI alone should not be considered a contraindication to resection.

On the contrary, colorectal disease is typically parenchymal and indicates aggressive biologic behavior affecting DFS and OS, even with a complete cytoreduction. Additionally, 36% of patients will develop extra-abdominal systemic failure [2], and a PCI of 12 or greater, or 3 or more areas of HI with a colorectal primary predict poor OS [16]. Therefore, in patients with colorectal primaries, and similarly HGA lesions, we perform liver resection and CRS/HIPEC only in patients who receive upfront systemic chemotherapy, have no evidence of progression of disease on repeat imaging, and who have a low volume of resectable disease. In these cases, CRS functions as any other metastasectomy, while any role that HIPEC may have is probably related to controlling local recurrence within the peritoneal cavity.

With modern systemic chemotherapy resulting in improved survival outcomes, it is tempting to compare OS of CRS/HIPEC to systemic chemotherapy alone; however, this is not an accurate comparison. The survival benefit provided by CRS/HIPEC and liver resection is not in lieu of that provided by systemic chemotherapy, but is additive to it. A more appropriate comparison could be drawn between liver resection with CRS/HIPEC and second- or third-line chemotherapy, where median survival for second-line chemotherapy is 10–14 months, and for third-line is less than 3 months [24–26], as compared to the 13–35 months achievable through liver resection and CRS/HIPEC.

Due to the relative magnitude of both procedures and high complication profile, previous studies have cautioned against simultaneous resection or advocated for a staged approach with large resections [3, 5]. Recently, Cloyd et al. have proposed a staged approach to resection, as in colorectal cancer, due to high postoperative morbidity, increased operative times, and longer LOS in patients with HI compared to patients who undergo CRS/HIPC without liver resection [3]. However, a comparison of synchronous resection and staged resection has never been completed. Additionally, this study included a heterogenous cohort, with unknown PCIs and the majority of patients with an unknown primary. As PCI was unknown, increased operative time, LOS, and morbidity may be related to the extent of cytoreductive surgery, rather than liver resection itself. Moreover, while a staged approach may be possible for a small subset of colorectal primaries, for LGA primaries where the liver disease is superficial, a staged operative approach would be contraindicated.

Conclusions

Synchronous HI and PD is not an absolute contraindication to CRS/HIPEC in appropriately selected patients. In patients with LGA primaries, HI is generally superficial and functions as a marker for greater volume of disease, rather than contraindication to resection. In patients with colorectal or HGA primaries, HI is associated with decreased DFS and OS, but with the addition of preoperative systemic chemotherapy, a meaningful survival benefit can still be achieved with CRS/HIPEC. In our opinion, this benefit is predominantly derived from surgical resection, while HIPEC may have an effect in delaying local recurrence in the peritoneal cavity. In all colorectal cancer cases, CRS/HIPEC should not be offered when a complete macroscopic cytoreduction cannot be achieved.

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Peritoneal Perfusion Techniques

17

Yaniv Berger, Harveshp Mogal, and Kiran Turaga

The use of intraperitoneal therapy was described as early as the eighteenth century, when English surgeon Christopher Warrick injected a mixture of water and wine into the peritoneal cavity of a woman suffering from intractable ascites [1]. In 1948, Karnofsky and colleagues used nitrogen mustard for palliative treatment of carcinomatous ascites. Weissberger reported the treatment results of intraperitoneal nitrogen mustard in patients with ovarian cancer in 1956. In 1978, Dedrick and colleagues studied the pharmacokinetic properties of intraperitoneal chemotherapy and discovered that certain cytotoxic drugs can penetrate 1–3 mm into tumor nodules. In the late 1970s, Spratt et al. created a model of hyperthermic intraperitoneal chemotherapy (HIPEC) in dogs and later performed the first HIPEC procedure in a human patient with pseudomyxoma peritonei [2]. Surgical and technical aspects associated with cytoreductive surgery (CRS) and delivery of intraperitoneal chemotherapy were further developed by Sugarbaker in the 1990s.

Over the past 3 decades, conventional intraperitoneal use of chemotherapy evolved into three different treatment strategies. In one, cytotoxic intraperitoneal agents that exert their effect rapidly are delivered intraoperatively and augmented with hyperthermia (HIPEC). In the second strategy, cytotoxic drugs are delivered throughout the first 4–7 postoperative days under normothermic conditions. This strategy is referred to as early postoperative intraperitoneal chemotherapy (EPIC); EPIC utilizes cell cycle-specific drugs that are maintained within the peritoneal cavity for long periods of time (usually 24 hours) between instillations. A third strategy, long-term bidirectional chemotherapy, combines the administration of intravenous and intraperitoneal chemotherapeutics for a long duration of time (approximately 6 months) [3]. The use of aerosolized chemotherapy is a novel modality of delivery of chemotherapy and is discussed elsewhere in the book.

CRS/HIPEC has become the most popular form of intraperitoneal chemotherapy delivery. This treatment modality has proved to be effective for patients with peritoneal carcinomatosis of gastrointestinal, gynecological, or primary peritoneal origin. The survival benefit associated with CRS/HIPEC has been demonstrated in animal experiments [4] as well as in multiple phase 2 studies and several randomized clinical trials performed in patients with colorectal [5], ovarian [6], and gastric cancers [7]. In the context of CRS/HIPEC, heated intraperitoneal chemotherapy is administered as an adjunct to curative cytoreduction. The rationale behind HIPEC under these circumstances is to expose residual peritoneal metastases of minimal volume (up to 1–3 mm) to

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Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_17

high concentration of regionally delivered heated chemotherapeutic agents. Given that the peritoneal-plasma barrier allows intraperitoneal drug concentrations that are 20–1000 times higher than those measured in the plasma [8], selective locoregional cytotoxicity can be achieved with minimal effect on systemic toxicity.

The role of cytoreduction is to completely resect macroscopic metastases and to lyse intra-abdominal adhesions in order to allow adequate distribution of the perfusate. HIPEC may be delivered by two main techniques—open vs. closed. The perfusion follows cytoreduction, which may include different peritonectomy procedures [9, 10] as well as resection of solid and tubular gastrointestinal organs, and traditionally before gastrointestinal anastomoses are created. This locoregional treatment requires a device that circulates the perfusate while maintaining stable high temperature. In order to achieve target tissue cytotoxic goals, and at the same time to prevent hyperthermia- or drug-associated morbidity and to ensure safety for the surgical team, several components should be precisely coordinated during HIPEC delivery, including flow, temperature, volume, and composition of perfusate. This chapter is aimed to review common technical aspects related to HIPEC delivery. Other forms of intraperitoneal drug delivery will also be discussed.

Rationale of Hyperthermia

Hyperthermia exerts its effects by several mechanisms. It has been known for many decades that hyperthermia has a direct cytotoxic effect specific to cancer cells. In modern medicine, early reports of regression of advanced malignancies treated with hyperthermia appeared in the nineteenth century. In the beginning of the twentieth century, localized hyperthermia was applied to treat cervical, uterine, and penile cancers [11]. The earliest experiment that documented the selective sensitivity of malignant cells to hyperthermia was performed by Lambert in 1912. This was followed by many other in-vivo studies. In 1963, Crile discovered that heating melanoma cells to 44 °C destroyed a high proportion of the tumor without affecting healthy tissues in rats [12]. Giovanella et al. have shown that hyperthermia has significantly greater lethal effect on colon cancer cells than on nonneoplastic intestinal cells [13]. The selective sensitivity of malignant cells to hyperthermia is attributable to cellular and molecular alterations that include selective induction of lysosomes, changes in microcirculation blood flow, inhibition of oxidative metabolism, acidic tumor microenvironment, and inhibition of RNA synthesis [11]. Nevertheless, given the fact that modern intraperitoneal chemotherapy uses moderate hyperthermia (less than 42.5 °C) for a relatively short duration of time, the anticancer effect attributable to the direct cytotoxicity of hyperthermia alone is not completely understood.

A second mechanism is the synergism between hyperthermia and certain chemotherapeutic drugs, such as mitomycin C, oxaliplatin, cisplatin, doxorubicin, melphalan, and gemcitabine [14]. Urano et al. have studied the thermal enhancement of multiple cytotoxic drugs in a mouse model and found that some drugs are markedly augmented in cytotoxicity by hyperthermia (Fig. 17.1) [15]. Balrogie et al. reported enhancement of drug-induced cell kill with moderate hyperthermia in a colon cancer cell line using cisplatin or mitomycin C [11]. Further in-vivo studies on the timing of hyperthermia have shown that heat and chemotherapy should be given together to show an effect [3]. Several mechanisms have been proposed to explain the interaction between hyperthermia and chemotherapy agents, including cell membrane damage by hyperthermia resulting in increased drug uptake, alteration of cellular metabolism, changes in drug pharmacokinetics, vascular effects (increased blood flow, vascular permeability, and vasodilatation), and inhibition of repair mechanisms.

A third mechanism by which hyperthermia exerts its effects is the improvement of drug tissue penetration [16]. Jacquet et al. have studied

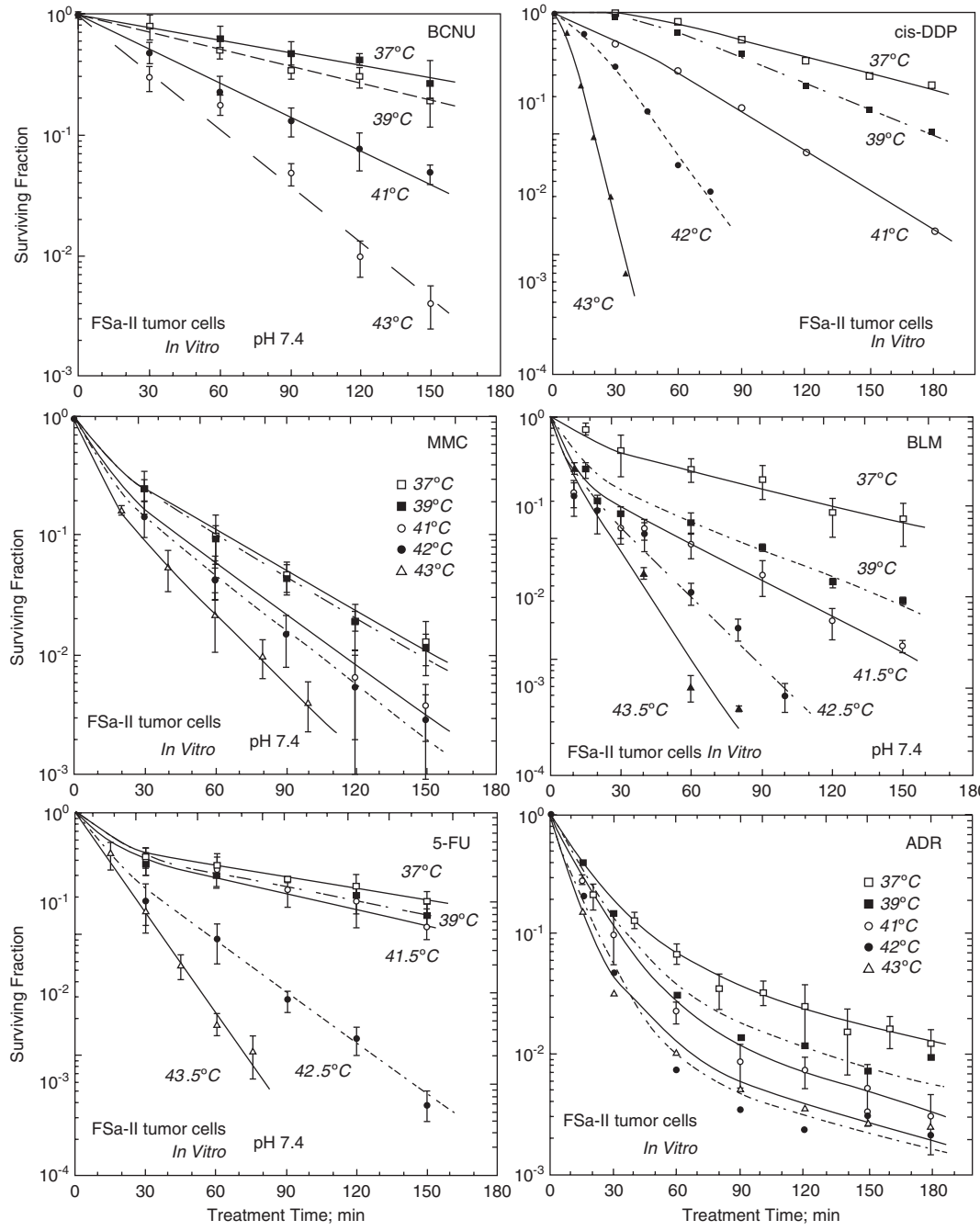

Fig. 17.1 Cell survival curves for mouse fibrosarcoma tumor cells treated with chemotherapeutic agents in vitro at various temperatures. Cell survivals were plotted as a function of treatment time of the agent. Drugs are indicated in each panel by the following abbreviations: BCNU, 1,3bis(2-chloroethyl)-N-nitrosourea; cis-DDP, cis-diamminedichloroplatinum; MMC, mitomycin; BLM, bleomycin; 5-FU, 5-fluorouracil; ADR, Adriamycin. (Adapted from: Urano et al. [15]; used with permission)

the tissue distribution of intraperitoneal doxorubicin in a rodent model and found that hyperthermia significantly increased doxorubicin tissue concentrations in different intra-abdominal organs [17]. Hyperthermia also induces immunomodulatory processes that improve antitumor immune responses, which include the generation of heat shock proteins, activation of antigen-presenting cells, and trafficking of lymphocytes [18].

Despite the above-mentioned potential benefits of hyperthermia, there is currently insufficient clinical evidence to support hyperthermic rather than normothermic perfusion. Human clinical trials are lacking and animal studies have generated conflicting results: in the influential study by Klaver et al. application of hyperthermia did not have a beneficial effect on survival when compared with normothermic drug delivery [4]. Conversely, other animal studies have shown that hyperthermia enhances diffusion in the peritoneum and other abdominal organs and reduces the extent and severity of peritoneal dissemination [19].

Chemotherapeutic Drugs

The effectiveness of HIPEC after cytoreduction is dependent on the presence of chemotherapeutic drugs in the perfusate. Klaver and colleagues have evaluated the necessity of the separate elements (hyperthermia and chemotherapy) of HIPEC in a rat model of colorectal peritoneal metastasis. Median survival in rats treated with intraperitoneal mitomycin C was significantly longer than those treated with CRS alone. In addition, the rats treated with chemoperfusion showed a lower tumor burden at autopsy [4].

Common chemotherapeutic agents in use are presented in Table 17.1. Although standard doses have been defined for HIPEC drugs, institutional protocols vary in the type and combination of drugs used, as well as in other perfusion parameters that modify pharmacokinetics. Nevertheless, some consensus guidelines have been established for colorectal cancer [20]. An ideal HIPEC drug should have proven cytotoxic efficacy and should be cell cycle-nonspecific, heat-synergistic, water soluble, and of high molecular weight in order to

Table 17.1 Properties of cytotoxic agents used during intraperitoneal chemotherapy

Drug	Molecular Weight (Daltons)	Intraperitoneal dose (mg/m^2)	Area under concentration-time curve ratio[a]	Drug Penetration distance	Thermal enhancement
Alkylating agents					
Mitomycin C	334.3	35	10–23.5	2 mm	+
Platinum compounds					
Cisplatin	300.1	90–250	13–21	1–3 mm	+
Carboplatin	371.3	350–800	1.9–5.3	0.5 mm	+
Oxaliplatin	397.3	460	3.5	1–2 mm	+
Antimicrotubule agents					
Paclitaxel	853.9	20–175	n/a	More than 80 cell layers	Not studied
Docetaxel	861.9	40–156	207	n/a	+
Topoisomerase interactive agents					
Mitoxantrone	517.4	28	15.2	5–6 cell layers	±
Doxorubicin	543.5	60–75	162	4–6 cell layers	+
Antimetabolites					
5-Fluorouracil	130.1	650	n/a	0.2 mm	–

From: Ceelen and Flessner [1]; used with permission

[a]Only data referring to clinical studies with hyperthermic chemoperfusion + and – refer to observed (or not) thermal enhancement of efficacy. Abbreviation: *n/a* not available

maintain favorable peritoneum/plasma concentration. Recently, protocols that combine concurrent administration of HIPEC with intravenous chemotherapy are gaining popularity; this is beneficial when the combination of agents has a synergistic effect on diffusion gradient. Repeated dosing of the chemotherapy agent has been used with mitomycin as another strategy to increase the retention of the intraperitoneal drug during chemoperfusion.

Generation of Hyperthermia and Flow

The synergism between hyperthermia and chemotherapeutic agents starts at a temperature of 39 °C and increases linearly as temperature raises, as shown in In-Vitro studies [21]; however, bowel tolerance to heat limits the maximum temperature applied during HIPEC. Shimizu and colleagues have studied the effect of local hyperthermia on the bowel in a rat model and found that treatment at 44 °C applied to the bowel was safe in terms of bowel integrity and healing of intestinal anastomoses, whereas treatment at 45 °C or 46 °C resulted in mortality rate of 90% and 100%, respectively [22]. The generalizability of this observation in animal models and the impact of longer duration of hyperthermia on bowel morbidity remain unclear. Retrospective studies in humans have shown that intra-abdominal temperatures above 42 °C [23] as well as high core body temperature [24] correlate with higher complication rate.

In order to generate hyperthermia, several proprietary perfusion systems have been developed and are commercially available [14]. These systems utilize closed-circuit pumps that deliver heated perfusate into the abdomen through inflow catheters with drainage being accomplished via outflow catheters. A heat exchanger that uses either electromagnetic induction or plate-heated water baths keeps steady hyperthermia of the inflow perfusate that results in average intraperitoneal temperatures of 41–43 °C. The temperature of the inflow solution is usually kept higher (44–48 °C) to allow for inadvertent radiant heat loss between the pump and the patient, with the goal of generating an outflow temperature between 40 °C and 42 °C [8, 16, 25–27]. The outflow catheters drain to a reservoir, where the perfusate can be collected in case of need. Temperature of the peritoneal cavity is measured via probes placed either directly in the peritoneum or in the outflow cannulas. During perfusion, core body temperature is measured via an esophageal temperature probe. Some groups advocate precooling of the patient by active measures such as cooling blankets in order to achieve core body temperatures of 34–35 °C before HIPEC [26], especially in procedures that involve prolonged duration of hyperthermia.

There is a general consensus among surgical oncologists that the desired level of intra-abdominal hyperthermia during HIPEC is 41–43 °C. However, other parameters such as flow rate, duration of perfusion, type of carrier solution, and chemotherapeutic drug dose and combination have not yet been standardized. While animal models have demonstrated the association between higher flow rates and favorable plasma/peritoneum AUC, whether this translates directly to improved efficacy of peritoneal perfusion in humans is unknown. Another finding from animal models is that higher flow rate during HIPEC leads to rapid achievement and maintenance of goal peritoneal temperatures [28]. The desired flow rates during HIPEC are 600–1500 mL/min [27].

Volume, Carrier Solution, and Duration

The volume of the carrier solution affects drug concentration and hence may influence the absorption of the drug from peritoneum and injured tissues [25]. While 3 L has been suggested as standard based on consensus guidelines for colorectal cancer, some experts argue that the volume of the carrier solution should be

adjusted based on body surface area especially in the open technique, with a recommended range between 1.5 L/m^2 and 2 L/m^2 [25, 29]. Elias et al. have shown that a volume increase from 2 L/m^2 to 2.5 L/m^2 resulted in a dramatic decrease in oxaliplatin concentration and absorption in open perfusions [25]. Most closed perfusions utilize 2–4 L of carrier solution. In cases where bicavitary (peritoneal and pleural) chemoperfusion needs to be performed, the perfusate volume should be increased to 4.5 L [27]. Cytoreductive procedures that result in a breach of the natural boundaries of the peritoneal space, such as total gastrectomy with resultant opening up of the mediastinal space, abdominoperineal resection, or hysterectomy with exposure of the peritoneum to the exterior, should be followed by appropriate restoration of the peritoneal space so as to minimize loss of volume during chemoperfusion. This would involve performing the esophago-jejunal anastomosis, closure of the perineum and vaginal cuff prior to perfusion so as to avoid loss of perfusate volume and inadequate perfusion. Similarly, when resection of a stoma site or a major portion of the abdominal wall is performed, temporary closure of the defect should be achieved either by direct approximation of the skin, use of adhesive barriers (Ioban or Tegaderm), or placing outflow cannulas through the defect with subsequent cinching around the cannula to minimize volume loss. Alternatively, conversion from a closed to an open technique may be considered in situations where adequate temporary closure cannot be obtained [27].

Several carrier solutions are in clinical use for chemoperfusion, and type may vary according to institutional protocols. Most teams use isotonic perfusate such as lactated ringers or 1.5% peritoneal dialysate. The downside of isotonic solutions is the inability to maintain a prolonged high intraperitoneal volume [21]. In addition, normal saline can cause hyperchloremic acidosis. Hypotonic carriers have shown promising results in in-vitro experiments. However, Elias et al. have demonstrated in a human pharmacokinetic study that hypotonic carriers did not increase tumor penetration of oxaliplatin but were associated with a high incidence of peritoneal bleeding and thrombocytopenia [30]. Hypertonic solutions allow slower clearance of intraperitoneal fluid. In an animal model, Pestieau et al. demonstrated that by using hypertonic or high molecular carrier solution, the exposure of intraperitoneal cancer cells is prolonged and drug availability at the peritoneal surface is increased [31]. The main drawback of hypertonic solutions is the fluid shift into the peritoneal cavity. Oxaliplatin was thought to be unstable in chloride-containing solutions, and therefore was delivered routinely with 5% dextrose solution. Given that glucose-containing solutions may lead to hyperglycemia and electrolyte disturbances, perioperative glucose levels should be carefully monitored when using 5% dextrose or dextrose-containing peritoneal dialysate. Recently, chloride-containing carrier solutions have been found to be safe and effective as a medium for oxaliplatin [32].

The duration of HIPEC may vary from 30 min to 120 min, depending on institutional protocol, pharmacokinetics of the chemotherapeutic agent, and some patient-related factors such as cell counts and renal function. HIPEC procedures administered with oxaliplatin and irinotecan (30–60 minutes) are usually shorter than those administered with mitomycin C (60–120 minutes).

Delivery Techniques

The Open Technique

Experts believe that there is not enough evidence in the literature that supports the superiority of one perfusion technique over the others in terms of outcome, morbidity, and safety to the operating room personnel [26].

The open technique is sometimes referred to as the “Coliseum” technique, and is mainly

popular in cancer centers in Europe and Asia. In the open technique, following cytoreduction a long running monofilament suture is used to secure the skin of the laparotomy incision to an elevated self-retaining retractor ring. A plastic sheet with a slit in its center is incorporated into the suture to cover the laparotomy opening. This arrangement suspends the abdominal wall creating a coliseum-like structure (Fig. 17.2). The slit enables the introduction of a double-gloved hand into the solution and stirring of the perfusate during HIPEC, allowing increased exposure of organs and peritoneal surfaces to heated drug as well as gentle manipulation of viscera by the surgeon. Inflow and outflow catheters are placed through the lateral abdominal wall. A smoke evacuator is placed beneath the plastic cover in order to aspirate potential drug aerosol. At the end of perfusion, the fluid is evacuated, the skin is reopened, and retractors are placed again. Gastrointestinal anastomoses are then performed and closure of the abdominal wall takes place.

The main advantage of the open technique is the effective distribution of heated chemotherapy throughout the abdominal cavity, although oncological benefit has not been proven in trials. Disadvantages include potential exposure of the surgical team to chemotherapy (by direct contact or inhalation), accelerated heat loss of the HIPEC perfusate through the laparotomy wound, and the time needed to construct the "Coliseum." Although the open technique was proven to be safe for operative room personnel [33], safety guidelines are needed that include the use of disposable sheets and drapes, restriction of personnel inside the operating room and wearing protective barrier garments (protective disposable gown, shoe covers, eye wear, high power filtration mask, and non-permeable double gloves) [34]. Open technique has largely been abandoned across centers in the US given that there is no data for its superiority over the closed technique, relatively complex set-up and potential concerns with repeated chemotherapeutic exposure of operating room personnel during chemoperfusion.

A technique of using peritoneal cavity expander (PCE), described by Fujimura et al. [35], is a modification of the open technique. The PCE, which was specifically developed for the treatment of gastric peritoneal carcinomatosis, is an acrylic cylinder with built-in inflow and outflow catheters. During HIPEC delivery, the PCE allows the bowel to float within the perfusate-filled cylinder and more uniform heat distribution is achieved compared with the closed technique. Disadvantages of this technique include oozing around the wound, insufficient exposure of parietal peritoneum to perfusate, and the relative complexity of this apparatus [8, 26].

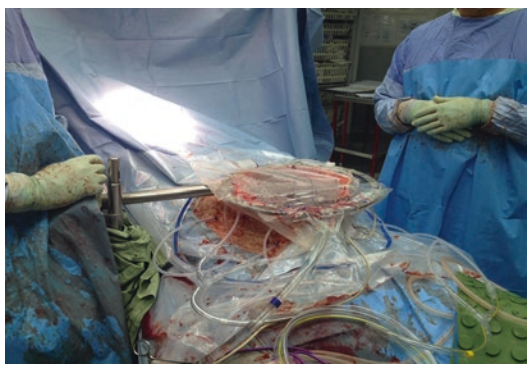

Fig. 17.2 The open (coliseum) technique

The Closed Technique

The closed technique (Fig. 17.3) is employed in the majority of US centers performing HIPEC. After cytoreduction, inflow and outflow catheters are introduced into the abdominal cavity directly through the midline incision or alternatively, through separate incisions in the lateral abdominal wall. The skin alone or all layers of the laparotomy incision (in case gastrointestinal anastomoses have already been performed) are then sutured to ensure a watertight closure. The abdomen is then filled with

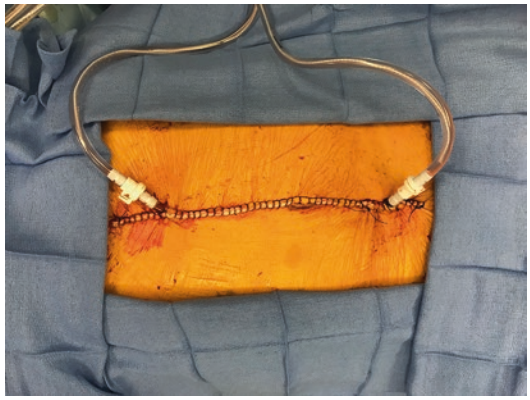

Fig. 17.3 The closed technique

the carrier solution and the perfusion cycle begins. Once goal temperature is achieved, the drugs of choice are added to the reservoir. During the procedure, the abdominal wall may be gently agitated in order to optimize heat and drug distribution.

Advantages of the closed technique include minimal heat loss that enables rapid achievement and easier maintenance of hyperthermia, better protection of the surgical team from chemotherapy exposure, sparing of time (mainly if definitive closure of the abdominal wall is performed before perfusion) and the theoretical potential of improved drug penetration secondary to increased intra-abdominal pressure; pharmacokinetic studies in rats have demonstrated that higher intra-abdominal pressure increases tissue uptake of doxorubicin [36] and cisplatin [37]. Disadvantages include lack of uniform drug and heat distribution that may result in dangerous pooling of overheated chemotherapy in dependent abdominopelvic regions on one hand, and insufficient treatment of other regions on the other hand [29, 38]. Non-uniform distribution of perfusate was demonstrated in methylene blue studies as well as thermal homogeneity studies [38]. In addition, the closed technique obviates the possibility of continued cytoreduction during perfusion and requires greater troubleshooting expertise [27]. Moreover, the closed technique may be associated with higher blood concentrations of cytotoxic agents leading to myelosuppression [39].

The timing of gastrointestinal reconstruction in patients undergoing CRS/HIPEC is controversial. Traditionally, bowel anastomoses were performed after chemoperfusion to prevent implantation of cancer cells into the anastomoses; however, this oncological benefit remains theoretical. There is also a concern that HIPEC itself may compromise the integrity of anastomosis, although the risk of anastomotic leak was not found to be higher in teams performing their anastomoses before HIPEC [26]. On the other hand, performing bowel reconstruction at the end of HIPEC leads to suboptimal surgical conditions, as the bowel is edematous and the surgical team may be tired. Currently, some cancer centers have adopted the concept of performing gastrointestinal reconstruction prior to HIPEC, which enables definitive closure of all layers of abdominal wall prior to chemoperfusion and facilitates earlier termination of the operation.

Given the fact that HIPEC is a complex procedure involving multiple physical and pharmacokinetic parameters, interruptions in chemoperfusion may occur that occasionally require the assistance of an experienced perfusionist. Common troubleshooting techniques that can be undertaken during HIPEC are presented in Table 17.2.

Laparoscopic HIPEC

Laparoscopic surgery has several roles in the context of HIPEC. Firstly, laparoscopy is sometimes employed at the beginning of cytoreductive surgery or as a separate diagnostic procedure aimed to accurately quantify the intra-abdominal tumor burden and to spare inoperable patients the morbidity associated with a non-therapeutic laparotomy [40]. Secondly, laparoscopy may be used for complete cytoreduction and delivery of HIPEC in selected patients with limited peritoneal disease. In addition, HIPEC may be delivered laparoscopically for prophylactic purposes [41]. Laparoscopic perfusion is a subtype of the closed perfusion, in which inflow and outflow

Table 17.2 Common troubleshooting techniques during chemoperfusion

Issue	Steps
High inline pressures	Check inflow cannulas that could get kinked during positioning. Check the purse-string suture to ensure that it is not occluding the line. Reset and reprime the line. If perfusion already begun, it is possible that viscera might be occluding the tip. In a closed perfusion, attempt to spin the cannulas gently to allow relief of inline pressure. If persistent, might need to stop perfusion
Drop in reservoir volume or loss of volume to abdomen	Check the outflow cannula and confirm that it is not kinked or obstructed from the stitch. In highly mucinous tumors, mucin can occlude the outflow lines or reservoir. This may need to be flushed. If the aforementioned reasons are unlikely then, this error usually occurs when the abdomen is more capacious than the perfusate volume added or if there is a diaphragmatic or perineal opening. This may require interruption of perfusion. Adding volume to the perfusate or reducing the flow rate can counter some of the leaks
Target temperature is not reached	Likely due to malposition of the temperature probes. Measure outflow temperature to confirm heated solution is delivered. Inflow temperature can be increased, but excessive increase could lead to visceral injury.
Systemic hyperthermia above 39 °C	Ensure that bair huggers are placed on ambient rather than off. Maximize the cooling blanket temperature. This can be dropped almost to 40 °F provided there is a cloth barrier between the patient and cooling blanket. Decrease temperature of IV fluids. Ice packs can be used near the head. Reduce temperature of inflow perfusate.
Flow rates not reached	Check inflow and outflow cannulas as outlined earlier. Ensure perfusate volume is adequate, may need to add volume. Very viscous perfusions due to mucin may need change of reservoir filter. May need to interrupt perfusion and use numerous inflow/outflow cannulas.

Adapted from: Turaga [27]. Used with permission

catheters are introduced through the 5–12 mm port sites (Fig. 17.4), or alternatively, through a single port hand-assistance incision.

Laparoscopic HIPEC may be also utilized as a palliative procedure for debilitating malignant ascites. Malignant ascites is common among patients with terminal stages of peritoneal carcinomatosis and may cause severe quality of life impairment. In this patient population, laparoscopic HIPEC may result in control of ascites and symptomatic relief in the majority of cases [42, 43]. This procedure has been described in patients with gastrointestinal, ovarian, and primary peritoneal cancers. Some patients may need repeat procedures to achieve ascites control [44]. In all published studies, only minimal perioperative morbidity was reported.

Neoadjuvant Intraperitoneal and Systemic Chemotherapy (NIPS)

NIPS is a treatment strategy developed by Yonemura and colleagues in order to increase the rate of complete cytoreduction in gastric cancer patients. Patients with overt peritoneal carcinomatosis or positive cytologic examination were included in this protocol, which consisted of administration of normothermic intraperitoneal chemotherapy through a peritoneal port system (introduced under local anesthesia) combined with synchronous infusion of systemic chemotherapy via a peripheral vein. This regimen was repeated weekly for 2–6 cycles, depending on tumor response or the status of peritoneal cytology. Patients who responded to NIPS were offered

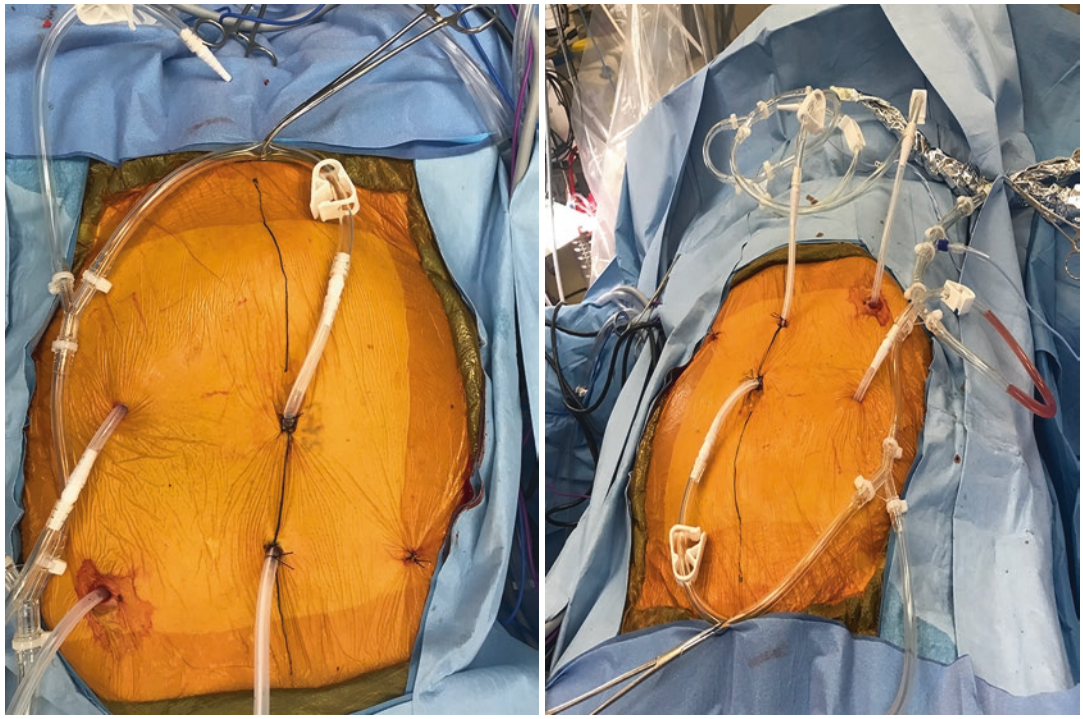

Fig. 17.4 Laparoscopic administration of HIPEC

to undergo laparotomy with cytoreduction [45]. A similar strategy, combining intraperitoneal paclitaxel with oral S-1 and intravenous paclitaxel, was described by Ishigami and colleagues; this neoadjuvant treatment course was repeated every 3 weeks for a median of 4 (2–18) cycles and gastrectomy was performed in responders (64% of the patients). The same regimen of chemotherapy was restarted after surgery [46]. A report by Canbay et al. summarized the experience gained with 194 NIPS procedures; 152 patients who had negative cytology after treatment underwent cytoreduction, of those 102 patients (67.7%) were completely cytoreduced. There was a significant overall survival difference between patients who underwent cytoreduction vs. those who did not—15.8 months vs. 9.7 months, respectively [47].

The reported median overall survival time for patients who underwent complete cytoreduction following NIPS is 20.5–30.5 months [46, 48]. Bidirectional chemotherapy has also been shown to palliate symptomatic ascites in this patient population. Recently, a protocol of neoadjuvant laparoscopic HIPEC with or without NIPS has been described in patients with gastric cancer: patients who underwent two cycles of neoadjuvant laparoscopic HIPEC were found to have significantly lower PCI score at laparotomy [49].

Normothermic Perfusion Techniques

Normothermic intraperitoneal chemotherapy may be delivered in the form of NIPS (discussed earlier), early postoperative intraperitoneal chemotherapy (EPIC), or long-term postoperative intraperitoneal chemotherapy. The advantage of normothermic intraperitoneal chemotherapy, as opposed to HIPEC, is its repeated delivery which allows consistent cytotoxic effect on cancer cells. In addition, the prolonged instillation cycles associated with EPIC allow administration of cell cycle-specific agents.

EPIC is typically administered following cytoreductive surgery on the first or second post-

operative day, for a duration of 4–7 days. The diluted chemotherapeutic agent is administered through operatively placed drains, retained in the abdomen for 23 hours, and then drained for 1 hour prior to re-administration. EPIC protocols have been developed for gastrointestinal malignancies, ovarian cancer, and mesothelioma [50]. The most common used agent for gastrointestinal cancers is 5-FU. This cell cycle-specific agent has a high intraperitoneal/intravenous AUC ratio resulting in approximately 250-fold greater exposure [51]; its disadvantage of short half-life is overcome by the repeated administration.

A comparative animal study by Klaver et al. has shown that both EPIC and HIPEC were effective in prolonging survival in rats when compared to cytoreduction alone [52]. This finding was supported by retrospective clinical studies in which EPIC was found to prolong survival in patients with colorectal [53] and gastric cancer [54] compared to cytoreductive surgery without perioperative intraperitoneal chemotherapy. The addition of EPIC after HIPEC was found to be associated with survival benefit for patients with low-grade appendiceal mucinous neoplasms [55] or appendiceal adenocarcinoma [51] when compared with HIPEC alone. Conversely, other reports suggest that the use of EPIC after HIPEC results in increased morbidity and is unlikely to affect survival outcomes.

Several randomized controlled trials have shown that long-term delivery of intraperitoneal chemotherapy, administered periodically in combination with systemic chemotherapy, significantly improves progression-free and overall survival in patients with small-volume residual ovarian cancer, when compared with systemic therapy alone [56–58]. In addition, long-term intraperitoneal chemotherapy for a duration of 6 months was associated with improved survival in patients with malignant peritoneal mesothelioma [59].

Conclusion

There are several techniques for the delivery of intraperitoneal chemotherapy, prominent among which is the closed technique delivery with potentiating hyperthermia. Ongoing studies regarding components of therapy such as volume, temperature, and carrier fluid might ascertain the most effective combination.

Acknowledgments Joseph Skitzki for his expertise in hyperthermia.

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18 Operative Pearls for Cytoreduction of the Difficult Abdomen and Pelvis

Marc Pocard

Introduction

The recent advance in the treatment of peritoneal metastasis is based on two simple surgical observations: morbidity must be controlled, and complete elimination of mortality is the only acceptable direction for practice; also, surgery must be complete (CC0 resection) with no residual tumor. Achieving complete cytoreductive surgery (CRS) of peritoneal metastasis requires a specific operative strategy [1, 2]. As a specific organ, the peritoneum requires specific surgical skills. Operative pearls for CRS of the difficult abdomen and pelvis are reported in that chapter. One of the difficulties is related to the fact that CC0 resection is difficult to predict.

Prediction of Operative Difficulty

Part of the difficulty could be related to prior surgery. A score has been proposed by Paul Sugarbaker to underline the fact that every prior surgical procedure decreases the rate of success of CC0 cytoreduction [3]. The prior surgical score (PSS) estimates the extent of previous surgical intervention by quantitating surgical dissection within 9 abdominopelvic regions (small bowel is excluded from the PCI abdominal regions). If during prior surgery only 1 region had been dissected, the PSS is at 1. If during prior surgery 2–5 abdominopelvic regions have been dissected, the PSS is 2. If ≥5 of the 9 abdominopelvic regions have been dissected, the PSS is 3. PPS is at 0 if only biopsy was performed by laparoscopy, CT-guided biopsy, or paracentesis with cytology. The PSS is a composite score of all previous surgeries, and by convention, it is additive for all previous surgical procedures in the number of abdominopelvic regions [4]. The construction of the PSS is easy to understand and help the surgeon to anticipate difficulty. The peritoneum is a barrier and must be preserved. If not, peritoneal metastasis can progress and invade the next structure behind the peritoneum: the ureter, diaphragm, or liver pedicle.

Of course, surgeons and radiologist develop many methods to select patients regarding the possibility to perform complete CRS. The group of the MD Anderson Cancer Center at Houston has proposed for an appendix tumor a score based on computed tomography scan findings, which are thought to predict incomplete cytoreduction [5]. Using a similar process, the French RENAPE group published a score that predicts the non-CC0 resectability in case of pseudomyxoma [6]. The thickness of tumor burden can be measured on preoperative multidetector-row computed tomography (MDCT) in five predetermined areas. The MDCT score is the sum of the five measures and is higher in unresectable disease [median 46.2 mm (range 27.9–74.6) vs.

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Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_18

0.0 mm (range 0.0–14.0), $p < 0.001$]. A threshold of 28 mm yields sensitivity, specificity, positive predictive value, and negative predictive value of 94, 81, 81, and 94% in the building cohort and 80, 68, 59, and 85% in the validation cohort, respectively.

Another recent publication focuses on colorectal cancer peritoneal metastases on the MDCT regarding the involvement of the perihepatic region (OR; 3.63, $p = 0.047$) and extensive small bowel involvement (OR; 9.90, $p = 0.019$) to predict non-CC0 possibility [7]. Another recent score was proposed for ovarian cancer using four criteria that were independently associated with incomplete CRS, confirmed by surgery [8]. Interestingly, that score, similar to other scores, uses MDCT, but innovatively, it uses clinical and biological information, including BMI ≥ 30 kg/m2 (adjusted odds ratio [aOR], 3.07; 95% confidence interval [95% CI], 1.0–9.6) and CA125 > 100 IU/L (aOR, 3.99; 95% CI, 1.6–10.1), for prediction of a non-CC0 possibility [8].

All available information is best analyzed in a preoperative meeting bringing together radiologists and surgeons, including sometimes specialist surgeons such as liver surgeons or urologic surgeons. Whatever the specific case, some aspect of the surgery of the peritoneum needs to be controlled by the surgeon in any occasions.

We report next that technical aspect of the peritoneum surgical CRS technique.

To Be Used on Demand

Liver Mobilization Is the Key

Because a majority of CRSs are performed with a midline incision, liver mobilization is specific and requires control of small tumor implants that could be close to the vena cava or behind the segment 1. The strategy is to mobilize the liver from the left lobe to the posterior part of the right lobe, using a strategy close to the anatomist Claude Couinaud's description, based on a circular motion. The first step is to protect the stomach with a compress behind the left lobe touching the diaphragm. Insertion of the Glisson capsule is sectioned from the middle to the insertion of the left lobe. The left lobe is mobilized, and the gastrohepatic ligament is opened to control segment 1 and its posterior part. The posterior part of segment 1 is exposed to treat a small implant that could be on the vena cava or on the diaphragm. The posterior part of the liver pedicle is then palpated. The mobilization goes to the right part of the liver. The insertion of the Glisson capsule is sectioned, and the upper part and the posterior part are sectioned progressively to obtain a complete mobilization of the liver, offering a complete vision of the vena cava. In case of tumor implants, the liver is the only plane to follow. There is nothing on that plane, no viscera, and no tumor. At the end, tumor implants could be resected on the diaphragm or in the abdominal wall, but the liver must be mobilized totally beforehand. Tumor implants could be located at different place on the liver, including any junction with ligament insertion, or any segment limitation—control it meticulously (Figs. 18.1 and 18.2).

Tumor implants can be resected by peritoneal stripping of the undersurface of the right diaphragm. Starting from the midline incision makes stripping easier. The only key for the stripping is the tension put on the peritoneum (Fig. 18.3).

In case of associated liver metastasis, wedge resection is possible. If the metastases are deeper, using thermal ablation with radiofrequency or microwave is a good option. Radiofrequency/

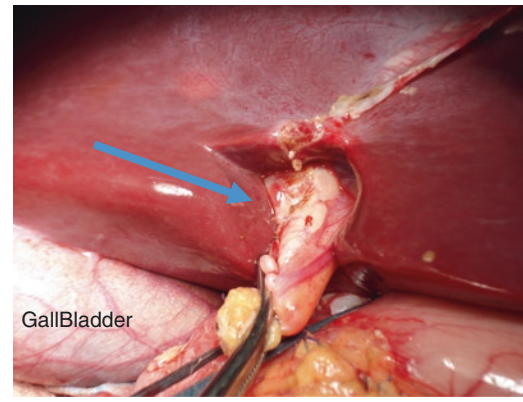

Fig. 18.1 Tumor implants could be located at different place on the liver, including any junction with ligament insertion (blue arrow)

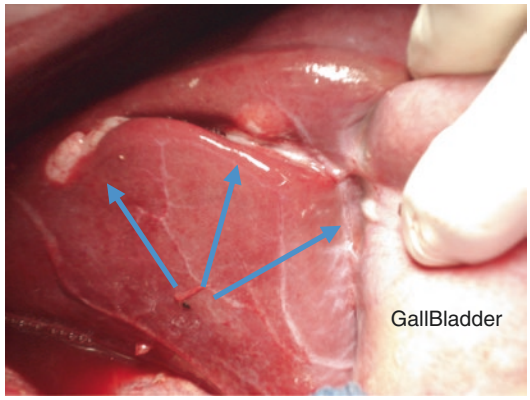

Fig. 18.2 Tumor implants (blue arrows) could be located at different place on the liver, including gallbladder, or any segment limitation—control it meticulously and resect ligaments deep in the liver

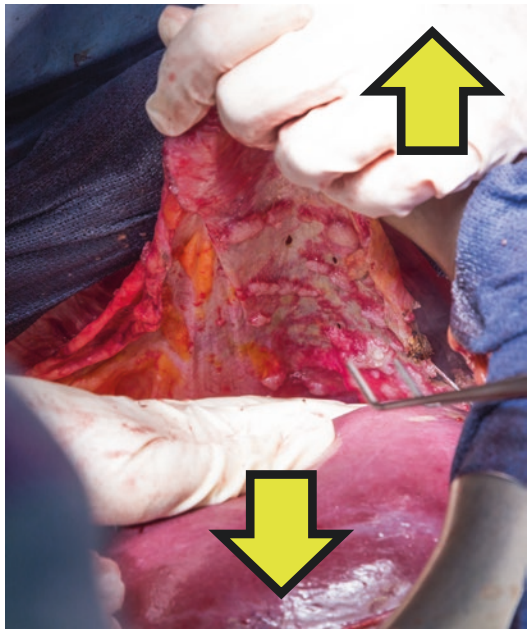

Fig. 18.3 The only key for the stripping is the tension put on the peritoneum

microwave ablation is probably nearly as efficient as surgical resection if (1) the lesion is far away from vascular structures (no temperature decrease induced by the blood flow), (2) the lesion has a large diameter but less than 2.5 centimeters (destruction margins are obtained), and (3) peroperative echography technique is controlled by the surgeon. The point of thermal ablation with radiofrequency is to decrease the risk of bleeding in the postoperative course and to avoid massive liver resection as a parenchyma-saving procedure.

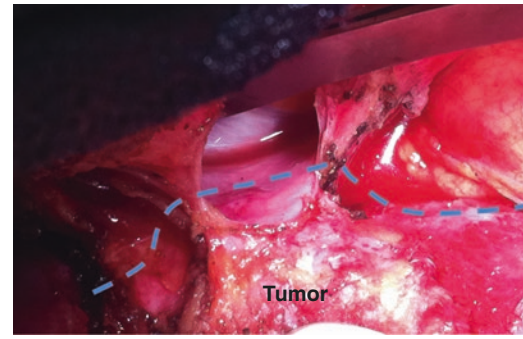

Fig. 18.4 Involvement of the pericardial area. This place had to be resected as proposed in the figure, following the dissection line (blue line)

If the liver surface is covered by tumor implants, different solutions have been proposed to expose the liver plane. The first solution is to destroy by electrocautery (not on coagulation function, but on the highest section possible) with a big ball tip. That dissection requires a smoke vacuum cleaner. The tumor implant destruction is obtained when the surface of the liver becomes soft and smooth. The second solution is a Glisson capsulectomy, which is done with limited incision and a second resection under the capsule [9, 10]. That solution is hemorrhagic but could be controlled with pressure from a wet compress.

If the tumor is invasive, implants may be located in and adherent to the tendinous central portion of the hemidiaphragm. In that situation, the tissue must be resected and the diaphragm opened. Caution must be taken to prevent tumor spillage into the thoracic cavity. This is particularly difficult to control in pseudomyxoma patients. An elliptical excision of the tendinous portion of the diaphragm is required (Fig. 18.4). The defect is closed with interrupted sutures, which must be complete to avoid the liquid going into the chest during the hyperthermic intraperitoneal chemotherapy (HIPEC) procedure. If the resection is more than fifteen square centimeters, it is better to put a mesh (Gore Tex) than to try to close the defect because the result will be a

nonmovable diaphragm that could dramatically decrease the postoperative diaphragm function.

The liver pedicle could be hard to clean. Remember that it is always possible to divide the left and right liver following the umbilical ligament. Involvement of the pericardial area is possible and identified during liver mobilization. This place had to be resected as proposed in Fig. 18.4, following the dissection line. Only a very limited portion of the pericardium could be resected to avoid oncologic limitation.

Left-Angle Colonic Mobilization Is Easy If You Save the Pancreas from Minor Trauma

The left-angle colonic mobilization could be complex because of patient factors (prior surgery, or BMI) or because of the disease. However, that surgery is well known by the surgeon. If difficult, you can start with omentum resection to offer simple access to the posterior part of the stomach. That access is important because it offers a solution to control the peritoneum in front of the tail of the pancreas. The risk of postoperative pancreatic fistula is important and could happen even without major trauma, but the risk increases with HIPEC. If you have any doubt regarding pancreatic trauma, put a drain to provide information in the postoperative course and to offer a drainage solution in case of fistula.

Splenic Resection—Can It Be Avoided?

The left diaphragmatic region is less affected than the right by carcinomatosis implants. However, implants could be present and not simple to identify. The only good reason to perform a splenectomy is hilar involvement that is not resectable because of vessel involvement. The hilum could be affected. In contrast, the localization behind the spleen must be treated, if possible, with complete spleen mobilization and resection without splenectomy. Splenectomy increases the postoperative complication rate [11].

Reconstruction After Ureteral Resection During HIPEC Surgery: Reimplantation with Ureteroneocystostomy Seems Safer than End-to-End Anastomosis

The rate of cases requiring ureteral resection is probably less than 8% [12]. Ureteral resection is necessary in case of specific involvement and must be done if the affected part of the ureter is small. In cases of extensive ureteral involvement, this is general fascia involvement (as in case of gastric carcinomatosis) rather than a tumor peritoneal nodule that pushes on a specific place. In case of fascia involvement, the CRS cannot be completed. On the other hand, a unique tumor nodule can be detected on CT because of a ureter dilatation, even if it is too small to detect by other means (Fig. 18.5). That case must be considered because the oncologic prognosis is better. The last situation is a lymph node involvement on the lateral part of the pelvis that affects the ureter. In that situation, if a lymphadenectomy was performed before (as for ovarian cancer), resection could be impossible without vascular associated resection, for which the oncologic benefit is limited.

In case of ureter resection, an end-to-end suture is possible if the resection is less than 2 or 3 centimeters, but a 22% rate of fistulas in ureteral sutures has been reported [12]. If the ureter affected is below the vessels of the pelvis and no

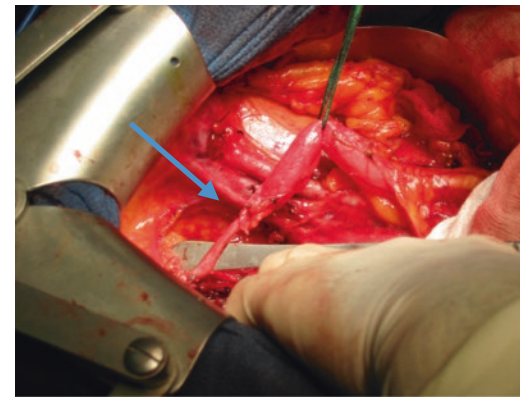

Fig. 18.5 Unique tumor nodule (blue arrow) can be detected on CT because of a ureter dilatation, even if carcinomatosis is too small to be detected by palpation

radiotherapy had been done before, a reimplantation with uretero-neocystostomy is possible with a dissection of the bladder. Comparing the result of the different methods for anastomosis, reimplantation seems to be better, with fewer fistulas [13].

A specific situation is the case where a reimplantation is not possible and end-to-end anastomosis cannot be achieved. If the renal function of the contralateral kidney is good, the diseased kidney could be left in-situ with a ligated ureter. In my experience, if no prior drainage is put on the kidney, the ureter can be closed without doing anything to the kidney. Progressively, the kidney will involute, usually with no pain and no infection, if no drain had been done before. The point of the choice to avoid nephrectomy is to decrease the surgical trauma, decrease tumor implantation risk in a cavity, and have a backup solution in case of renal insufficiency. It is possible to go back with a tube and to perform a renal-to-bladder tube interposition. A subcutaneous pyelovesical bypass is probably better for quality of life than a nephrostomy [14].

Douglas Pouch Resection Without Rectal Resection

The peritoneum of the anterior mid-rectum, just up to the end of the Douglas pouch, is covered by a layer of fat that allows a peritonectomy at this side without the need for rectal resection. To do this, in case of a limited or moderate extent of peritoneal metastasis in the pelvis, a visceral-sparing peritonectomy with the rectum stripped of peritoneum, but left in place with no resection, is possible. It is easier to start with the peritoneum of the top, around the bladder, and up to the ureter and to progress to the Douglas pouch. This maneuver is possible with a cul-de-sac resection even after uterus resection and transection of the posterior part of the vagina. All the peritoneum is stripped, including the peritoneum of the posterior vagina (the most difficult place) as the anterior part of the rectum. This technique is time-consuming, possibly more than a pelvectomy [15], but is organ preserving and affords the best quality of life after (Fig. 18.6).

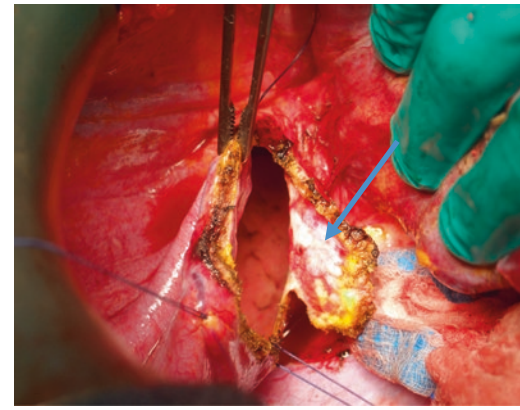

Fig. 18.6 An elliptical excision of the tendinous portion of the diaphragm is required

Inguinal Canal Control: Do Not Forget It

The inguinal canal can keep a peritoneal small nodule isolated for a long time, which can progress after a long non-clinical-detection period. During every laparotomy, the canal should be explored and disease resected. Recurrence does not mean that a new peritoneal dissemination had occurred if the recurrence is on the inguinal canal [16].

To Be Decided Before Cytoreductive Surgery

Unusual Major Associated Procedures: On the Same Surgery Except Liver?

Unusual procedures could be necessary during a cytoreductive surgery because of specific situations and because it is a complex matter to consider a second surgery. Cytoreductive surgery induce always completes liver mobilization and small mesentery mobilization in front of lombo-aortic space. The mobilization of liver structures is the only solution that makes certain that no small nodule exists. It is easy to understand that in case of associated procedures, all must be done during the same operation or many months after. Major liver resection has been done by some

teams but abandoned because of excessive morbidity. In case of secondary liver resection, after CRS and HIPEC, a non-adhesive mesh could be used [17].

In case of associated procedures, such as resection of a massive thrombus on the vena cava, resection or interruption of the vena cava must be performed during the HIPEC. That situation must be anticipated, and a second surgeon expert associated with the surgical team must be called on. The concept of associating an expert surgeon is the only way to control the risk of increasing morbidity, even if you are able to perform the technique.

Total Gastrectomy Is Possible: Hiatal Surgery, May Be?

Total gastrectomy is possible and could be planned in specific situations. Some surgeons consider that in case of major pseudomyxoma, this could be a solution. Some others consider it in case of gastric primary. Usually, gastric resection will be limited. In case of total gastrectomy, some key points are mandatory. The nutritional status of the patient must be well evaluated before surgery and could delay the surgery if it needs to be corrected. Total gastrectomy induces a weight loss of 10 kilograms, whatever the body weight is before.

During surgery, the small bowel mobilization is major, with no mesenteric involvement. In this case of involvement, anastomosis will be quite difficult. At the end of the surgery, abdominal tube drainage is important on the left subdiaphragmatic space, as usual, but more on the duodenum section. In our experience, we have had more fistulas with the duodenum than with the esophagus.

Hiatal surgery could be associated, but the extensive dissection of the inferior mediastinal area could open the pleural cavity. That cavity needs to be closed before the HIPEC. If not identified, the liquid of the HIPEC can go into the pleural space during the procedure and induce specific difficulties for anesthesiology and for the intra-abdominal procedure because the abdomen is empty. In contrast, the opening of the pericardiac area is not complex to manage, the risk of liquid drop is limited, and the opening is always recognized during the procedure (Fig. 18.4).

Pelvectomy: Organize Before to Share Expertise

Pelvectomy is possible and can be performed if you control morbidity and consider the oncological situation controlled. If a bladder resection is necessary, as in the case of involvement of the junction of the two ureters, a reconstruction is necessary. Case reports have been published, and there is no specificity for the reconstruction. Regardless of the association of a second expert surgeon, at that time a urologist is mandatory to control the morbidity as much as possible. The same idea could be implemented if you have a complete colonic and rectal resection and you need to perform an ileo-anal anastomosis. If you are not familiar with that surgery, a second expert in colorectal surgery is mandatory.

In the case of posterior pelvectomy or rectal resection with an R1 resection requiring postoperative radiotherapy, a solution could be to place a pelvic prosthesis to empty the pelvis. The concept is to exclude the pelvis from the risk of irradiation to the small bowel. It is possible to perform the HIPEC procedure with the prosthesis technique described before [18].

Abdominal Wall Resection: Use Biological Mesh

Abdominal wall resection could be important in the case of scar involvement (Fig. 18.7). A classical situation is the resection of a cancer of the appendix during an emergency procedure. If the surgeon did not recognize the cancer risk during the initial surgery, the risk of tumor deposition on the lateral incision is high. Development of the tumor is progressive and not painful at the beginning. The CT scan could interpret the tumor as an inflammatory process after the surgery. At the end, extended involvement of the abdominal wall requires extended muscle resection, but the skin

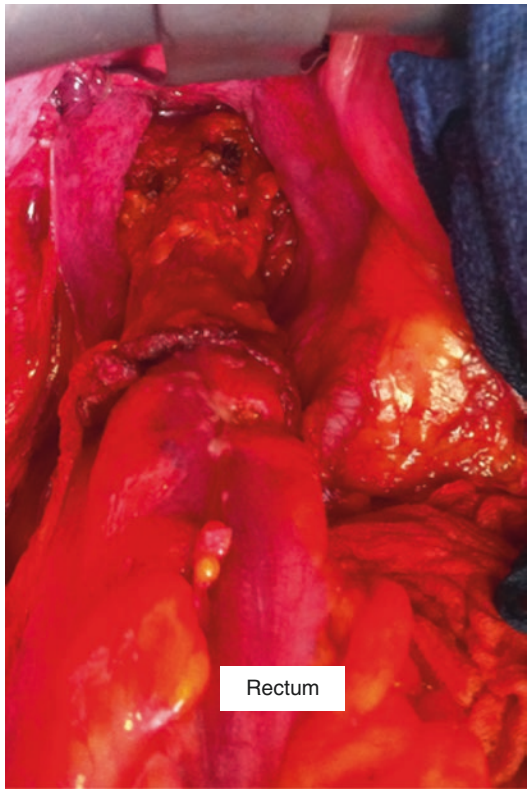

Fig. 18.7 Douglas pouch resection without rectal resection—in that case, high rectum had to be resected because of involvement, but low and middle rectum is preserved

resection is limited. To close the abdomen, using a biological mesh is a solution with probably less risk of tumor progression than synthetic mesh use. The price of that mesh is a limitation, and drainage is necessary because of a highly inflammatory postoperative reaction.

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19 Novel Techniques and the Future of HIPEC (Immunotherapy, Viral Therapy)

Joal D. Beane and David L. Bartlett

Introduction

The peritoneal dissemination of a patient's cancer portends a dismal prognosis and presents unique challenges to both the patient and the treating clinician. With these challenges come a unique opportunity for regional therapy. Cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) has been shown to improve survival in select patients [1–3]. Despite advances in operative technique, chemotherapy, and perfusion regimens, many patients present with unresectable disease and tumor recurrence is frequent for those who undergo CRS/HIPEC [4, 5]. For these patients, investigators are developing novel therapies that utilize the body's own immune system to rid the body of cancer. This chapter reviews immunotherapies currently under investigation as a regional therapy for the treatment of peritoneal carcinomatosis including antibody-, T-cell, and viral-based immunotherapies.

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Brief History

The ability of the immune system to rid the body of cancer has long been proposed, but only recently understood. Physicians dating back to the thirteenth century have described the spontaneous regression of cancer, and in 1891, Dr. William Coley described a patient with sarcoma who underwent the spontaneous tumor regression following an infection with *Streptococcus pyogenes* [6, 7]. These observations led him to perform experiments trying to induce an immune response with intratumoral injections of inactivated *Streptococcus pyogenes* and *Serratia marcescens*. Coley was able to induce durable responses in multiple patients but lacked an understanding of the biological basis for these responses. This, combined with the risk of infecting patients with his treatment, resulted in harsh criticism from the scientific community, and the use of immunotherapy to treat cancer was not pursued until almost a century later (Fig. 19.1).

In 1976, a potent T-cell activator called interleukin-2 (IL-2) was discovered. The use of IL-2 in cell culture media allowed scientists to grow and study T cells for the very first time. After studying the ability of T cells to induce regression of hepatic and pulmonary metastases in a murine model, Rosenberg et al. were the first to report the efficacy of high-dose IL-2 for the treatment of cancer in patients with metastatic disease [8]. This led to the approval of IL-2 by the U.S. Food

Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_19

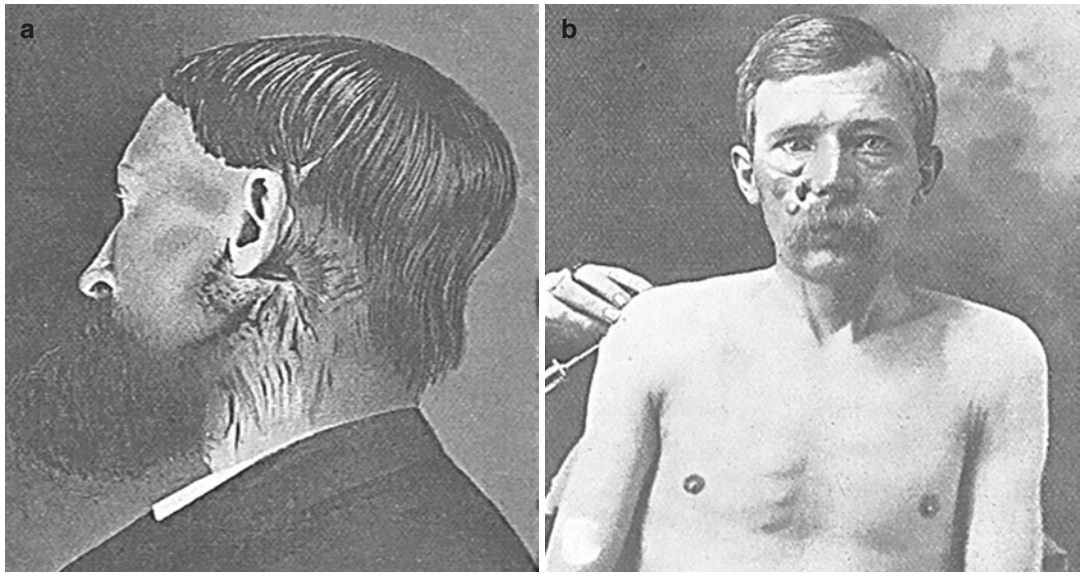

Fig. 19.1 Two patients treated with Coley's experimental therapy. Both patients had durable tumor responses (**a**). The patient on the left (**a**) responded after a single injection, and the patient on the right required 63 injections for the response seen in figure (**b**). (Reprinted with permission from Cancer Research Institute/Proceedings of the Royal Society of Medicine 01/1910/3 (Surg Sect): 1–48)

and Drug Administration (FDA) in patients with metastatic renal cell carcinoma in 1991, and in those with metastatic cutaneous melanoma in 1998. While durable complete responses were observed, there were significant toxicities associated with the high doses of IL-2.

During the same period Rosenberg et al. were using IL-2 to induce tumor regression through the activation of T cells, Milstein and Kohler were investigating the use of antibody-based therapies to specifically target the immune system to the desired cell type [9]. Their pioneering work laid the foundation for others who would later develop Cituximab—an antibody that binds CD20 on the surface of malignant B cells, activating natural killer cells, and resulting in apoptosis and complement-mediated cytotoxicity [10]. Cituximab was the first monoclonal antibody approved by the FDA for non-Hodgkin's lymphoma in 1997.

More recent advances include vaccines designed to induce immunity against tumor antigens by eliciting an effector response from cytotoxic T cells. Sipuleucel-T was the first cancer vaccine for castration-resistant prostate cancer that was approved in 2010 by the FDA [11]. Another breakthrough came with the discovery of the immune checkpoint inhibitors Ipilimumab and Nivolumab. Both are antibodies that prevent tumor-mediated inhibition of in vivo T cells. By binding and neutralizing the T-cell receptors that cancer cells exploit to cause inactivation (CTLA-4 and PDL-1, respectively), the T cells are released from their inactivated state and able to lyse cancer cells [12, 13]. Finally, adoptively transferred T cells harvested from resected tumors have been shown to possess antitumor efficacy by recognizing mutated antigens expressed on cancer cells. These were first pioneered by Rosenberg et al. for the treatment of metastatic melanoma (Fig. 19.2), but now have been used for the treatment of less immunogenic epithelial cancers including HPV-associated cervical cancer, cholangiocarcinoma, and hormone receptor positive breast cancer [14–17]. These advances and their ability to induce durable responses have created substantial enthusiasm within the scientific community for the use of immunotherapy for the treatment of cancer. A novel immunotherapy to treat peritoneal malignancies has the potential to

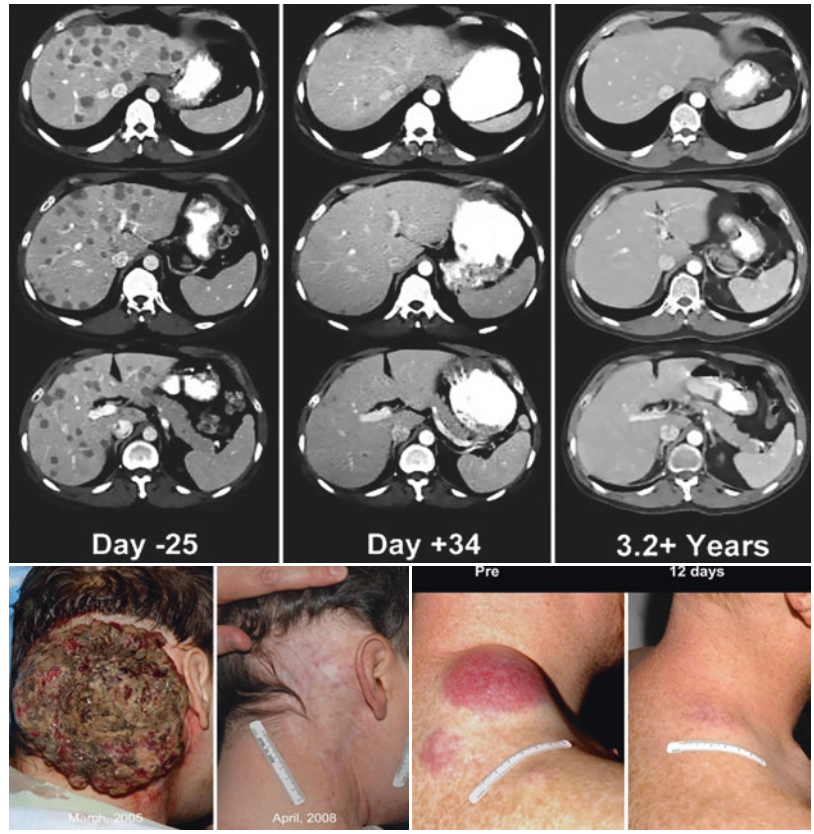

Fig. 19.2 Objective responses following the adoptive transfer of tumor-infiltrating lymphocytes in patients with metastatic melanoma. (Reprinted from Rosenberg and Dudley [85], with permission from Elsevier)

transform care of these patients and ultimately improve outcomes. Advances in immunotherapies and their application as a regional approach for the treatment of advanced peritoneal malignancies are the focus of this chapter.

Rational for Intraperitoneal Immunotherapy for Peritoneal Carcinomatosis

Peritoneal carcinomatosis is an advanced form of tumor metastases whereby cells have a predilection to spread throughout the abdominal cavity and peritoneum. There are several characteristics of the peritoneum that make it an ideal location to induce an immune response to cancer. These include a greater number of immunocompetent lymphocytes, higher proportion of CD8+ T cells to CD4+ T cells, and the ability to secrete the proinflammatory cytokines interleukin-1, interleukin-6, prostaglandin E2, and others including interleukin-2 and interferon-gamma [18–20]. Taken together, these findings suggest the peritoneal cavity provides a fertile landscape for both innate and adaptive immune responses that could be exploited to induce tumor regression.

In addition to the unique ability of the peritoneum to induce an immune response to cancer, a regional approach to immunotherapy can be used to more directly target tumor cells and increase doses while avoiding the toxicity associated with systemic administration. The feared complication with immunotherapeutic agents is the induction of autoimmunity that can be difficult to reverse and result in lasting consequences. These are well described, and include pneumonitis, hepatitis, colitis, pancreatitis, and thyroiditis among others [21]. Complications are often controlled with immunosuppressive medications such as corticosteroids and

antihistamines, but in some cases, the effects are irreversible [22]. As such, using regional immunotherapy in patients with peritoneal carcinomatosis has the potential to improve the immune response to cancer while avoiding systemic toxicity.

Advances in the field of cancer immunotherapy and gene therapy over the last three decades have provided a novel class of therapies with immeasurable potential. Today, multiple strategies to harness an immune response to cancer are available and include antibody-, T-cell-, and viral-based approaches.

Antibody-Based Therapies

Trifunctional Antibodies

A trifunctional antibody is a monoclonal antibody that contains two antigen-binding sites and an Fc domain that enables the interaction with three different cell types. Catumaxomab is a trifunctional antibody with specificity for CD3 on the surface of T cells and a surface antigen found on some tumor cells called epithelial cell adhesion molecule (EpCAM). Catumaxomab simultaneously binds human EPCAM-expressing tumor cells along with CD3 positive T cells, accessory macrophages, natural killer cells, and/or dendritic cells to induce an immune complex and tumor cell eradication via perforin-mediated lysis, antibody-mediated phagocytosis, and cytokine release (Fig. 19.3) [23, 24]. Catumaxomab was found to have efficacy for the treatment of malignant ascites, and clinical trials of patients with ovarian and non-ovarian peritoneal carcinomatosis with ascites resulted in prolonged puncture-free survival (46 vs 11 days, hazard ratio = 0.254: $p < 0.0001$) [25, 26]. In a subgroup analysis of patients with gastric cancer, Catumaxomab appeared to improve survival (71 vs 44 days, $p = 0.03$). In addition, Catumaxomab has been shown to induce tumor regression when given as an intraperitoneal injection in a preclinical mouse model of gastric cancer and in several case reports of patients with metastatic cancer (Fig. 19.4) [23, 27, 28]. Taken together, these findings have led to a multi-center, randomized, phase II study of intraperitoneal Catumaxomab in patients following resection of limited peritoneal carcinomatosis from gastric cancer. The primary endpoint is 2-year overall survival and the results have not been reported [29].

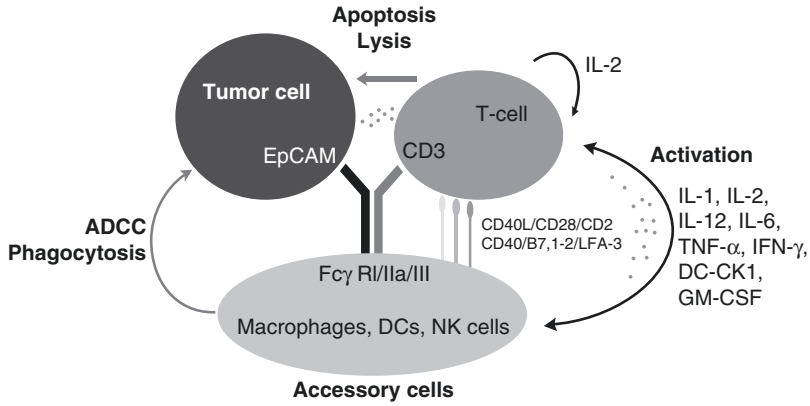

Fig. 19.3 Proposed mechanism of the trifunctional antibody Catumaxomab. Catumaxomab simultaneously binds human EPCAM-expressing tumor cells along with CD3-positive T cells, and accessory macrophages, natural killer cells, and/or dendritic cells to induce an immune complex and tumor cell eradication via perforin-mediated lysis, antibody-mediated phagocytosis, and cytokine release. (Reprinted from Seimetz [24], 2011 under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0))

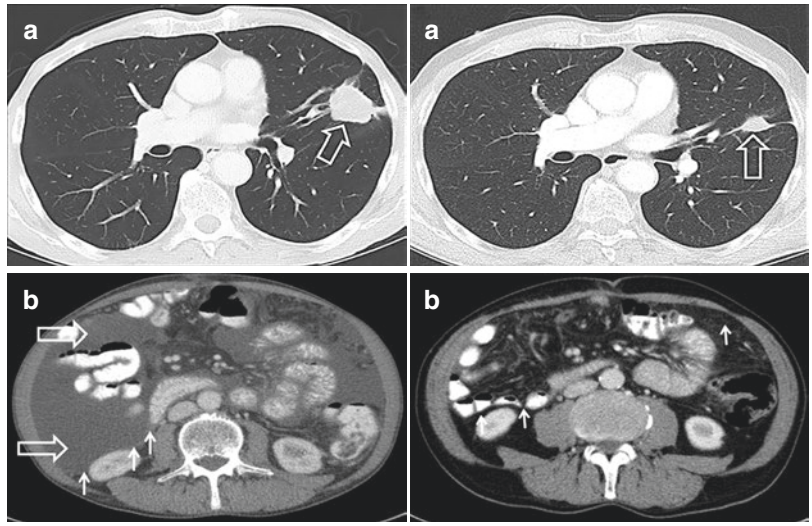

Fig. 19.4 Case report of a systemic response to intraperitoneal Catumaxomab. A 78-year-old patient with metastatic colon cancer and peritoneal carcinomatosis was unable to tolerate palliative chemotherapy. Intraperitoneal Catumaxomab was started and the patient remained puncture free for 1 year. In addition to improving his ascites, a pulmonary lesion decreased in size to nearly completely resolve on images taken later in his course. (Reprinted from Bezan et al. [28], 2013 under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0))

Radionucleotide-Labeled Antibodies

Investigators have attempted to deliver toxic doses of irradiation directly to tumor cells lining the peritoneum by taking advantage of the ability of antibodies to bind to a specified target. By conjugating a radionucleotide to an antibody with specificity for an antigen expressed exclusively on the surface of tumor cells, one can administer a cytotoxic dose of irradiation while avoiding off-target toxicity. This approach is termed radioimmunotherapy and was effective in inducing tumor regression and improving survival in multiple preclinical animal model studies [30, 31]. Radioimmunotherapy has been evaluated prospectively as an adjuvant therapy in patients with peritoneal carcinomatosis of ovarian origin, but has failed to improve survival or time to relapse [32].

In addition to failing as an efficacious clinical treatment for patients with peritoneal carcinomatosis, other challenges including off-target toxicity, insufficient tumor uptake, and formidable pharmacokinetics remain significant barriers [33]. Using radioimmunotherapy as a regional therapy within the peritoneum has ameliorated some of this toxicity. However, bone marrow suppression and off-target toxicity remain [34]. A few others are currently investigating the use of more targeted therapies to both the tumor and tumor microenvironment, as well as using different radionucleotide particles including alpha particles, fractionating doses, and pre-targeting approaches [35]. Proof of concept for radioimmunoconjugates is readily available, and the technology has the potential to improve outcomes in patients with peritoneal carcinomatosis [36]. However, radioimmunotherapy for patients with peritoneal carcinomatosis remains experimental until further optimization is achieved.

Immune Checkpoint Inhibitors

T cells express surface proteins that when activated reduced effector function thereby reducing the adaptive immune response. T-lymphocyte-associated protein-4 (CTLA-4) and programmed

cell death receptor-1 (PD-1) are two such surface receptors that some cancers can activate as a means to evade the host immune response [37, 38]. Antibodies CTLA-4 and PD-1 have been approved by the FDA and used systemically to induce tumor regression and successfully treat patients with metastatic melanoma [12, 13]. More recently, antibodies to PD-1 and/or its ligand on the tumor, PDL-1, have shown efficacy in multiple histologies including renal cell carcinoma, urothelial cell carcinoma, non-small-cell lung cancer, Hodgkin's lymphoma, hepatocellular carcinoma, mismatch repair-deficient colorectal cancer, and head and neck carcinoma [39–44].

While multiple PD-1/PDL-1 inhibitors are approved for systemic administration, there has been interest in using these antibodies in conjunction with other immunomodulators as a regional therapy in patients with peritoneal metastases. Using a preclinical mouse model of peritoneal carcinomatosis from colon cancer (CT26 cell line), Ma et al. compared survival in mice treated with either the systemic administration or intraperitoneal administration of the checkpoint-inhibiting antibodies anti-CTLA-4 and anti-PDL-1 with or without IL-18 [45]. They found improved survival in mice treated with intraperitoneal administration of anti-PDL-1 antibodies and/or anti-CTLA-4 antibodies compared to mice treated with control IgG, and that these improvements in survival could be increased with that addition of intraperitoneal IL-18 [45].

T-Cell Therapies

The ability of adoptively transferred tumor-specific T cells to induce durable tumor regression is well established in melanoma and other solid tumors (Fig. 19.2) [8, 15–17]. Tumor-specific T cells can be isolated from resected tumor specimens (tumor-infiltrating lymphocytes) or can be generated from naïve peripheral blood lymphocytes through either peptide stimulation or genetic engineering. Finally, tumor-specific T cells can be isolated from peripheral blood, but the ability to use these to induce tumor regression remains uncertain [46].

The intraperitoneal administration of tumor-infiltrating lymphocytes (TIL) has been used in patients with peritoneal carcinomatosis, with minimal success. The presence of TIL in ovarian cancer carries prognostic value and researchers have sought to use TIL as a means to treat patients with advanced stage disease [47]. The approach involves the harvesting of TIL from resected metastatic tumors, expanding the cells ex vivo, and then injecting them as an intraperitoneal suspension. While innovative, many of the earlier trials using TIL for patients with ovarian cancer and peritoneal metastases were fraught with difficulties and ultimately failed to demonstrate clinical efficacy. Several of the trials used cultures of TIL that had not been screened for tumor reactivity and/or had been cultured ex vivo for significant periods of time, while other trials failed to accrue and/or failed to demonstrate a significant difference in survival [48–50]. Given the challenges, the approach ultimately failed as a viable treatment option. The adoptive transfer of TIL has the potential to be a curative therapy based on the results from other histologies and remains under investigation as a regional therapy for patients with advanced peritoneal malignancies.

Despite the discouraging results early on using TIL, more recent discoveries have advanced the field of adoptive T-cell therapy by creating more avenues to generate tumor-reactive T cells. These advances have resulted in novel T-cell therapies that are less dependent on the ability to harvest and culture TIL from resected tumors. Tumor reactive T cells can now be generated ex vivo using peptide stimulation of tumor-naïve autologous CD4(+) effector cells isolated from peripheral blood. Peptide-stimulated effector T cells have been used to induce tumor regression in patients with metastatic ovarian cancer. Dobrzanski et al. reported the outcomes of four patients with advanced ovarian cancer treated with an intraperitoneal injection of autologous CD4+ effector T cells with specificity for epithelial mucin-1 (MUC1). After three monthly intraperitoneal infusions of MUC-1-specific effector T cells, they observed a subsequent decrease in CA-125 levels in all four patients and an improvement in overall survival [51]. One patient had a

complete durable response that was ongoing at the time of a later publication [52].

Tumor reactive T cells can also be generated using gene therapy. Tumor-naïve T cells can be isolated from peripheral blood and then transduced or transfected with a T-cell receptor (TCR) or chimeric antigen receptor (CAR) that when expressed provides the T cell with specificity for an antigen expressed on cancer cells [53–55]. T cells are then able to bind and eradicate tumor cells with high levels of specificity. Both TCR and CAR T-cell therapies are effective, and recently, a CAR-T-cell targeting CD-19 (Tisagenlecleucel) has been approved by the FDA for relapsed or refractory diffuse large B-cell lymphoma and acute lymphoblastic leukemia. The advantage of CAR-T cells is that the receptor can bind a target antigen in the absence of a major histocompatibility complex and is thus not restricted by an individual human leukocyte antigen (HLA) complex [55]. The durable and complete responses of T-cell-based therapies combined with the versatility afforded by genetic engineering have led to a significant amount of enthusiasm for CAR-T-cell therapies for the treatment of patients with cancer.

CAR-T cells have been used as a regional therapy for glioblastoma and for colorectal liver metastases with some efficacy in select patients and is an attractive approach for patients with peritoneal carcinomatosis [56]. Several preclinical studies have shown promising results using an intraperitoneal infusion of CAR-T cells. In a mouse model of colon cancer peritoneal carcinomatosis, Katz et al. found improved tumor killing when anti-carcinoembryonic antigen (CEA) CAR-T cells were given as an intraperitoneal injection compared to an intravenous injection. More so, when mice were re-challenged with intraperitoneal tumor injections, those treated with regional CAR-T cells demonstrated a significant reduction in tumor growth [57]. Another study investigating the use of CAR-T cells with specificity to the epithelial cell adhesion molecule (EpCAM) reported eradication of established ovarian xenografts and improved survival in mice following the administration of a single intraperitoneal dose of CAR-T cells [58].

In addition to providing naïve T cells with tumor specificity, gene therapy can be used to manipulate T-cell effector function [59, 60]. Yeku et al. generated CAR-T cells directed against Muc-16 (expressed in human ovarian cancer cells) that are capable of secreting the proinflammatory cytokine IL-12 [61]. The goal was to further enhance the effector function of the CAR-T cells in order to overcome the hostile, immunosuppressive tumor microenvironment. They found that their "armored" CAR-T cells proliferated better, resisted apoptosis, and were more resistant to endogenous PD-L1-induced inhibition. More so, the T cells exhibited increased antitumor efficacy resulting in improved survival in a syngeneic mouse model of ovarian peritoneal carcinomatosis. Not only can gene therapy instill tumor specificity, but it has the potential to modify T-cell effector function in order to overcome the immunosuppressive tumor microenvironment within the peritoneal cavity.

Significant strides have been made using the adoptive transfer of T cells as a regional therapy, but challenges remain. Similar to the antibody-based immunotherapies discussed above, one of the limitations of T-cell-based therapies is identifying tumor-specific targets that are not expressed on normal host tissues. On-target, off-tumor T-cell reactivity has occurred using genetically modified T cells and resulted in significant toxicity for patients due to shared antigens between host tissues and the tumor cells that the T cells are designed to eradicate [62, 63]. For this reason, identifying a limited number of targets on cancer cells that are not expressed in normal human cells has stifled research efforts. However, a recent breakthrough came when investigators at the National Cancer Institute were able to isolate and enrich T cells reactive to mutated neoantigens expressed exclusively on a patient's cancer cells. By screening for these neo-antigen reactive T cells and subsequently enriching the TIL population for these T cells, Tran et al. were able to adoptively transfer these T cells to a patient with metastatic cholangiocarcinoma and induce tumor regression [16].

This proof-of-concept approach has now been repeated in other histologies and provides a new avenue for identifying novel tumor-specific targets [17, 64]. Identifying targets in this way has the potential to improve response rates and minimize on-target, off-tumor host toxicity for patients with peritoneal surface malignancies as well.

Oncolytic Viral Therapies

Oncolytic viral therapy is another class of immunotherapy being investigated as a regional therapy for patients with peritoneal carcinomatosis [65]. Oncolytic viruses are viruses that selectively bind cancer cells and elicit tumoricidal effects [66]. Tumor cell lysis can occur directly after viral infection, intracellular replication, and ensuing oncolysis or indirectly by targeting a cancer cell for immune-mediated destruction. In addition, the potential for an oncolytic virus to induce a systemic antitumor effect via the adaptive immune response makes it an attractive option for the treatment of patients with metastatic cancer [65, 66].

Oncolytic viruses include both native viruses and genetically engineered/recombinant viruses that bear transgenes capable of tailoring the immune response to viral infection. Both types of viruses have been investigated and the safety and efficacy are well established. Talimogene lahperparepvec (Imlygic) is a herpes simplex oncolytic virus that expresses granulocyte-macrophage colony-stimulating factor (GM-CSF) and in 2015 was approved by the FDA for the treatment of advanced stage melanoma [67]. In patients with hepatocellular cancer, an intralesional injection of 10^9 plaque forming units (pfu) of vaccinia-GM-CSF resulted in a 15% response rate and prolonged survival (14.1 months vs 6.7 months, $p = 0.02$) when compared to lower doses (10^8 pfu) [68]. In addition to the efficacy, oncolytic viruses are safe. Numerous viral strains have been used either systemically, as an intratumoral injection, intrapleural infusion, or intraperitoneal infusion in phase I studies with acceptable safety profiles [68–72].

One advantage to using oncolytic viruses as a regional therapy is the avoidance of circulating antibodies and complement that effectively neutralize the virus, resulting in premature immune clearance and reduced delivery. In a preclinical lung-metastases mouse model, intravenous administration of an oncolytic reovirus reduced metastatic tumor growth, and its effectiveness was drastically reduced in mice that had been preimmunized [73]. The effectiveness of the reovirus could then be rescued by simultaneously administering the immune-suppressive drug cyclosporine A. This finding has been further supported in other mouse models and in humans from a phase I trial where reovirus (RT3D) was studied in patients with advanced stage cancers [74, 75]. White et al. found neutralizing anti-reoviral antibodies in all but one patient and the median fold increase in neutralizing antibody titers was 250 (range of 9–6437-fold increase). Using oncolytic viruses as a regional therapy provides the theoretical advantage of avoiding neutralizing viral antibodies and complement, while exposing malignant cells to a higher concentration of virus.

The use of oncolytic viruses as a regional therapy for patients with peritoneal carcinomatosis is an ongoing area of research where significant strides are being made. In 2002, Vasey et al. were one of the first to report using an oncolytic virus as regional therapy for the treatment of patients with recurrent ovarian cancer. Following the intraperitoneal administration of an adenovirus that selectively replicates in cells deficient in p53 (ONYX-015), no tumor response was identified, but adenovirus DNA was detected in patient blood samples up to 10 days after the final infusion, suggesting continued viral replication.

Since this initial publication, others have prospectively examined the role of regional therapy with oncolytic adenoviruses in patients with peritoneal metastases. In a dose escalation study of 21 patients, Kimball et al. evaluated the clinical activity and toxicity associated with the intraperitoneal administration of an infectivity-enhanced conditionally replicative adenovirus (CRAd). At a follow-up of 1 month, 15 (71%) of the patients

had stable disease, and of these 15, seven were noted to have a decrease in their serum CA-125 levels. In four patients, this decrease was greater than 20%. There were no partial or complete responses based on RECIST criteria, and adverse effects were well tolerated, with no grade 3 or 4 toxicities reported [76]. In another study, Kim et al. treated ten patients with metastatic ovarian cancer with intraperitoneal doses of an adenovirus (Ad5/3-Δ24) that had enhanced ovarian cancer infectivity. After three consecutive daily doses, they found the therapy was well tolerated and of eight evaluable patients, six had disease stabilization based on RECIST criteria. In addition, three of these patients had a decrease in their CA-125 [77].

In addition to adenoviruses, other types of oncolytic viruses have been used as an intraperitoneal infusion including an oncolytic measles virus (MV). Based on its preclinical efficacy in mouse models of ovarian cancer, Galanis et al. used an MV that expressed CEA (MV-CEA) as a marker in order to indirectly measure its activity when administered to patients with Taxol and platinum-refractory recurrent ovarian carcinoma [78]. Twenty-one patients were treated with an intraperitoneal injection every week for 4 weeks for up to six cycles. They were able to measure a dose-dependent increase in CEA in both peritoneal fluid and serum, suggesting continued viral replication. In addition, dose-dependent stable disease was observed in 14 patients with a median duration of 92.5 days. Like previous trials, they found a significant decrease in CA-125 in 5 patients, and the median survival of patients treated was 12.2 months compared to an expected median survival of 6 months.

Oncolytic viruses have been used as a regional therapy for other tumor histologies as well. Lauer et al. used an indwelling peritoneal catheter to administer a marker gene-expressing oncolytic vaccinia virus (GL-ONC1) in patients with advanced peritoneal carcinomatosis from either peritoneal mesothelioma, gastric cancer, or primary peritoneal carcinoma [79]. Using reporter genes, investigators were able to measure tumor cell infection, in-patient viral replication, and oncolysis. They found that treatments were well tolerated with no dose-limiting toxicities, and in eight of nine patients, viral replication of GL-ONC1 and subsequent oncolysis were observed as indicated by the release of GL-ONC1-encoded transgenic ß-glucuronidase. Only four patients completed all four cycles of therapy as designed. Of these, two had stable disease based on RECIST 1.1 criteria. Like previous trials, GL-ONC1 treatment induced a humoral anti-viral response that increased over time and resulted in neutralizing activities in the patients treated.

From the experience to date, three principles have been proposed for viral immunotherapies to be successful. These include (1) specific replication and lysis of tumor cells, (2) creation of an inflammatory response capable of recruiting the adaptive immune system, and (3) release and exposure of tumor-associated antigens to induce an effector response and create memory. The latter two appear to present the greatest challenge and have been the focus of efforts to improve oncolytic viral therapy. While neutralizing antibodies reduces the efficacy by preventing viral infection of cancer cells distant to the site of virus administration, the immunosuppressive tumor microenvironment further prevents the recruitment and activation of an adaptive immune response.

Current strategies to enhance the immune response to oncolysis include the creation of recombinant oncolytic viruses and combinatorial immunotherapy [80–84]. Our lab has constructed a novel oncolytic vaccinia virus (VVDD) that expresses the chemokine CXCL11 [80]. Intraperitoneal administration in a murine AB12 mesothelioma model led to increased numbers of tumor-specific T cells in the tumor microenvironment, but also increased the number of tumor-specific CD8+ T cells in the spleen and other lymph organs. The treatment resulted in improved tumor efficacy and prolonged survival. Another approach is combining oncolytic viruses with additional forms of immunotherapy. Liu et al. combined an oncolytic poxvirus with PDL-1 blockade in mouse models of ovarian and colon cancer and found increased CD8+ and CD4+ T cells with increased IFN-γ, granzyme B, and perforin expression. In addition, there were fewer

regulatory T cells and fewer exhausted PD1+ CD8+ T cells that led to reduced tumor burden and improved survival (Fig. 19.5) [81]. While the tumor microenvironment provides a formidable obstacle, there are innovative strategies currently under investigation that hold promise. Multiple phase I trials are underway and will continue to advance the field of viral immunotherapy.

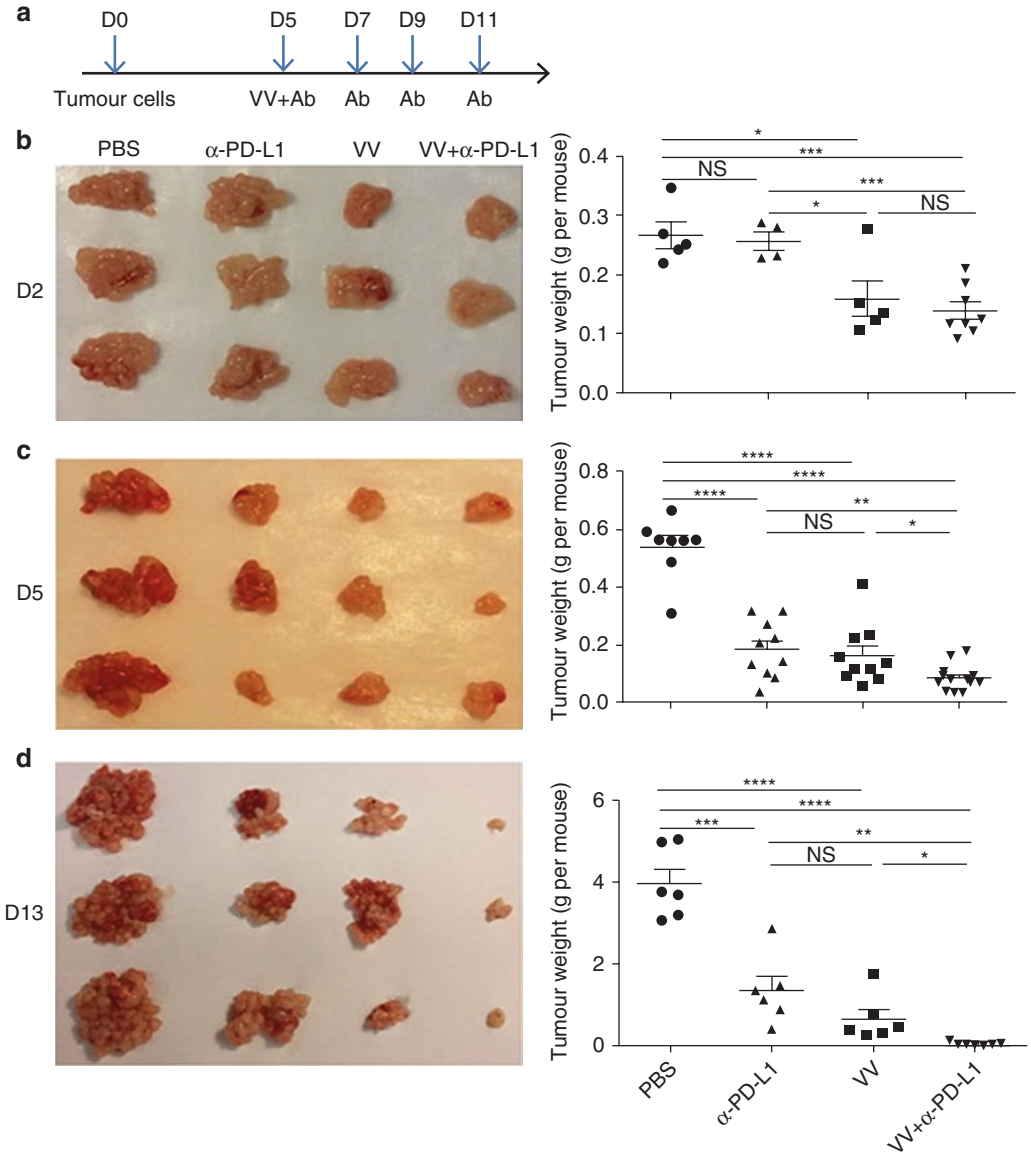

Fig. 19.5 A combinatorial approach to regional immunotherapy using oncolytic vaccinia viruses and the immune checkpoint inhibitor α-PD-L1. Representative tumor responses of B6 mice inoculated with MC38-luc cancer cells (Day 0) and treated with PBS, α-PD-L1 antibody (Ab), vaccinia virus (VV), or VV plus α-PD-L1 Ab. Mice were sacrificed at days 2, 5, and 13 after first treatment and tumors were collected and weighed. The experimental design is shown in figure (**a**). Photos of harvested tumors and plots of tumor weights on day 2 (**b**), day 5 (**c**), and day 13 (**d**) are shown. Data are presented as individuals and means and analyzed using the Student's *t*-test ($*p < 0.05$; $**p < 0.01$; $***p < 0.001$; $****p < 0.0001$; NS: not significant). (Reprinted from Liu et al. [81], 2017 under the terms of the Creative Commons Attribution License https://creativecommons.org/licenses/by/4.0/))

Conclusion

In summary, regional immunotherapy is a promising approach currently under investigation for patients with advanced peritoneal malignancies. Advances in the field of cancer immunotherapy and gene therapy over the last three decades have provided a novel class of therapies with immeasurable potential. Today, multiple strategies to harness an immune response to cancer are available and include antibody-, T-cell-, and viral-based approaches. Each has its respective challenges but also unique advantages to overcome the immunosuppressive tumor microenvironment and induce an immune-mediated tumor response. For this reason, a combinatorial approach to immunotherapy is an attractive and an ongoing focus of investigation. Based on the increasing number of durable responses observed with available immunotherapies, the implications for regional immunotherapy in patients with advanced peritoneal malignancies are broad.

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Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC)

20

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PIPAC is an innovative method of intraperitoneal drug administration that has pharmacological advantages due to local administration and physical laws. The first clinical use of the method was by M.A. Reymond in Germany at the end of 2011 [1].

"Therapeutic Capnoperitoneum"

The concept of "therapeutic capnoperitoneum" is to apply therapeutic substances to the closed abdominal space that is filled with carbon dioxide during a laparoscopy. This allows different therapeutic effects to be achieved, e.g., pain management, prevention of adhesions, prevention of tumor recurrence, etc. Up to now, conventional chemotherapeutic substances [2], nanomolecules [3], siDNA [4], and siRNA [5] have been administered as pressure aerosols.

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Principle of PIPAC

The major limitations of intraperitoneal chemotherapy with fluids are the low tissue penetration and inhomogeneous distribution [6]. Instead of distributing the chemotherapeutic substances in the abdomen in the form of a fluid solution, in PIPAC, the drug solution is nebulized in carbon dioxide to create an aerosol. Aerosols consist of two phases: a fluid phase (droplets) and a gaseous phase. Because gases distribute homogeneously within a closed space (according to Fick's first law [7]), there is a more even concentration of the drug throughout the entire abdominal cavity than with a fluid solution. The aerosol is applied to the abdominal cavity under pressure so an artificial pressure gradient is created between the intraperitoneal space and the interstitium of the peritoneal tumor [8]. A direct consequence is that absorption in the peritoneum is improved [9–11]. The intraperitoneal pressure applied thus compensates for the increased interstitial fluid pressure of the tumors, which limits the absorption of medication in solid tumors and potentially contributes to chemoresistance [12] (Table 20.1).

Surgical technique for PIPAC

A normothermic capnoperitoneum with a pressure between 12 and 15 mmHg is generated using a Veress needle or a mini laparotomy. A 5-mm and a 12-mm balloon trocar (Kii®, Applied Medical,

Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_20

Düsseldorf) are inserted. A staging laparoscopy is conducted, the peritoneal cancer index (PCI) is determined, ascites is suctioned off, multiple biopsies are taken from all 4 quadrants, and a local peritonectomy is performed if necessary. Peritoneal cytology may be taken. A nebulizer (Capnopen®, Capnomed GmbH, Villingendorf) is connected to an angio injector (Accutron HP®, MedTron AG, Saarbrücken) and inserted into the abdomen via a trocar. The system is checked for tightness. The chemotherapeutic solution is aerosolized and the system is kept closed in this stationary condition for 30 min (application time). Then, the aerosol is suctioned off through a closed exhaust system and disposed of (Fig. 20.1).

Table 20.1 Postulated advantages of PIPAC over other chemotherapy techniques

Advantages of PIPAC technique
Homogeneity of drug distribution
Depth of tissue penetration and tissue drug concentration
Dose reduction, therefore limited local and systemic toxicity
Can be repeated
Feasible in most patients, also with limited liver or renal function
Objective assessment of tumor response, including tumor profiling and individualized therapy
Simple and easy to perform
Cost-effectiveness
Preserves quality of life

Indications

Intraperitoneal chemotherapy (as PIPAC) is used for the palliative treatment of isolated peritoneal metastases, especially as second- or third-line treatment if there is tumor progression under systemic chemotherapy [13–16]. In a retrospective analysis of a total of 832 procedures, 41.1% of the indications for PIPAC were for peritoneal metastases of gastric cancer, 22.7% for ovarian cancer, 20.1% for colon cancer, 5.6% for appendix cancer, 5% for peritoneal mesothelioma, and 5.3% for other indications, in particular hepatobiliary and pancreatic tumors [2]. However, for patients in satisfactory general condition with only peritoneal metastases, as complete as possible surgical removal of the tumor (cytoreductive surgery—CRS) followed immediately by lavage of the abdominal cavity with a hyperthermic chemotherapy solution (HIPEC) should be attempted. In individual cases, the PIPAC method can also be applied before CRS and HIPEC, as has been reported for colorectal cancer [17].

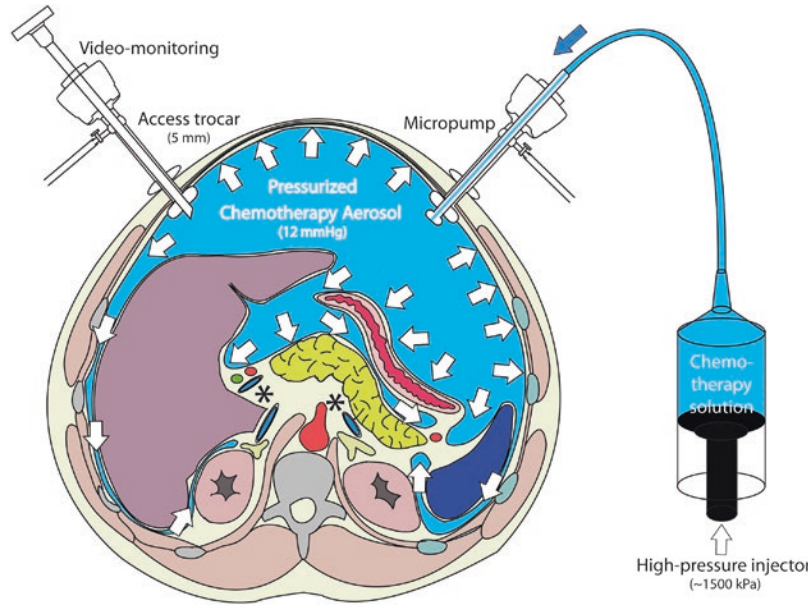

Fig. 20.1 Principle of PIPAC. During a staging laparoscopy, an aerosol cytostatic agent is applied in the abdominal space using a nebulizer. The application of the aerosol allows the relatively even distribution of the substance. Increased pressure (12 mmHg) ensures deeper penetration into the tissue

In combination with systemic chemotherapy (XELOX, FLOT), PIPAC has also been studied as first-line treatment for peritoneal metastases of gastric cancer [18, 19]. Other indications for PIPAC are intolerance or severe side effects of palliative systemic chemotherapy, patient's refusal of systemic chemotherapy, or organ toxicity (e.g., kidney failure) that precludes the further use of platinum-based chemotherapeutic agents.

Treatment Regimen

For palliative treatment, repeated cycles of PIPAC at intervals of 6–8 weeks are usually administered. In retrospective analyses, a median number of 3 PIPAC cycles/patient were usually administered (range 1—15). If there is high-grade or complete histological regression, the treatment-free interval can possibly be increased to 12 weeks. Criteria for discontinuation are peritoneal tumor progression under PIPAC and the development of visceral metastases [20].

Assessment of the Treatment Response

The response to treatment is assessed radiologically (in studies using the latest RECIST criteria), macroscopically (Peritoneal Cancer Index, PCI), and/or histologically. The applicability of the RECIST criteria is problematic because of the limited information from tomographic techniques on the extent of peritoneal metastases [21], especially for small-volume lesions associated with gastrointestinal tumors [22]. Although the "Peritoneal Cancer Index" (PCI) is used all around the world to determine the extent of peritoneal metastases [23], it is only conditionally suitable for assessing remission after PIPAC, because it can be difficult to distinguish between vital peritoneal lesions and secondary avital peritoneal scars macroscopically. The most suitable method is the direct histological comparison of sequential biopsies before the individual applications of PIPAC using the "Peritoneal Regression Grading System (PRGS)" [24] (Fig. 20.2).

Chemotherapeutic Agents Used

For peritoneal metastases of colorectal cancer and for appendix cancer, intraperitoneal oxaliplatin is administered at an arbitrary dosage of 92 mg/m^2 body surface [15]. This dosage was derived from a HIPEC dosage with an 80% reduction of the dosage [25]. Two dose-finding studies are currently being conducted to determine the optimal dosage of oxaliplatin [26, 27]. For all other indications (ovarian [28], stomach [13], mesothelioma [29], hepatobiliary [30], and pancreatic [16, 31] tumors), a combination of low-dose doxorubicin and cisplatin is currently used. The defined dosage after a dose-escalation study for doxorubicin is 2.1 mg/m^2 body surface and for cisplatin 10.5 mg/m^2 body surface [32]. The use of taxanes (nab-paclitaxel) is currently being studied in a phase I–II trial for gastrointestinal and ovarian peritoneal metastases [3]. Comprehensive clinical reports on the use of these substances as PIPAC have been published [2, 33].

Combination of PIPAC with Systemic Chemotherapy

In most treatment centers, PIPAC is also administered in combination with systemic chemotherapy [2]. Previous reports show that combination of PIPAC and systemic chemotherapy is well tolerated [1, 33, 34]. The systemic chemotherapy is generally paused 2 weeks before PIPAC, but can be restarted shortly afterward [2]. In case of the systemic administration of angiogenesis inhibitors, a 4-week pause is recommended because of the known risk of sometimes lethal bowel perforations [35].

Current Clinical Evidence

The current clinical evidence for PIPAC is based on results of one phase I study [32] and five phase II studies published up to now [20, 28, 36–38]. In addition, a total of 67 preclinical studies, case reports, and prospective and retrospective case series have been published [39]. Moreover, a

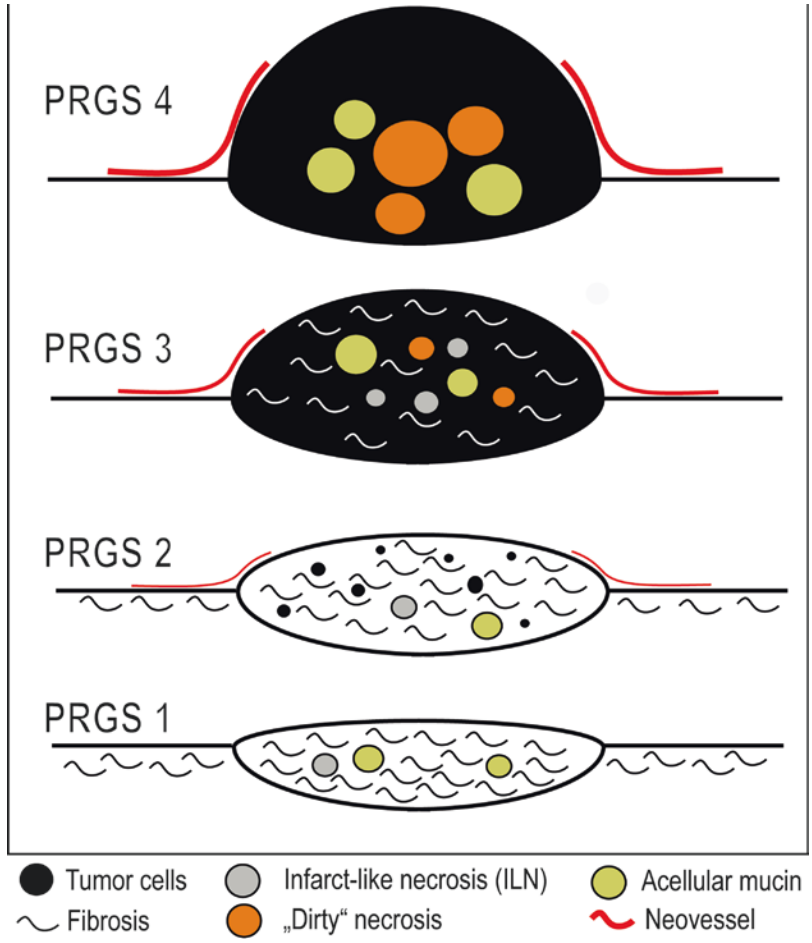

Fig. 20.2 Peritoneal Regression Grading Score (PRGS). PRGS is a 4-tier scoring system for objectifying the effects of systemic and/or intraperitoneal chemotherapy on peritoneal metastases

prospective, international, multicenter PIPAC registry (NCT03210298) has been created in 1996, with 1791 PIPAC procedures entered as of 9/2018 (data on file).

Feasibility

The technical feasibility of the PIPAC technique depends on the degree of entero-enteric and entero-parietal adhesions. In pre-operated patients, abdominal access is not possible in 0–17% of cases due to adhesions or it is not possible to create sufficient working space to apply the chemotherapeutic agent effectively [40]. This rate is considerably higher in patients with prior CRS and HIPEC. After PIPAC alone, no adhesions were reported; secondary non-access is rare, so it is usually possible to use the same incisions again for repeated PIPAC cycles.

Tolerability

The PIPAC technique is generally well tolerated. The international standard is a hospital stay of currently 3 days [40]. At Ghent University (Belgium), the patients are generally discharged the next day [41]. In a phase II trial, 80% (28/35) and 89% (24/27) of the patients were discharged within 24 h after the first and the third PIPAC, respectively [20].

Safety

The PIPAC technique was recently classified as safe in two systematic reviews [40, 42]. However, surgical or chemical-toxic complications may occur rarely. The surgical complications include incisional hernias (up to 4%) [28], enteral access lesions (0–3%) [13, 28], subcutaneous toxic emphysema (0–4%) [41], or tumor recurrences through the incision sites (1%) [40]. The chemical-toxic complications include local and systemic toxicity. Unlike the previously available intraperitoneal chemotherapy methods, which are frequently associated with gastrointestinal side effects, pain, fever, and infections [40], PIPAC is generally very well tolerated [20], despite the induced chemical peritonitis and accompanying inflammatory reaction [41]. The most common accompanying symptom is temporary mild-to-moderate abdominal pain [13, 14, 28, 40, 41]. In individual cases (especially after administration of oxaliplatin), severe, stabbing pain has been reported [15]. The acute bowel toxicity of the technique is low. The only postoperative, non-iatrogenic bowel perforations in the PIPAC register occurred with a colon stent or with a combination of systemic treatment with angiogenesis inhibitors (PIPAC registry, data on file). There is generally no deterioration of existing gastrointestinal symptoms such as nausea/vomiting, constipation, diarrhea, or loss of appetite [18, 42]. In retrospective analyses, intraoperative anaphylactic shock occurs as a reaction to the chemotherapeutic agents or other drugs in statistically 1 of 300 PIPAC cycles.

Efficacy

After PIPAC as sole treatment for pretreated patients with peritoneal metastases, response rates in CT imaging (RECIST) of 62% for recurrent ovarian cancer (ITT) [28] and of 40% for recurrent stomach cancer (ITT) [36] have been reported. The histological response rates in peritoneal metastases previously treated with systemic chemotherapy are comparatively high in the corresponding studies (ovarian cancer 62–88%, colorectal cancer 71–86%, and stomach cancer 70–100%) [40]. Less often, even complete radiological and/or histological remission is achieved (Fig. 20.3).

Survival

As the sole treatment of patients with peritoneal metastases in gastric cancer in the second to fifth line of treatment, the median survival after the first PIPAC was 8.4 months [36]. In combination with palliative systemic chemotherapy, the median survival with peritoneal metastases of gastric cancer was 15.4 months [13], 13.0 months [18], and 19.5 months [35]. For peritoneal metastases of ovarian cancer in the third to eighth line of treatment, the median survival was 11 months [28] or 14 months [14]. Although these results are encouraging, the data on survival after PIPAC must be interpreted with caution due to the lack of data from randomized trials. The results of ongoing, randomized trials of gastric cancer [43, 44] and ovarian cancer [45] are pending.

Patient-Related Outcomes

The PIPAC technique results in control of the symptoms in approx. 60% of patients [43] and can lead to stabilization/improvement of the quality of life [14, 20, 28, 42], especially in patients in whom repeated PIPAC applications are possible and who are affected by considerable ascites at the start of treatment. The nutritional condition can also be stabilized under PIPAC treatment [46].

Prospects

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a comparatively new method for intraperitoneal administration of medication. It is currently used for palliative care and is being tested for peritoneal metastases of gastrointestinal and gynecological tumors. Initially usually

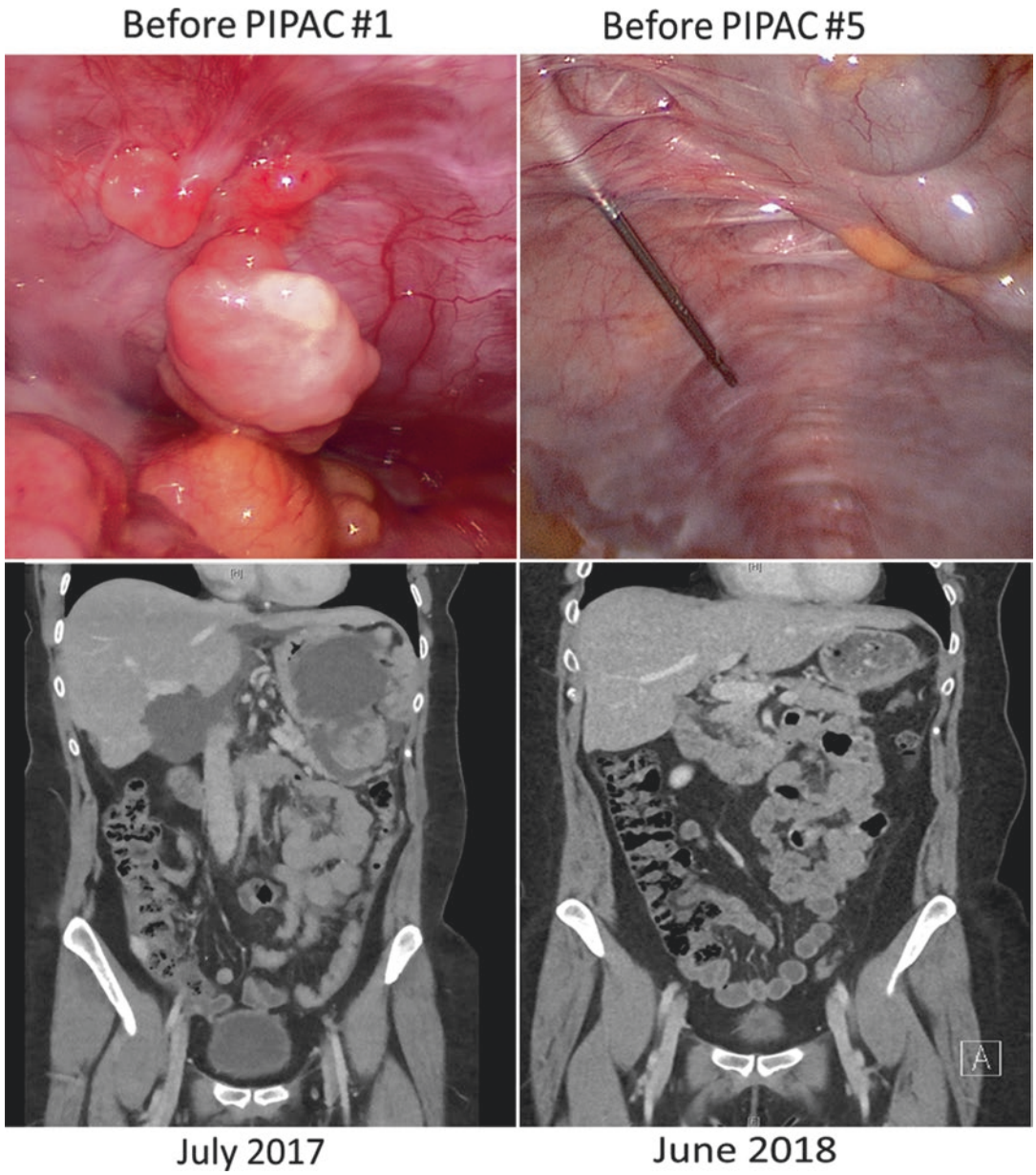

Fig. 20.3 Example of a complete macroscopic, histological, and radiological tumor regression after PIPAC with cisplatin and doxorubicin in the salvage situation. A 40-year-old woman with yolk sack tumor, progressive under systemic immunotherapy after 5 lines of palliative chemotherapy, 3 bone marrow transplantations, and 2 cytoreductive surgeries. Complete tumor response 6 weeks after PIPAC#1. The patient is alive 15 months after PIPAC#1 without evidence of disease (pictures before PIPAC#5)

conducted as individual treatment attempts, the PIPAC technique is now in clinical use in specialized cancer centers all around the world. Many different substances can be administered with this generic method. The number of preclinical studies, patient cohorts, and clinical studies that have been published is increasing. The first randomized trials of patients with peritoneal metastases from ovarian or gastrointestinal cancer are already being conducted. PIPAC appears to

be safe and well tolerated. However, it remains difficult to assess the effectiveness of this method without randomized trials and to specify evidence-based indications at this time.

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Part IV

Liver Infusional and Perfusional Therapies

21

The History of Isolated Hepatic Perfusion for Liver Metastases and Current Indications for Use

Callisia N. Clarke, H. Richard Alexander Jr., Edward J. Quebbeman, and T. Clark Gamblin

Introduction

Liver metastasis is frequently a lethal disease state in patients with metastatic colorectal cancer, ocular, melanoma, and neuroendocrine tumors. While surgical resection has been shown to improve survival, many patients present with excessive liver tumor burden confined to the liver and are deemed inoperable. Isolated hepatic perfusion (IHP) was first employed more than 50 years ago as a regional treatment in diffuse liver metastases not amenable to surgical resection. The technique administers high doses of cytotoxic chemotherapy to the liver after complete vascular isolation, limiting the systemic toxicity while treating the entire affected field. However, the technique has not been widely adopted due to technical complexity, associated morbidity and mortality, and the lack of demonstrated benefit in many disease states especially in the era of more effective systemic chemotherapy and targeted agents. In this chapter, we will review the history of IHP, its development and initial clinical trial results, as well as current techniques, indications, and expectant outcomes.

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Historical Perspectives and Rationale for Isolated Hepatic Perfusion

The single most important driver in the development of IHP for regional treatment of liver metastasis was the observation by Breedis and Young in 1954 that while benign hepatocytes largely derived their blood supply from portal venous flow, liver metastases were fed primarily by the hepatic arteries [1]. This discordance in blood supply drove many to hypothesize that delivery of chemotherapy via the hepatic arteries could decrease metastatic liver tumor burden with relative sparing of the normal liver. Thus, the concept of regional liver perfusion for metastasis was born.

The technical challenges of regional liver perfusion would delay testing of this hypothesis. However, in the late 1950s, Ryan et al. [2] and Creech et al. [3] successfully performed the first isolated regional perfusion for cancer in eight patients with metastatic melanoma of the lower extremities. Their description of this new technique included vascular isolation of leg by accessing either the femoral artery and vein or the external iliac artery and vein [3]. They delivered the drug, phenylalanine mustard, via

Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_21

an extracorporeal system consisting of a pump and an oxygenator, at much higher concentrations without significant systemic toxicity. The clinical result was significant; many patients showed a partial response and "several [lesions] disappeared completely." [3] Later, Stehlin would demonstrate the synergistic effects of chemotherapy and hyperthermia in regional limb perfusions for cancer, and the two treatment strategies became a standard approach for regional therapy [4].

Robert Ausman, at Roswell Park Memorial Institute, expanded on this technique and was credited with performing the first isolated hepatic perfusion in 1961; first perfecting the technique in dogs before moving to human clinical trials [5, 6]. In his paper, he described the arterial access method as trans-splenic arterial cannulation with ligation of the gastroduodenal and left gastric artery as well as occlusion of the celiac artery and suprarenal aorta [6]. The vena cava was occluded above and below the liver. Five patients underwent liver perfusion for liver metastasis with nitrogen mustard. One died 3 weeks after the procedure from a myocardial infarction, two patients with metastatic gastrointestinal adenocarcinomas eventually succumbed to their disease, and the remaining two patients (one metastatic carcinoid, one unknown histology) tolerated the procedure well though there was no mention of survival outcomes [6]. Despite this relative success, more than a decade would pass before the procedure resurged as a viable treatment option in patients with unresectable liver disease.

In the late 1970s, Joseph Skibba and Edward Quebbeman at the Medical College of Wisconsin would again bring IHP to the forefront in management of incurable liver metastases. While hyperthermia and chemotherapy were being widely employed in regional perfusions of the extremity, little was known about the safety and tolerability of hyperthermia in the liver. They sought to address this knowledge gap by investigating the effect of hyperthermia facilitated by IHP. Previous preclinical studies had demonstrated that hyperthermia, even in the absence of cytotoxic drugs, would selectively induce cellular injury and death in cancer cells when compared to normal tissues [7]. Skibba et al. were able to prove that hepatic hyperthermia to 43 °C could be tolerated with little effect on normal liver function in dogs [8]. With these two principles in mind, Skibba and Quebbeman performed the first human clinical trial of hyperthermic isolated liver perfusion in patients with unresectable primary and secondary liver malignancies [9]. Eight patients underwent hyperthermic liver perfusion to temperatures of 42–42.5 °C for 4 hours. There was one postoperative death due to liver failure, while the remaining seven patients only had transient increases in transaminases and liver function tests [9]. Six patients (five with metastatic colon cancer and one with cholangiocarcinoma) demonstrated response to treatment as evidenced by tumor necrosis and experienced meaningful improvement in survival with overall survival ranging from 12 to 14 months. One patient with metastatic colon cancer did not respond to therapy and died of disease at 4 months [9].

These and other small cohort studies were pivotal in the renewed interest in hyperthermic isolated liver perfusion in the 1990s. Alexander et al. [10] reported their experience with hyperthermic IHP using high-dose melphalan and TNFα[alpha] for 60 minutes in 34 patients with unresectable liver cancers (26 colorectal, 4 ocular melanoma, 1 leiomyosarcoma, 2 unknown primary adenocarcinoma, and 1 hepatocellular carcinoma). They demonstrated acceptable safety and tolerability with a 75% response rate and durability of responses for up to 9 months (Fig. 21.1) [10]. More significantly, they reported a refined technique with shunting of the portal blood flow to the axillary vein using external venovenous bypass, arterial inflow via the gastroduodenal artery, and documented complete vascular isolation of the liver using I-131-labelled human serum albumin [10]. There was one treatment-related mortality in the study. Marinelli et al. [11] had similar responses in their study of IHP using mitomycin C and melphalan in nine patients with colorectal cancer liver metastasis (CRCLM). However, four

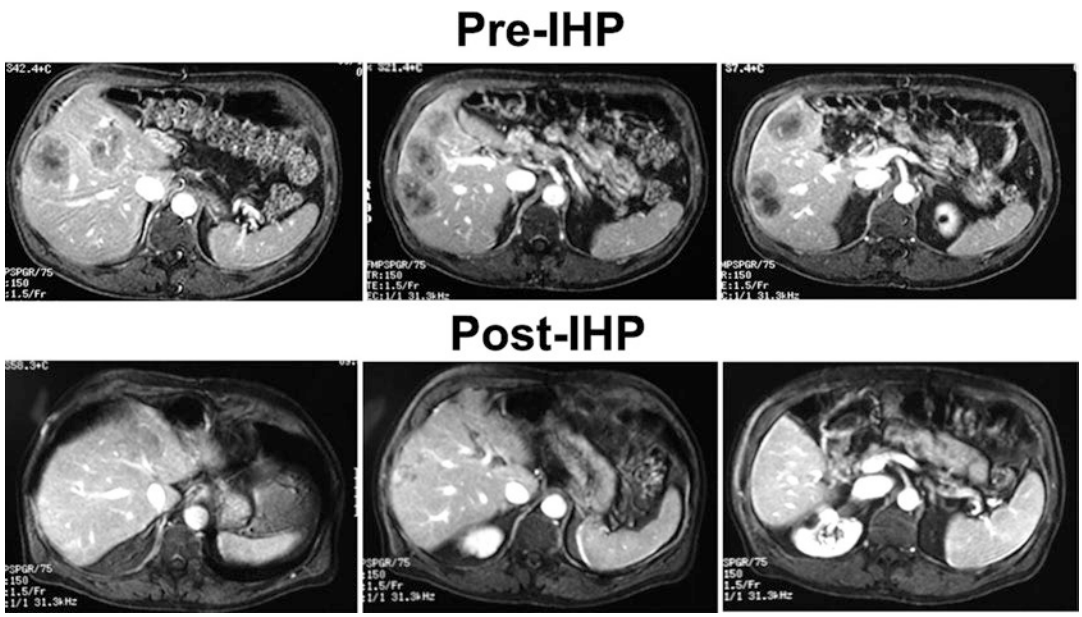

Fig. 21.1 Dr. Alexander et al. reported excellent outcomes in patients with liver metastases treated with hyperthermic isolated hepatic perfusion and high-dose melphalan with TNFα[alpha] for 60 minutes. Response rates of 75% were observed in this cohort as evidenced in this figure of a study patient with metastatic colorectal cancer who had near-complete response in the lesions. Responses in this study were durable for up to 9 months [10]. The pre-IHP scans pictured here were obtained at presentation and post-IHP scans were obtained at 1 year after perfusion

patients in the mitomycin treatment arm developed hepatic venous thrombosis, one resulting in death [11]. For this reason, mitomycin C was no longer studied in IHP.

Contemporary Surgical Technique

Patient Selection and Preoperative Planning

Contemporary IHP techniques in most centers utilize the gastroduodenal artery for hepatic inflow and the inferior vena cava (IVC) for outflow. Additionally, to establish a venovenous bypass circuit, the authors endorse using the internal jugular vein and the femoral vein, though variations may include similar venous access via the axillary or saphenous vein (Fig. 21.2). Approximately 20% of patients will present with aberrant hepatic arterial anatomy [12]. Although aberrant anatomy does not preclude eligibility for hepatic perfusion, careful consideration must be given in these cases to avoid catastrophic vascular injury. For this reason, it is critical to clearly delineate the hepatic arterial and venous anatomy prior to surgery. This is most commonly achieved using multidetector-row helical computed tomography (CT) imaging with thin sections through the liver and dual-phase contrast with late arterial and portovenous phases. This allows for high-resolution imaging of the liver vasculature, as well as detection of extrahepatic metastases, particularly nodal and lung metastases, which could render patients ineligible for IHP [13]. Magnetic resonance imaging (MRI) can also provide useful information regarding compromised liver reserve due to fibrosis and/or fatty liver disease, as well increased sensitivity in detection of peritoneal metastasis [14–16]. Because of the known risks of venous thrombosis and bile duct anomalies associated with liver perfusion, only patients with good performance status, intact synthetic and excretory function, and adequate functional liver reserve should be considered for IHP [11, 17, 18].

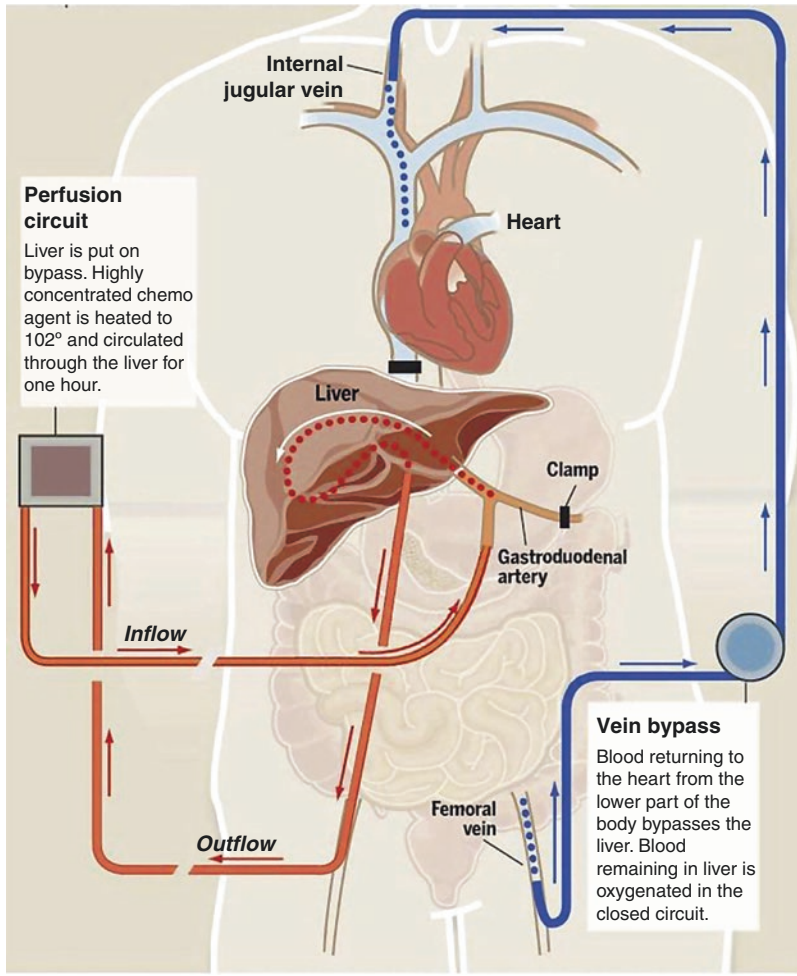

Fig. 21.2 Illustration of isolated hepatic perfusion circuit with venovenous bypass circuit outlined in blue using the right internal jugular and left femoral veins as access sites. The extracorporeal hepatic perfusion circuit is outlined in red with the inflow catheter positioned in the gastroduodenal artery and the isolated retrocaval inferior vena cava providing outflow. Vascular clamps are placed on the common hepatic artery and the suprahepatic inferior vena cava. (From Fauber J. Froedtert, doctors try using heat, chemo to halt liver cancer. *Milwaukee Journal Sentinel*. 2011; with permission. Available at: http://www.jsonline.com/news/health/froedtert-doctors-try-using-heat-chemo-to-halt-liver-cancer-id2qg37–134220898.html. Accessed 1 June 2019)

Surgical Technique

Anesthetic considerations include general anesthesia to facilitate surgery and the need for venovenous bypass with consequent systematic anticoagulation. Fluid management should be judicious to avoid hepatic engorgement, though the significant volume restriction often employed in liver resection surgery is not necessary. Epidurals for postoperative pain control are not used due to the increased risk of epidural hematoma secondary to systemic anticoagulation.

At the Medical College of Wisconsin, we employ a combined open and percutaneous technique. After general anesthesia is induced, an 8-French (F) central venous catheter is placed in the left internal jugular vein for administration or medications, fluid, and blood products. The right internal jugular vein is percutaneously accessed, and a 17F to 19F catheter is advanced into the

central circulation for venovenous bypass access. The abdomen and bilateral groins are then prepped and draped.

A diagnostic laparoscopy is used to rule out peritoneal metastasis, distant nodal disease, and liver pathology such as fibrosis, significant steatosis, or sinusoidal congestion which represent contraindications for IHP. A laparotomy is then performed; we prefer a right subcostal incision with a midline extension if needed. A cholecystectomy is often performed if the gallbladder is in situ to ameliorate the risk of cholecystitis. The right and left lobes of the liver are then completely mobilized, and all collateral veins or accessory arteries are clamped or ligated. The phrenic vein, all venous tributaries from the retrohepatic IVC, and the right adrenal vein are ligated and divided.

A generous Kocher maneuver is performed exposing the IVC to the level of both renal veins. A Rummel tourniquet is then placed around the infrahepatic IVC for outflow control. The suprahepatic IVC is dissected free above the hepatic veins to allow for unobstructed placement of an angled vascular clamp. The portal dissection is performed to clearly delineate the structures within the porta hepatis. Specifically, the common hepatic artery, proper hepatic artery, and the gastroduodenal artery (GDA) should be circumferentially dissected. Since the GDA serves as the cannulation site for arterial inflow, we recommend a length of at least 2 cm of the vessel be dissected and exposed. Angled clamps should be selected to occlude the common hepatic artery and the entire portal triad.

Both femoral veins are percutaneously accessed and wires placed into circulation. Heparin is administered for systemic anticoagulation to achieve and maintain an activated clotting time of 300–400 seconds. A 17F to 19F catheter is placed in the left femoral vein with the tip positioned in the left common iliac vein, and the venovenous bypass circuit is completed by attaching this and the right IJ catheter to the centrifugal pump. A 14F catheter is advanced in to the right femoral vein and the tip positioned in the retrocaval IVC below the suprahepatic IVC clamp.

The GDA is then accessed and a 5F catheter advanced into the vessel with the tip at the junction of the proper hepatic artery. The perfusion circuit is then completed by placing the previously selected vascular clamps across the common hepatic artery, portal triad, and suprahepatic IVC. The infrahepatic IVC is secured with the Rummel tourniquet around the retrocaval catheter to achieve complete hepatic isolation. Temperature probes are placed into the left and right lobes of the liver to monitor hyperthermia. Venovenous bypass is initiated and oxygenated pH balanced liver perfusion begins via the GDA with flow rates of 400–700 mL/min. Inline arterial pressures are maintained at 150 mmHg or less. Perfusate leakage can be detected by monitoring the stability of the reservoir volume. While there may be subtle fluctuation in reservoir volume attributed to liver capsular expansion, any significant decrease in reservoir volume indicates perfusate leakage. To troubleshoot fluctuations in reservoir volume, first check all vascular clamps and catheters to ensure complete liver isolation was achieved. Additionally, ensure all collateral and accessory vessels have been ligated. The reservoir volume must be constant before the chemotherapy drug is added to the perfusate.

The perfusate is also warmed to achieve liver parenchyma temperatures of 39.5–40 °C. Once cytotoxic chemotherapy (usually melphalan) has been administered, the liver is perfused for 60 minutes. Arterial and venous blood gases are obtained throughout perfusion to maintain a perfusate pH between 7.2 and 7.3. At the completion of perfusion, the liver is flushed with crystalloid and colloid, and fresh frozen plasma is administered. The vascular clamps are removed and the GDA decannulated. The vessel is either ligated or prepared for hepatic arterial pump insertion if indicated. Venovenous bypass is terminated, the cannulas removed, and systemic anticoagulation reversed. Postoperative monitoring typically occurs in the intensive care unit and includes close attention to synthetic liver function, hematologic derangements, glycemic homeostasis, and other signs of significant hepatocyte injury.

Current Clinical Indications

Ocular Melanoma

Ocular melanoma is the most common malignancy of the eye and accounts for 3–6% of all melanoma cases [19, 20]. These tumors typically arise within the pigmented uveal tract which includes the iris, the choroidal plexus, and the ciliary body. Ocular melanoma represents a distinct subset of melanoma with varying genomic drivers, clinical characteristics, patterns of metastasis, and response to therapy [19, 21–23]. Metastasis occurs in 30–60% of all cases with the most common site being the liver via hematogenous spread [19, 20, 24]. Prognosis in the setting of stage IV disease is poor with overall survival rates of approximately 2 months if left untreated [25]. Resection of isolated liver disease offers the best chance for prolonged survival, but liver metastases are often diffuse with bilobar distribution. Systemic options for these patients are limited as immunotherapy and BRAF targeted drugs that work well in cutaneous melanoma are usually ineffective [26, 27]. IHP has been shown to improve survival in metastatic ocular melanoma; the summary of evidence is outlined in Table 21.1. The SCANDIUM trial is the first randomized clinical trial to evaluate IHP in metastatic uveal melanoma and is ongoing [28].

Colorectal Cancer Liver Metastasis

Approximately 140,000 patients will be diagnosed with colorectal cancer each year in the United States, and 40–50% will present with liver metastasis, either at the time of diagnosis or later in their disease course [29]. More effective systemic therapies have resulted in improved survival, but surgical resection is still the only modality with potential for cure [30]. IHP has been widely studied in the setting of unresectable colorectal liver metastasis (CRCLM), both as a definitive treatment to halt disease progression and improve survival and as a means to potentially downstage and facilitate later resection. There is wide variation in the cytotoxic drugs used. Initial trials primarily evaluated the effect of melphalan with or without TNFα[alpha], while more recent studies using oxaliplatin have also shown favorable outcomes. The role of IHP in CRCLM continues to evolve, and data strongly suggests that all patients should receive upfront systemic chemotherapy as response rates and duration of disease control have vastly improved with the routine use of newer agents, including irinotecan, cetuximab, panitumumab, and bevacizumab [31–33]. Some studies have demonstrated equivalent outcomes of IHP compared to systemic chemotherapy, further supporting the use of IHP as salvage treatment only [17]. If IHP is

Table 21.1 Contemporary studies of isolated hepatic perfusion in patients with metastatic ocular melanoma confined to the liver

Author, year	N	Agent	Response rate	Median survival (mos.)
Vogl et al. (2017) [39]	18	Melphalan	44%	9.6
de Leede et al. (2016) [40]	30	Melphalan ± oxaliplatin	NR	10
Ben-Shabat et al. (2016) [41]	68	Melphalan ± TNFα[alpha]/cisplatin	67%	22
Hughes et al. (2016)[a, b] [42]	65	Melphalan	36.4%	10.6
Forster et al. (2014)[b] [43]	10	Melphalan	50%	12.6
Olofsson et al. (2014) [28]	34	Melphalan	68%	24
Varghese et al. (2010) [44]	17	Melphalan	50%	11.9
van Etten et al. (2009) [45]	8	Melphalan	37%	11
Rizell et al. (2008) [46]	27	Melphalan	70%	7.5
Noter et al. (2004) [47]	8	Melphalan ± TNF	50%	9.9
Alexander et al. (2000) [48]	22	Melphalan ± TNF	62%	11

NR Not reported

[a]Randomized crossover trial including ocular (89%) and cutaneous melanoma (11%). Sixty-five patients underwent IHP

[b]Percutaneous IHP

employed in CRCLM treatment, additional hepatic arterial drug delivery techniques such as hepatic artery infusion pump placement may also be utilized. A summary of clinical data of IHP in CRCLM is outlined in Table 21.2.

Other Diseases

Studies in other disease states have also suggested a benefit for IHP in select patients. Fukumoto et al. [34] and Arai et al. [35] reported their experience with two-stage treatment of multifocal HCC utilizing IHP to downstage disease. They report response rates of approximately 70% and improved overall survival of 25 months in patients completing all intended therapy [34, 35]. Grover et al. [36] also reported their experience with melphalan, TNFα[alpha], and IHP for treatment of unresectable liver metastases for gastroenteropancreatic neuroendocrine tumors (GEP-NET). They reported a 50% response rate in thirteen patients with a median actuarial survival of 48 months [36]. However, the re-emergence of liver transplantation, the advent of peptide receptor radionuclide therapy (PRRT), and the development of more effective systemic agents such as everolimus have provided more treatment options for patients with metastatic GEP-MET and are associated with meaningful long-term outcomes [37, 38].

Summary

IHP is a safe and effective liver-directed therapy that may be employed in select patients to treat unresectable liver metastasis. Response rates exceed 50% in most study cohorts, and morbidity and mortality are acceptably low using contemporary techniques. IHP takes advantage of preferential hepatic arterial blood supply in the vast majority of metastases and allows for concentrated cytotoxic drug delivery to the tumor. For patients with unresectable ocular melanoma, who have no effective systemic agents, IHP offers improved response rates and overall survival. In CRCLM, systemic chemotherapy remains the standard of care for first-line therapy, and IHP should only be carefully integrated into the treatment algorithm of select patients. While studies have demonstrated good safety with IHP, these results have been observed in highly specialized centers with experience with this and other regional therapies. Expertise and good patient selection are needed for acceptable short-term and long-term outcomes.

Table 21.2 Studies of isolated hepatic perfusion with or without hepatic arterial infusion in patients with metastatic colorectal cancer confined to the liver

Author, year	N	Agent	Response rate (%)	Median survival (mos.)
Magge et al. (2013)[a] [49]	12	5-FU + oxaliplatin	82	NR [1 yr 90.9%, 2 yr 71.6%]
van Iersel et al. (2010) [17]	99	Melphalan	47	25
Alexander et al. (2009) [50]	120	Melphalan ± TNFα[alpha]	61	17.4
Zeh et al. (2009)[a] [51]	13	Oxaliplatin	66	25
van Iersel et al. (2008) [52]	105	Melphalan	50	24.8
van Iersel et al. (2007)[a] [53]	30	Melphalan	41	16.9
Alexander et al. (2005)[a] [54]	25	Melphalan	60	12
Rothbarth et al. (2003) [55]	71	Melphalan	59	28.8
Alexander et al. (2002) [56]	7	Melphalan ± TNFα[alpha]	71	19.7
Vahrmeijer et al. (2000) [57]	24	Melphalan	29	19
Marinelli et al. (1996) [11]	9	Mitomycin C	22	17

NR Not Reported

[a]Hepatic arterial infusion used adjunctively

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Pump-Based Hepatic Arterial Infusional Therapy

22

Sebastian Mondaca and Nancy E. Kemeny

Introduction

The history of hepatic arterial infusion (HAI) chemotherapy for treatment of patients with metastatic colorectal cancer (mCRC) began over 30 years ago, and since then its development has been challenging in terms of improving the logistics of the procedure and conducting clinical trials to demonstrate its efficacy [1]. Initially, pump therapy was used without concomitant systemic therapy, and there were concerns about progression of disease outside the liver. In this review we will discuss how these problems have been addressed leading to the development of new programs of this treatment modality across North America and Europe. We will also describe relevant aspects of the procedure and summarize most relevant evidence supporting current indications.

Rationale

The rationale of HAI is based on the differential perfusion of liver metastases, which are perfused by the hepatic artery, while the portal vein supplies the normal liver parenchyma [2]. Another relevant aspect is the possibility to infuse drugs with important first-pass extraction which minimize systemic exposure [3]. Because hepatic arterial blood flow has a high regional exchange rate (100–1500 mL/min), drugs with a high total body clearance and short plasma half-life are more useful for hepatic infusion. Floxuridine (FUDR) is a fluoropyrimidine with a shorter half-life and greater first-pass effect compared to 5-fluorouracil (5-FU). It has been demonstrated that 94–99% FUDR is extracted during the first pass, compared to 19–55% 5-FU [4]. The mean tumor FUDR levels are 15-fold higher when this drug is injected via the hepatic artery compared to portal vein [5]. Oxaliplatin HAI has also been associated with favorable pharmacokinetic profile in rabbit models [6]. Of note, first-pass extraction limits both systemic toxicity and systemic benefit from chemotherapy with FUDR, and therefore HAI has been combined with systemic treatment, which has demonstrated to be safe and effective [7–9].

Pump Insertion and Treatment Administration

HAI can be done by using either hepatic arterial port or a percutaneously placed catheter connected to an external pump, or to a totally implantable pump. Early studies with percutaneously placed hepatic artery catheters were associated with high risk of clotting as well as bleeding [10]. The development of a totally implantable pump allowed long-term HAI with good patency

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Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_22

of the catheter and the hepatic artery and a low incidence of infection (Fig. 22.1). Thorough preoperative planning is relevant before considering a patient for HAI. A computed tomography (CT) scan of the chest, abdomen, and pelvis must rule out extrahepatic disease. Selection of patients with low-burden extrahepatic disease for this therapy must be done very carefully [11, 12]. A CT angiogram must be performed before the procedure to determine a suitable arterial anatomy and assures that the portal vein is patent. During surgery, the abdomen must be explored to rule out extrahepatic disease, and the tip of the catheter is placed at the origin of the gastroduodenal artery, which is ligated distally. Placement of the catheter too distally in this artery leaves a segment continuously exposed to chemotherapy increasing risk of thrombosis. Placement of the catheter into the hepatic artery also may promote thrombosis [12]. The arterial collaterals to stomach, duodenum, and pancreas are identified and ligated. A cholecystectomy must be performed to prevent chemotherapy-induced cholecystitis. An intraoperative injection of methylene blue dye is used to evaluate flow immediately after placement, and postoperatively technetium-99 m is infused through the side port of the pump to assess adequate bilobar perfusion and rule out leaks (Fig. 22.2). In some cases, patients need embolization treatment by interventional radiology to correct these problems. Usually, the pump is placed in a subcutaneous pocket, preferably on the left side. Complications after the procedure are seen rarely and include the following: arterial injury leading to hepatic artery thrombosis (2.4%); misperfusion to the stomach, duodenum, or pancreas (1.7%); pump pocket hematoma (0.4%); and pump pocket infection (1%). Some

Fig. 22.1 Types of implanted infusion pumps. (**a**) codman pump; (**b**) medtronic pump

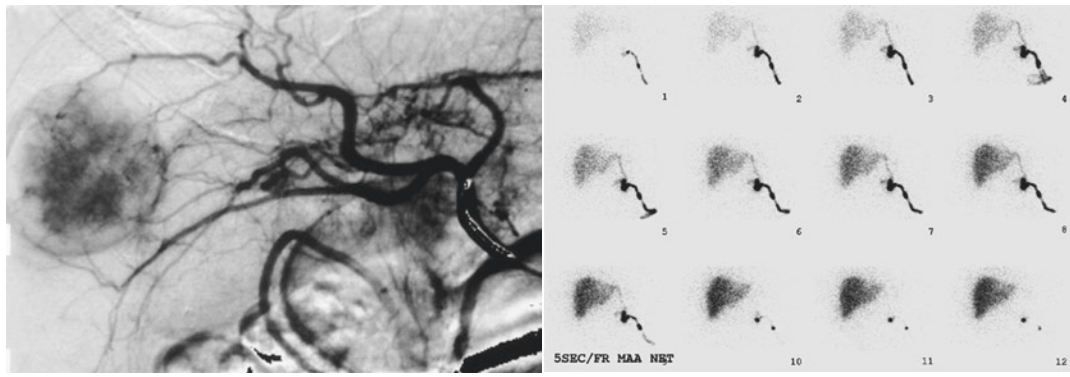

Fig. 22.2 Arteriography showing the tumor derives supply from hepatic artery (left panel). Perfusion scan with isotopically labeled technetium albumin particles to document flow distribution (right panel). These particles are trapped in the first arteriolar-capillary bed encountered

complications, particularly the ones occurring early after the procedure, can be salvaged [13]. Among late complications, pump pocket infection, catheter thrombosis, and peptic ulceration are the most frequent ones. After successive trials at Memorial Sloan Kettering Cancer Center (MSKCC) assessing different dosing and modulation strategies of FUDR, a defined protocol was established that has been used for the last 25 years [14, 15]. In patients receiving HAI for conversion to resectability, a 4-week cycle is used, whereas in patients receiving adjuvant therapy after liver resection, a 5-week cycle is preferred. In both situations, FUDR is delivered in a 14-day infusion at 0.12 mg/kg × pump volume/flow rate with concomitant dexamethasone. On Day 15, an infusion of heparin (30.000 units) is administered via the pump to complete the 4- or 5-week cycle. During treatment, total bilirubin, alkaline phosphatase, and aspartate transaminase (AST) are used to monitor biliary toxicity and adjust dosing accordingly.

HAI in Colorectal Cancer

Colorectal cancer (CRC) is the third most common cancer in the United States, and in 2017, there were an estimated 135,000 new cases, and 50,000 patients died from this disease [16]. In mCRC, HAI has been explored in three settings: as adjuvant treatment after resection, as a treatment for conversion to resectability, and as palliative treatment in chemotherapy-refractory patients. Over the last decades, the resection of colorectal liver metastases (CLM) has become standard of care with an increase in the number of patients getting resection. Initially, only patients with one to three metastases were resected [17], however, now in large institutions patients with more lesions can be resected as long as enough normal liver can be left behind and the frontiers for this indication are continuously being pushed [18].

Adjuvant HAI After Resection CLM

In patients who underwent liver metastasectomy the risk of recurrence is high, and the main site of recurrence is the liver [19, 20]. Perioperative systemic chemotherapy with FOLFOX has shown a benefit in disease-free survival (DFS) in these patients, but a benefit in overall survival (OS) has not been clearly demonstrated [21]. Several trials have studied adjuvant liver-directed therapy with mostly positive results (Table 22.1). A recent systematic review included nine trials that assessed the benefit of adjuvant HAI for patients who underwent resection of CLM. The chemotherapy regimens used with HAI included FUDR (five studies), 5-FU (three studies), and oxaliplatin/iri-

Table 22.1 Summary of individual studies of adjuvant HAI in colorectal cancer

Study	Types of study	Samples	Study treatments	Results (primary outcomes)
Kemeny N [50]	RCT	74 vs 82	HAI FUDR + Sys Ch	2-y OS 86% vs 72% $P = 0.03$
Bolton [51]	Nonrandomized	36	HAI FUDR + Sys Ch	5-y OS 31% (19–50)
Goere [52]	Nonrandomized	44 vs 54	HAI Oxa/Iri + Sys Ch	3-y OS 75% vs 62% $P = 0.17$
House [53]	Nonrandomized	125 vs 125	HAI FUDR + Sys Ch	5-y DSS 76% vs 55% $P < 0.01$
Kemeny M [54]	RCT	53 vs 56	HAI FUDR + Sys Ch	4-y RFS 46% vs 25% $P = 0.04$
Kusonoky [55]	RCT	30 vs 28	HAI 5-FU + Sys Ch	5-y OS 59% vs 27% $P < 0.001$
Lorenz [56]	RCT	113 vs 113	HAI 5-FU	OS 34.5 vs 40.8 mo $P = 0.15$
Onaitis [43]	Nonrandomized	21 vs 71	HAI FUDR + Sys Ch	2-y OS 61% vs 53% $P = 0.58$
Tono [57]	RCT	9 vs 10	HAI 5-FU + Sys Ch	3-y DFS 67% vs 20% $P = 0.045$
Koerkamp [23]	Nonrandomized	785 vs 1583	HAI FUDR + Sys Ch	HR OS 0.67 (0.59–0.76)[a]
Lygidakis [58]	RCT	62 vs 60	HAI Mito + 5-FU + IL2	5-y DFS 60 vs 35% $P = 0.0002$

Abbreviation: *RCT* randomized clinical trial, *HAI* hepatic arterial infusion, *FUDR* floxuridine, *5-FU* 5-fluorouracil, *Sys Ch* systemic chemotherapy, *OS* overall survival, *Oxa* oxaliplatin, *Iri* Irinotecan, *RFS* relapse-free survival, *DFS* disease-free survival, *DSS* disease-specific survival, *HR* hazard ratio, *vs* versus, *mo* months

[a]Adjusted by propensity score

notecan (one study), and the pooled hazard ratio (HR) for OS was 0.75 (95% CI, 0.56–0.99). This systematic review concluded that adjuvant HAI therapy has a benefit both in OS and DFS [22]. A recent study from MSKCC compared 785 patients who underwent a complete resection of CLM and received HAI with 1583 who did not receive this therapy. Despite more advanced disease in the HAI group, the 10-year OS in these patients was 38% compared to 24% in the group without HAI ($P < 0.001$). In the HAI group, there was a higher proportion of patients with node-positive tumors (65% versus 59%; $P < 0.001$), more patients with greater than five lesions (19% versus 12%; $P < 0.001$) and more patients with clinical risk score greater than three (55% versus 42% $P < 0.001$). The median survival was 67 and 44 months in the HAI and systemic-only groups ($P < 0.001$), respectively. The HR adjusted by propensity score demonstrated longer OS with HAI: 0.67 (95% CI, 0.59–0.76). The patients who benefited the most in terms of OS from this intervention were the ones with node negative tumors (129 months with HAI versus 51 months without; $P < 0.001$) and low clinical risk score of recurrence (89 months with HAI versus 53 months without; $P < 0.001$) [23].

HAI to Convert Unresectable CLM

In patients with unresectable CLM, systemic treatment has been proposed as an effective strategy for conversion to resectability, particularly for patients with involvement of critical structures. In such cases, response rate is critical to achieve negative margins after resection, and a strong correlation between response rate and resectability has been demonstrated [24]. The most active systemic regimens have shown an overall response rate around 50–60% in this setting [25, 26]. Initial studies of HAI FUDR in patients with mCRC showed a response rate between 42% and 47%, which compared favorably to the response achieved in the systemic chemotherapy arms at that time [27, 28]. Subsequent studies that have combined HAI with modern systemic regimens have demonstrated higher responses ranging from 64% to 100% [29]. In a cohort of 49 patients with unresectable CLM treated at a single institution with HAI FUDR and concurrent systemic chemotherapy (oxaliplatin and irinotecan), the response rate was 92%. Furthermore, the resectability rate was 47%, and the median survival was 51 months in the treatment-naive group and 35 months in the group that previously received chemotherapy [30]. These encouraging results were replicated in a phase II trial in which bevacizumab was added to the systemic treatment. In the first 24 patients who received bevacizumab, there was increased risk of biliary toxicity and no impact on other clinical outcomes; therefore, the remaining patients did not receive this biologic [31]. In a recent French trial, HAI with irinotecan, oxaliplatin, and 5-FU associated with systemic cetuximab showed an objective response rate of 41% in patients with unresectable *KRAS* wild-type CRC after a first-line systemic treatment and led to resection in 30% of them [32]. Determining resectability is highly variable among different institutions, with nonuniform criteria for selection of patients. However, it seems that patients with both extrahepatic disease and more than 10 liver lesions have particularly bad prognosis and very low chance of long term DFS [33].

HAI in Chemotherapy-Refractory CRC

The options for treating refractory mCRC are limited and there remains an unmet need for new treatments. In a retrospective review, 110 patients with mCRC refractory to oxaliplatin, irinotecan, and fluorouracil-based treatments were treated with HAI FUDR with or without concomitant systemic treatment and had a response rate of 33% and a PFS of 6 months. Acknowledging the limitations of cross-trial comparisons, this result compares favorably to other alternatives in chemotherapy-refractory mCRC such as regorafenib or TAS-102, which have a progression-free survival around 2 months and response rate lower than 5% [34, 35].

HAI in Intrahepatic Cholangiocarcinoma

Intrahepatic cholangiocarcinoma (ICC) is an aggressive gastrointestinal malignancy, and surgery is the only approach with curative potential. Unfortunately, a minority of patients are resectable upon diagnosis and most patients present with locally advanced or metastatic disease. Locoregional therapies are considered appropriate for patients with locally advanced unresectable tumors, and there is emerging data supporting ablative radiotherapy, transarterial chemoembolization, and radioembolization [36–38]. Initial studies conducted more than 20 years ago suggested a benefit for HAI in locally advanced ICC [39], and modern series have confirmed these results. A recent retrospective review of 78 patients, who underwent treatment with combined HAI and systemic chemotherapy, showed that overall survival was longer compared to patients who received systemic treatment alone (30.8 versus 18.4 months, respectively, $P < 0.001$) [40]. In a phase II trial, 34 unresectable patients (26 ICC and 8 hepatocellular carcinoma) were treated with HAI FUDR. Overall response rate was 47% (54% in ICC), and OS was 29 months [41]. Similarly, in a series of 11 unresectable ICC patients treated with HAI with 5-FU and oxaliplatin, 5 had a partial response, and 3 were able to undergo complete resection [42]. Currently at MSKCC, a phase II trial is assessing the efficacy and safety of HAI FUDR combined with systemic gemcitabine and oxaliplatin in unresectable ICC (NCT01862315).

Toxicity of HAI

Hepatobiliary toxicity is the most frequent adverse event seen with HAI FUDR and is a frequent cause of dose reductions and stopping treatment [43]. The etiology of this toxicity is ischemic and inflammatory effect on the bile ducts. The bile ducts are particularly sensitive to HAI chemotherapy, because, like hepatic tumors, they derive their blood supply almost exclusively from the hepatic artery. The addition of dexamethasone during treatment has had a relevant impact on decreasing biliary toxicity [44]. Clinically, biliary toxicity is manifested as elevations of AST, alkaline phosphatase, and bilirubin levels. Elevation of AST level is an early sign of toxicity, whereas elevation of the alkaline phosphatase or bilirubin is evidence of more severe damage [45]. In the early stages of toxicity, hepatic enzyme elevations will return to normal after the drug is stopped. In more advanced cases, jaundice might not resolve. In a review of 393 consecutive patients who received HAI FUDR on prospective protocols at MSKCC, the incidence of biliary sclerosis was 5.5% (16 of 293) in the adjuvant setting and 2% (2 of 100) in patients with unresectable disease [46]. Close monitoring of liver function test and strict adherence to treatment protocol are paramount to avoid severe toxicity. Another relevant complication is peptic ulcer disease, which can be reduced via careful dissection of these collaterals at the time of pump placement. However, even without radiologically visible perfusion of the stomach and duodenum, mild gastritis and duodenitis can occur. To avoid these complications, patients are treated with prophylactic proton pump inhibitors. Myelosuppression does not occur with intrahepatic FUDR, but HAI mitomycin C through the side port may produce minor decrease in platelet counts. Nausea, vomiting, and diarrhea do not occur with HAI FUDR. If diarrhea occurs, shunting to the bowel should be suspected [45].

Future Directions

The widespread implementation of HAI treatment has been challenging given its logistics and learning curve to reduce operative complications and hepatobiliary toxicity. Moreover, the problems of conducting randomized trials of an intervention that involves a surgical procedure have been well described [47]. However, thanks to the persistent effort of few centers in America and Europe, modern data support its benefit in selected patients, and new institutions are emerging with particular interest in this treatment

modality. In the following years, emergent data will refine this approach leading to more homogeneous regimens. While FUDR is the most used drug for HAI in the United States, in Europe, it is seldom used because of concerns about biliary toxicity, and it is replaced by oxaliplatin or 5-FU [48]. Likewise, there is no clarity about the best systemic regimen to combine with HAI. Intense regimens such as FOLFOXIRI or combinations with anti-EGFR monoclonal antibodies have also demonstrated high response rate and increased resection rate [26, 49]; therefore, they could be explored as induction regimens followed by HAI in unresectable patients. Given the difficulty of conducting randomized clinical trials to address multiple unanswered questions regarding HAI, the development of multi-institutional prospective registry may be an alternative to generate high-quality data.

Conclusion

After decades of research, HAI has emerged as a plausible alternative therapy with compelling data of efficacy and should be considered in all CRC patients with unresectable and resected liver-confined metastatic disease, where it is available. It has known toxicity and procedure-related complications, which can be minimized with specific technical expertise and knowledge in surgical, radiologic, nursing, and medical oncologic aspects of the procedure.

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Percutaneous Transcatheter Particle Therapies

23

Grace C. Lee, T. Clark Gamblin, and Motaz Qadan

Introduction

While surgical resection is considered the gold standard for hepatocellular carcinoma (HCC), fewer than 20 percent of patients have resectable disease [1, 2]. Liver transplantation is another curative option. However, the supply of donor organs is severely limited in the United States [3]. Furthermore, in the majority of patients with unresectable disease, chemotherapy is associated with systemic toxicities without appreciably improving survival [4–6].

In the setting of unresectable disease, there has been an increasing role for transarterial particle therapies in the management of hepatic malignancies. These therapies include conventional transarterial chemoembolization (cTACE), chemoembolization with drug-eluting beads (DEB-TACE), bland transarterial embolization (TAE), and radioembolization or selective internal radiation therapy (SIRT) with Yttrium-90 (Y90) [7]. All of these techniques rely on the fact that the hepatic artery is the predominant blood supply to liver tumors, while normal liver parenchyma receives most of its blood supply from the portal vein [8]. Therefore, by infusing therapeutics and embolic agents into the hepatic artery, transarterial techniques reliably target tumors while sparing the healthy surrounding liver parenchyma (Fig. 23.1) [7].

Developed in the 1970s and initially only used for palliation in patients with unresectable and chemorefractory tumors, regional therapies are increasingly being used with surgery for a curative intent, as a bridge to transplantation or tumor resection [8, 9]. Furthermore, potential clinical applications have expanded beyond HCC to include intrahepatic cholangiocarcinoma and liver metastases from colorectal cancer, ocular melanoma, neuroendocrine tumors, and gastrointestinal sarcomas [1, 10]. In this chapter, percutaneous transcatheter particle therapies and an evidence-based approach with the available data are discussed.

Conventional Transarterial Chemoembolization (cTACE)

Background and Technique

Conventional transarterial chemoembolization (cTACE) involves the catheter-based infusion of chemotherapeutics to tumor-feeding arteries,

GCL was supported by the National Institutes of Health T32 Research Training in Alimentary Tract Surgery grant DK007754–13.

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Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_23

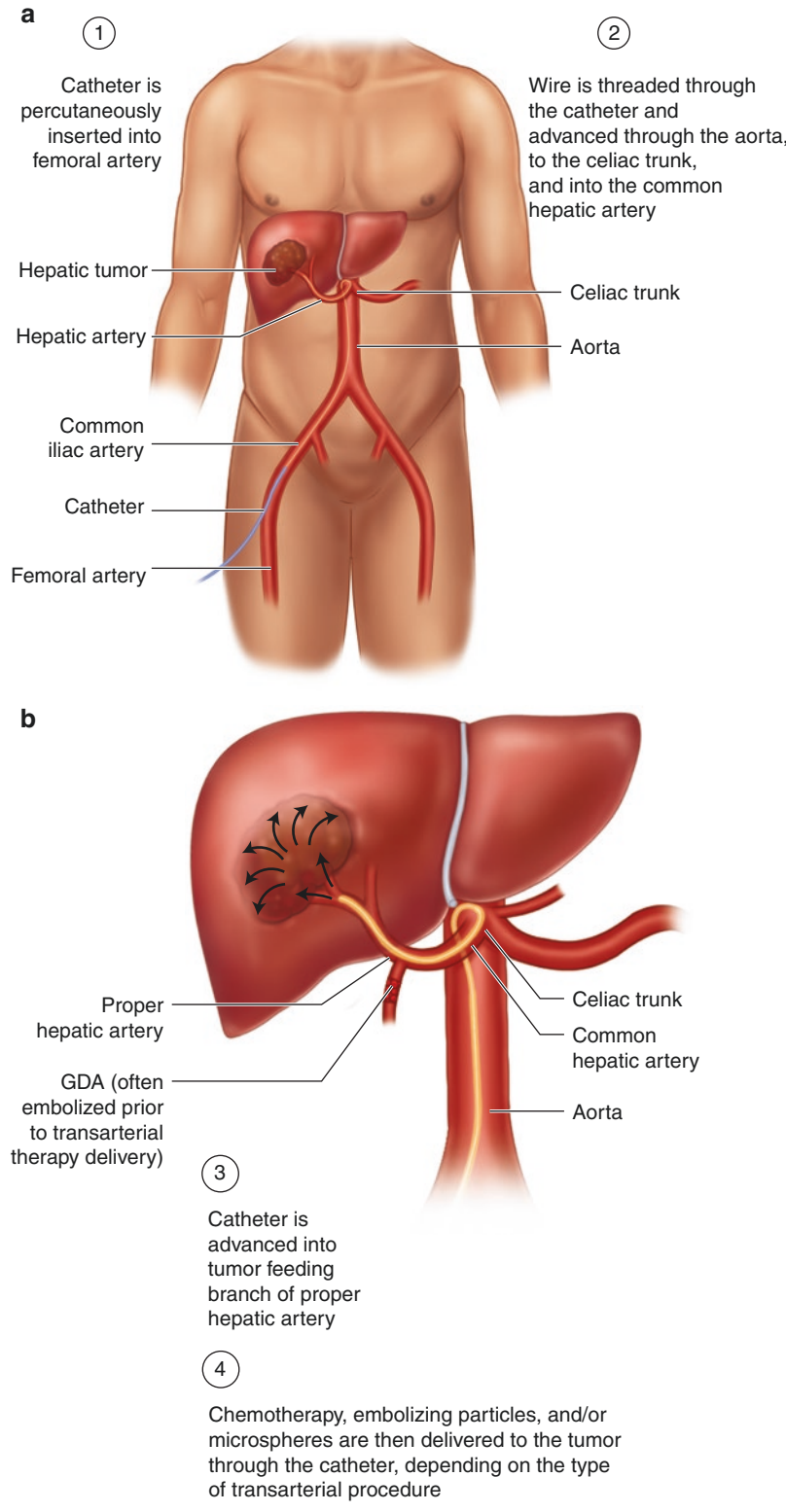
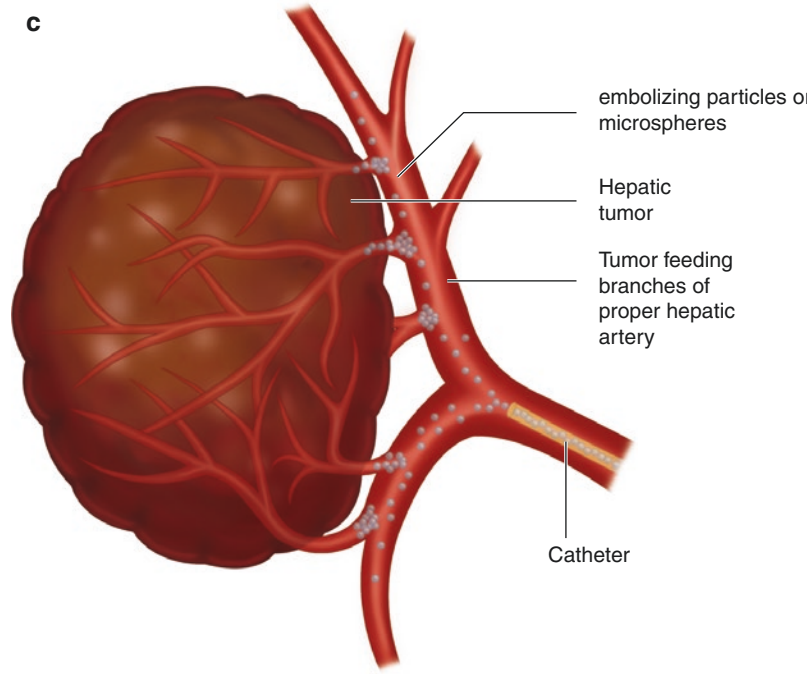


Fig. 23.1 Technical aspects of performing transarterial therapies for hepatic tumors. (**a**) First, a catheter is percutaneously inserted into the femoral artery. The wire is threaded through the catheter and advanced to the celiac trunk, and into the common hepatic artery. (**b**) The catheter is advanced into tumor-feeding branches of the proper hepatic artery. Chemotherapeutic agents, embolizing particles, and/or microspheres are then delivered to the tumor through the catheter, depending on the type of transarterial procedure. (**c**) These embolizing particles or microspheres lodge in small tumor-feeding arterial branches, causing partial ischemia to the hepatic tumor

Fig. 23.1 (continued)



⑤ Embolizing particles and microspheres lodge in tumor feeding arterial branches, causing partial ischemia to the hepatic tumor

followed by the embolization of the hepatic artery with particles designed to render the tumor ischemia [1]. This technique achieves peritumoral drug concentrations twice as high as hepatic arterial infusion without embolization, with decreased systemic toxicity and prolonged detectable tumor drug levels for up to 1 month after cTACE [11–13].

The most commonly used single chemotherapeutic agent for cTACE is doxorubicin, though many interventional radiologists in the United States use a combination of cisplatin, doxorubicin, and mitomycin [8]. Lipiodol, an iodinated ester that acts as an emulsifying agent and preferentially binds tumors cells, is often added to the chemotherapeutic mixture as well [7]. Embolization of the tumor-feeding arteries is then performed, using either temporary occluding options such as Gelfoam or more permanent options such as polyvinyl alcohol particles or microspheres (Embozene and Embospheres) [8]. There has been no demonstrated difference in survival based on type of embolic agent, although patients who receive Gelfoam often receive more treatments than those treated with polyvinyl alcohol [14].

Of note, some advocate that embolization should preserve some arterial flow to the tumor, as complete tumor ischemia may paradoxically stimulate tumor growth via the upregulation of vascular endothelial growth factor and hypoxia-inducible factor 1 [15, 16]. Due to this possibility, studies examining the potential of combining TACE with newer biologics that target these hypoxia-induced tumor pathways are underway [8]. Maintaining patency of the hepatic artery after cTACE also allows multiple TACE treatments to be performed, as repeated treatments have been shown to increase patient survival [17–19].

Most centers assess liver function and tumor response after cTACE every 4–12 weeks [8]. After successful TACE, tumor size does not always decrease; therefore, treatment response

and tumor necrosis are often assessed by lack of contrast enhancement on computed tomography (CT), lipiodol deposition in the tumors, or diffusion-weighted uptake using magnetic resonance imaging (MRI) [20, 21].

Most patients can be safely discharged the day after cTACE is performed. The procedure is generally well-tolerated, with the most common adverse event being postembolization syndrome, which occurs in 3.8–10% of patients [8]. Symptoms of this syndrome include right upper quadrant pain, nausea, vomiting, fatigue, and fever, which usually resolve in 7–10 days. Other serious but rare complications include acute liver failure, acute renal failure, encephalopathy, hepatic or splenic abscess, tumor rupture, and pulmonary lipiodol embolism [8, 22].

Role of Conventional TACE in Palliative Treatment of Unresectable HCC

Over the past three decades, cTACE has become widely used in the treatment of patients with unresectable HCC. Though early randomized controlled trials (RCTs) of cTACE produced equivocal results, they were conducted during the evolution of the technique, were underpowered, and were insufficiently treated patients in the chemoembolization arms with fewer treatments relative to current practice [23, 24]. Two pivotal RCTs have since been conducted, which demonstrated a significant survival benefit in patients with locally advanced HCC, preserved liver function, and adequate performance status who underwent cTACE compared to best supportive care. Lo et al. randomized 80 Asian patients to either chemoembolization (cisplatin, Lipiodol, and Gelfoam) or symptomatic treatment [18]. The patients in the chemoembolization group received a median of 4.5 treatments. TACE was associated with significant improvements in overall survival (1 year, 57% vs. 32%; 2 year, 31% vs. 11%; $p = 0.006$). The other trial, by Llovet et al., randomly assigned 112 European patients to chemoembolization (doxorubicin and Gelfoam), embolization (Gelfoam alone), or conservative treatment [19]. The authors also found significantly improved overall survival in the chemoembolization group compared to conservative treatment (1 year, 82% vs. 63%; 2 year, 63% vs. 27%; $p = 0.009$), with a hazard ratio (HR) of 0.47 ($p = 0.025$).

Recent meta-analyses have also demonstrated a consistent survival benefit associated with cTACE in patients with unresectable HCC. Llovet et al. performed a meta-analysis of 7 RCTs (545 patients) and found a significant survival benefit from chemoembolization with cisplatin or doxorubicin (odds ratio (OR) 0.42, $p = 0.017$), with objective treatment responses observed in 35% of patients [4]. Marelli et al. identified 175 studies assessing transarterial therapies for HCC and found that 1-year and 2-year overall survival after TACE was 62% and 42%, respectively [22]. Their meta-analysis of nine RCTs also confirmed that TACE was associated with an improvement in survival (OR 0.7, $p = 0.003$). The most recent Cochrane meta-analysis by Oliveri et al. in 2011 included nine trials and found that TACE was not associated with a significant survival benefit (HR 0.81, 95% confidence interval (CI) 0.64–1.02, $p = 0.07$) [25]. Criticisms of this meta-analysis focused on study selection, specifically inclusion of early RCTs when patient selection, procedural techniques, and treatment repetition were still being refined [26, 27]. Repeat analysis of only the three most recent trials found that TACE was associated with a significant survival benefit (HR 0.79, 95% CI 0.63–1.00) [18, 19, 27, 28].

Other Clinical Applications of Conventional TACE

Though historically only used as palliative therapy for patients with unresectable HCC, cTACE has been explored as a bridge to liver transplantation. Patients with cirrhosis and whose tumor is within the Milan criteria are often listed for transplantation. However, dropout rates can be high at over 20% due to tumor progression [29]. Two small studies of patients listed for transplantation within the Milan criteria found that preoperative TACE decreased or eliminated the risk of tumor

progression while awaiting transplant [3, 30]. Furthermore, two promising studies demonstrated that TACE may be used in carefully selected patients outside of the Milan criteria to downstage tumors and subsequently enable eligibility for transplantation [31, 32]. Pretransplant TACE does not appear to be associated with worse outcomes following hepatic transplantation, including similar rates of postoperative complications, overall survival, and disease-free survival [33, 34].

Conventional TACE is also being investigated for its potential to make inoperable tumors amenable to resection. A study of 49 patients who received transarterial therapy, mostly TACE, and who subsequently underwent salvage surgery found that 42.9% had recurrence after surgery, though 1-, 3-, and 5-year survival rates were 98%, 64%, and 57%, respectively [35]. Interestingly, another study of 82 patients who were downstaged after receiving TACE found that salvage surgical resection was associated with a survival benefit in those with a partial response to TACE but offered no survival benefit in patients who had a complete response to TACE [36]. Therefore, salvage surgery after successful tumor downstaging by TACE may improve survival in carefully selected patients with initially unresectable HCC.

Other clinical applications of TACE include potential use as salvage therapy for intrahepatic tumors recurrences after resection, although results from small studies comparing salvage TACE to percutaneous ablation are mixed [37, 38]. There may also be a role for adjuvant TACE after resection, as postoperative TACE has been associated with improved overall survival and disease-free survival in meta-analyses [39]. TACE has also been used to treat unresectable colorectal liver metastases, with favorable results in patients with good performance status and no extrahepatic disease [1].

In conclusion, the technique of conventional TACE has been refined since it was introduced over three decades ago. It has become a standard-of-care option for patients with HCC not amenable to resection, as multiple recent trials demonstrate an association between improved survival and cTACE in patients with unresectable HCC compared to systemic chemotherapy or best supportive treatment alone [6, 18, 19, 22]. Additional roles exist in tumor downstaging to permit transplantation and/or resection, as well as tumor salvage in the setting of recurrence.

Transarterial Chemoembolization with Drug-Eluting Beads (DEB-TACE)

An adaptation of conventional TACE combines chemotherapy arterial infusion and delivery of embolic agents into one step by loading microspheres, beads, and other types of embolizing particles with chemotherapeutic drugs. These particles gradually release the drug over time, with the goal of delivering drug to the tumor in a precise, controlled, and sustained manner (Fig. 23.2) [8]. This technique is called transarterial chemoembolization with drug-eluting beads (DEB-TACE), and often uses doxorubicin as the chemotherapeutic of choice. It offers a favorable pharmacokinetic profile, as it leads to higher intra-tumoral levels of doxorubicin and increased tumor necrosis, but with lower plasma concentrations of doxorubicin compared to cTACE [40, 41]. DEB-TACE has also been shown to deliver high concentrations of doxorubicin to as far as 200 μm from the bead edge for at least 1 month, thus enabling prolonged contact time of the drug with tumor [42].

Early retrospective studies were promising, demonstrating an association with improved survival after DEB-TACE compared to cTACE in patients with HCC [43, 44]. One study found higher treatment response after DEB-TACE compared to cTACE ($p < 0.001$), longer time-to-progression in the DEB-TACE group ($p = 0.018$), and no statistically significant difference in liver toxicity between the two groups [45]. However, these favorable results after DEB-TACE were not seen in subsequent RCTs. The largest trial, the PRECISION V study, included 212 patients with HCC and found higher rates of tumor response after DEB-TACE compared to cTACE, but the differences were not statistically significant

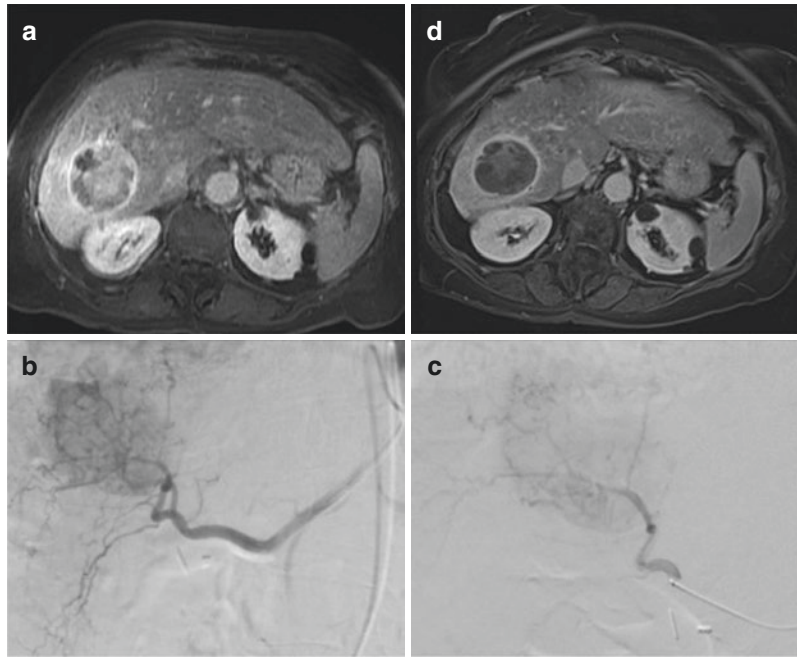


Fig. 23.2 An 84-year-old woman with a 5.7 cm right lobe hepatocellular carcinoma initially underwent SIRT however was found to have residual enhancing tumor on liver MRI (**a**), and subsequently underwent DEB-TACE. (**b**) Super-selective catheterization and angiography of the right hepatic artery was performed. (**c**) Next, super-selective angiography and chemoembolization using drug-eluting beads of the posterior branch of the right hepatic artery was performed. (**d**) Liver MRI 1 year after DEB-TACE demonstrated decreased size and favorable treatment response of the lesion. (Courtesy of Kei Yamada, MD)

(p = 0.11) [46]. Two smaller RCTs comparing DEB-TACE to cTACE also found no significant difference in tumor response [47, 48]. Nevertheless, the PRECISION investigators did find that DEB-TACE was associated with reduced liver toxicity ($p < 0.001$) and decreased doxorubicin-related side effects ($p = 0.0001$) [46, 49]. A subsequent analysis of long-term results by the PRECISION investigators found no difference in tumor response, time-to-progression, adverse events, or overall survival [50]. Two meta-analyses again found no difference in tumor response, survival, or adverse events when comparing DEB-TACE to cTACE [51, 52].

Therefore, DEB-TACE appears to offer equivalent survival and tumor response compared to cTACE, with potentially less systemic toxicity. In this context, many groups have adopted DEB-TACE for unresectable HCC, and it is currently being evaluated with irinotecan-eluting beads for metastatic colorectal cancer to the liver [53].

Bland Transarterial Embolization (TAE)

Bland transarterial embolization (TAE), in which embolic agents are selectively delivered to the tumor-feeding arteries without associated chemotherapy, thus inducing tumor ischemia, has been proposed as an alternative to conventional TACE and DEB-TACE. Numerous retrospective and prospective studies have been performed comparing cTACE to bland TAE, none of which show any difference in overall survival between the two modalities [54–59]. A recent trial by Meyer et al. compared 86 patients who were randomized to TAE or TACE and found improved tumor response in the TACE group ($p = 0.04$), but no difference in median overall survival (17.3 vs. 16.3 months, $p = 0.74$) or median progression-free survival (7.2 vs. 7.5 months, $p = 0.59$) [57]. A retrospective analysis of 405 patients in the Veterans Affairs cohort who underwent either

TACE or TAE also found no difference in median overall survival (20.1 vs. 23.1 months, $p = 0.84$) [59]. Additionally, a meta-analysis of three trials found no survival difference between patients treated with TACE versus TAE [22].

The debate over whether the addition of a chemotherapeutic agent affects disease response or survival has continued even after the introduction DEB-TACE. An RCT by Malagari et al. compared 41 patients who received doxorubicin DEB-TACE with 43 patients who received TAE with BeadBlock and found a longer time to progression for patients in the DEB-TACE group (42.4 vs. 36.2 weeks, $p = 0.008$), but did not assess survival [60]. A more recent trial by Brown et al. compared 51 patients who were treated with BeadBlock with 50 patients who received doxorubicin DEB-TACE and found no difference in adverse events, tumor response, progression-free survival, or overall survival [61].

Therefore, due to the lack of apparent survival difference between bland embolization and conventional TACE, some authorities favor treating patients with unresectable HCC with TAE alone [61]. However, other groups state that there is insuffieicnt data to ascertain the impact on survival, and since some studies have shown improved tumor response after TACE compared to TAE, it recommends treating patients with TACE unless patients have comorbidities that would prevent chemotherapy use [62].

Selective Internal Radiation Therapy (SIRT) with Y-90

Background and Technique

Though external beam radiation therapy has been used in the treatment of many types of malignancies, the *external* application of radiation has proven less feasible in hepatic malignancies due to high rates of radiation-induced liver disease when administered at tumoricidal doses [63]. To address this limitation, the technique of radioembolization or selective internal radiation therapy (SIRT) was developed in the 1960s [64], in which radioactive glass or resin microspheres are delivered via a catheter into tumor-feeding branches of the hepatic artery, thus delivering doses as high as 150 Gy to hepatic tumors while sparing normal liver parenchyma [65].

Yttrium-90 (Y-90), a pure beta particle emitter with a half-life of 64 hours and tissue penetration of 2.5–10 mm, is embedded into two commercially available microspheres (Thera-Spheres and SIR-Spheres). Thera-Spheres (BTG Medical, Ottawa, Canada) are glass spheres, 20–30 μm in size, that are approved for HCC treatment. SIR-Spheres (Sirtex Medical, Wilmington, MA, USA) are made of resin, 20–60 μm in size, and are approved for treatment of colorectal liver metastases. Of note, the particles are not designed to be embolic, as SIRT requires continued blood flow in order to generate free radicals from the ionization of water molecules by the beta radiation [65, 66].

Patient evaluation prior to SIRT includes CT scans of the chest, abdomen, and pelvis to rule out extrahepatic disease. Triphasic liver CT or MRI is necessary to evaluate tumor location and size, ensure there is adequate liver reserve, and assess for variant vascular anatomy [66]. CT scans are also helpful in identifying tumor characteristics associated with favorable response to SIRT, including well-defined tumor margins and central hypervascularity [67]. Patients then undergo mesenteric angiography 1–3 weeks before SIRT, which enables careful arterial mapping as well as coil embolization of extrahepatic collateral arteries (such as the gastroduodenal artery, right gastric artery, cystic artery, and accessory left gastric artery) that may otherwise lead to off-target tissue damage if not occluded prior to SIRT [68]. Finally, patients undergo Technetium-99 m labeled macroaggregated albumin scans to assess for hepatopulmonary or splanchnic shunting (Fig. 23.3). If there is a high degree of shunting, then SIRT is contraindicated due to the risk of extrahepatic radiation exposure, including the risk of radiation-induced pneumonitis. If the shunt is small, it may be embolized and reassessed with a repeat scan prior to SIRT [66, 69].

During the SIRT procedure itself, hepatic angiography is again performed and the radioactive microspheres are now delivered to tumor-feeding arteries under fluoroscopic guidance (Fig. 23.4).

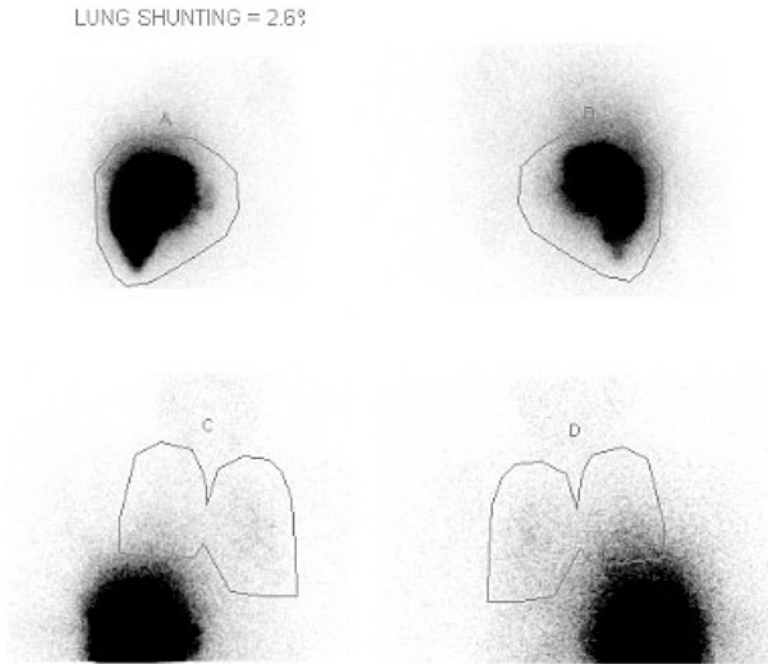


Fig. 23.3 Before SIRT, patients undergo Technetium-99 m labeled macroaggregated albumin scans to assess for hepatopulmonary or splanchnic shunting. SIRT is contraindicated if there is a high degree of shunting due to risk of extrahepatic radiation exposure. This scan demonstrates distribution of radiotracer in the right hepatic lobe. In panels **A** and **B**, the black line is a general outline of the liver. Panel **A** is an anterior view of the abdomen, while panel **B** is a posterior view of the abdomen. In panels **C** and **D**, the black lines are general outlines of the lungs. Panel **C** is an anterior view of the chest, while panel **D** is a posterior view of the chest. Estimated lung shunting was 2.6%. There was no radiotracer distribution elsewhere suggestive of non-target embolization. This patient later underwent SIRT. (Courtesy of Kei Yamada, MD)

Patients then undergo a single-photon emission CT (SPECT) scan to assess the distribution of the microspheres in the tumor [65]. Tumor response is evaluated using triphasic CT or liver MRI 1, 3, and 6 months after SIRT, using the World Health Organization (WHO) criteria, Modified Response Evaluation Criteria in Solid Tumors (mRECIST) [70], or the European Association for the Study of the Liver (EASL) Criteria [71].

SIRT is often well tolerated and performed as an outpatient procedure [66]. The most common complication is postembolization syndrome, which occurs in 20–55% of patients and includes abdominal pain, nausea, vomiting, fatigue, and low-grade fever that develop days to weeks after SIRT treatment [72]. More serious complications include radiation-induced liver disease (0–4% of patients) [73], biliary complications (<10%) [74], and gastric or small bowel injury (3%) [75] due to radioembolization through unrecognized collaterals to the stomach and duodenum. Radiation-induced pneumonitis is rare (<1%) [76]. Transient lymphopenia has also been noted but has not been associated with increased risk of infection [77].

Role of SIRT in the Treatment of Unresectable HCC

Early studies established the safety and feasibility of SIRT for unresectable HCC. In a pivotal study by Salem et al., 291 patients with HCC received 526 SIRT treatments (mean 1.8 per patient) [78]. The authors reported a 30-day mortality rate of 3%, with tumor response rates of 42% by WHO criteria and 57% by EASL criteria. Time to progression was 7.9 months, and median survival was 17.2 months in patients with Child-Pugh A disease

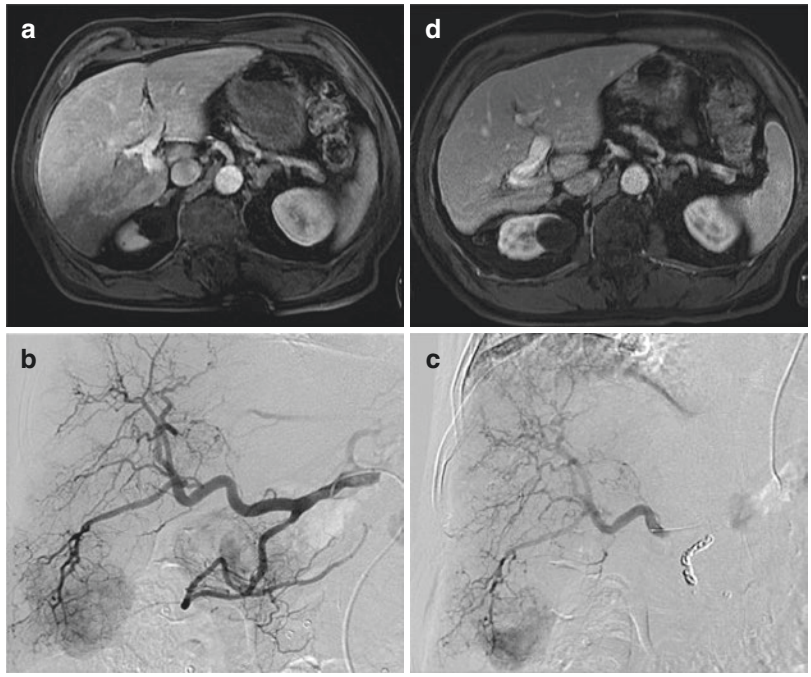


Fig. 23.4 A 73-year-old man was diagnosed with biopsy-proven hepatocellular carcinoma (**a**) and underwent SIRT. (**b**) Super-selective catheterization and angiography of the right hepatic artery was performed. (**c**) Next, super-selective angiography and radioembolization of the right hepatic artery using Yttrium-90 coated microspheres was performed. Coils from the GDA embolization performed prior to SIRT are visible. (**d**) Liver MRI 17 months after SIRT demonstrated excellent treatment response of the lesion. (Courtesy of Suvranu Ganguli, MD)

and 7.7 months in those with Child-Pugh B disease. Sangro et al. enrolled 325 patients with HCC who underwent SIRT at 8 European centers, and reported a median overall survival of 12.8 months, with 30-day mortality rate of 6.8% [79].

Subsequent studies have compared SIRT to TACE in patients with HCC, finding similar survival outcomes but fewer symptomatic side effects after SIRT. Lance et al. examined 73 patients with HCC who underwent either SIRT or TACE [80]. They found no significant difference in median survival (8.0 vs. 10.3 months, $p = 0.33$). However, postembolization syndrome was more severe and led to greater hospitalizations in the TACE group. In a large RCT, Salem et al. assigned 179 patients with HCC to cTACE or SIRT and found that patients in the SIRT group had significantly longer median time to progression than patients in the cTACE group (>26 vs. 6.8 months, $p = 0.001$; HR 0.122, $p = 0.007$) [81]. Both groups had similar tumor response rates (87% vs. 74%, $p = 0.4$) and similar median overall survival (18.6 vs. 17.7 months, $p = 0.99$), while the cTACE patients were more likely to develop diarrhea or hypoalbuminemia. Improved quality of life scores with SIRT have also been reported elsewhere [82].

Though SIRT was initially only used for palliation, the utility of SIRT in downstaging HCC tumors for curative surgical therapy has been reported. In 1 study of 21 patients with stage T3 HCC who underwent SIRT, 6 patients were downstaged and were treated with curative intent (4 patients underwent liver resections, 2 underwent liver transplantation) [83]. The six patients who underwent curative-intent therapy after SIRT had significantly improved survival compared to those who only received SIRT. Another study identified 12 patients who were downstaged after SIRT and subsequently underwent liver resection [84]. The authors noted that average length of stay was 7 days, readmission rate was 42%, and 90-day morbidity and mortality were 42% and 8%, respectively.

These smaller studies prompted the larger, multicenter, Post-SIR-Spheres Surgery Study (P4S), which was published in 2017 [85]. This retrospective analysis of 100 patients with primarily HCC or metastatic colorectal cancer found that, after SIRT, 71 patients went on to undergo liver resection and 29 received a liver transplant. One-fourth of patients experienced a Grade 3+ complication, 7% developed liver failure, and 90-day mortality rate was 4%. Given the pre-existing operative risk of these generally higher-risk patients, these morbidity and mortality rates were noted to be acceptable, suggesting that liver resection after SIRT is safe and feasible in carefully selected patients.

Role of SIRT in Treatment of Colorectal Liver Metastases

Radioembolization has also been clinically applied to unresectable and chemorefractory colorectal liver metastases (CRLM), with promising results. It was first tested as single-line therapy in patients with CRLM who had failed multiple prior trials of systemic chemotherapy. For example, Nace et al. examined 51 patients with CRLM who had failed 2 regimens of systemic chemotherapy and then underwent SIRT [86]. Over three-quarters of patients had either stable disease or a partial response, and median overall survival was 10.2 months after the initial SIRT treatment. Bester et al. compared 339 patients with chemorefractory liver metastases who underwent SIRT to 51 patients who received best supportive care [87]. Median overall survival was significantly longer in patients who underwent SIRT (12.0 vs. 6.3 months, $p < 0.001$), with an acceptable rate of complications.

Other groups have extensively evaluated the combination of SIRT with systemic chemotherapy for patients with unresectable CRLM, including a phase I study that established dosing protocols for Y-90 SIRT with systemic fluorouracil and leucovorin [88]. Single-institution retrospective studies demonstrated an improved treatment response in patients who received SIRT plus systemic therapy over systemic therapy alone, including a cohort of 133 patients with unresectable CRLM who underwent SIRT [89]. In this group, 1% of patients had a complete response, 31% partial response, 31% stable disease, and 37% progressed. Combined modality therapy with SIRT and systemic therapy were associated with an improved treatment response ($p = 0.007$). A phase III randomized trial by Hendlisz et al. confirmed these findings [90]. The authors randomized 44 patients with unresectable, chemorefractory CRLM to intravenous fluorouracil alone or SIRT plus fluorouracil and found that median time for tumor progression was significantly longer in the SIRT group (2.1 vs. 4.5 months, HR 0.51, $p = 0.03$). Number of grade 3 or 4 toxicities and median overall survival were not significantly different between the two groups.

SIRT appears to be a promising therapy for unresectable HCC and CRLM, with similar survival, potentially improved tumor response, and better tolerability when compared to TACE [80–82]. Liver resection after SIRT has also been shown to be safe and feasible in patients whose tumors could be downstaged to the point of resectability [85].

Conclusions

Percutaneous transcatheter particle therapies have become essential in the care of patients with unresectable hepatic malignancies, both for palliation and as a bridge to potential curative therapy. Conventional TACE has been associated with improved survival in patients with unresectable HCC [6, 18, 19, 22], and preoperative cTACE has been shown to decrease the risk of tumor progression while awaiting transplantation [3, 30]. DEB-TACE offers similar tumor response rates and survival rates as cTACE with fewer local toxicities and systemic side effects [46, 49]. There appears to be no survival difference between bland TAE and cTACE, leading some groups to favor bland TAE to avoid chemotherapy-related exposure [54–59]. SIRT has also demonstrated promising results, with similar survival rates as TACE but with longer time to progression, better tolerability, and better quality of life than TACE [80–82].

Widely used in the management of patients with HCC and colorectal liver metastases, applications for these transarterial particle therapies are expanding to intrahepatic cholangiocarcinoma and liver metastases from ocular melanoma, neuroendocrine tumors, and gastrointestinal sarcomas [1, 10]. Clinicians are also pushing the boundaries by administering TACE in the adjuvant setting and administering SIRT to increase tumor resectability [39, 85]. Given the multimodal approach of hepatic tumors and breadth of available treatments, including a variety of transcatheter therapies, discussion of treatment options in multidisciplinary tumor boards (including surgical oncologists, transplant surgeons, medical oncologists, radiation oncologists, interventional radiologists, and hepatologists) and careful patient selection are critical [62, 66]. In this era of personalized medicine, future studies will hopefully delineate which patients will benefit most from these transarterial therapies [7].

Acknowledgments The authors would like to acknowledge Dr. Suvranu Ganguli and Dr. Kei Yamada, both of the Department of Radiology, Massachusetts General Hospital, Boston, MA, for providing the images used in Figs. 23.2, 23.3, and 23.4.

Conflicts of Interest The authors have no conflicts of interest to disclose.

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Hepatic Perfusion: Surgical and Catheter

24

Stephanie H. Greco and H. Richard Alexander Jr.

Introduction

Effective treatment of isolated and unresectable liver metastases remains a significant challenge in the field of oncology. In 2018, there were estimated 140,250 new cases of colorectal cancer in the United States (SEER data), and approximately 50% of patients will develop liver metastases over the course of their lifetime [1]. The majority of patients will harbor unresectable metastases. Approximately 46–93% of patients with NETs have liver metastases at the time of presentation [2]. In patients with ocular melanoma, liver metastases are common, and up to 80% will have metastatic disease confined to the liver [3]. Liver metastases are associated with a dismal prognosis with a median overall survival less than 1 year [3]. Although less common, several other cancers can spread to the liver, including soft-tissue sarcoma, renal cell, and breast cancer. Even with improvements in systemic biological agents and chemotherapy, survival for patients in these clinical settings remains poor.

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The liver-directed therapies that are under development for the treatment of patients with primary and metastatic unresectable liver tumors include hepatic arterial infusion (HAI), isolated or percutaneous hepatic perfusion (IHP or PHP), radiofrequency ablation, transarterial embolization (TAE), and selective internal radiation. Several of these therapies, including IHP, take advantage of the unique vascular supply of hepatic tumors, which derive their blood flow primarily from the hepatic arterial circulation [4]. This allows for tumors to be targeted for treatment through the hepatic artery while limiting both systemic toxicity and toxicity to the normal liver. This chapter will review the techniques of both IHP and PHP and their use in the treatment of liver metastases in colorectal cancer, neuroendocrine tumors, and melanoma. It will also review the most updated data from randomized clinical trials, as well as discuss future directions in this field of cancer treatment.

Development of Isolated Hepatic Perfusion and Initial Clinical Results

The concept of vascular isolation and regional perfusion of a cancer-burdened organ or region of the body was first described by Creech and Krementz in 1958, and was made possible only through the development of extracorporeal oxygenated bypass circuits [5]. Creech and Krementz demonstrated that high-dose chemotherapy could

Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_24

Table 24.1 Selected series of early isolated hepatic perfusion studies

Author/year	Trial type	Agents	Histology	*N*	CR (%)	PR (5)	Comments
Alexander (1998)	Phase II	Melphalan TNF	Multiple, primarily colorectal	34	3	72	TNF used safely
Hafström (1994)	Phase II	Melphalan Cisplatin	Multiple, primarily melanoma	29	0	20	5 patients survived >3 years
Lindnér (1999)	Phase I	Melphalan TNF	Multiple	11	0	27	MOS 20 months
Marinelli (1998)	Phase I/II	Melphalan Mitomycin C	Colorectal	59	2	8	Mitomycin C high toxicity; Melphalan MOS 18 months

N sample size, *CR* complete response, *PR* partial response, *MOS* median overall survival

be delivered via isolated limb perfusion with limited systemic exposure and observed antitumor effects. In 1969, Stehlin et al. demonstrated synergistic effects of hyperthermia and chemotherapy in regional limb perfusion, and therefore, the combination of hyperthermia and chemotherapy has become standard in isolation perfusion [6]. In 1961, Dr. Robert Ausman, at the Roswell Park Memorial Institute (now known as the Roswell Park Cancer Institute), described a technique for IHP in humans [7]. The technique was first refined in a canine model and was then tested in five patients with various hepatic malignancies. Although there was no long-term follow-up and the morbidity was significant, a therapeutic effect was likely observed in two patients. Because of the significant morbidity and potential mortality associated with IHP, the technique did not have much clinical development over the following three decades. Several studies evaluating small numbers of patients were published during this time, but patient selection criteria and perfusion parameters were variable [8–10].

In the early 1990s, interest in the field of regional perfusion was renewed using a combination of melphalan and tumor necrosis factor alpha (TNF). When administered via limb perfusion, very high response rates were observed in patients with extremity melanoma or sarcoma [11]. During the 1990s, several studies were published reporting results using improved techniques in IHP in patients with unresectable liver malignancies [12–15]. One report was that of a Phase II study which evaluated the use of melphalan, TNF, and moderate hyperthermia in patients with unresectable malignancies confined to the liver [12]. Thirty-four patients were treated and there was one treatment-related mortality. The majority of patients (76%) had CRC liver metastases, and 60% had received prior systemic or regional treatment. The overall response rate (RR) was 75% and was observed even in patients with advanced disease or those who had prior treatment (Table 24.1).

Technique of IHP

IHP using the open approach is a complex surgical procedure. The right and left lobes of the liver are extensively mobilized and the inferior vena cava (IVC) below the liver is exposed via a Kocher maneuver. The right lobe of the liver is mobilized medially to visualize the entire retrohepatic vena cava to the level of the diaphragm; venous tributaries from the retroperitoneum to the IVC including the right adrenal vein and phrenic vein are ligated. The porta hepatis structures are completely exposed. The IHP circuit is shown in (Fig. 24.1).

After systemic anticoagulation using heparin, a veno-venous bypass circuit is created from the saphenous vein to the axillary vein to maintain systemic venous return during IHP as the retro-hepatic vena cava is temporarily occluded. A catheter is inserted in the retro-hepatic vena cava and serves as the venous outflow for the hepatic perfusion circuit. The portal vein (PV) and common hepatic artery (CHA) are occluded with vascular clamps. The inflow for the perfu-

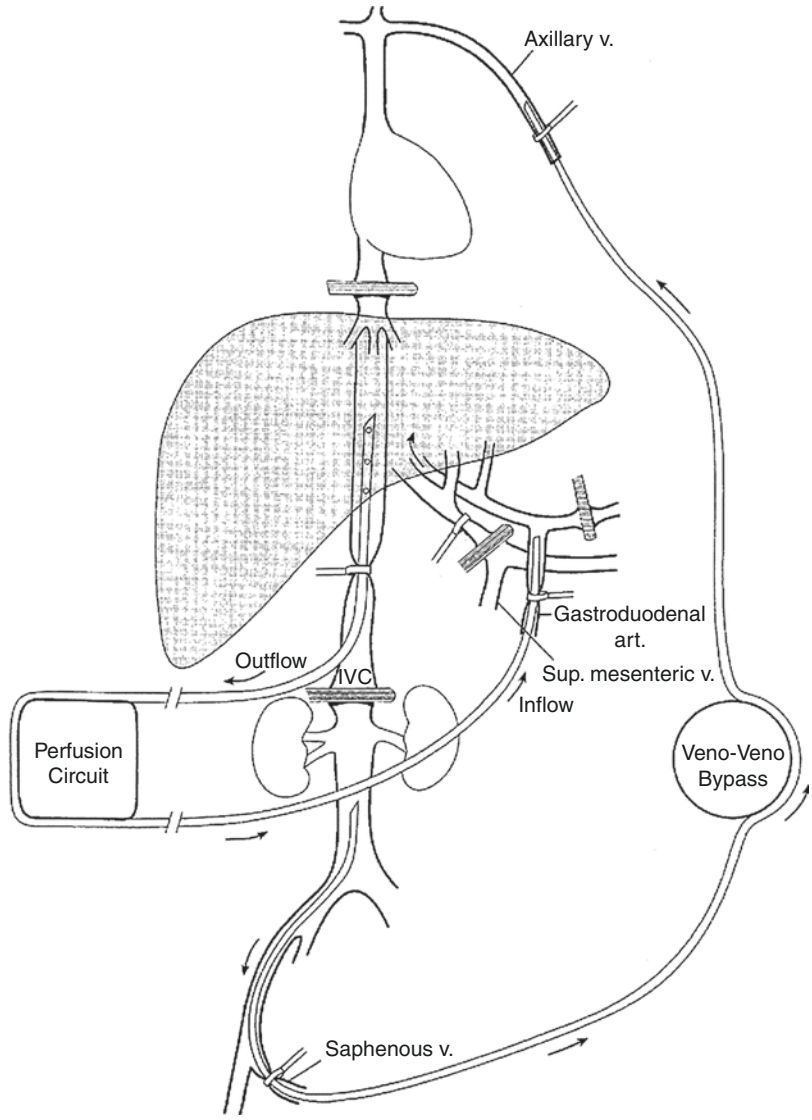


Fig. 24.1 Illustration of the IHP circuit; the extracorporeal perfusion device is shown on the patient's right. Arterial inflow to the hepatic artery is via the gastroduodenal artery, and venous outflow is collected via a cannula placed in an isolated segment of the retro-hepatic inferior vena cava (IVC). Vascular occluding clamps are shown on the IVC above and below the liver and on the hepatic artery. On the patient's left is the veno-venous bypass circuit that shunts blood from the infrahepatic IVC to the systemic circulation (via the axillary vein) using a centrifugal pump

sion is via the gastroduodenal artery (GDA). Complete isolation of the liver is achieved by placing a vascular clamp across the suprahepatic vena cava. Temperature probes are placed directly into the liver parenchyma on the right and left side to monitor hyperthermia during the procedure. The perfusion circuit for the open technique consists of a roller pump, membrane oxygenator, and a heat exchanger. The perfusate consists of 700 milliliters (mL) of a balanced salt solution and one unit of packed red blood cells (roughly 300 mL). A unit of packed red blood cells is necessary to ensure adequate oxygen delivery to the hepatic parenchyma during the perfusion. The heat exchanger is used to warm the perfusate to maintain hepatic parenchymal temperatures between 38.5 °C and 40 °C. Flow rates of >400 mL per minute should be achieved, and optimal flow rates are 600–800 mL per minute. The perfusion continues for 60 minutes and then the liver is flushed with crystalloid and colloid. The vascular structures are decannulated and repaired and normal liver perfusion is restored.

IHP for CRC Liver Metastases

Because of the relatively high frequency of patients with unresectable CRC liver metastases, the majority of studies that have evaluated IHP are in patients with CRC. These studies have utilized multiple types of chemotherapy including mitomycin C [15], oxaliplatin [16], and melphalan with and without TNF [15, 17–22]. There are two large series that have evaluated IHP in patients with unresectable CRC liver metastases [17, 20]. The results of IHP in 120 patients with unresectable CRC liver metastases using IHP with melphalan alone (n = 69), melphalan and TNF (n = 41), or TNF alone (n = 10) have been reported [17, 20]. The majority of patients (80%) had been treated with chemotherapy prior to IHP. There were five (4%) treatment-related mortalities; response was evaluable in 114 patients. The overall RR was 59% with a median time to hepatic progression of 7.0 months. Patients who received HAI therapy after IHP had a longer time to hepatic progression than those patients who did not. Median overall survival (OS) was 17.4 months. With respect to OS, only the use of HAI after IHP and a preoperative carcinoembryonic antigen level of ≤30 ng/mL were significant on multivariate analysis. Similar outcomes were reported in 105 patients with unresectable CRC liver metastases treated with a fixed dose of 200 mg of melphalan in the circuit [20]. The overall RR was 50%. The median OS was 24.8 months.

A case-control study that compared the use of IHP with melphalan to systemic chemotherapy in patients with unresectable CRC liver metastases has been reported [21]. The systemic chemotherapy group consisted of 111 patients who were treated with CApecitabine, IRinotecan, and Oxaliplatin (CAIRO). There was no significant difference in OS between the two groups. The authors of this study concluded that systemic therapy remains the standard of care for management of patients with unresectable CRC liver metastases and that IHP should be considered in the context of prospective clinical trials. However, the role for IHP in patients who are refractory to systemic chemotherapy is not well known. In a series of 25 patients with unresectable CRC liver metastases refractory to irinotecan-based therapy, IHP results in an overall RR of 60%, and the median duration of response in the liver was 12 months [19]. The median OS was 12 months, with a 2-year survival of 28%.

IHP for Ocular Melanoma

Approximately 30–60% of patients with ocular melanoma will develop liver metastases [23–27]. The options for systemic treatment in these patients are limited in number and efficacy [28–31], and although surgical resection has been attempted in very selected patients with modest results [32–34], most patients have diffuse metastases many of which are not visible on imaging studies (Fig. 24.2). Given the limited alternative treatment options, multiple studies have evaluated the use of IHP in these patients.

IHP in patients with ocular melanoma and unresectable hepatic metastases using escalating doses of melphalan with and without TNF has been reported [35]. Patients generally had advanced disease with a median number of metastatic nodules of 25 (range, 5–50), a mean percentage of hepatic replacement of 25% (range, 10–75%), and the mean size of the largest lesion being >7 cm. The overall RR was 62% including two complete responses (9.5%). Of those patients treated with melphalan alone, 7 out of 10 (70%) had a response, while 6 out of 11 patients (54%) treated with melphalan and TNF had evidence of a radiographic response. There was one treatment-related mortality (5%). The median PFS was 9 months in all patients and was significantly longer in patients who received TNF (14 months versus 6 months, p = 0.04). The OS was 11 months.

A report of outcomes in 29 patients with metastatic ocular melanoma to the liver using IHP with melphalan alone showed similar results [36]. The overall RR was 62% with three CRs (10%). On multivariate analysis, only baseline lactate dehydrogenase (LDH) was identified as a significant independent prognostic factor for survival, suggesting that baseline LDH level may

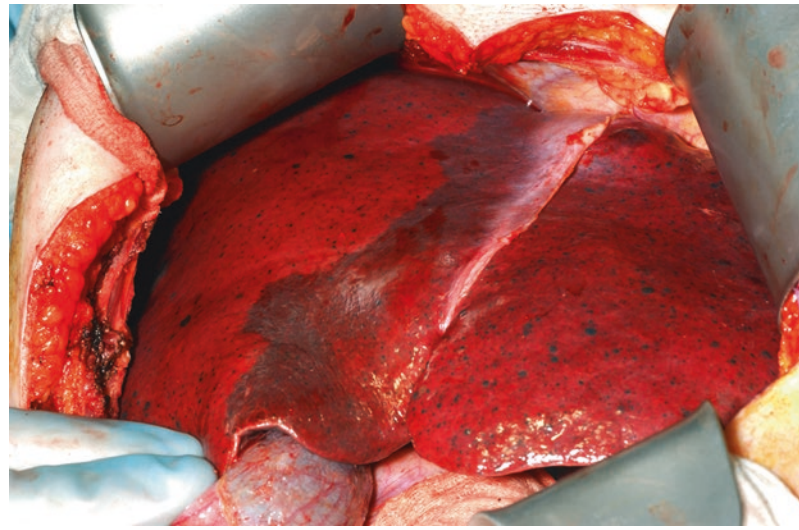


Fig. 24.2 Example of progressive tumor biology and diffuse pattern of metastatic spread in a patient with ocular melanoma hepatic metastases

Table 24.2 Summary of selected trials of IHP for hepatic metastases in ocular melanoma

Author/year	Trial type	Agents	*N*	CR (%)	PR (%)	Comments
Alexander (2000)	Phase II	Melphalan TNF	22	9.5	52	MOS 11 months; median response duration better with TNF (14 vs. 6 months); 5% mortality
Alexander (2003)	Phase II	Melphalan	29	10	52	0% mortality
Noter (2004)	Phase II	Melphalan	8	0	50	MOS 9.9 months
van Iersel (2008)	Phase II	Melphalan	12	0	33	MOS 10 months

N sample size, *CR* complete response, *PR* partial response, *MOS* median overall survival

have a role in patient selection. Smaller series in the literature have also reported similar results. In eight patients treated with IHP with high-dose melphalan (200 mg), the overall RR was 50%, and the median OS was 9.9 months [20, 37]. It appears that in patients with unresectable ocular melanoma liver metastases, response rates of >50% can generally be obtained using IHP with melphalan with and without TNF, with mortality rates of <5% and transient morbidity (Table 24.2).

IHP for Neuroendocrine Tumors

While surgical resection of metastatic neuroendocrine cancer is effective and can improve 5-year survival rates to greater than 50%, complete surgical resection is usually difficult since patients often present with multifocal or bilateral disease in the liver [38–41]. The use of IHP to treat 13 patients with neuroendocrine hepatic metastases showed an overall RR of 50% and a median OS of 48 months [42]. Given the effectiveness of surgical resection and other liver-directed therapies [39, 43–46] in the management of patients with neuroendocrine liver metastases, it is unlikely that IHP will only play a significant role in the management of patients.

Percutaneous Hepatic Perfusion

Percutaneous hepatic perfusion (PHP) was initially utilized in a clinical setting almost 30 years ago. Its feasibility was first demonstrated in a porcine model by Curley and colleagues and in 1994, Ravikumar et al. conducted a feasibility trial to evaluate PHP in patients with hepatic metastases [47]. Fifty-eight PHP procedures were performed on 21 patients using either

5-fluorouracil (5-FU) or doxorubicin. Twelve patients received dose escalation of 5-FU and nine received dose escalation of doxorubicin. The chemotherapeutic agents were infused into the liver in a volume of 250 mL over a 15- to 30-minute interval. Treatment was repeated every 3 weeks for two courses and if disease response was documented without dose-limiting toxicity, patients received two additional courses. There were no treatment-related mortalities. Hypotension was the most common toxicity, occurring in 78.5% of procedures. Notably, hepatic toxicities were minimal with only transient elevations in liver enzymes. In patients treated with doxorubicin, two had significant responses. In the other patients, 17 of 19 had progression of hepatic tumors and 1 had stable disease at the time of last follow-up. This study established the feasibility of PHP for the use of regional therapy for treating hepatic metastases, but due to lack of evidence of efficacy, the technique was largely abandoned until the early 2000s when it was reevaluated in a series of clinical studies.

Technique of PHP

Melphalan is delivered to the hepatic parenchyma via a percutaneously placed catheter positioned in the proper hepatic artery. The hepatic venous outflow is collected and filtered before being returned to the systemic circulation. Usually, the procedure is performed under a general anesthetic. Three cannulas are placed for treatment: a right subclavian vein or jugular venous catheter for return of blood to the systemic circulation, a femoral artery cannula which is advanced into the proper hepatic artery for infusion of chemotherapy, and a femoral vein cannula for placement of the fenestrated double-balloon catheter positioned in the retro-hepatic vena cava that collects hepatic venous effluent.

A visceral angiogram is performed before treatment and the GDA and other accessory vessels are embolized to ensure that the drug delivery is exclusively to the liver. On very rare occasions, aberrant hepatic arterial anatomy is encountered which requires infusion of melphalan into two feeding arteries sequentially by repositioning the inflow catheter midway through treatment. A double-balloon catheter is advanced from the femoral vein into the retro-hepatic vena cava (Fig. 24.3). The venous catheter has several design features that allow the hepatic venous effluent to be isolated, collected, and filtered through an extracorporeal filtration system before being returned to the systemic circulation via the cannula in the neck (Fig. 24.3). The patient is systemically anticoagulated with intravenous heparin and the cephalad balloon is inflated with dilute contrast containing saline and "seated" under fluoroscopic control at the atrial-caval junction until the inferior aspect of the balloon is slightly indented. The caudal balloon is inflated to isolate the retro-hepatic inferior vena cava. Contrast material is then injected into the catheter to confirm that the hepatic venous system is isolated between the balloons. A centrifugal pump is then used to obtain flow rates of approximately 500–600 mL/minute through the circuit. Once this is accomplished, the filtration system is brought on-line.

A melphalan dose of 3 mg/kg of ideal body weight with a maximum dose of 250 mg diluted to 2 mg/mL is administered via a power injector and the infusion rate is set so that the drug will be delivered over 30 minutes. During treatment, the infusion is briefly interrupted once or twice and a small amount of contrast is injected through the arterial catheter to ensure that it is still in correct position. A small amount of nitroglycerin can be infused to relieve arterial vasospasm as needed. Once the melphalan infusion is complete, the arterial catheter is removed but filtration of hepatic venous effluent continues for an additional 30 minutes. At that time, the filtration system is stopped, the balloons are deflated, and the venous catheter is removed. The patient usually emerges from general anesthesia in the suite, is extubated, and taken to the intensive care unit for monitoring.

PHP is a complex procedure that has some potential risks associated with it. To minimize risk, the responsibilities of the various specialists involved including the anesthesiologist, interven-

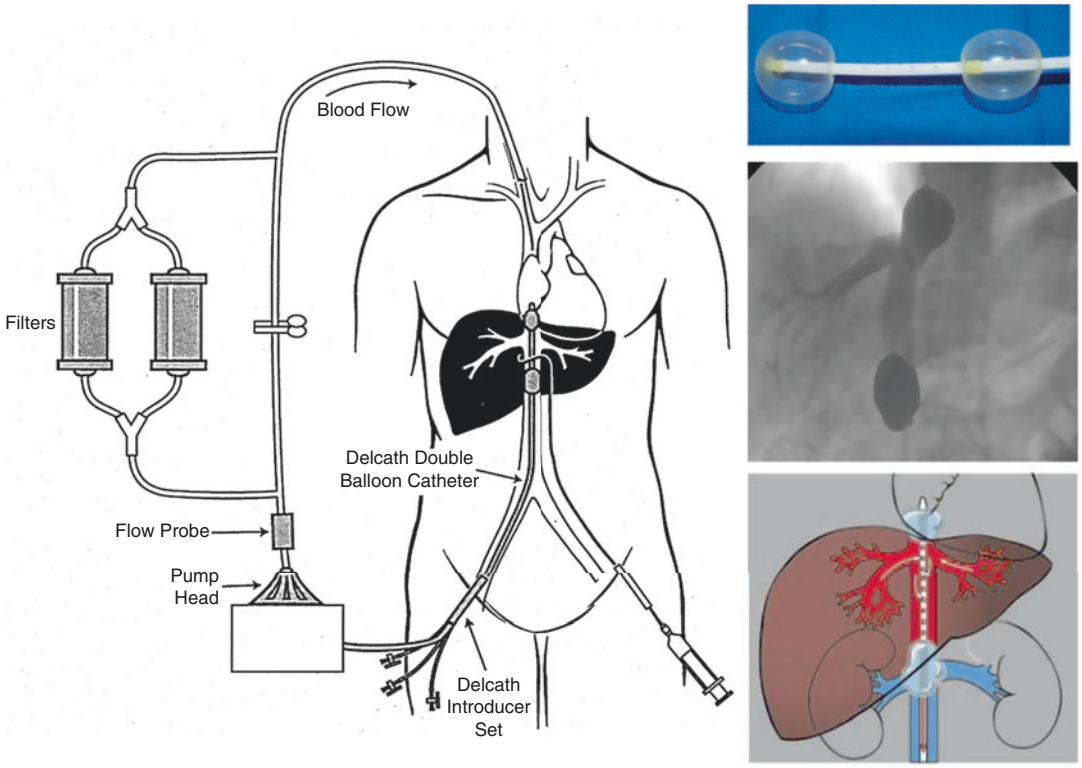


Fig. 24.3 Illustration of the PHP technique. The left side shows the overall schema of PHP with placement of the arterial and venous catheters and the filtration system on the patient's right side. Note that blood returns to the patient from the filtration system run by a centrifugal pump via a catheter in the subclavian or jugular vein. Bottom right shows a picture of the hepatic venous catheter fenestrations between two balloons, and the top panel shows an intra-procedural X-ray confirming isolation of the hepatic venous system

tional radiologist, perfusionist, pharmacy personnel, specialized nursing services, and the surgical or medical oncologist must be coordinated. Hypotension is almost always encountered during the procedure when both when the venous balloons are inflated and when the filters in the bypass circuit are activated. The mechanism for the hypotension is thought to be due to decreased venous return and filtration of catecholamines. The hypotension responds to cardiopressor support and hemodynamic parameters can usually be restored quickly. The anesthetic management of the hemodynamic and metabolic alterations that occur during PHP has been described by Miao et al. [9]. They reviewed the treatment of 51 patients who underwent 136 PHPs at the NCI in Bethesda, Maryland. Based on data from this study, there were decreases in mean arterial blood pressure, central venous blood pressure, and increases in heart rate which resolved at completion of the procedure. Patients received norepinephrine in 13% of PHPs, phenylephrine in 70%, or both agents in 11%. Compared to baseline values, there were also transient decreases in bicarbonate and pH which returned toward baseline by the end of the procedure. Activated clotting times must be monitored regularly during the procedure and additional heparin must be administered as needed. Patients may experience a drop in core body temperature and the use of a heating blanket during the procedure is routine. After the procedure, the patients require correction of anticoagulation with fresh frozen plasma and platelets. Once this is accomplished, the vascular access sheaths are removed. During the first 24 hours, a resuscitation pathway that includes aggressive correction of coagulopathy, pulse checks, and other parameters should be followed.

First Phase I Trial with Melphalan

A Phase I dose-escalation study of melphalan in patients with unresectable primary or metastatic hepatic malignancies has been reported [31]. In total, 28 patients received treatment, of whom the mean age was 49 years and male and female genders were equally represented. Ten patients had metastatic ocular melanoma, 3 had cutaneous melanoma, and 15 had other types of tumors including colorectal, neuroendocrine, renal cell, and other cancers. The eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status ≤2, a serum bilirubin <2.0 mg/dL, a platelet count >100,000, and a serum creatinine level ≤1.5 mg/dL. The study excluded patients with biopsy-proven cirrhosis or significant portal hypertension, but those with limited extrahepatic disease were eligible. The study used melphalan which is ideal for PHP since its peak perfusion concentrations are 10- to 100-fold higher than the maximally tolerated peak systemic levels and was associated with high response rates when used in IHP [13, 48]. In this study, 12 patients were initially treated with 2.0 mg/kg followed by 16 patients with escalating doses (increased in 0.5 mg/kg increments) to a maximum tolerated dose of 3.0 mg/kg. Periprocedural complications were low. Most patients were ambulatory and tolerating a regular diet within 24 hours of their procedure.

At 3.5 mg/kg, a dose-limiting toxicity of neutropenia and thrombocytopenia was observed. Grade 3/4 neutropenia occurred in 66% of treatments in these patients, requiring filgrastim in three cases. There was also an increase in grade 3/4 thrombocytopenia in this group, some of which required platelet transfusions. Among the seven patients who received 3.0 mg/kg, the defined maximum safe tolerated dose, 58% of (11 of the 19) treatments were associated with transient grade 4 neutropenia requiring filgrastim administration. In the 12 patients treated at a dose of 2.0 mg/kg, transient grade 3/4 neutropenia was seen after approximately 50% of treatments and grade 3/4 thrombocytopenia was seen in one third of patients. Based on these toxicities, growth-factor support is now usually administered prophylactically. Hepatic toxicities were infrequent and universally transient in this study, and there were no renal, cardiac, or pulmonary toxicities observed. Notably, of the 10 patients with ocular melanoma, 50% had an objective tumor response and two patients had a complete response documented at 10 and 12 months. In addition, two of the four patients with hepatic metastases from neuroendocrine tumors had ongoing partial responses occurring at 5 and 7 months and one had an ongoing minor response at 10 months.

In summary, the Phase I feasibility study of PHP utilizing melphalan demonstrated the safety of the procedure and identified the MTD as 3.0 mg/kg. This is a greater dose than can be utilized in either systemic or intraoperative regional administration due to bone marrow toxicity. Based on pharmacokinetic studies, at the MTD the mean filter efficiency was 78.5%. This process allows greater doses to be given without increasing toxicity. In addition, only 14 of the 74 treatments had hepatic toxicity, indicating that even with direct, regional therapy the healthy liver parenchyma is not at increased risk. Although the goal of this study was not to assess impact of PHP on survival, there was an overall response rate of 29.6% including two complete responses.

Phase II Clinical Evaluation of PHP

A Phase II study of PHP was subsequently conducted at the NCI. Of the 57 patients enrolled, tumor histology included metastatic colorectal cancer, primary liver cancer, metastatic ocular melanoma, and metastatic neuroendocrine tumors. Results of the 23 patients with metastatic neuroendocrine cancer who underwent 68 PHP treatments with melphalan have been reported in abstract form [49]. The majority of patients had advanced liver disease, with a median number of 15 metastases, a mean size of largest lesion 4.8 cm, and greater than 25% hepatic replacement in almost half of the patients. The overall radiographic response rate was 79% including a 68% partial and 11% complete radiographic response rate. The median actuarial overall survival was 40 months.

Pivotal Phase III Evaluation of PHP for Patients with Melanoma Liver Metastases

A multicenter, randomized controlled trial comparing PHP with melphalan (PHP-Mel) versus best alternative care (BAC) was conducted in 93 patients between 2006 and 2009 [50]. The NCI coordinated the study and enrolled the first 33 patients. The primary end point was hepatic progression-free survival (hPFS) assessed by an independent review committee (IRC). Eligibility criteria included unresectable, biopsy-proven, melanoma liver metastases, ECOG performance status ≤2, serum bilirubin <2 mg/dl, platelet count >100,000, serum creatinine <1.5 mg/dl, and liver function tests <10 times upper limit of normal. Patients with limited extrahepatic disease with progressive liver disease that was life-limiting were eligible. Forty-four patients received PHP-Mel and 49 received BAC, which included systemic chemotherapy, embolization, and supportive care. Crossover to PHP-Mel was allowed. The study was powered to detect a difference in median progression-free survival of 4 months. Subjects in the PHP-Mel group received treatment every 4–8 weeks when hematologic toxicity was grade 2 or less, with a maximum of six procedures. Patients were followed and imaged at 6 weeks ±2 week intervals. Response and survival were assessed at predetermined intervals.

The two groups were well matched with respect to demographic, previous treatment, and disease characteristics (Table 24.3). Of note, almost 90% of patients enrolled had ocular melanoma, and most had advanced disease (51% had five or more lesions, mean hepatic replacement with tumor of 31.6%). Most patients had not received prior regional therapy. Of the 44 patients in the PHP-Mel arm, 92% were treated (median number of treatments = 3), and 18%

Table 24.3 Demographics of Phase III trial

Category	PHP-Mel (*N* = 44)	BAC (*N* = 49)	Treatment group comparison *p* value
Age (years)			0.9534
Median (range)	55.0 (33–74)	56.0 (31–77)	
Gender, *n* (%)			0.4797
Male	23 (52.3%)	22 (44.9%)	
Female	21 (47.7%)	27 (55.1%)	
ECOG performance status			0.0284
0	28 (63.6%)	42 (85.7%)	
1	13 (29.5%)	6 (12.2%)	
Site of primary tumor			0.8577
Ocular	39 (88.6%)	44 (89.8%)	
Cutaneous	5 (11.4%)	5 (10.2%)	
Duration of hepatic metastasis (months)			
Mean ± SD	4.6 ± 7.7	4.6 ± 5.5	
Hepatic tumor burden, %			0.5342
Median (range)	32.5 (5–85%)	25.0 (5–90%)	
Site of metastases, n (%)			0.9305
Hepatic only	27 (61.4%)	28 (57.1%)	
Hepatic and extrahepatic	17 (38.6%)	21 (42.9%)	
Previous treatment (for liver metastases) n (%)			
Chemotherapy/immunotherapy	8 (18.2%)	10 (20.4%)	0.9008
Regional therapy[a]	4 (9.1%)	3 (6.1%)	0.7038

Adapted from Hughes et al. [50]; used with permission
PHP-Mel percutaneous hepatic perfusion with melphalan, *N* sample size, *BAC* best alternative care, *ECOG* Eastern Cooperative Oncology Group
[a]Included chemoembolization, radioembolization, or ablation

completed 4 treatments. In the BAC group, 50% had chemotherapy with dacarbazine/temozolomide, 22% had chemoembolization, and 18% had supportive care. Twenty-eight of 49 patients crossed over to PHP-Mel, but only 25/28 received treatment. The results demonstrated statistically significant improvements in hPFS and overall PFS in patients treated with PHP compared to BAC (Fig. 24.4) (hPFS 7.0 vs. 1.6 months, $p < 0.001$; oPFS 5.4 vs. 1.6 months, $p = 0.0001$). The overall response rate (ORR) was 27.3% in the PHP-Mel group vs. 4.1% in the BAC group ($p = 0.003$) and the median duration of objective response was 6.4 vs. 3.7 months. An example of the response to PHP in ocular melanoma is shown (Fig. 24.5). The median overall survival with PHP-Mel was 10.6 months vs. 10.0 months with BAC. However, in a subgroup analysis the median OS was 13.1 months in BAC patients who crossed over and received PHP-Mel treatment. The median time to liver progression on the BAC arm was 1.6 months, and 8.4 months

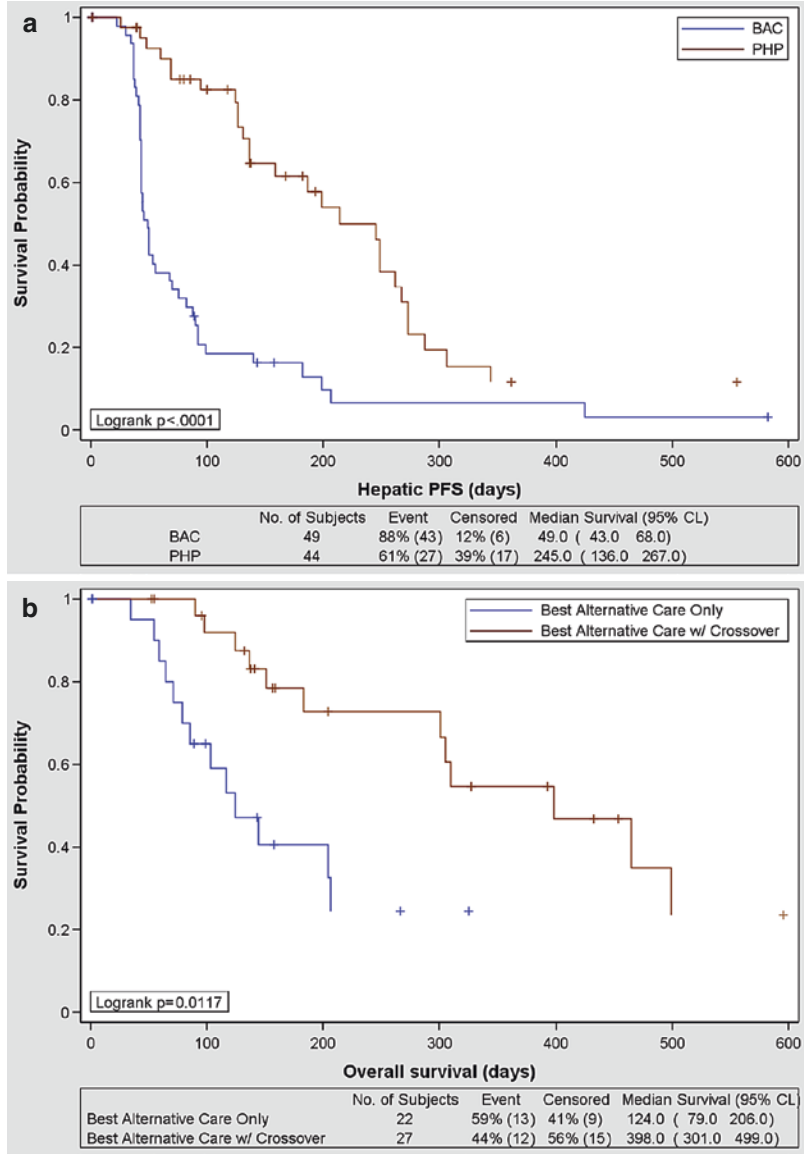
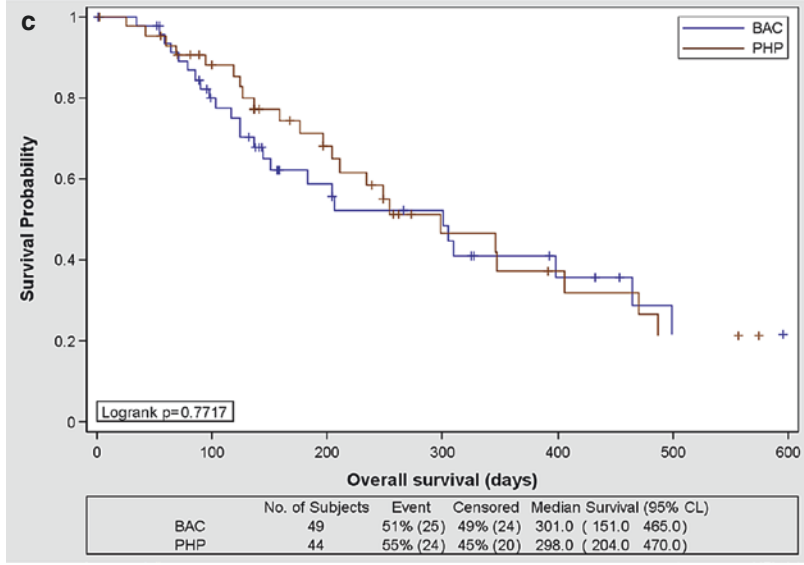


Fig. 24.4 Outcomes of Phase III trial [50] including progression-free survival (PFS) (Panel **a**) and overall survival (Panels **b** and **c**). BAC best alternative care, PHP percutaneous hepatic perfusion

Fig. 24.4 (continued)



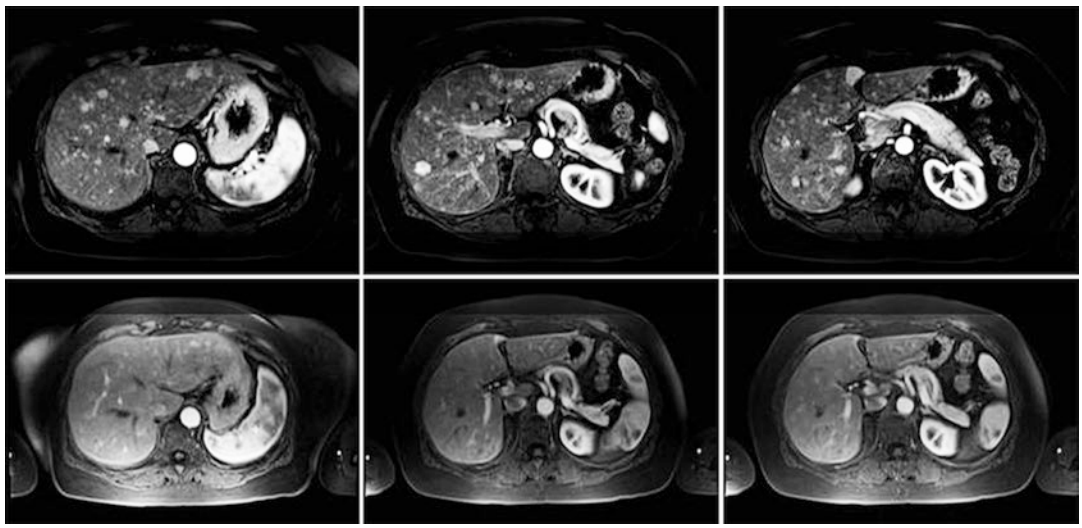


Fig. 24.5 MRI showing near-complete regression of metastatic ocular melanoma after percutaneous hepatic perfusion over 2 years

in those who crossed over and received PHP-Mel, indicating the ability of the treatment to salvage patients after disease progression. Adverse events were mainly related to platelet sequestration and hemodilution, often requiring transfusion. Postprocedural adverse events were observed in 91% of patients in the PHP-Mel group, which were primarily grade 3/4 neutropenia, thrombocytopenia, and anemia. Hepatic dysfunction occurred in 14% of patients and was self-limited. A third of patients discontinued PHP-Mel due to adverse events and there were three overall deaths, two from bone marrow suppression, and one from progressive hepatic failure. Overall, this study showed a statistically significant improvement in both hepatic and overall disease progression with PHP-Mel treatment. Although patients who crossed over from BAC had the best overall survival (13.1 vs. 10.6 months), this is likely confounded by selec-

tion bias, and the study was not designed with the ability to assess survival advantage due to the crossover criteria. Toxicities were frequent but manageable in the majority of cases.

Other Studies

There have been several other studies which have evaluated the efficacy of PHP, mostly in retrospective single or multi-institutional reviews. Forster et al. retrospectively reviewed data from 10 patients with unresectable melanoma or sarcoma hepatic metastases at Moffitt Cancer Center [51]. They reviewed 27 total treatments, median of 3 treatments per patient. Five of ten subjects had ocular melanoma, only one patient had sarcoma. Median hPFS was 240 days, 90% of patients had stable disease or partial responses, and 40% were alive at 11.5 months. Myelosuppression was the most common toxicity, which was treated on an outpatient basis. The authors concluded that PHP was a safe and promising treatment for selected patients. Similarly, Vogl et al. reported the results of 14 patients at 2 European centers who were treated between 2012 and 2013 with 3.0 mg/kg of melphalan by PHP [52]. All patients had hepatic metastases from solid malignancies including ocular or cutaneous melanoma, cholangiocarcinoma, and breast or gastric cancer. One complete response (cholangiocarcinoma), six partial responses (ocular and cutaneous melanoma), and five stable responses (ocular melanoma and breast cancer) were observed. Toxicities were similar to those previously reported. Interestingly, in this series, a second-generation filter was used in select patients which was designed to increase melphalan extraction efficiency. In these patients, toxicity was reduced, and recovery was enhanced. This second-generation filter was first reported in a porcine model in 2014 [53] and has an extraction efficiency of 99%, superior to first-generation filters, used in the first reported studies, which had a mean extraction rate of 77% [54]. A subsequent European study by the same group in 2016 in 18 uveal melanoma patients achieved partial or stable responses in 83% of patients, with median overall survival of 9.6 months and median progression-free survival of 12.4 months. Grade 3/4 toxicities were temporary, and patients had high self-reported satisfaction rates [55].

More recently, Karydis et al. reported similar results in a retrospective analysis of 51 patients at 4 centers (2 in England, 2 in the United States) [56]. Fifty-one patients with metastatic uveal melanoma who had 134 treatments (median of 2) with melphalan-PHP (M-PHP) between 2008 and 2016 were included. Previous systemic or liver-directed treatments were included in the eligibility criteria, as was extrahepatic disease, only if it was nonprogressive or amenable to ablative therapies. Forty-nine percent of patients achieved a partial response by RECIST, and 5.9% had a complete response. Median oPFS and hPFS were 8.2 and 9.1 months, respectively, and median overall survival was 15.1 months. There were no treatment-related deaths. The use of the second-generation filter may have reduced late bone marrow suppression. Significantly, overall survival was 65% at 1 year versus 38% in the previous trial.

In summary, these studies in concert with the Phase III trial show that PHP with melphalan can provide durable responses in patients with unresectable hepatic metastases. Progression-free survival can be improved, and treatments can be repeated. Toxicities, although significant, are self-limited and manageable. Further studies are needed to assess the efficacy of PHP on overall survival, and to evaluate the efficacy of treatment in patients with other solid malignancies, as the majority of patients in these studies had ocular melanoma. In addition, PHP is a highly technical procedure which requires multidisciplinary care at a highly specialized center but may be considered as multimodality treatment approach in highly selected patients.

Current Ongoing Trials and Future Directions

Currently, the value of PHP in the United States remains controversial, although this therapy has been approved and is in use in several European

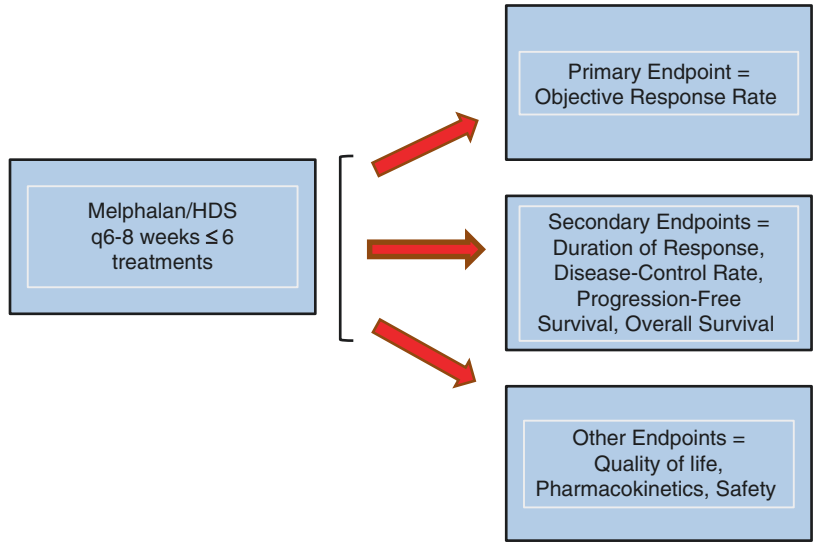


Fig. 24.6 Schema of FOCUS Trial

countries. However, there are several ongoing Phase III clinical trials, which will help assess the long-term efficacy of PHP and also evaluate its utility in comparison with more modern alternative therapies such as immunotherapy. The randomized controlled FOCUS trial (NCT02678572) started enrolling patients in 2016 and aimed to compare PHP versus best alternative care (TACE, dacarbazine, ipilimumab, or pembrolizumab) in patients with ocular melanoma and unresectable liver metastases. The primary outcome is overall survival, and secondary outcomes will include progression-free survival and objective response rates. This trial has recently been changed to a single-arm trial (Fig. 24.6). A second trial (NCT03086993) will compare PHP versus standard of care chemotherapy (cisplatin/gemcitabine) for patients with unresectable intrahepatic cholangiocarcinoma. Lastly, there is an observational study (NCT03266042) which will retrospectively evaluate safety and efficacy data from participating institutions who have used PHP with melphalan and the second-generation filter, which has been in use since 2011.

In summary, previous studies have demonstrated efficacy and safety of this technique, and its minimally invasive approach and reproducibility are advantageous. Use of the technique is limited by its familiarity only at highly specialized centers and the lack of large volume randomized controlled trials in comparison with other modern therapies. However, reconsideration of PHP as a useful therapy is warranted as the use of regional therapies has become more common as part of integrated cancer treatment.

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25 Percutaneous and Port Delivered Arterial Infusional Therapy for Liver Tumors

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Introduction

Limited hepatic primary cancer or metastases in the liver are now treated with resection [1], thermal ablation [2], or transplantation [3] for possible cure. For more diffuse cancer predominantly in the liver, intra-arterial chemotherapy delivered either as isolated hepatic perfusion (IHP) or hepatic arterial infusion (HAI) has been used clinically with impressive results. Intra-arterial chemotherapy can be classified mainly into four categories (Table 25.1): (1) surgical isolated perfusion, (2) percutaneous isolated perfusion, (3) pump HAI, and (4) percutaneous or port HAI. The most common agents for these therapies are shown in Table 25.2.

HAI and IHP aim to take advantage of the benefits of a systemic therapy by treating the whole organ with high concentration local chemotherapy, while avoiding the systemic toxicities. These therapies seek to utilize the unique dual perfusion of the liver to increase local drug concentrations at tumor sites without exposing the patient to systemically high doses. Though the liver parenchyma receives 30% of its blood flow from the hepatic artery and 70% from the portal venous system, cancers in the liver are almost exclusively arterially fed [4]. Therefore, by infusing chemotherapy directly into the hepatic artery, cancerous deposits can be preferentially targeted with theoretical sparing of a large portion of normal liver parenchyma. These techniques have the benefit of treating the whole organ and being able to target large tumor deposits, bulky or highly numerous tumor deposits, and micrometastases that would otherwise be unable to be targeted by regional therapies such as ablation or resection. The presence of extrahepatic disease is a relative contraindication to these infusional regional therapies, as the extrahepatic disease would go unaddressed [5].

Infusional Therapies

Surgical Isolated Hepatic Perfusion

IHP can be clinically executed by either the surgeon or the interventional radiologist, and involves using agents that are highly toxic to both tumor and normal tissues, and consequently have relatively low therapeutic index. These agents must have extensive and lasting effects on cancer, even with just a short direct exposure, as the treatment is only administered during the procedure. The maximal dose of melphalan delivered via IHP can be four times higher than

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Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_25

Table 25.1 Methods of hepatic arterial delivery of tumoricidal agents

Method	Agents	Rationale for use	Complexity and invasiveness	Ease of repeated administration
Isolated surgical perfusion	Melphalan, TNF, adriamycin	*For highly toxic agents*: complete prevention of leakage into systemic circulation necessary Agents must have high anticancer efficacy with short exposure	Highly invasive Hospitalization Long recovery	Hard to repeat
Isolated radiologic perfusion	Melphalan, TNF, adriamycin	*For highly toxic agents*: prevention of leakage into systemic circulation necessary Agents have to have high anticancer efficacy with short exposure	Less invasive than ISP Big hemodynamic effects with vascular isolation Not ideal for patients with cardiovascular disease	High effort to repeat but less onerous than ISP
Pump infusional therapy	FUDR	High extraction of FUDR allows high tumor exposure to agent without systemic toxicity Because of small volume of infusion pumps, only appropriate for agents that are highly soluble such as FUDR	Requires surgical implantation of pump Pump not available worldwide. FUDR not available outside the USA	Clinic procedure. Low intensity
Catheter/port infusional therapy	5-FU, oxaliplatin, cisplatin, adriamycin	Extraction of chemotherapies on first pass through liver allows for increased efficacy while minimizing systemic toxicity	More misperfusions than surgical implantation Eliminates the cost of pump Mostly percutaneous outpatient procedure	Outpatient radiologic procedure for catheter-based delivery Clinic procedure for port delivery

Notes: *FUDR* floxuridine, *5-FU* 5-fluorouracil, *TNF* tumor necrosis factor

Table 25.2 Chemotherapies and biologic agents for intra-arterial delivery

Drug	Delivery	Mechanism of action	Increased exposure with HAI (fold increase)
FUDR	Pump infusion	Thymidylate synthase inhibitor – cell cycle dependent	100–400
5-Fluorouracil	Catheter infusion	Thymidylate synthase inhibitor – cell cycle dependent	5–10
Mitomycin C	Catheter infusion	Bioreductive alkylation and inhibits DNA synthesis and function – not cell cycle dependent	6–8
Oxaliplatin	Catheter infusion	Platinum-DNA adducts, DNA repair inhibition	4–5
THP adriamycin	Catheter infusion/ isolated perfusion	DNA polymerase alpha inhibitor	20
Cisplatin	Catheter infusion	Platinum-DNA adducts, DNA repair inhibition	4–7
Doxorubicin	Catheter infusion/ isolated perfusion	Binds to DNA, topoisomerase II inhibitor, DNA polymerase alpha inhibitor	2
Melphalan	Isolated perfusion	Alkylating agent that binds to DNA and prevents DNA synthesis and repair	4
TNF-alpha	Isolated perfusion	Hemorrhagic necrosis through cellular effects	NA

Notes: *FUDR* floxuridine, *5-FU* 5-fluorouracil, *THP* Taxol® + Herceptin® + Pertuzumab, *TNF* tumor necrosis factor

the dose perfused via systemic veins and it is even possible to infuse drugs whose use via the intravenous route is contraindicated, such as TNF-alpha [6]. The surgical approach was the traditional approach for IHP. This involves a large open surgery, during which the liver is put on vascular bypass and infused with the treatment drug. To learn more about this procedure, please see Chap. 27. The surgical procedure to put the liver on vascular bypass is extensive, however, requiring lengthy recovery, and difficult to repeat. Few centers perform these procedures at present.

Percutaneous IHP

The emergence of interventional radiology and new catheter-based technology has allowed development of a percutaneous IHP procedure. Percutaneous hepatic perfusion is performed with a specialized double-balloon IVC catheter system and an extracorporeal charcoal filter. In this system, three percutaneous catheters are placed in the femoral artery, the femoral vein, and the internal jugular vein. The double-balloon catheter is placed with the lower balloon in the retro-hepatic IVC and the cephalad balloon in the cavoatrial junction, for hepatic isolation and hepatic effluent aspiration [7]. With this system, the hepatic effluent is captured, filtered, and then returned to the systemic circulation via a veno-venous bypass circuit. Because of this effluent filtration, agents such as melphalan, which are highly toxic if leaked in large amounts into the systemic circulation, can still be used for therapy as the vast majority of the drug is removed from circulation prior to reinfusion. Significant hemodynamic instability may still result as the liver is placed on bypass, with occlusion of the vena cava. IHP remains a relatively morbid method of delivering chemotherapy, even when performed percutaneously. However, because it is less invasive than surgical IHP, these treatments can be repeated every 4–8 weeks.

Pump HAI

Another technique for limiting systemic toxicity is utilizing HAI via subcutaneous pump for regional introduction of drugs with high hepatic first-pass extraction. This allows the liver itself to be exposed to treatment dose medication and then remove the majority of the drug prior to systemic exposure. Because of these pharmacodynamics, there is no need to put the liver on bypass, since little of the chemotherapy passed the liver into the systemic circulation. FUDR is one of the most widely studied drugs for HAI as FUDR has 95% first-pass liver metabolism. Because of this, HAI with FUDR is able to be dosed to yield 100–300× tumor exposure compared to systemic infusion, with little FUDR entering the systemic circulation (Table 25.2) [8]. The high solubility of FUDR also permitted a 30-day dose of this drug to be sufficiently small in volume to fit in a subcutaneous infusion pump.

Results from many trials show pump HAI to be highly effective therapy for colorectal metastases to the liver, cholangiocarcinomas, and hepatocellular carcinomas (Chap. 24). This method requires surgery for implantation of the pump, and consequently the morbidity, cost, and recovery associated with the procedure. In recent years, both the supply of pumps and that of FUDR have become difficult.

Catheter and Port HAI

The advances in interventional radiology now allow percutaneous access to the hepatic artery either from the axillary, subclavian, or femoral arteries which can be utilized for HAI. These catheters can be either placed percutaneously for each delivery of cancer treatment, or catheters can be placed and then connected to arterial ports for later repeated delivery of chemotherapy in an oncology clinic. This is the least invasive method of delivering arterial therapies to cancers in the liver and is the main subject of the discussions in this chapter. We will discuss the data gathered for use of this form of HAI in the palliative, adjuvant therapy, and neoadjuvant settings.

Catheter/Port Hepatic Arterial Infusion

The premise of these minimally invasive methods of delivery of chemotherapy is still based on increasing local drug concentrations in tumor deposits, while avoiding systemic side effects. When performed with care, percutaneous implantation provides equivalent or superior results to operative placement of ports, while avoiding laparotomy and surgical morbidity. Prior to percutaneous port placement, hepatic arterial anatomy must be identified, and occlusion of replaced hepatic arteries, GDA, and right gastric artery is needed to prevent acute gastric mucosal lesions from chemotherapy exposure, and to ensure infusion of chemotherapy in the whole liver through a single artery. Though cholecystectomy is often performed when open placement of hepatic arterial access is utilized, it has been demonstrated that systemic occlusion of the cystic artery is not necessary. Additionally, some recommend technetium-99 scintigraphy or angiography after access has been achieved to ensure that the entire liver is being perfused without extrahepatic diffusion.

For port or catheter-delivered hepatic arterial chemotherapy, the most common agents used have been oxaliplatin and 5-fluorouracil (5-FU). When administered with HAI, oxaliplatin has been shown to have lower peak plasma platinum levels than that with systemic therapy, and intrahepatic levels that are 4.3 times higher than with systemic therapy. Oxaliplatin has demonstrated a liver extraction ratio of 0.47 [9]. Conversely, HAI is less suitable for medications like irinotecan, where first-pass metabolism is required to form its active metabolite, which would result in very low active metabolite at the tumor sites when using HAI [10].

Though there are high success rates of placement of access for HAI, high rates of access complications still exist. The success rate of percutaneous femorally placed access is 94–99% [11]. However, 21% of percutaneously placed ports/catheters and 34% of surgically placed ports/catheters result in complications leading to discontinuation of HAI. Additionally, regional complications of HAI therapy include hepatitis, gastritis, duodenitis, and biliary sclerosis. These complications have been shown to reach between 20% and 89% of patients in various studies, though many are transient and without long-term consequence, many such complications result in the discontinuation of HAI therapy.

Pharmacokinetic Basis for HAI Using Oxaliplatin

A pivotal animal study of agents for HAI was conducted to compare intra-arterial hepatic administration (IAH) versus intravenous (i.v.) administration of oxaliplatin and cisplatin in a VX2 tumor model in rabbits. White New Zealand female rabbits with VX2 tumors implanted in their livers were treated with either cisplatin (4 mg/kg) or oxaliplatin (6 mg/kg) administered by IAH or i.v. and platinum pharmacokinetic parameters measured by atomic absorption spectrometry. After IAH oxaliplatin administration, a significant decrease in systemic platinum and a significantly higher tumor platinum was found after arterial infusion when compared with i.v. oxaliplatin administration. No differences in pharmacokinetic parameters or platinum tissue accumulation were apparent between the IAH and i.v. administration with cisplatin. This is the basis of using oxaliplatin via HAI [12].

Hepatic Colorectal Metastases

Unresectable Metastatic Colorectal Cancer to the Liver

Data for catheter- and port-based HAI for metastatic colorectal cancer have emerged mainly from France and from Japan. In France, the agent chosen for use in HAI was oxaliplatin, while investigators from Japan favored 5-FU. The most important studies in the palliative setting are summarized in Tables 25.3 and 25.4.

HAI Oxaliplatin Therapy

In 2005, Ducreux et al. reported a phase II study evaluating concomitant administration of oxaliplatin by HAI (100 mg/m^2) and intravenous (i.v.) FU plus leucovorin according to the LV5FU2 protocol (leucovorin 200 mg/m^2, FU 400 mg/m^2 i.v. bolus, FU 600 mg/m^2 with a 22-h continuous infusion on days 1 and 2 every 2 weeks) (Table 25.3). Inoperable patients with metastatic colorectal cancer restricted to the liver, without previous treatment with oxaliplatin, were treated via surgically implanted ports. Treatment was continued until disease progression (PD) or toxicity. Twenty-six patients were treated with 200 courses of therapy (median: 8 courses; range: 0–20 courses). The most frequent toxicity was neutropenia. The main toxicity related to HAI was pain. The intent-to-treat objective response rate was 64% (95% CI, 44–81%; 18 of 28 patients). Median overall and disease-free survival times were 27 and 27 months, respectively. No doubt, the combination of oxaliplatin HAI and FU + leucovorin according to the LV5FU2 protocol is feasible and effective in patients presenting with isolated hepatic metastases of colorectal cancer [13].

In 2008, Boige et al. reported on a series of 44 patients with unresectable CRLM and history of

Tables 25.3 Arterial infusional oxaliplatin therapy for unresectable colorectal cancer liver metastases (palliative therapy)

Study	Treatment	Setting	Response	Survival	Complication
Ducreux et al. [13] *N* = 26 Surgically placed ports	Oxaliplatin by HAI intravenous (i.v.) FU plus leucovorin according to the LV5FU2 protocol every 2 weeks	Phase II palliative therapy Unresectable colorectal liver metastases	The intent-to-treat objective response rate was 64% (95% CI, 44–81%; 18 of 28 patients).	Median survival: 27 months PFS: 27 months	Neutropenia Pain for HAI infusion
Boige et al. [14] *N* = 44 Surgical ports Percutaneous catheters	Bimonthly with HAI oxaliplatin (100 mg/m^2 2 h) combined with i.v. LV and i.v. bolus and infusional 5-FU (modified LV5FU2 regimen)	Unresectable colorectal liver metastases 98% had previously received systemic chemotherapy	PR: 62% 7 patients became resectable (16%)	PFS: 7 months OS: 16 months	Grade 3–4 neutropenia: 43% Grade 2–3 neuropathy: 43% Grade 3–4 abdominal pain: 14%
Lim et al. [10] *N* = 61 Surgical ports Percutaneous catheters	HAI oxaliplatin plus systemic therapy of 5-FU, leucovorin, with or without antibodies	Retrospective study 4 institutions Unresectable colorectal liver metastases 95% previously treated 82% previous oxaliplatin	Tumor response rate in 1st- and 2nd-line was 26.5% and 3rd- and 4th-line was 11%. A secondary R0 resection was possible in 10 cases (16.4%) allowing a 2-year survival of 80%	Median overall survival (OS) in 1st- and 2nd-line was 13.5 months 3rd- and 4th-line it was 8.3 months Median PFS in 1st- and 2nd-line was 9 months and 3rd- and 4th-line it was 6 months (P = 0.0037)	Grade 3–4 clinical toxicities: 16% 9.8% of neurotoxicity Grade 3–4 biological toxicities: 24.6% and 22.2% with neutropenia Catheter complications: 31%

(continued)

Table 25.3 (contined)

Study	Treatment	Setting	Response	Survival	Complication
Tsimberidou et al. [15] $N = 57$ Percutaneous transfemoral catheters	HAI oxaliplatin 60 mg/m^2 to 175 mg/m^2 and intra-arterial heparin 3000 IU (Day 1); leucovorin 200 mg/m^2 i.v. and 5-FU 300 mg/m^2 bolus plus 600 mg/m^2 i.v. (Days 1 and 2); and bevacizumab 10 mg/kg i.v. (Day 3)	Phase I study Unresectable metastatic colorectal liver cancer Median prior therapies: 3	PR: 11% SD: 32%	–	MTD of HAI oxaliplatin: 140 mg/m^2 Dose-limiting toxicities: grade 4 thrombocytopenia ($n = 1$) grade 4 hypokalemia ($n = 1$) at 150 mg/m^2 ($n = 5$) 33 patients (58%) had no toxicity >grade 1 Most common toxicities were thrombocytopenia ($n = 19$), fatigue ($n = 15$), nausea/vomiting ($n = 6$), constipation ($n = 6$), and diarrhea ($n = 4$)

systemic chemotherapy failure. Treatment consisted of bimonthly HAI with oxaliplatin (100 mg/m^2 for 2 h) combined with i.v. LV and i.v. bolus and infusional 5-FU (modified LV5FU2 regimen). Of the 44 patients (median age 56 years; median number of prior systemic chemotherapy regimens: 2, with a range of 1–5). Patients received a median of nine cycles of HAI oxaliplatin and i.v. modified LV5FU2 (range 0–25). Toxicity included grade 3–4 neutropenia (43%), grade 2–3 neuropathy (43%), and grade 3–4 abdominal pain (14%). There were 24 partial responses (62%) among the 39 assessable patients, including 17, 12, and 12 patients who had failed to respond to prior systemic chemotherapy with FOLFIRI, FOLFOX, or both, respectively. Tumor response allowed conversion to resectable/ablatable in eight patients (18%). Median progression-free survival (PFS) and overall survival (OS) were 7 and 16 months, respectively. Thus, HAI oxaliplatin and i.v. LV5FU2 are clearly feasible, safe, and effective, even in patients who have failed modern chemotherapy [14].

In 2017, Lim et al. evaluated the feasibility, efficacy, and tolerance of HAI in a multicenter study and also showed encouraging results. Sixty-one patients with unresectable hepatic CRC were included: 95% had previously received systemic chemotherapy and 82.8% had previous oxaliplatin treatment. HAI oxaliplatin was combined with intravenous (i.v.) 5-FU with leucovorin alone (43.3%) or combined with other i.v. chemotherapies or monoclonal antibodies (56.7%). Grade 3–4 clinical toxicities included neurotoxicity (9.8%) and neutropenia (22.2%). Catheter-related complications were observed in 31.1%. Tumor response rate in 1st- and 2nd-line was 26.5% and 3rd- and 4th-line was 11%. Median overall survival (OS) in 1st- and 2nd-line therapy was 13.5 months, and in 3rd- and 4th-line therapy it was 8.3 months. Median PFS in 1st- and 2nd-line therapy was 9 months, and in 3rd- and 4th-line therapy it was 6 months (HR, 0.53; 95% CI, 0.18–0.659; $P = 0.0037$). A secondary R0 resection was possible in 10 cases (16.4%) allowing a 2-year survival of 80% [10].

An American experience was also published by Tsimberidou et al. in 2010. Delivery of HAI oxaliplatin was via femoral catheters that were removed after each infusion. In this phase I study of hepatic arterial infusion (HAI) oxaliplatin combination therapy in patients with advanced cancer and liver metastases, 57 patients were treated (30 women: 27 men; median age: 57 years). Patients received a median of three prior therapies (range, 1–7 prior therapies). The most common cancer was colorectal ($n = 29$).

Overall, 204 cycles were administered (median per patient, 2 cycles; range, 1–17 cycles). Treatment consisted of escalating doses of HAI oxaliplatin 60 mg/m^2 to 175 mg/m^2 and intra-arterial heparin 3000 IU (Day 1); leucovorin 200 mg/m^2 intravenously (iv) and 5-FU 300 mg/m^2 bolus plus 600 mg/m^2 i.v. (Days 1 and 2); and bevacizumab 10 mg/kg i.v. (Day 3). The maximum tolerated dose (MTD) of HAI oxaliplatin was 140 mg/m^2. Thirty-three patients (58%) had no toxicity greater than grade 1. The most common toxicities were thrombocytopenia (n = 19), fatigue (n = 15), nausea/vomiting (n = 6), constipation (n = 6), and diarrhea (n = 4). Four patients (7%) had a partial response (PR), and 32 patients (58%) had stable disease (SD), including 15 patients (48%) who had SD for ≥4 months. Of 28 patients with colorectal cancer, three patients (11%) had a PR and nine patients (32%) had SD for ≥4 months [15].

It is clear that such arterial therapies resulted in a higher incidence of severe oxaliplatin-related lesions (SOxL), including sinusoidal obstruction syndrome and regenerative nodule hyperplasia. In a study involving patients with initially unresectable CRLM who had undergone hepatic resection after at least six cycles of oxaliplatin-based chemotherapy administered either via HAI (n = 18) or i.v. (n = 50), resected specimens were examined for the presence of oxaliplatin-related lesions. Encouragingly, a complete pathologic response (CPR) was observed significantly more often after HAI (33 vs. 10%, P = 0.03). However, SOxL had occurred more frequently in patients in the HAI group versus the i.v. group, 66 and 20%, respectively (P < 0.001). On a well-balanced cohort, HAI was associated with higher chance of complete pathologic response (CPR) (odds ratio 9.33, 95% confidence interval 1.59–54.7) but also higher risk of SOxL (odds ratio 13.7, 95% confidence interval 3.08–61.3).

Of note, a CPR markedly enhanced overall survival (OS) and disease-free survival (median OS of 114 vs. 42 months, P = 0.02; median disease-free survival of 51 vs. 12 months, P = 0.002). Patients with SOxL did not experience different outcome (median OS of 42 vs. 50 months, respectively; P = 0.92). Thus, HAI of oxaliplatin increases the likelihood of a CPR at the cost of a higher incidence of SOxL in patients with initially unresectable CRLM. What will the higher incidence of SOxL translate into clinically is still not fully known [16].

5FU-Based HAI Therapy

The Japanese experience on HAI has been based on infusion of 5-Fluorouracil (5-FU). In 2009, Seki et al. reported on arterial chemotherapy delivered by a radiologically placed port via the axillary artery (Table 25.4). In this retrospective study of 20 patients with unresectable hepatic colorectal cancer, the patients were treated with hepatic arterial infusion (HAI) chemotherapy followed by systemic therapy using oxaliplatin plus 5-FU (1000 mg/m^2 weekly) and then with FOLFOX thereafter (FOLFOX4, n = 13; modified FOLFOX6, n = 7). Toxicity of HAI chemotherapy was generally mild. Of 20 patients, adverse events leading to treatment discontinuation occurred in only one patient (5%) during HAI therapy, while nine patients (45%) exhibited adverse events during FOLFOX therapy. Objective response rates for HAI chemotherapy and FOLFOX were 85.0% and 35.0%, respectively. Median time to progression was 11.6 and 5.1 months, respectively. Median overall survival was 30.1 months. The sequence of HAI 5-FU chemotherapy followed by FOLFOX is clearly active against metastatic colorectal cancer and is well tolerated [17].

Iguchi et al. in 2011 reported on the use of HAI 5-FU delivered via surgically placed port. In this small (n = 3) study on patients with very large liver tumor burden, HAI 5FU (1000 mg/m^2) was administered weekly by continuous 5-h infusion. After three HAI cycles administered over three consecutive weeks, the mean alkaline phosphatase levels decreased from 969.3 IU/l to 422 IU/l due to shrinkage of the liver metastases. The investigators used such HAI therapy to shrink tumor prior to starting FOLFOX. Two patients succumbed 488 and 333 days after hepatic arterial infusion chemotherapy (HAIC) was initiated. A third patient is still alive and has been followed up for 1215 days. This suggests

Table 25.4 Arterial infusional 5-FU therapy for unresectable colorectal cancer liver metastases (palliative therapy)

Study	Treatment	Setting	Response	Survival	Complication
Seki et al. [17] *N* = 20 Transaxillary arterial ports	HAI chemotherapy until disease progression (5-fluorouracil, 1000 mg/m^2 intra-arterial infusion, weekly) and then with FOLFOX thereafter (FOLFOX4, *n* = 13; modified FOLFOX6, *n* = 7)	Unresectable metastatic colorectal liver metastases	PR: 85%	Median survival: 30.1 months	Only one patient required stoppage of HAI therapy
Arai et al. [19] *N* = 25 Percutaneous port	Intra-arterial 5-FU (1000 mg/m^2) was administered on days 1, 8, and 15 of each treatment cycle. The dose of systemic irinotecan on days 1 and 15 was escalated from 75 mg/m^2	Phase I-II	RR: 72%	Median survival: 49.8 months	No DLT Grade 3 or higher adverse events included hyperglycemia (15%), elevated gamma-glutamyl transpeptidase levels (15%), and neutropenia (9%)
Arai et al. [20] *N* = 27 Subclavian artery ports	5-FU at 1000 mg/m^2 over 5 h via hepatic arterial infusion on a weekly schedule.	Unresectable colorectal liver metastases	CR: 14% PR: 29% SD: 28% RR: 43% DCR: 79%	PFS: 203 days OS: 560 days	The most common grade 3 or 4 hematological and non-hematological toxicities were total bilirubin level elevation (10.4%) and gamma-glutamyl transferase level elevation (10.4%)
Goi et al. [21] *N* = 10 Femoral catheters	HAIC (5-FU and LV administered once weekly)	Unresectable colorectal liver metastases	PR: 30% SD: 40%	Median survival: 9 months	–
Sato et al. [22] *N* = 6 Port	Escalating doses of oxaliplatin for levels 1 and 2 were set at 50 and 100 mg/m^2, respectively, and were combined with fixed doses of intravenous 5-FU (200 mg/m^2 bolus and 2400 mg/m^2/46-h continuous infusion) and l-LV (200 mg/m^2)	Phase I-II Unresectable colorectal liver metastases	Liver disease control rate: 70%	–	RD for oxaliplatin by HAI in combination with intravenous 5-FU and l-LV was 100 mg/m^2

Notes: *RR* overall response rate, *DCR* disease response rate, *CR* complete response, *PR* partial response, *SD* stable disease, *CRCLM* colorectal cancer liver metastases, *DLT* dose-limiting toxicity, *HAI* hepatic arterial infusion, *LV5FU2* leucovorin plus 5-fluorouracil regimen [29], *RD* recommended dose

that combined use of HAIC followed by standard systemic chemotherapy is a feasible strategy for highly advanced cases of liver tumor with hepatic dysfunction [18].

Arai et al. reported in 2013 on the feasibility of image-guided delivery of 5-FU through HAI (1000 mg/m^2) administered on days 1, 8, and 15 of each treatment cycle and systemic irinotecan (on days 1 and 15 it was escalated from 75 mg/m^2) in a multicenter phase I/II study. Twenty-five patients were treated with no dose-limiting toxicity that was encountered during phase I. The recommended dose (RD) of irinotecan was set at 150 mg/m^2. Grade 3 or higher adverse events included: hyperglycemia (15%), elevated gamma-glutamyl transpeptidase (GGTP) (15%), and neutropenia (9%). The response rate and median survival time were 72% and 49.8 months (95% CI, 27.5–78.1 months), respectively. HAI 5-FU and systemic irinotecan can be delivered safely with good tumor response and survival [19].

These investigators updated their experience in 2015, reporting a prospective multicenter study delivering HAI 5-FU (1000 mg/m^2 over 5 h weekly). Results from 77 eligible patients were reported. Response included complete response (CR) in 4 patients, PR in 29, 28 with stable disease, and 15 with progressive disease. The overall RR was 42.9% and the disease control rate (DCR) was 79.2%. The median PFS and OS times were 203 and 560 days, respectively. Grade 3 or 4 toxicities included hyperbilirubinemia (10.4%) and high GGTP (10.4%). This study demonstrated that HAI as a method of delivering chemotherapy to colorectal liver metastases is safe and effective [20].

Goi et al. in 2015 looked at HAI 5FU in patients with tumors refractory to systemic chemotherapy (FOLFOX/FOLFIRI) or to additional molecularly targeted therapies for progressive disease. Hepatic infusion catheters were placed percutaneously. In this 10 patient study, HAI (5-FU and LV) was administered once weekly. Of the 10 subjects, 3 (30%) showed partial response and 4 (40%) showed stable disease. The disease control rate was 70%. Eight subjects had improved quality of life. Survival time ranged from 2 to 16 months (median, 9 months). Thus, HAI 5FU chemotherapy can be used in patients with systemic chemotherapy-resistant colorectal cancers with liver metastases [21].

Sato et al. in 2018 assessed HAI in a phase I/II trial in patients with refractory tumors and used HAI oxaliplatin combined with intravenous 5-FU and l-leucovorin (l-LV). A catheter-port system for HAI was placed by the interventional radiologist percutaneously. In phase I, escalating doses of oxaliplatin for levels 1 and 2 were set at 50 and 100 mg/m^2, respectively, and were combined with fixed doses of intravenous 5-FU (200 mg/m^2 bolus and 2400 mg/m^2/46-h continuous infusion) and l-LV (200 mg/m^2). In phase I, none of the six enrolled patients exhibited DLT. RD for oxaliplatin by HAI was estimated as 100 mg/m^2. In phase II, seven additional patients were enrolled. In patients receiving RD (n = 10), the disease control rates for total lesions and liver lesions were 30% and 70%, respectively. However, the 6-month survival rate and the overall survival time were only 53.3% and 6.9 months, respectively. The conclusion from this study was that HAI therapy is certainly feasible [22].

Downstaging for Resection

Goere et al. reported on the use of HAI oxaliplatin chemotherapy to convert patients from unresectable to resectable. The chemotherapy regime administered was oxaliplatin (100 mg/m^2 IA over 2 h), with systemic leucovorin (200 mg/m^2) and i.v. 5FU (2400 mg/m^2 over 2 days). Twenty-three patients of a total of 87 patients were rendered resectable by this regimen (26%). The main criterion for unresectability was massive liver involvement (86% of patients) with most patients having synchronous tumors (85%) and bilateral metastases (89%). Resection in the 23 patients was associated with no postoperative mortality and a morbidity rate was 35%. Five-year overall survival was 56% in the resected group versus none in the nonresected group ($P < 0.0001$). After a median follow-up of 63 months, intrahepatic recurrence occurred in ten patients among the 23 operated patients. HAI of oxaliplatin with systemic 5-FU and leucovorin offers an opportunity to convert initially unresectable isolated colorectal liver metastases to resectable and possibly curable [23].

HAI as Adjuvant Therapy

HAI chemotherapy has also been used as adjuvant therapy after liver resection (Table 25.5). The premise of this treatment is that such adjuvant regimens directly treat the organ at highest risk of residual disease. Liver disease is also frequently the most dominant site of disease burden in terms of cause of death.

Goere et al. in 2013 reported on the use of oxaliplatin-based HAI chemotherapy in association with systemic fluoropyrimidine as adjuvant therapy after liver resection. The trial was conducted by investigators from Institut Gustave Roussy. Therapy was delivered via arterial ports, which were placed at the time of surgery. Through the ports, oxaliplatin chemotherapy was delivered over 2 h with each cycle. Ninety-eight patients, who had undergone curative resection of at least four colorectal liver metastases, were included. Forty-four patients (45%) had received postoperative HAI combined with systemic 5-FU (HAI group)

Table 25.5 Studies of adjuvant arterial infusion and resectable colorectal cancer liver metastases

Study	Setting	Survival	Complication	Major findings
Goere et al. [24] $N = 98$	Retrospective comparison of subjects who were able to receive adjuvant HAI oxaliplatin vs not >3 CRLM	After a median follow-up of 60 months (51–81 months), 3-year overall survival was slightly higher in the HAI group (75% vs 62%, $P = 0.17$) Three-year disease-free survival was significantly higher in patients in the HAI group than those in the i.v. group (33% vs 5%) $P < 0.0001$	HAI chemotherapy was discontinued because of toxicity ($n = 8$), HAI catheter dysfunction ($n = 6$)	In the multivariate analysis, adjuvant HAI chemotherapy and an R0 resection margin status were the only independent predictive factors for prolonged disease-free survival
House et al. [25]	125 patients underwent resection of CRLM followed by adjuvant HAI-FUDR plus dexamethasone (Dex) and concurrent systemic chemotherapy including oxaliplatin or irinotecan. These patients were compared retrospectively to 125 consecutive patients who received modern systemic chemotherapy alone	Recurrence-free survival at 5y was at 79% for the HAI group vs 55% in the control group (adjuvant systemic therapy) Estimated 5-year overall RFS for the HAI + Sys patients was 48%, compared to 25% for the Sys group, $P < 0.01$ 3-year DSS = 86% 5-year DSS = 75%	25% of the patients in the HAI group presented complications; these included 2 arterial pseudoaneurysms, 2 gastrointestinal ulcerations, and 1 biliary sclerosis	Adjuvant HAI chemotherapy group showed an overall RFS of 52 m vs 23 m for systemic adjuvant group

Notes: *DSS* Disease-specific survival, *HAI* hepatic arterial infusion, *HAI-FUDR* hepatic arterial infusional floxuridine, *RFS* recurrence-free survival, *Sys* adjuvant systemic therapy

and 54 patients (55%) had received "modern" systemic chemotherapy (i.v. group). The two groups were similar in terms of age, gender, and stage of the primary. The median number of HAI cycles received per patient was 7 (range, 1–12). Twenty-nine patients (66%) received at least six cycles of HAI oxaliplatin, and 22 patients (50%) received the full planned treatment. For the remaining 22 patients (50%), HAI chemotherapy had been discontinued because of toxicity ($n = 8$), HAI catheter dysfunction ($n = 6$), an early recurrence ($n = 6$), and patient's refusal ($n = 2$). After a median follow-up of 60 months (51–81 months), 3-year overall survival was slightly higher in the HAI group (75% vs 62%, $P = 0.17$). Three-year disease-free survival was significantly longer in patients in the HAI group than those in the i.v. group (33% vs 5%, $P < 0.0001$). Adjuvant HAI chemotherapy and an R0 resection margin status were the only independent predictive factors for prolonged disease-free survival. The conclusion was that postoperative HAI oxaliplatin combined with systemic chemotherapy after curatively intended surgery of colorectal liver metastases is feasible and may improve disease-free survival [24].

A study by House et al. puts in perspective the other adjuvant therapies. In this study, the authors compared 125 patients who underwent resection of CRLM followed by adjuvant HAI-FUDR plus dexamethasone (Dex) and concurrent systemic chemotherapy including oxaliplatin or irinotecan, with 125 consecutive patients who received modern systemic chemotherapy alone after liver resection. The median follow-up for all patients

was 43 months. There were no differences in clinical risk score, disease-free interval, size of largest CRLM, number of CRLM, or pre-hepatectomy CEA level between the two groups. Adjuvant HAI-FUDR was associated with improved overall survival, liver recurrence-free survival (liver RFS), and disease-specific survival (DSS) rates. For the adjuvant HAI-FUDR group, the 5-year liver RFS, overall RFS, and DSS were 75%, 48%, and 79%, respectively, compared to 55%, 25%, and 55% for the systemic alone group ($P < 0.01$). On multivariate analysis, adjuvant treatment including HAI-FUDR was independently associated with improved liver RFS (HR = 0.34), overall RFS (HR = 0.65), and DSS (HR = 0.39), $P < 0.01$.] [25].

Adjuvant HAI-FUDR through a pump combined with modern systemic chemotherapy is independently associated with improved survival compared to adjuvant systemic chemotherapy alone. It seems that intra-arterial chemotherapy using oxaliplatin via a port can also improve outcome.

Hepatocellular Carcinoma

HAI has also been tested for primary cancers of the liver. The vast majority of the studies have involved hepatocellular carcinoma. Most of these studies have been for patients with portal vein thrombosis, a population for which embolic therapies are associated with prohibitive morbidity and mortality.

In a study from the Sun Yat Sen University, researchers looked at the use of infusional oxaliplatin in the treatment of patients with HCC in the setting of portal vein thrombosis. This prospective single-arm phase II study was conducted to determine whether HAI chemotherapy of oxaliplatin, 5-FU, and leucovorin added to sorafenib could improve on the results of sorafenib monotherapy. Hepatic arterial chemotherapy was delivered by percutaneously placed catheters. Thirty-five patients were treated with sorafenib 400 mg orally twice a day, oxaliplatin 85 mg/m^2 HAI on day 1, leucovorin 400 mg/m^2 HAI on day 1, and 5-FU 2800 mg/m^2 on days 1 and 2, repeated every 21 days. The 3-, 6-, and 12-month PFS rates were 83%, 52%, and 23%, respectively. The median PFS and overall survival was 6.7 and 13.2 months, respectively. The objective response rate was 40%, and the disease control rate was 77%. Five (14.3%) patients achieved conversion to complete resection after the study treatment, and one of them experienced a pathological complete response. There were no deaths and grade 3–4 toxicities consisted of elevated AST (31.4%), hand-foot syndrome (17.1%), thrombocytopenia (14.3%), and neutropenia (8.6%). The combination treatment met the prespecified endpoint of a 3-month progression-free survival rate exceeding 65% and was clinically tolerable [26]. Thus, HAI therapy represents a promising therapy in this population since the median progression-free survival (PFS) of patients with HCC and major portal vein tumor thrombosis treated with sorafenib monotherapy is no more than 3 months (Table 25.6).

In a study from the Beijing Cancer Hospital, the Yunnan Second People's Hospital, and the Baotou Cancer Hospital, Zhu et al. combined embolization with infusional chemotherapy for 86 patients with HCC in the setting of cirrhosis and portal vein thrombosis. Infusional chemotherapy was performed for 2 h through the same catheter used for embolization. The HAI treatment that consisted of oxaliplatin (50 mg in 250 mL of glucose) was infused by pump for 4 h, followed by raltitrexed (2 mg in 100 mL of 0.9% saline) infusion by pump for the next 1 h. Complete responses (CRs), partial responses (PRs), stable disease (SD), and disease progression (PD) for intrahepatic disease were observed in 0, 45, 20, and 21 patients, respectively. The 1-, 2-, and 3-year overall survival rates of the 86 patients were 40.7%, 22.1%, and 8.1%, respectively, and the median survival time was 8.7 months. However, 28 cases had variceal hemorrhage after embolization, with 19 occurring in the first 3 months and 14 died. Fourteen patients developed intractable ascites. These complications are not unlike those seen for embolization performed in the setting of portal vein thrombosis [27]. These data further support consideration of infusional therapy in this patient population.

Table 25.6 Arterial infusion for HCC with portal vein thrombosis (PVT)

Study	Treatment	Setting	Response	Survival	Complication
Kim et al. [28] *N* = 36 6 institutions Implanted port system	5-FU (500 mg/m^2) for 5 h on days 1~3 and cisplatin (60 mg/m^2) for 2 h on day 2 Treatment sessions were repeated every 4~8 weeks Compared to TACE group: lipiodol doxorubicin q 4–8 weeks	Patients with intractable, advanced HCC with major portal vein invasion or bilobar involvement Progressing after previous embolic therapy Multicenter, prospective study from January 2006 to January 2008	HAI group CR: 0 PR: 17% TACE group: CR: 0 PR: 0	Median survival, 193 vs. 119 days (P = 0.026)	Fever, abdominal discomfort, and nausea were common Gastrointestinal/hepatic symptoms and neutropenia/thrombocytopenia were the most serious HAIC group: Neutropenia and thrombocytopenia were more common TACE group had higher frequency of frequency of hepatitis and hyperbilirubinemia
He et al. [26] *N* = 35 Percutaneous catheter	Oral sorafenib 400 mg BID HAI treatment: oxaliplatin 85 mg/m^2 HAI from hour 0 to 2 on day 1 leucovorin 400 mg/m^2 HAI from hour 2 to 3 on day 1 and 5-FU 400 mg/m^2 HAI bolus at hour 3 and then 2400 mg/m^2 over 46 h on days 1 and 2	Prospective single-arm phase II study Patients with unresectable HCC and major portal vein tumor thrombosis	CR: 3 patients had CR of tumor 3 patients had CR of the PVTT Objective response rate: 40% Disease control rate: 77.1% Five (14.3%) patients achieved conversion to resection with one complete pathological response	The 3-, 6-, and 12-month PFS rates were 82.9, 51.4, and 22.9%, respectively The median PFS and overall survival was 6.7 and 13.2 months	LFT abnormality ≥ grade 3: 11 of the 35 patients (31.4%) Other grade 3 and worse toxicities: Hand-foot syndrome (HFSR, 6 patients, 17.1%), thrombocytopenia (5 patients, 14.3%) neutropenia (3 patients, 8.6%) esophageal hemorrhage (3 patients, 8.6%)
Zhu et al. [27] *N* = 86 Percutaneous catheter	Combined HAI and TACE The catheter was kept in the hepatic artery after TACE HAI oxaliplatin (50 mg in 250 mL of glucose) was infused by pump for 4 h, followed by raltitrexed (2 mg in 100 mL of 0.9% saline) infusion by pump for the next 1 h	Hepatocellular carcinoma (HCC) with major portal vein tumor thrombus (MPVTT)	CR: 0 PR:45% SD:20% PD:21%	Median survival time was 8.7 months 1-year survival: 41% 2-year survival: 22% 3-year survival: 8%	Acute variceal hemorrhaging 28 cases exhibited variceal hemorrhaging after TACE 19 of these complications occurred within 3 months, 14 of these patients died intractable ascites: 14 cases

Notes: *CR* complete response, *mRECIST* modified Response Evaluation Criteria in Solid Tumors Group, *PFS* progression-free survival, *PR* partial response, *PVTT* portal vein tumor thrombus, *TACE* transarterial chemoembolization

Direct Comparison with Transarterial Embolic Therapy

Kim et al. reported a direct comparison of HAI delivered by implanted port system over a 2-h period to TACE. The aim of this study was to compare the effectiveness and safety of high-dose HAI and conventional TACE using doxorubicin for advanced HCC. The HAI group consisted of 36 patients from six institutions, with good liver function, but also with main portal vein invasion (including vascular shunt), infiltrative type, bilobar involvement, and/or refractory to prior conventional treatment (TACE, radiofrequency ablation, or percutaneous ethanol injection), and documented progressive disease. Patients received 5-FU (500 mg/m^2 on days 1~3) and cisplatin (60 mg/m^2 on day 2 every 4 weeks) via an implantable port system. For comparison, 31 patients treated by TACE with characteristics similar to those in the HAI group were recruited. Patients underwent a transarterial infusion of doxorubicin every 4~8 weeks. Six patients (8.9%) achieved a partial response and 20 patients (29.8%) had stable disease. The objective response rate (complete response plus partial response) was significantly better in the high-dose HAI group than in the TACE group (16.7% vs. 0%, $P = 0.030$). Overall survival was longer in the high-dose HAI group than in the TACE group (median survival, 193 vs. 119 days; $P = 0.026$). There were no serious adverse effects in the HAI group, while hepatic complications occurred more often in the TACE group. Thus, HAI may be a less morbid and effective procedure compared to conventional TACE using doxorubicin in patients with intractable, advanced HCC [28].

Conclusion

Interventional radiology now allows for added possibilities in delivering regional liver-directed therapies. Many studies have demonstrated that these techniques are safe and viable, though not without complications. These therapies target directly the area of disease, aim to limit systemic toxicities, and utilize inherent characteristics of the liver's circulatory system and metabolism in order to maximize their treatment effect on liver tumors. Such infusional therapies may be useful even for patients with portal vein thrombosis. Thus, for patients with unresectable liver predominant metastases or primary cancer, HAI may reduce tumor burden, prolong life, and on rare occasions downstage patients for potentially curative resection.

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26 Regional Therapies in Hepatocellular Carcinoma and Cholangiocarcinoma

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Hepatocellular Carcinoma

Introduction

Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver with a rising global incidence and mortality due to chronic liver disease, partly from overall growth and increasing age of the population [1]. Geographically, East Asia and sub-Saharan Africa account for about 85% of cases [2]. Majority of HCCs are attributed to known etiologies, most commonly chronic hepatitis B (HBV) and C virus (HCV), alcoholic cirrhosis, and aflatoxin exposure. Additional causes of cirrhosis, such as nonalcohol steatohepatitis (NASH) and genetic diseases (e.g., hemochromatosis, alpha-1-antitrypsin deficiency), also contribute to the development of HCC. Chronic HBV infection is the etiology of the maximum number of HCC diagnoses worldwide, while HCV, alcoholic cirrhosis, and NASH are the main causes in the western population. Approximately one-third of patients with cirrhosis will develop HCC, with estimated annual risk factor of 1–8% that cirrhosis will progress to HCC [2].

Treatment options for HCC are limited and surgical options such as resection or transplantation offer the only potentially curative interventions, but surgery is not always feasible. Resection is the treatment of choice in noncirrhotic patients as they can tolerate major hepatectomies, but this accounts for only about 5% of patients in western countries and up to 40% in Asian countries [2, 3]. Residual liver function and elevated risk of complications from major surgery must be considered in cirrhotic patients, and resection is generally reserved for patients with solitary tumor, adequate liver function (Child-Pugh class A), model for end-stage liver disease (MELD) score <10, without portal hypertension, and adequate future liver remnant (FLR) volume [2]. In nonresectable patients who meet the Milan criteria (one lesion ≤5 cm or up to 3 lesions ≤3 cm, no macrovascular invasion, no extrahepatic disease), or for early-stage HCC in the setting of Child-Pugh class B or C, liver transplantation is another surgical option. Transplant, however, is limited by graft shortage and limitations of patient selection. In such patients, locoregional therapies are widely performed as nonsurgical treatments for HCC because of their minimal invasive approach and potential effectiveness (Table 26.1).

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Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_26

Table 26.1 Locoregional therapies in HCC

Study	Type	Comparison	Results
Pompili et al. [4]	Multicenter retrospective analysis 136 RFA cases 108 PEI cases	RFA vs. PEI	5-year survival 72.9% vs. 64.7% 5-year recurrence 49% vs. 73.3%
Shibata et al. [10]	RCT 36 patients (48 lesions) RFA 36 patients (46 lesions) MWA	MWA vs. RFA	Treatment sessions 2.4 vs. 1.1 Complete therapeutic response 89% vs. 96% ($p = 0.26$) Residual foci of untreated disease 17.4% vs. 8.3% ($p = 0.2$)
Shi et al. [11]	Single-institution retrospective analysis 224 patients 117 MWA cases 107 surgery cases	MWA vs. surgery	1-year OS 94% vs. 94% 3-year OS 70% vs. 72% 5-year OS 52% vs. 60% 1-year DFS 77% vs. 85% 3-year DFS 38% vs. 57% 5-year DFS 18% vs. 31% DFS significantly higher with surgery in tumors 3–5 cm, no difference in OS
Llovet et al. [20]	RCT 112 patients 37 TAE 40 TACE 35 supportive care	TACE vs. TAE vs. supportive care	1-year OS 82% vs. 75% vs. 63% 2-year OS 63% vs. 50% vs. 27%
Lammer et al. [22]	RCT 201 patients 93 DEB-TACE 108 TACE	DEB-TACE vs. TACE	Complete response 27% vs. 22% Objective response 52% vs. 44% Disease control 63% vs. 52%
Golfieri et al. [23]	RCT 177 patients 89 DEB-TACE 88 TACE	DEB-TACE vs. TACE	1-year OS 86.2% vs. 83.5% 2-year OS 56.8% vs. 55.4% Post-procedure pain more severe in TACE
Peng et al. [27]	RCT 189 patients 94 TACE and RFA 95 RFA alone	TACE with RFA vs. RFA alone	Overall survival HR 0.525 ($p = 0.002$) RFS HR 0.575 ($p = 0.009$)
Brown et al. [31]	RCT 101 patients 51 TAE 50 DEB-TACE	TAE vs. DEB-TACE	RECIST response 5.9% vs. 6% Adverse events 38% vs. 40% Median PFS 6.2 vs. 2.8 months ($p = 0.11$) Median OS 19.6 vs. 20.8 months ($p = 0.64$)
Meyer et al. [33]	RCT 86 patients	TAE vs. TACE	RECIST response 13.2 vs. 32.6% ($p = 0.04$) Median OS 17.3 vs. 16.3 months ($p = 0.74$) Median PFS 7.2 vs. 7.5 months ($p = 0.59$)
Salem et al. [37]	Single-institution retrospective review 245 patients 123 TARE 122 TACE	TARE vs. TACE	Response rate 49% vs. 36% ($p = 0.104$) TTP 13.3 vs. 8.4 months ($p = 0.046$) Median OS 20.5 vs. 17.4 months ($p = 0.232$)
Salem et al. [38]	Prospective observational study 56 patients 29 TARE 27 TACE	TARE vs. TACE	Equivalent QOL ($p = 0.055$) Better social and functional well-being ($p = 0.019$, $p = 0.031$) with TARE TACE patients had lower tumor burden ($p = 0.018$)

Table 26.1 (continued)

Study	Type	Comparison	Results
Salem et al. [39]	RCT 45 patients 24 TARE 21 TACE	TARE vs. TACE	Median TTP >26 vs. 6.8 months ($p = 0.0012$) Rate of necrosis 87% vs. 74% ($p = 0.433$) Median OS 18.6 vs. 17.7 months ($p = 0.99$)
Chow et al. [40]	RCT 360 patients 182 TARE 178 sorafenib	TARE vs. systemic sorafenib	Median OS 8.8 vs. 10 months ($p = 0.36$) Severe adverse events 27.7% vs. 50.6% ($p < 0.001$)
Vilgrain et al. [41]	RCT 459 patients 237 TARE 222 sorafenib	TARE vs. systemic sorafenib	Median OS 8 vs. 9.9 months ($p = 0.18$) Serious adverse events 77% vs. 82%
Ben-Josef et al. [49]	RCT 128 patients	Conformal RT with hepatic arterial floxuridine	Median OS 15.8 months 3-year survival 17%
Kwon et al. [50]	Single-institution retrospective review	Cyberknife radiosurgery	59.6% complete response 26.2% partial response 1-year OS 92.9% 3-year OS 58.6%

Abbreviations: *RCT* randomized control trial, *OR* odds ratio, *OS* overall survival, *RD* risk difference, *RFS* recurrence-free survival, *RR* relative risk, *RT* radiation therapy, *TTP* time to progression

Ablation

The purpose of most locoregional therapies is to cause selective tumor necrosis. A few different ablative approaches exist, including chemical ablation, thermal ablation, or cryoablation [2]. One of the first techniques utilized was percutaneous ethanol injection (PEI), which causes tumor necrosis by dehydration of cells and denaturation of proteins. While ethanol ablation is able to induce necrosis in most tumors smaller than 2 cm, there is greater than 70% 5-year recurrence rate and almost 50% local tumor progression rate [4]. Radiofrequency ablation (RFA) induces cell death by heat generated from high-frequency alternating current. One advantage of RFA to ethanol ablation is that the effects of RFA extend beyond the tumor tissue, creating a margin of tumor-free tissue.

Both RFA and PEI are associated with relatively low complication rates, but RFA was shown to be superior to PEI with better complete response rate (CR) of 65.7% vs. 36.2% ($p < 0.05$) and better 3-year local recurrence rate of 14% vs. 34% ($p < 0.05$) [5]. Additional meta-analyses have shown that overall survival (risk difference 0.116) and local control (risk difference 0.21 at 3 years) were better with RFA than with PEI [6], especially for tumors larger than 2 cm, with overall mortality hazard ratio of 0.53 and recurrence odds ratio of 0.27 when comparing RFA to PEI [7].

RFA has also been compared to surgical resection as first-line treatment for HCC [8, 9], and there was no difference in mortality between the two treatments. While different studies reported in one meta-analysis had discordant outcomes in terms of recurrence and disease-free survival, overall survival was not statistically different between RFA and resection [8]. A Cochrane review also did not find a statistically significant difference in all-cause mortality between RFA and resection, but rate of serious adverse events was significantly lower in RFA (1.7% vs. 23.3%) while cancer-related mortality was lower with surgery (17.4% vs. 37.4%) [9].

Another modality of ablation is microwave ablation (MWA), which uses electromagnetic energy and is more resistant to heat sink effect, meaning its efficacy is not as likely to be diminished by blood vessels. In one randomized trial comparing RFA and MWA, there were no significant differences between the two procedures with respect to complication rates, therapeutic effects,

or rates of residual untreated disease, although MWA required higher number of treatment sessions [10]. Another randomized trial comparing with MWA and surgical resection showed that there was no significant difference in 1-, 3-, and 5-year overall survival between MWA and surgery for tumors up to 5 cm, but disease-free survival was significantly higher in surgery group for tumor size between 3 and 5 cm [11].

Additional ablation techniques under investigation include laser ablation, and irreversible electroporation. In irreversible electroporation, high-current electrical pulses are used to induce pore formation in the plasma membrane leading to cell death. In patients who underwent transplantation for HCC, electroporation led to complete pathologic necrosis in most tumors while preserving bile ducts [12, 13]. An important limitation of ablation is that tumors may not be amenable to treatment based on location, such as subcapsular HCC. However, given the noninferior outcomes after ablation compared to resection, the National Comprehensive Cancer Network (NCCN) guidelines include ablation as a potentially curative treatment modality for HCC ≤3 cm [14]. For tumors larger than 3 cm, alternative therapies are recommended in addition to or instead of ablation.

Arterially Directed Therapies

Transarterial therapies for HCC include bland embolization, chemoembolization, and radioembolization. These therapies involve selective catheter-based infusion of particles targeted to the branches of the hepatic artery that are feeding the segment of liver where the tumor may be located. Currently available arterially directed therapies for HCC include transarterial bland embolization (TAE), transarterial chemoembolization (TACE), TACE with drug-eluting beads (DEB), and transarterial radioembolization with yttrium-90 (Y90) microspheres. Among these, TACE is the most commonly used treatment modality for unresectable HCC [15, 16]. TACE works by intraarterial infusion of a cytotoxic drug followed by embolization of the blood vessel leading to ischemia, as primary liver tumors derive their blood supply from the arteries whereas liver parenchyma is supplied by the portal system. The most commonly used cytotoxic agents in conventional TACE are doxorubicin, epirubicin, cisplatin, or miriplatin as a single agent [17]. TACE offers survival benefits compared to best supportive care when comparing 2- [18], 3- [19], and 5-year [20] survival. In an attempt to improve treatment efficiency of TACE, DEB-TACE was developed with the idea that calibrated doxorubicin-carrying microspheres have a more sustained drug delivery [21]. While one study showed that DEB-TACE has a better toxicity profile and radiographic tumor response [22], another study showed no difference in overall survival, median number of procedures, tumor response, or incidence and severity of adverse events except for lower rates of post-procedure abdominal pain with DEB-TACE [23]. A meta-analysis of seven studies totaling 693 patients also concluded no difference in outcome between TACE and DEB-TACE [24]. However, in patients with advanced cirrhosis, biliary injuries and liver damage may be more frequent with DEB-TACE [25].

As with surgical resection and ablation, patient selection is an important factor for TACE. Patients with declining performance status or severe decompensated liver failure are unlikely to benefit from TACE. Other risk factors for worsening hepatic function after TACE include serum bilirubin >2 mg/dl and tumor burden greater than 50% of total liver volume. The best candidates for TACE have limited disease without vascular invasion or metastasis and are asymptomatic with Child-Pugh stage ≤B [2]. Combination of TACE or DEB-TACE with RFA has been shown to improve overall and recurrence-free survival compared to RFA alone if the tumor is larger than 3 cm [26–28].

There is no definitive data to determine the frequency at which patients should receive TACE, but regular treatments at 2-month intervals may induce liver failure in many patients [29]. Currently, repeat TACE is only recommended when residual HCC is detected on contrast-enhanced CT. Furthermore, if desired treatment

effect is not achieved after two rounds or if the tumor progresses with treatment, TACE should not be repeated [2].

TAE, in contrast to TACE, utilizes occlusion of the blood supply to the tumor without the use of cytotoxic agents. Several studies [30–33] and meta-analysis/systematic review [18, 34] have not shown significantly different outcomes between TAE and TACE or DEB-TACE. However, in clinical practice, TACE is utilized for treatment of unresectable HCC in most instances [2].

The final modality of arterially directed therapy to be discussed is TARE, also called selective internal radiation therapy. Rather than using cytotoxic agents, TARE utilizes radioactive embolic materials such as 131-iodine Lipiodol or microspheres with Y90, which is the most commonly used method. Y90 emits beta particles, a form of high-energy and low-penetration radiation. This technique is newer, more complex compared to other transarterial therapies, and involves coordination between multiple disciplines including interventional radiology, nuclear medicine, and physics [2], meaning it is not as widely available as TAE or TACE. Preliminary hepatic artery angiography is performed, and radiation dosage to the tumor and surrounding tissue as well as tracer distribution and hepatopulmonary shunt are calculated using technetium-99 m (^{99m}Tc) macroaggregated albumin [35]. Contraindications to proceeding with TARE include severe lung shunting and extrahepatic uptake of ^{99m}Tc. Bilirubin >2 mg/dl increases the risk of radiation-induced liver disease with Y90 [36]. Comparing TARE to TACE, small retrospective studies indicate that TARE has favorable toxicity profile, longer time to progression, better tumor control, and increased quality of life, but it does not offer benefit in terms of overall survival [37–39]. Two additional trials have compared TARE to sorafenib, which is the first-line systemic therapy for HCC, demonstrating higher tumor response, longer progression-free survival and time to progression, and lower rates of adverse events with TARE [40, 41]. However, there was no difference in overall survival. The biggest reported complications of TARE include cholecystitis, bilirubin toxicity, radiation-induced liver disease, gastrointestinal ulcers, and abscess formation [35].

One patient population in which locoregional therapy is frequently utilized is those awaiting transplant for unresectable early-stage HCC as a bridging therapy and those who do not meet transplant criteria in attempt to downstage the tumor. In patients who are awaiting transplant, the recommendation is that locoregional therapy be given if the anticipated wait time until transplant is greater than 6 months [42], but in practice, the majority of patients receive some form of locoregional therapy during the wait period. The use of bridging therapy aims to reduce the risk of dropout due to progression; however, some studies have failed to show a significant difference and had high risk of bias [43]. Furthermore, the use of bridging therapy did not change mortality, overall survival, recurrence rate, or recurrence-free survival compared to transplant alone [43]. While it is not possible to directly compare results of patient with American Joint Committee on Cancer (AJCC) T3 HCC (>1 lesion, at least one lesion >5 cm) receiving transplant with or without locoregional therapy as T3 patients are not eligible for transplantation, other studies comparing the outcome of transplant alone for T2 HCC (solitary lesion >2 cm with vascular invasion or multiple tumors all ≤5 cm) and downstaging therapy followed by transplant in T3 HCC have reported increased 1- and 5-year survival rates with downstaging therapy but no difference in 3-year survival or recurrence-free survival at 1 and 5 years [44–46]. Quality of evidence for all studies looking at locoregional therapy in pretransplant setting was low, and given the lack of randomization, it is possible that there was a selection bias for those patients who received locoregional therapies.

In unresectable patients who are not candidates for transplant, locoregional therapies are the preferred treatment option with demonstrated benefit in the overall survival from TACE [18–20, 47]. Addition of radiation therapy, another form of noninvasive regional therapy, may provide added benefit in treating HCC. While radiation therapy is associated with risk of radiation-induced liver disease, advances in technology

that allow for more targeted radiation such as intensity-modulated radiation therapy (IMRT) and stereotactic body radiation therapy (SBRT) have allowed for delivery of radiation to the tumor while limiting the exposure of the surrounding normal tissue [48]. In a phase II trial using radiation therapy in combination with fluorodeoxyuridine via continuous hepatic artery infusion as a radiosensitizer, median survival for patients with HCC was 15.2 months compared to historical figure of 8 months [49]. Another non-comparative study using radiation therapy in patients with nonresectable HCC who were not eligible for ablation showed in-field complete response of 59.6%, 1- and 3-year survival rates of 92.9% and 58.6%, respectively, and in-field progression-free survival rate of 72% and 67.5% at 1- and 3-years, respectively [50]. A Cochrane review comparing TACE alone to TACE and radiation therapy reported improved 1-year all-cause mortality and complete response rate with combination therapy, which also had higher risk of elevated alanine aminotransferase and bilirubin levels [51].

Cholangiocarcinoma

Introduction

Cholangiocarcinoma, or cancer of the biliary tract, is more rare but aggressive form of primary liver malignancy, and the incidence of intrahepatic cholangiocarcinoma (ICC) is also rising while incidence of hilar and distal extrahepatic cholangiocarcinoma is decreasing [52]. While it is considered a rare cancer in most of the world (fewer than 6 cases per 100,000 people), it has a higher incidence in China, Korea, and Thailand [52]. Contrary to HCC, most cholangiocarcinomas arise in patients without appreciable risk factors [53]. Some of the known risk factors for cholangiocarcinoma include primary sclerosing cholangitis, liver fluke infection, choledochal cysts, hepatolithiasis, thorotrast (radiocontrast used in 1930–1950s) exposure, alcohol, and HBV or HCV infection [54]. ICC is often asymptomatic and discovered at a later stage.

Given that patients with ICC present at advanced stages, surgery is an option only in 15–30% of cases but median survival is 3 months without treatment [55]. Contraindications to surgical intervention include multifocal disease, lymph node metastases beyond porta hepatis, and distant metastasis. Even after resection, recurrence rate in ICC is high [56]. Furthermore, transplantation is not pursued for unresectable ICC due to poor outcomes including median survival of 5 months, 1-year survival rate of 13.9%, and recurrence rate of 54% [57–60].

Indications for resection in ICC include localized disease and solitary lesions that allow for sparing of at least two contiguous liver segments with resectability ranging from 15–30% [54]. Even after resection, recurrence rates are 61–71% and 5-year survival rates are 23–61% [56, 61]. General locoregional therapy principles for ICC mirror the management for HCC, but there are fewer studies due to the rarity of the disease. In unresectable ICC, chemotherapy offers limited benefits; hence, locoregional therapies may be offered in attempt to control disease progression, especially considering that major source of mortality in ICC is related to local progression leading to liver failure or biliary complications [54]. Currently, locoregional therapies available for the management of ICC include RFA, TACE, DEB-TACE, and TARE with Y90 (Table 26.2).

Ablation

In ICC, thermal ablation may offer some benefit as a treatment, although no comparative studies have been performed. In patients who were ineligible for surgical resection, ablation led to a median overall survival of 33 months and 29% 5-year survival in one retrospective study, compared to historical median survival of 6–12 months in unresectable ICC [62]. A meta-analysis reported similar findings with pooled 5-year survival of 24% and progression rate of 21% [63]. In treating recurrent disease, ablation showed no difference in overall survival compared to repeat resection if the tumor is smaller than 3 cm [64], and 5-year overall

Table 26.2 Locoregional therapies in ICC

Study	Type	Comparison	Results
Fu et al. [62]	Single-institution retrospective review 17 patients (26 lesions)	RFA only	Early necrosis 96.2% Median RFS 17 months Median OS 33 months 1-year survival 84.6% 3-year survival 43.3% 5-year survival 28.9%
Zhang et al. [64]	Single-institution retrospective review 109 patients 77 ablation 32 repeat resection	Ablation (RFA and MWA) vs. repeat resection	No significant difference in OS ($p = 0.996$) No significant difference in DFS ($p = 0.692$) For tumors >3 cm, resection had improved OS ($p = 0.037$) Major complication rate higher in repeat resection ($p < 0.001$)
Xu et al. [65]	Single-institution retrospective review 18 patients (25 lesions)	Ablation (RFA and MWA) only	Complete ablation 92% 1-year OS 36.3% 3-year OS 30.3% 5-year OS 30.3% Survival better for primary ICC compared to recurrent disease
Scheuermann et al. [67]	Single-institution retrospective review 273 patients 130 resection 32 TACE 111 systemic chemotherapy or best supportive therapy	TACE vs. surgery	Median survival and OS comparable between TACE and surgery if lymph node positive or positive margins
Kiefer et al. [68]	2-center retrospective study 62 patients	TACE vs. TACE with systemic therapy	Median OS 16 vs. 28 months ($p = 0.02$)
Kuhlmann et al. [69]	Retrospective review 67 patients 26 DEB-TACE 10 TACE 31 systemic	DEB-TACE vs. TACE	PFS 3.9 vs. 1.8 months OS 11.7 vs. 5.7 months
Rafi et al. [72]	Single-institution retrospective review 19 patients	TARE	Median OS from first treatment 11.5 months Partial response rate 11% Stable disease rate 68% Progressive disease rate 21%
Al-Adra et al. [73]	Systematic review	TARE	Median weighted OS 15.5 months Partial response rate 28% Stable disease rate 54%
Gangi et al. [74]	Single-institution retrospective review 85 patients	TARE	Median OS from first treatment 12 months Partial response rate 6.2% Stable disease rate 64.2% Progressive disease rate 29.6%
Konstantinidis et al. [78]	Single-institution retrospective review 236 patients	HAI and systemic therapy vs. systemic therapy alone	Response rate 59% vs. 39% ($p = 0.11$) OS 30.8 vs. 18.4 months ($p < 0.001$)

Abbreviations: *DFS* disease-free survival, *OR* odds ratio, *OS* overall survival, *PFS* progression-free survival, *RFS* recurrence-free survival

survival rates after ablation of recurrent and primary disease were 30.3% and 62.5%, respectively [65].

Arterially Directed Therapies

Many small retrospective studies have examined the outcomes after different transarterial therapies in unresectable ICC. Conventional TACE extended median survival from 3.3 to 12.2 months when compared to supportive care [66]. When comparing conventional TACE or DEB-TACE to surgical resection with positive margins or positive nodal disease, there was no difference in survival outcome [67]. Addition of systemic chemotherapy to conventional TACE (mitomycin C, doxorubicin, and cisplatin) led to an increase in overall survival from 15 months to 28 months [68]. Single-agent TACE, on the other hand, led to 5.7 months of overall survival and 1.8 months of progression-free survival, whereas DEB-TACE led to overall survival of 11.7 months and progression-free survival of 3.9 months [69]. A meta-analysis reported weighted cumulative median overall survival of 13.4 months from first TACE treatment and 15.7 months from diagnosis [70].

Radioembolization with Y90 is another treatment option for unresectable ICC. In patients who had undergone multiple other therapies including surgery, radiation, chemotherapy, or other locoregional therapies, TARE led to overall survival of 22 months from first treatment with 36.4% of tumors demonstrating partial response and 51.5% remaining stable [71]. The time to TARE from initial diagnosis was 21.2 months. However, in patients who did not respond to systemic chemotherapy, TARE led to median survival of 11.5 months with lower rates of tumor response [72]. A systematic review reported weighted overall median survival of 15.5 months, partial response rate of 28%, and stable disease in 54% with TARE [73]. In another single-institution retrospective study of 85 patients, median overall survival after TARE was 12 months, with improved outcomes in patients with better performance status (Eastern Cooperative Oncology Group, or ECOG, score of 0–1), solitary disease, well-differentiated tumor, and absence of extrahepatic metastasis [74], again highlighting the importance of patient selection.

There is no current evidence to support the use of TACE over TARE in ICC, and they have demonstrated comparable overall survival [75, 76]. However, there are other clinical factors that must be considered when choosing TACE or TARE as the treatment option for unresectable ICC. For example, prior biliary intervention may increase the risk of liver abscess with TACE, whereas infectious complications are rare with TARE [77]. TARE, on the other hand, is not recommended for patients who have received prior radiation therapy in the same field, but TACE can be used safely in such circumstances.

Hepatic artery infusion (HAI), which involves surgical placement of hepatic artery pump and allows for continuous administration of cytotoxic agents into the hepatic artery, can also be considered in unresectable ICC. In a meta-analysis, HAI was shown to provide the longest median overall survival of 22.8 months compared to TARE (13.9 months), TACE (12.4 months), and DEB-TACE (12.3 months) [76]. Complete and partial response rate was also the highest for HAI at 56.9% compared to TARE (27.4%) and TACE (17.3%), but grade III and IV toxicity was also more frequent. HAI may also improve overall survival when combined with systemic chemotherapy compared to chemotherapy alone [78].

Complications and Contraindications

Locoregional therapies for hepatic malignancies are generally well tolerated. Most common complications from percutaneous RFA in a multicenter study from Italy were peritoneal bleeding, tumor seeding, abscess formation, bowel perforation, hemothorax, and/or rapid hepatic decompensation with overall major complication rate of 2.2% and mortality rate of 0.3% [79]. Tumor location is a relative contraindication for ablation. If the tumor is superficial and close to the

bowel, there is an increased risk of thermal injury to the gastrointestinal tract which may be avoided with certain maneuvers such as intraperitoneal dextrose injection, but, if the tumor is within 1 cm of a main biliary duct then RFA is contraindicated [80]. Other contraindications to RFA include intrahepatic ductal dilatation, bilioenteric anastomosis, anterior exophytic tumor, and coagulopathy that cannot be treated [80].

Some of the more common complications from any arterially directed therapy include liver failure, injury to the vessels, and postembolization syndrome, characterized by pain, fever, and/or nausea [81]. Postembolization syndrome is more common to TAE/TACE compared to TARE. Absolute contraindications to TACE include decompensated cirrhosis, hepatofugal flow, involvement of entirety of both lobes, and impaired renal function (creatinine ≥2 mg/dl or creatinine clearance <30 ml/min) [82]. TARE contraindications are elevated total bilirubin >2 mg/dl and reduced albumin <3 g/dl indicating inadequate functional liver reserve and significant hepatopulmonary shunting [83]. Treatment options for patients with unresectable HCC/ICC who are also not eligible for locoregional therapies include systemic therapy and enrollment in clinical trials.

Conclusion

HCC and ICC represent two distinct cases of primary liver cancer. While surgical resection remains the only potentially curative intervention, many patients present with unresectable disease. Locoregional therapies, such as ablation, TACE, DEB-TACE, and TARE have been utilized to treat unresectable HCC and ICC with varying degree of success in improving outcomes. Overall consensus is that these interventions offer improved oncologic outcomes in specific patient populations, and they are recommended as treatment options by different groups including NCCN, American Association for the Study of Liver, and European Association for the Study of Liver. Additional studies are needed in order to definitively address whether one form of locoregional therapy is superior to another and whether locoregional therapy in combination with other systemic therapies will improve outcome.

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27 Regional Therapies for Hepatic Melanoma Metastases

T. Susanna Meijer, Alexander L. Vahrmeijer, and Mark C. Burgmans

Introduction

Worldwide, each year 1.7% of all newly diagnosed primary malignancies (excluding nonmelanoma skin cancer) and 0.7% of all cancer deaths are accounted for by cutaneous melanoma [1]. Although the vast majority of melanomas (~90%) arise through malignant transformation of melanocytes within the skin, they occasionally arise from melanocytes located in the uveal tract of the eye (~5%), which is composed of the iris, ciliary body, and choroid (Fig. 27.1). In rare cases, melanoma develops within mucous membranes or meninges, or is diagnosed in a metastatic setting with an unknown primary site [2–4].

Although uveal melanoma accounts for only 5% of all melanomas, it accounts for 13% of all deaths caused by melanoma [5]. This is closely related to the large number of uveal melanoma patients that will eventually develop metastases (up to 50%) while there is no effective systemic therapy [6]. The prognosis for metastatic cutaneous melanoma patients has improved significantly with the introduction of immunotherapy and BRAF-targeted therapy, but these therapies are not effective in patients with uveal melanoma [7].

Cutaneous melanoma and uveal melanoma have a different metastatic pattern and biological behavior. While cutaneous melanoma initially spreads to regional lymph nodes after which any organ can be affected through lymphatic and/or hematogenous spreading, uveal melanoma spreads purely hematogenously as the eye has no lymphatic vessels [7–9]. When uveal melanoma patients are diagnosed with metastatic disease, the liver is affected in more than 90% of cases and remains the only site of metastases in about 50% [6]. On the contrary, metastatic cutaneous melanoma is rarely liver-dominant and hepatic metastases occur in only 10–20% of patients [7–9]. Because the survival of most patients with metastatic uveal melanoma is determined by the status of the disease in the liver, liver-directed therapies play a key role in the management of these patients. Systemic treatment is the treatment of choice for most patients with metastatic cutaneous melanoma.

Hepatic metastases from cutaneous melanoma and uveal melanoma also differ in terms of mutation status. Activating mutations in the *BRAF* oncogene are most common in cutaneous melanoma (50–60%), making the majority of patients eligible for treatment with *BRAF* inhibitors. Combining *BRAF* inhibitors with *MEK* (mitogen-activated protein kinase) inhibitors resulted in an objective response rate (ORR) of

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Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_27

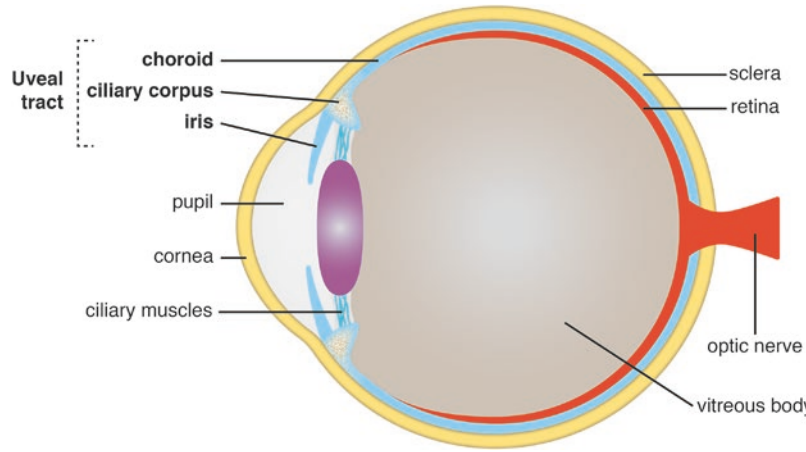

Fig. 27.1 Uveal tract. The uveal tract or uvea is a vascular and pigmented layer of tissue located between the outer layer (cornea and sclera) and inner layer (retina) of the eye. The uvea is composed of three components that are continuous with one another: the iris, ciliary corpus, and choroid

70%, median progression-free survival (PFS) of 14.9 months, and overall survival (OS) of 22.3 months [1, 10]. Typical for all *BRAF* inhibitor-based therapies is the rapid tumor response that occurs within days to a few weeks, making them particularly beneficial in patients with symptoms and/or rapidly progressive disease. *BRAF*-targeted therapy is not an option for metastatic uveal melanoma, which does not harbor *BRA*F mutations. Mutations in genes encoding the G-protein-alpha subunits *GNAQ* or *GNA11* are characteristic for uveal melanoma metastases (80–90%), but these remain difficult targets for systemic therapy. The introduction of mutation independent immune-checkpoint inhibitors against *CTLA4* (ipilimumab) and *PD-1* (pembrolizumab, nivolumab) has further improved OS in patients with metastatic cutaneous melanoma including those without *BRAF* mutations. Unfortunately, also these immune-checkpoint inhibitors have not been able to improve OS in metastatic uveal melanoma [11].

Liver-directed therapies may be considered when the liver is the only or dominant site of metastatic disease. In this chapter, we will highlight the liver-directed therapies that are currently used for the treatment of hepatic melanoma metastases, focusing on metastases from cutaneous melanoma and uveal melanoma. Treatment reports for liver-directed therapies in melanoma literature are, however, often dominated by or restricted to uveal primaries. We will briefly discuss the techniques and give an overview of published literature.

Liver-Directed Therapies: Arterial Therapies

The liver has a unique dual blood supply. Approximately 70–80% of the blood supply to the liver parenchyma is derived from the portal vein and the hepatic arteries supply the remaining 20–30%. In contrast, most hepatic malignancies have a dominant or exclusive vascular supply from the hepatic arteries. When a drug or embolic agent is delivered through the hepatic artery, this will mainly affect the liver malignancies with relative sparing of the normal liver parenchyma.

All arterial therapies share the same common advantage of being an intensified treatment to both radiologically visible and occult tumors (micrometastases), while systemic toxicity is limited. Established arterial therapies in the treatment of hepatic melanoma metastases include the following:

- Hepatic arterial infusion (HAI)
- Transarterial chemoembolization (TACE)
- Transarterial radioembolization (TARE)
- Percutaneous hepatic perfusion with melphalan (M-PHP)

Hepatic Arterial Infusion (HAI)

In this procedure, also referred to as intra-arterial chemotherapy (IAC) or transarterial chemotherapy (TAC), tumor cell necrosis is induced by the direct cytotoxic effect of chemotherapeutics. It is a repeatable procedure in which the number of received cycles depends on clinical response and the occurrence of toxic effects.

Table 27.1 gives an overview of studies on HAI as treatment of hepatic melanoma metastases [12–19]. The most frequently used chemotherapeutic agent is fotemustine (Muphoran®), generally administered at a dose of 100 mg/m^2 over 4 hours. Two different techniques have been used. In some studies, an implantable catheter connected to a subcutaneous access chamber (Port-A-Cath) was surgically placed into the hepatic artery through the gastroduodenal artery. This was accompanied by ligature or occlusion of collateral arteries and prophylactic cholecystectomy [12, 14]. In other studies, femoral access was achieved by an interventional radiologist after which a microcatheter was placed in the hepatic arterial tree and chemotherapeutics were administered [15, 16, 18, 19].

As shown in Table 27.1, for uveal melanoma the ORR ranges from 0–40% and the median OS from 2.9–21 months. The unfavorable outcomes reported by Boone et al. are partly explained by the fact that their patients had very advanced disease with a median lactate dehydrogenase (LDH) level at baseline of 654 IU/L. They were already found ineligible for M-PHP due to hyperbilirubinemia (n = 8), hepatomegaly due to massive tumor infiltration (n = 5), and prior M-PHP (n = 1) [18]. However, 3/14 patients (21%) had nearly 1-year survival after treatment, suggesting a potential benefit for a subset of patients. Leyvraz et al. demonstrated in a randomized trial that intra-arterially infused fotemustine has a higher ORR and longer PFS compared to intravenous (IV) treatment [17]. However, this did not translate into a significant improved OS. As expected, severe hematologic toxicity was less frequent in the HAI than IV arm; grade 3–4 thrombocytopenia in 21.2% versus 42.1% and neutropenia in 28.7% versus 62.6%. The nonhematologic toxicity was mainly related to HAI therapy, with abdominal pain grade ≥3 in 12.1% of patients, and gastric ulcers in 3%. In addition, 31.8% of patients had a catheter-induced complication and 4.5% had liver toxicity grade ≥3. The two reported deaths, one case of septic shock and one case of mesenteric artery thrombosis followed by sepsis, both occurred in the HAI arm.

Transarterial Chemoembolization (TACE)

Classical TACE involves the injection of an emulsified mixture of a chemotherapeutic agent and oily contrast medium, which acts as a drug carrier, into the tumor-feeding arteries. Although the oily contrast medium (ethiodized oil or Lipiodol®) has some embolic effects itself, an additional embolic agent is generally administered to achieve stasis in the target vessel. By slowing the drug efflux from the hepatic circulation, embolic agents increase the drug concentration delivered to the tumor and increase the duration of drug exposure. In addition, embolic agents cause occlusion of tumor-feeding arteries, which promotes ischemia and tumor necrosis [11]. Common used embolic agents are gelatine sponge (GS), polyvinyl alcohol particles (PVA), and microspheres. GS causes transient embolization with recanalization occurring within approximately 2 weeks, while PVA and microspheres are considered permanent embolic agents [20].

Drug-eluting beads have been increasingly used over the past years. They are nonresorbable microspheres that can be pre-loaded with chemotherapeutic agents such as doxorubicin and irinotecan, and are available in different sizes. In contrast with classical TACE, drug-eluting beads allow for a one-step process in which the chemotherapeutic and embolic agent are delivered simultaneously. Drug-eluting beads lead to a more sustained drug release and lower concentrations of chemotherapeutics in the systemic circulation than in classical TACE [21, 22].

Absolute contraindications for TACE include insufficient portal vein inflow, hepatic encephalopathy, and jaundice. Relative contraindications

Table 27.1 Overview of studies on HAI (≥10 patients) as treatment for hepatic melanoma metastases

First author (year)	Study design	Melanoma type	No. pts (median no. procedures)	Chemotherapeutic agent	ORR	Median PFS (mo)	Median OS (mo)
Leyvraz (1997) [12]	Phase II	UM	31 (6)	Fotemustine	40%	NR	14
Peters (2006) [13]	Phase II	UM	101 (8)	Fotemustine	36%	NR	15
Siegel (2007) [14]	RS	UM (n = 18), CM (n = 12)	30 (8)	Fotemustine	Total 30%, UM 28%, CM 33%	NR	UM 22, CM 12 (*n.s.*)
Heusner (2010) [15]	RS	UM	61 (4[a])	Melphalan/combination of melphalan and additional agent[b]	Reported for each chemoperfusion session no.; max. 30% (4th session)	NR	10
Farolfi (2011) [16]	RS	UM (n = 18), CM (n = 5)	23 (4[a])	Fotemustine/carboplatin	UM 16.7%, CM NR	UM 6.2, CM NR	UM 21, CM NR
Leyvraz (2014) [17]	Randomized phase III	UM	86 HAI (4), 85 IV (3)	Fotemustine (intraarterial vs intravenous)	HAI 10.5%, IV 2.4%	HAI 4.5, IV 3.5, (p = 0.002)	HAI 14.6, IV 13.8 (*n.s.*)
Boone (2018) [18]	RS	UM	14 (2)	Melphalan	7%[c]	NR	2.9
Vera-Aguilera (2018) [19]	Phase I/II	UM (n = 16), CM (n = 9), mucosal (n = 1), unknown (n = 1)	30 (NR)	Nab-paclitaxel	UM 0%, CM 11%, mucosal 0%, unknown 100%	NR	6.5

CM cutaneous melanoma, *HAI* hepatic arterial infusion, *IV* intravenous, *mo* months, *NR* not reported, *n.s.* not significant, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *RS* retrospective, *UM* uveal melanoma

[a]Mean no. of procedures per patient

[b]Melphalan during 1st cycle, combination of melphalan and additional agent (fotemustine, dacarbazine, mitomycin, doxorubicin, or gemcitabine) during other cycles

[c]Based on 7/14 patients

include extrahepatic disease, <50% healthy liver tissue, biliary obstruction, LDH level >425 IU/L, aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) level >5 × upper limit of normal (ULN), and total bilirubin >2.0 IU/L [20].

Table 27.2 gives an overview of studies on TACE as treatment of hepatic melanoma metastases [23–38]. For cutaneous melanoma, Ahrar et al. reported an ORR of 39%, median PFS of 6 months, and median OS of 7.7 months. Responders showed a significant longer OS than those who did not respond to TACE (14.08 versus 7.4 months in patients with stable disease (SD), and 8.5 months in patients with progressive disease (PD), $p = 0.031$) [34].

Studies with more than 20 patients with metastatic uveal melanoma reported an ORR ranging from 14% to 46%, median PFS from 3 to 8 months, and median OS from 5.2 to 28.7 months. Again, several studies found a significant longer OS in responders than in nonresponders [23, 24, 26, 27, 30, 32, 33]. Interestingly, Sharma et al. reported that patients with lesions with a nodular angiographic appearance had a longer PFS and OS than patients with lesions that had an infiltrative appearance (PFS 249 versus 63 days; mean OS 621 versus 114 days; $p = 0.0002$) [28].

The wide variety in outcomes is probably due to differences in the type of chemotherapeutic drugs and embolic agents that were used, the number of procedures per patient, and the selection of patients. Firstly, although in some studies TACE was only offered after first-line systemic therapy had failed [29, 31], in other studies most patients were chemotherapeutic-naive [35–38]. In the study by Huppert et al. and Valpione et al., a considerable number of patients even received some sort of systemic therapy shortly before or after TACE [33, 36]. Secondly, although metastatic disease was liver-dominant in all patients, the percentage of patients with extrahepatic disease at the time of TACE varied from 0% to 75% [27, 37]. Finally, there was a considerable variation regarding tumor load in the liver, where tumor load was limited in most patients that were evaluated in studies reporting the longest OS [35, 38].

Commonly reported side effects of TACE were abdominal discomfort or pain, nausea and/or vomiting, (sub)febrility, and hepatotoxicity. Grade 3 thrombocytopenia was reported in 3–11% and may be partly attributed to the additional systemic chemotherapy [25, 26, 31]. Other serious adverse events are rare, but vascular thrombosis, splenic infarction, and acute renal failure due to tumor lysis syndrome have been reported [26, 31].

Transarterial Radioembolization (TARE)

In this procedure, also known as selective internal radiation therapy (SIRT), yttrium-90 (^{90}Y)-labeled microspheres are delivered into the hepatic arteries after which they eventually lodge in the end-arterioles of the tumor microvasculature. ^{90}Y is a high-energy β-emitting isotope with a mean soft-tissue penetration of 2.5 mm. As hepatic metastases are mainly perfused by the hepatic arteries, high radiation doses can be applied to the tumor while the nontumorous parenchyma is relatively spared. Two types of ^{90}Y-microspheres are commercially available: SIR-Spheres and TheraSpheres. SIR-Spheres (Sirtex, Sydney, Australia) are nonbiodegradable resin ^{90}Y-microspheres with a diameter of 20–40 μm and activity of 40–70 Bq per microsphere. TheraSpheres (MDS Nordion, Ottawa, Canada) are nonbiodegradable glass microspheres with a diameter of 20–30 μm and maximum activity of 2500 Bq per microsphere at the time of calibration. To achieve a similar dose, a much larger number of SIR-Spheres has to be administered compared to the number of TheraSpheres (typically 20–40 million SIR-Spheres versus 1.2 million TheraSpheres).

Holmium-166 poly(L-lactic acid) (^{166}Ho-PLLA) microspheres (QuiremSpheres®) were recently developed as an alternative for ^{90}Y-microspheres. In addition to emitting β-radiation for tumor destruction, ^{166}Ho-microspheres emit y-radiation and are paramagnetic. This gives them the advantage of being visible on both single-photon emission CT (SPECT) and MRI, which enables the use

Table 27.2 Overview of studies on TACE (≥10 patients) as treatment of hepatic melanoma metastases

First author (year)	Study design	Melanoma type	No. pts (mean no. procedures)	Drug(s)	Embolic agent(s)	ORR	Median PFS (mo)	Median OS (mo)
Mavligit (1988) [23]	RS	UM	30 (NR)	Cisplatin	PVA	46%	6	11
Bedikian (1995) [24]	RS	UM	44 (3[a])	Cisplatin ± additional agent[b]	PVA	36%	NR	6
Agarwala (2004) [25]	Phase I/II, dose-esc.	UM	19 (NR)	Cisplatin	± PVS	16%	NR	8.5
Patel (2005) [26]	Phase II	UM	30 (3[a])	BCNU	Ethiodized oil, GS	17%	8	5.2
Vogl (2007) [27]	PS, pilot	UM	12 (4.6)	MMC	Ethiodized oil, microspheres	25%	NR	21
Sharma (2008) [28]	RS	CM ($n = 3$), UM ($n = 17$)	20 (2.4)	Cisplatin, doxorubicin, MMC	Ethiodized oil, GS/PVA	0%	6.1	8.9
Fiorentini (2009) [29]	Phase II	UM	10 (1.5)	Irinotecan loaded drug-eluting beads		100%	NR	NR
Dayani (2009) [30]	RS	UM	21 (2.3)	MMC, cisplatin, doxorubicin	Ethiodized oil, GS/PVA	NR	NR	7.6 (mean)
Schuster (2010) [31]	RS	UM	25 (2)	Fotemustine/cisplatin	Ethiodized oil, starch microspheres	16%	3	6
Gupta (2010) [32]	RS	UM	125 (2)	Mostly cisplatin[c]	GS/PVA	27%[d]	3.8	6.7
Huppert (2010) [33]	PS, pilot	UM	14 (2.4)	Cisplatin/carboplatin[e]	PVA	57%	8.5	11.5
Ahrar (2011) [34]	RS	CM	42 (2)	Cisplatin/cisplatin, paclitaxel/paclitaxel	Gelfoam/PVA	39%	6	7.7
Edelhauser (2012) [35]	RS	UM	21 (3.3)	Fotemustine	Ethiodized oil, PVA	14%	7.3	28.7
Valpione (2015) [36]	RS	UM	58 (NR)	Irinotecan loaded drug-eluting beads[f]		28%	NR	16.5
Abbott (2017) [37]	RS	CM ($n = 9$), UM ($n = 3$)	12 (1)	Doxorubicin, MMC, cisplatin	Ethiodized oil, microspheres	NR	1.7	8.8
Shibayama (2017) [38]	RS	UM	29 (4)	Cisplatin	GS	21%	6	23

BCNU 1,3-bis(2-chloroethyl)-1-nitrosourea; *CM* cutaneous melanoma; *dose-esc.* dose-escalating study; *GS* gelatin sponges; *MMC* mitomycin *C; NR* not reported; *pt(s)* patient(s); *OS* overall survival; *PFS* progression-free survival; *PVA* polyvinyl alcohol particles; *PVS* polyvinyl sponges; *PS* prospective; *RS* retrospective; *TACE* transarterial chemoembolization; *UM* uveal melanoma

[a]Median

[b]In all TACE procedures ($n = 64$): cisplatin ($n = 44$), cisplatin + vinblastine ($n = 12$), cisplatin + dacarbazine + vincristine ($n = 2$), cisplatin + dacarbazine ($n = 3$), cisplatin + dactinomycin ($n = 3$)

[c]Cisplatin ($n = 122$), cisplatin + paclitaxel ($n = 2$), cisplatin + doxorubicin + MMC ($n = 1$)

[d]Based on 105/125 patients

[e]5/14 patients received systemic immuno-chemotherapy 2–4 weeks prior to TACE

[f]49/58 patients received systemic fotemustine, the induction phase starting within 3 weeks from TACE

of dosimetry and more personalized patient treatment. Because data on ^{166}Ho-radioembolization in the treatment of hepatic melanoma metastases have been very limited so far, this will not be discussed further in this chapter [39].

Radioembolization is preceded by preparatory angiography and administration of a test dose of 75–150 MBq ^{99m}Tc-macroaggregated albumin (^{99m}Tc-MAA). The angiography is used to map out the vascular supply of the tumor and, upon indication, perform coil embolization of hepaticoenteric anastomosis, such as the gastroduodenal and right gastric artery. After injection of ^{99m}Tc-MAA, planar SPECT imaging and SPECT/CT are performed to rule out extrahepatic shunts and assess ^{99m}Tc-MAA distribution in the liver. ^{99m}Tc-MAA particles are believed to be representative for the distribution of ^{90}Y microspheres, as they are fairly similar in size. Lung shunting with an estimated absorbed radiation dose of more than 30 Gray makes patients ineligible for TARE. Depending on the location of hepatic metastases, patients will receive whole-liver, lobar, or segmental treatment with microspheres. After treatment, a bremsstrahlung ^{90}Y-SPECT/CT is performed to evaluate the actual distribution of microspheres (Fig. 27.2).

TARE is mostly offered as salvage therapy in patients with PD following conventional chemotherapy, immunotherapy, and/or other liver-directed therapies. Prospective studies evaluating the efficacy of ^{90}Y radioembolization as treatment of hepatic melanoma metastases are lacking. A few small retrospective studies in which most patients suffered from hepatic metastases from uveal melanoma, have been published (Table 27.3) [40–48]. In uveal melanoma, reported ORR ranges from 6% to 70%, median PFS from 3.2 to 5.9 months, and median OS from 5.9 to 13.5 months.

In a study including 32 patients, Gonsalves et al. reported a median OS of 10 months (range 1.0–29.0) [41]. Patients were divided into three groups based on tumor burden within the liver at baseline: <25% (n = 25), 25–50% (n = 5), and >50% (n = 2). Patients with <25% tumor burden had a significantly longer OS than those with ≥25% tumor burden (10.5 versus 3.9 months; p = 0.0003). As might be expected, patients with complete response (CR), partial response (PR), or SD had a significantly longer OS than patients with PD (14.7 versus 4.9 months; p = 0.006). Moreover, patients with <25% tumor burden had a significantly longer PFS than patients with ≥25% tumor burden (6.4 versus 3.0 months; p = 0.03), and patients with CR, PR, or SD had a longer PFS than patients with PD following TARE (7.9 versus 3.1 months; $p < 0.0001$).

Common side effects are abdominal discomfort or pain, nausea, and vomiting, usually well manageable with analgesics and anti-emetics. Additionally, patients often suffer from fatigue during the first weeks after treatment. Severe complications such as gastric ulcers, liver failure, or cholecystitis are rare. Xing et al. reported two patients (7%) who developed major complications in the form of ascites and hepatic encephalopathy and eventually died due to liver failure within 1 month of ^{90}Y radioembolization [47]. Both patients had diffuse hepatic metastases and decompensated liver function with a high MELD score and Child-Pugh class C at the time of treatment.

Percutaneous Hepatic Perfusion with Melphalan (M-PHP)

Isolated hepatic perfusion (IHP) is a complex surgical procedure in which the liver is isolated from the systemic circulation by clamping the inferior vena cava (IVC) and portal vein, and ligation of IVC tributaries and arterial hepaticoenteric anastomoses. Subsequently, the liver is perfused with a high dose of melphalan that is injected through a catheter in the proper hepatic artery. For metastatic uveal melanoma, response rates of 37–52% have been reported [49–52]. High morbidity and mortality rates, however, prohibited a widespread application of IHP [53–56].

Percutaneous hepatic perfusion with melphalan (M-PHP) was developed by Delcath Systems Inc. (New York, USA) as a minimally invasive, repeatable, and safer alternative for IHP. M-PHP is performed under general anesthesia by a team

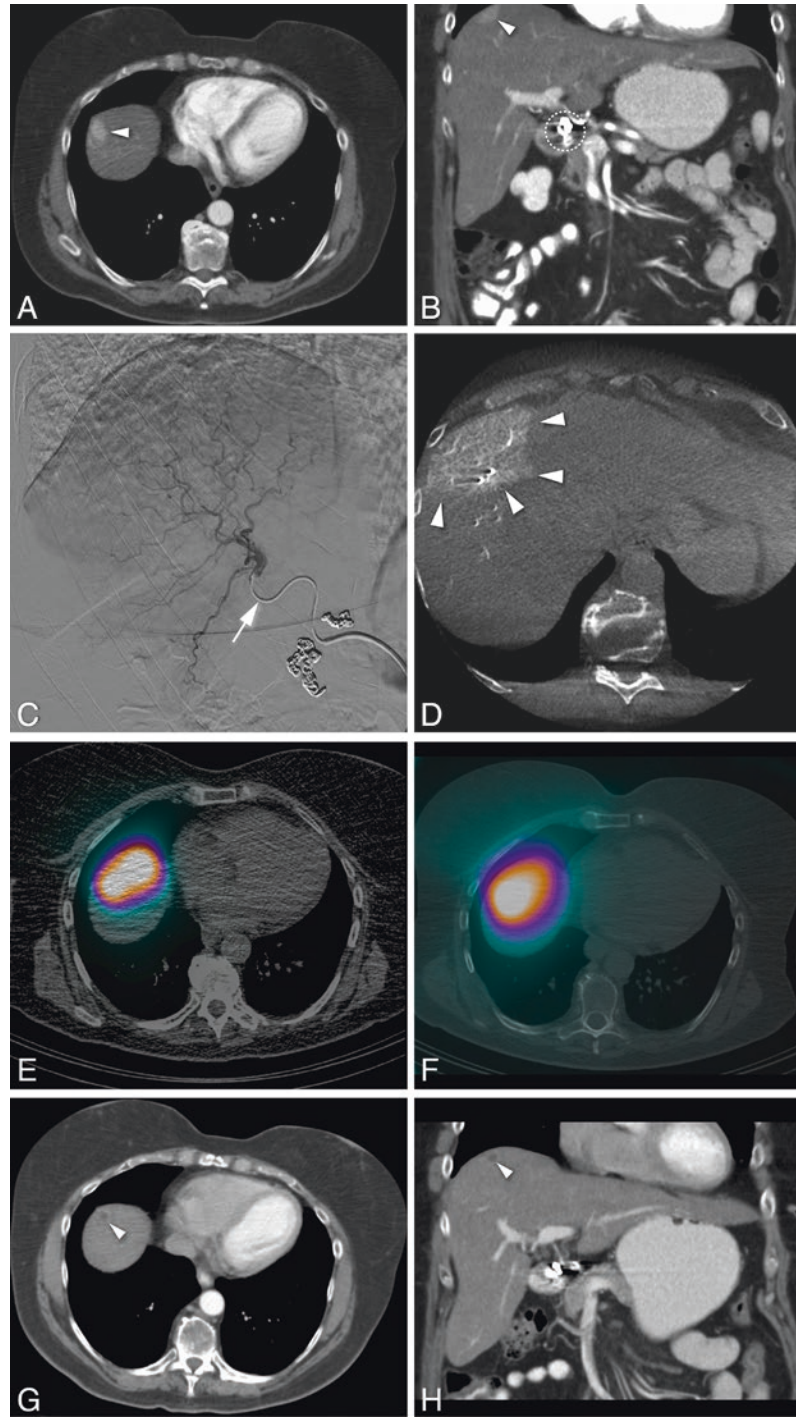

Fig. 27.2 Transarterial radioembolization with yttrium-90. 61-year-old female with multiple uveal melanoma metastases treated with two cycles of percutaneous hepatic perfusion with melphalan (M-PHP). Excellent response was seen with only one residual tumor in the hepatic dome. Thermal ablation was considered, but due to the limited size and location preference was given to segmental radioembolization. Axial (**a**) and coronal (**b**) CT images in arterial phase before treatment, showing a hypervascular lesion in segment 8 (*white arrowheads*). Note the coils (*dotted circle*) that were used to embolize the right gastric artery and gastroduodenal artery prior to M-PHP. (**c**) Angiographic image showing the microcatheter position (*white arrow*) during ^{99m}Tc-MAA infusion. (**d**) Enhanced treatment area highlighted on cone-beam CT (*white arrowheads*). (**e**) Axial ^{99m}Tc-MAA SPECT/CT image showing an adequate accumulation in the target lesion. (**f**) Axial bremsstrahlung ^{90}Y-SPECT/CT image demonstrating an intense ^{90}Y-accumulation in the lesion. Axial (**g**) and coronal (**h**) CT images in arterial phase 6 weeks after treatment, showing a marked devascularization and reduction in the size of the lesion (*white arrowheads*)

consisting of an interventional radiologist, anesthesiologist, and extracorporeal perfusionist. During the procedure, a microcatheter is placed in the hepatic artery at the intended location of infusion [57]. A double-balloon catheter is placed in the IVC through the common femoral vein. The cranial balloon is inflated to occlude the atriocaval junction and the caudal balloon is

Table 27.3 Overview of studies on TARE with ^{90}Y (≥10 patients) as treatment for hepatic melanoma metastases

First author (year)	Study design	Melanoma type	No. pts	Type of microsphere (dosage)	ORR	Median PFS (mo)	Median OS (mo)
Kennedy (2009) [40]	RS	UM	11	SIR-Spheres® (mean 1.55 GBq)	77%	NR	NR
Gonsalves (2011) [41]	RS	UM	32	SIR-Spheres® (mean 1.08 GBq)	6%	4.7	10
Piduru (2012) [42]	RS	CM (*n* = 5), UM (*n* = 7)	12	SIR-Spheres® (NR)	NR	NR	10
Klingenstein (2013) [43]	RS	UM	13	SIR-Spheres® (mean 1.78 GBq)	62%	NR	7
Memon (2014) [44]	RS[a]	CM (*n* = 4), UM (*n* = 7), rectal (*n* = 3), unknown (*n* = 2)	16	TheraSphere® (median 1.87 GBq)	24%	4.2	Total 7.6, UM 5.9, non-UM 10.7
Klungboonkrong (2015)[a] [45]	RS	UM	17	NR	NR	3.2	9.3
Eldredge-Hindy (2016) [46]	RS	UM	71	SIR-Spheres® (median right lobe 0.88, median left lobe 0.33)	9%	5.9	12.3
Xing (2017) [47]	RS	CM (*n* = 13), UM (*n* = 15)	28	SIR-Spheres® (mean 1.86 GBq)	18%	5.1	10.1
Tulokas (2018) [48]	RS	UM	16	NR (median 1.9 GBq)	17%	5.6	13.5

CM cutaneous melanoma, *GBq* gigabecquerel, *mo* months, *NR* not reported, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *RS* retrospective, *TARE* transarterial radioembolization, *UM* uveal melanoma
[a]Only abstract available

inflated in the infrahepatic IVC to prevent leakage of chemotherapeutics into the systemic circulation. In between the two balloons, the catheter has multiple side holes that are used to aspirate the chemosaturated blood returning through the hepatic veins. The aspirated blood is pumped through an extracorporeal hemofilter consisting of two activated carbon filters. After filtration, the blood is returned to the patient by a vascular sheath in the right internal jugular vein (IJV) (Fig. 27.3). Once all of the melphalan is infused, extracorporeal filtration is continued for 30 minutes to allow complete clearance of chemotherapeutics from the liver [57]. Because of the significant hemodynamic perturbations resulting from the combination of chemofiltration and IVC occlusion, hemodynamic monitoring and support during the procedure is crucial. Continuous arterial pressure is monitored by a cannula in the radial artery, and a triple-lumen line placed in the left IJV enables central venous pressure monitoring and infusion of sympathomimetics and fluids. The duration of the procedure is generally 3–4 hours (compared to 9 hours for IHP).

Patients undergoing M-PHP generally receive pretreatment angiographic evaluation (Fig. 27.4). Angiography is commonly performed several days in advance, and allows the interventional radiologist to: (1) identify possible extrahepatic tumor-supplying vessels, (2) plan an appropriate strategy for (micro)catheter positioning during treatment, and (3) perform prophylactic coil embolization of branches arising from the hepatic arterial bed (e.g., accessory left gastric artery, right gastric artery, and falciform artery) to prevent nontarget drug delivery and minimize the risk of side effects and complications.

In 2005, the results of a phase I dose-escalation study on M-PHP in 28 patients with primary and metastatic hepatic disease were published, establishing a maximum tolerated dose of 3 mg/kg body weight. In the 10 patients with metastatic ocular melanoma, an ORR of 50% was observed (two CR and three PR) [58].

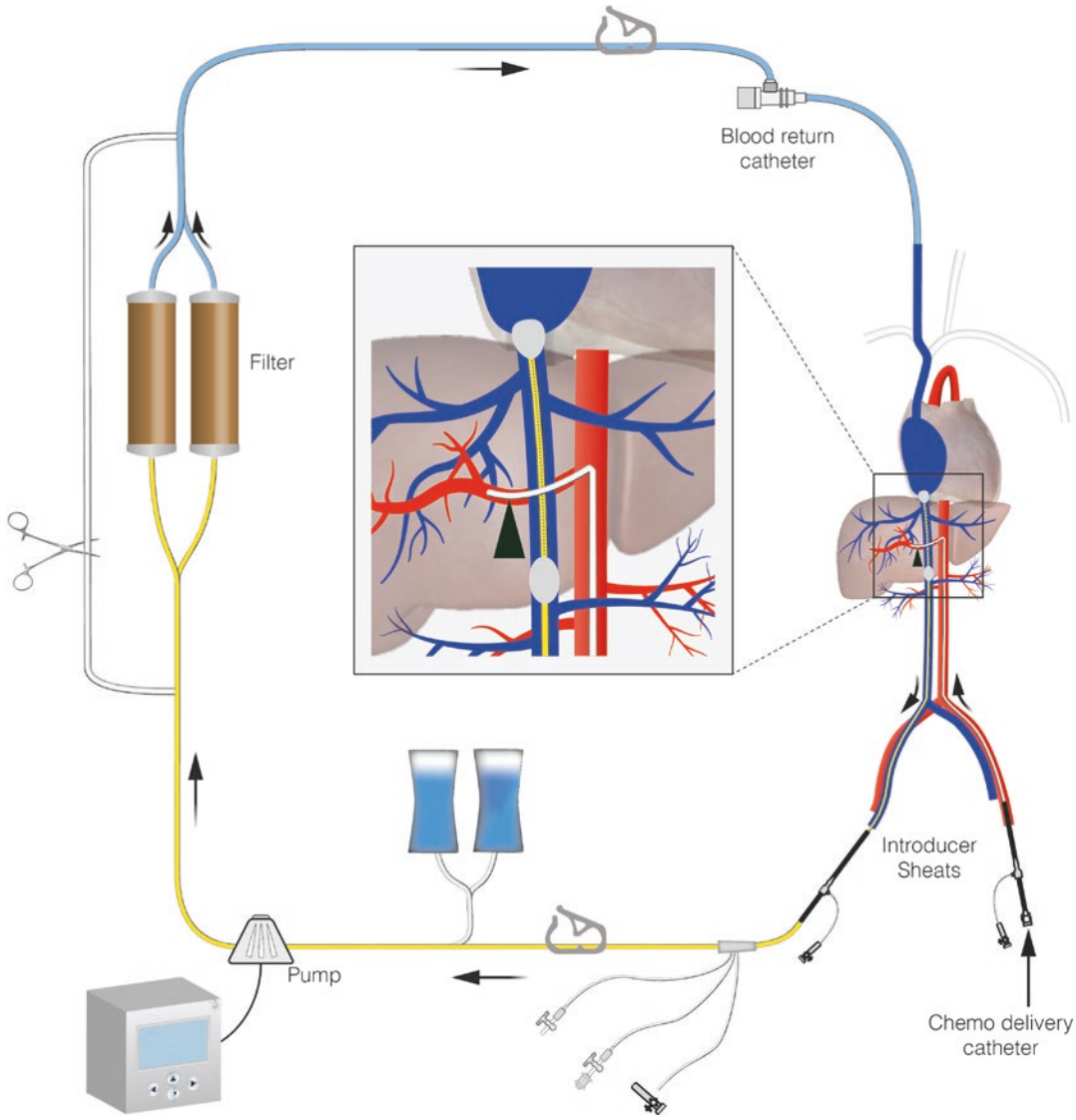

Fig. 27.3 Schematic overview of the setup of percutaneous hepatic perfusion. Chemotherapeutic drugs (melphalan) are infused through a microcatheter that is placed in the hepatic artery (*black arrowhead*). The chemosaturated blood returning through the hepatic veins is aspirated through side holes in the double-balloon catheter. An extracorporeal hemofiltration system, consisting of a pump and two activated carbon filters, is used to filter the chemotherapeutics from the blood. The filtered blood is returned to the patient via a sheath in the right internal jugular vein

In 2016, Hughes et al. published the results of a multi-center randomized controlled trial (RCT) comparing M-PHP with best alternative care (BAC) in patients with unresectable hepatic melanoma metastases [59]. The study included 93 patients with metastases from either ocular (n = 83) or cutaneous (n = 10) melanoma. Although in most patients (59.1%) metastases were confined to the liver, limited extrahepatic disease was not an exclusion criterion. Patients in the M-PHP arm (n = 44) underwent a maximum of six perfusions at 4–8-week intervals (median of three M-PHP procedures per patient). Patients in the BAC-arm (n = 49)

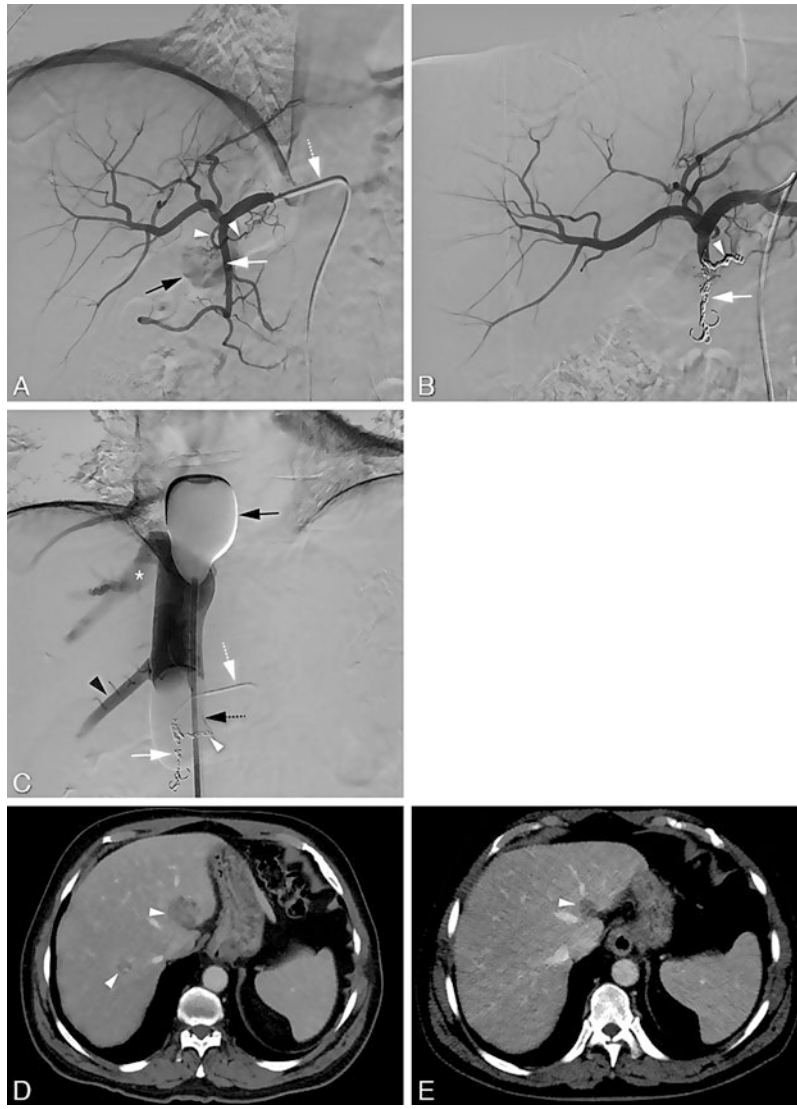

Fig. 27.4 Percutaneous hepatic perfusion with melphalan. A 66-year-old male with bilobar hepatic metastases from uveal melanoma. (**a**) Pretreatment angiographic image from the common hepatic artery (CHA) showing a right gastric artery (RGA, *white arrowheads*) and gastroduodenal artery (GDA, *white arrow*). Also the macrocatheter in the CHA (*dotted white arrow*) and duodenal bulb (*black arrow*) are seen. (**b**) Successful coiling of the RGA (*white arrowhead*) and GDA (*white arrow*). (**c**) Posteroanterior image during venography performed by injection of contrast medium through side holes of the double-balloon catheter. The cranial balloon (*black arrow*) is inflated at the atriocaval junction to prevent flow to the right atrium, and the caudal balloon (*dotted black arrow*) is inflated in the infrahepatic portion of the inferior vena cava (IVC) to prevent retrograde flow to the infrarenal IVC. A microcatheter is inserted through the macrocatheter (*dotted white arrow*) and placed into the proper hepatic artery for the infusion of melphalan. The right hepatic vein (*asterisk*) and accessory right inferior hepatic vein (*black arrowhead*) are opacified. Note the coils in the RGA (*white arrowhead*) and GDA (*white arrow*). (**d**) Axial CT image in portovenous phase before treatment showing a metastasis in liver segment 2 and segment 7/8 (*white arrowheads*). A third lesion in segment 6 is not shown. (**e**) Axial CT image in portovenous phase after two cycles of M-PHP showing reduction in size of the metastasis in liver segment 2 (*white arrowhead*). The other two lesions showed complete radiological response

received active treatment such as systemic chemotherapy, TACE, TARE, or surgery in 81.6%. A significant improved hepatic objective response (hOR), hepatic progression-free survival (hPFS), and overall progression-free survival (oPFS) were observed in patients treated with M-PHP compared to BAC. The hOR was 36.4% for M-PHP and 2.0% for BAC ($p < 0.001$), hPFS was 7.0 months for M-PHP and 1.6 months for BAC ($p < 0.0001$), and oPFS was 5.4 months for M-PHP and 1.6 months for BAC ($p < 0.0001$). Median OS was not significantly different (10.6 months for M-PHP versus 10.0 months for BAC), likely due to a high crossover rate from the BAC- to M-PHP-arm (57.1%). Despite the prophylactic administration of stem cell support, the majority of grade 3–4 adverse events (according to the Common Terminology Criteria for Adverse Events) were related to bone marrow suppression with neutropenia in 85.7%, thrombocytopenia in 80.0%, and anemia in 62.9%. Hepatic toxicity, as manifested by grade 3–4 bilirubin elevation, was observed in only 14.3% of patients and self-limiting. Rare complications included venous thrombosis, acute cholecystitis, and gastroduodenal ulcer. Four deaths were attributed to M-PHP: two resulted from bone marrow suppression, one was associated with hepatic failure due to PD, and one resulted from gastric perforation.

Recently, a retrospective study evaluating only patients with hepatic metastases from uveal melanoma ($n = 51$) was published [60]. In the majority of patients (84.3%), metastases were confined to the liver. A median of two M-PHPs per patient resulted in an ORR of 54.9% with PR in 43.1% ($n = 22$) and CR in 5.9% ($n = 3$). Median hPFS and oPFS were 8.1 and 9.1 months, respectively. Median OS was 15.3 months. Grade 3–4 neutropenia was observed in 31.3%, grade 3–4 thrombocytopenia in 31.3%, and grade 3–4 anemia in 29.4%. These low percentages of grade 3–4 hematologic adverse events in comparison with the RCT by Hughes et al. is probably due to the use of a new second-generation (GEN 2) filter that has been shown to increase melphalan extraction with almost 10%, reducing bone marrow suppression [61]. Additionally, the median number of M-PHPs per patients was lower than in the RCT.

These promising results were confirmed in a prospective study in which 35 patients received a total of 72 M-PHPs (median of two procedures at a 6–8 weeks interval) using the GEN 2 filter. Best overall response was CR in 3.1%, PR in 68.8%, SD in 12.5%, and PD in 15.6%. Median OS was 20.3 months. Median PFS and median hPFS were 8.1 and 10.9 months, respectively [62]. Although hematologic grade 3–4 events were seen in the majority of patients, these were all well manageable or self-limiting. Grade 3–4 thrombocytopenia, leukopenia, and neutropenia were seen in 54.5%, 75.6%, and 66.7% of patients, respectively. Grade 3 anemia was reported in 18.1%. There was one case of grade 3 hepatotoxicity with increased aminotransferases immediately after treatment, which normalized 1 week after treatment. Of all nonhematologic and nonhepatic grade 3 events ($n = 14$), posttreatment hemorrhage ($n = 2$; epistaxis and vaginal bleeding), febrile neutropenia ($n = 3$), and pulmonary emboli ($n = 2$) were most common. These patients were successfully treated with platelet transfusion, intravenous antibiotics, and low-molecular-weight heparin, respectively [63]. There was one nonhematologic grade 4 event. This was a case of sepsis due to bacterial pharyngitis with the formation of a retropharyngeal abscess, which was treated with intravenous antibiotics, immunoglobulins, and aspiration of the abscess.

Liver-Directed Therapies: Miscellaneous

Surgical resection and thermal ablation (TA) are considered the only curative treatments for hepatic melanoma metastases. Unfortunately, in most patients (>95%) resection or TA is no first-line treatment option because metastatic disease in cutaneous melanoma is often not liver-dominant, and patients with metastatic uveal melanoma most commonly present with diffuse liver disease (90–95%) [64, 65]. The few patients that are candidates are selected with MRI. Notably, for uveal melanoma, the sensitivity for detection of intraparenchymal hepatic metastases is 68–86% and only 41–54% for

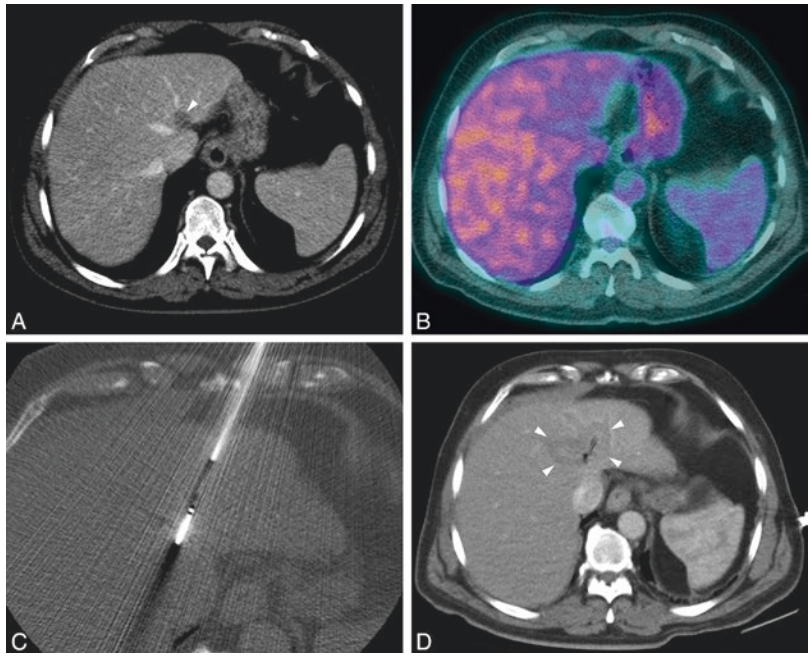

Fig. 27.5 Microwave ablation (MWA) of a solitary liver lesion. Same patient as in Fig. 27.4. A 66-year-old male who already received two cycles of M-PHP as treatment of bilobar hepatic metastases from uveal melanoma. Two metastases had shown complete radiological response, while a third metastasis in segment 2 (S2) was still visible. (**a**) Axial CT image in portovenous phase showing a hypodense lesion in S2 (*white arrowhead*). (**b**) Axial PET/CT image showing no increased 18F-FDG accumulation in S2. Despite this, it was decided to perform ablation to minimize the risk of recurrence. (**c**) Axial CT images during MWA, showing the positioning of the probe from anterior. (**d**) Contrast-enhanced CT immediately after MWA shows successful ablation (*white arrowheads*) with a peripheral ring of enhancement that usually disappears after a few weeks

metastases in the subcapsular regions of the liver [66]. A careful inspection of the liver surface during surgery is therefore essential. In particular, TA does play a role in patients with a few small residual lesions after showing a good radiological response upon arterial therapy (Fig. 27.5).

Table 27.4 gives an overview of studies on surgical resection and TA as treatment of hepatic melanoma metastases [65, 67–73]. The median OS after surgical resection ranges from 14–29 months for uveal melanoma [67–70, 73], and 24–27 months for cutaneous melanoma [67, 68]. The percentage of patients in whom complete microscopic resection (R0) was achieved varies between 13% in a study by Frenkel et al. and 95.8% in a study by Pawlik et al. In a large retrospective review by Mariani et al. that was conducted to evaluate the evolving surgical management of hepatic metastases from uveal melanoma, 255/798 (32%) patients with liver metastases underwent surgical resection. The authors underlined the importance of R0 resection, as this increased the median OS from 14 months, as was seen in the total cohort, to 27 months in the group with R0 resection ($p < 0.0001$) [69]. Although Frenkel et al. also found a longer median posthepatectomy survival in patients with R0 resection than in patients with R1/R2 resection (65.6 versus 16.6 months, $p = 0.14$), there was no statistical significance. In addition, they found no correlation between the status of the surgical borders (R0 or R1/2) and recurrence of the metastases ($p = 0.79$).

There have been several retrospective studies on surgical resection and/or TA in patients with hepatic melanoma metastases [65, 71, 73]. Doussot et al. found no significant difference in median OS between resection ($n = 32$) and percutaneous TA ($n = 16$) in patients with uveal and cutaneous melanoma: 26 months for resection

Table 27.4 Overview of studies on surgical resection and TA (≥10 patients) as treatment for hepatic melanoma metastases

First author (year)	Study design	Melanoma type	No. pts	Treatment	Median OS (mo)	R0/R1/R2 (%)
Adam (2006) [67]	RS	UM (n = 104), CM (n = 44)	148	Resection	UM 19, CM 27	83/8/9 (total)
Pawlik (2006) [68]	RS	UM (n = 16), CM (n = 24)	40	Resection[a]	UM 29, CM 24 (p = 0.2)	87.5/12.5/0 (UM) 95.8/4.2/0 (CM)
Mariani (2009) [69]	RS	UM	798	Resection (n = 255), no surgery (n = 543)	Resection 14, no surgery 8 R0 27, R1 17, R2 11 (p < 0.0001)	30/9/61
Frenkel (2009) [70]	RS	UM	74	Resection (n = 35), no surgery (n = 39)	Resection 23.0, no surgery 6.8 (p = 0.0001) R0 65.6, R1/R2 16.6 (p = 0.14)	13/NR/NR
Faries (2014) [64]	RS	UM (n = 121) CM (n = 957)	1078	Resection ± RFA (n = 58)[c], no surgery (n = 1020)	Resection ± RFA 24.8, no surgery 8 (p < 0.01)	NR
Doussot (2015) [71]	RS	UM (n = 22), CM (n = 26)	48	Resection (n = 32), percutaneous TA (n = 16)	Resection 26, TA 18 (p > 0.2)	94/NR/NR (total)
Akyuz (2015) [65]	RS	UM	44	Lap. resection (n = 2), lap. RFA (n = 14), systemic therapy (n = 28)	Lap. group 35, systemic therapy group 15 ($p \leq 0.0001$)	NR
Bale (2016) [72]	RS	UM (n = 6), CM (n = 14)	20	RFA[c]	UM 38, CM 11.6 (p = 0.063)	n/a
Mariani (2016) [73]	RS	UM	72	Resection (n = 57), RFA ± resection (n = 15)	Resection 27, RFA ± resection 28 (n.s.)	NR

Lap. laparoscopic, *mo* months, *NR* not reported, *OS* overall survival, *R0* microscopically complete resection, *R1* microscopically incomplete resection, *R2* macroscopically incomplete resection, *RFA* radiofrequency ablation, *RS* retrospective, *TA* thermal ablation

[a]26/40 patients received additional perioperative systemic therapy

[b]9/58 of surgical patients had ocular primaries as did 112/1020 patients in the nonsurgical group (p = 0.27)

[c]In 19% of cases, extrahepatic disease was resected at the time of hepatic resection. All patients with cutaneous melanoma received additional systemic chemotherapy

versus 18 months for TA (p > 0.2) [71]. Four patients in the resection group received an additional resection of extrahepatic metastatic disease and portal lymphadenectomy was performed in eight patients. R0 resection was achieved in 30 patients (93.8%). Percutaneous TA included radiofrequency ablation (RFA, n = 8), microwave ablation (n = 6), and cryoablation (n = 2) along with additional transarterial hepatic embolization in three cases. Notably, patients in the TA group presented with more adverse disease characteristics with a significantly shorter interval between primary melanoma diagnosis and treatment for liver metastases (11 versus 31 months; p = 0.011) and more often had extrahepatic disease (56.3% versus 18.8%; p = 0.008). Nine out of 48 patients with extrahepatic disease received systemic therapy at the time of the procedure. Patients without extrahepatic disease tended to have a longer OS and PFS. Extrahepatic disease was associated with a significantly worse OS in the resection group (p = 0.034).

In a paper by Bale et al., a retrospective review of 20 patients was presented, with a total of 75 hepatic melanoma metastases that were treated with RFA [72]. Primary tumors were uveal in 6 patients and cutaneous in 14 patients. A median number of two lesions (range 1–14) per patient with a median size of 1.7 cm (range 0.5–14.5) were treated. Most lesions (89.3%) were <3 cm. A total of 34 ablation sessions were performed with a median of one session per patient (range 1–4). There were no procedure-related deaths. Three cases of pleural effusion requiring pleural drainage were reported. Computed tomography 1 month after initial therapy demonstrated successful ablation in 89.3% (67/75). Residual tumor was retreated in three patients, resulting in a secondary success rate of 93.3% (70/75). Overall local recurrence rate was 13.3%. During follow-up, 10/20 patients developed liver recurrence at any location and 9/20 developed extrahepatic metastases. The median OS following initial RFA was 19.3 months with a large, but not statistically significant, difference between patients with cutaneous and uveal melanoma (11.6 versus 38 months, $p = 0.063$). The median disease-free survival for all patients was 9.5 months. The authors conclude that RFA is a good alternative for resection due to the high potential for local cure and promising effects on survival with minimal morbidity and mortality.

Summary

In this chapter, we discussed several liver-directed therapies that are currently used for the treatment of hepatic melanoma metastases. These therapies can be considered when the liver is the only or dominant site of metastatic disease. Treatment reports for liver-directed therapies in melanoma literature are dominated by studies on patients with uveal primaries as these patients often present with metastases that are confined to the liver. Although considered the only curative treatment, in most patients (>95%), surgical resection or thermal ablation is no first-line treatment option. There is no current consensus on what liver-directed therapy would be the best practice for patients with hepatic melanoma metastases, but M-PHP has been studied most extensively. M-PHP is the only treatment with proven efficacy in a randomized controlled trial on patients with hepatic metastases from melanoma.

Acknowledgments The authors thank Gerrit Kracht for his help in producing the figures.

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Complications of Intra-Arterial Regional Liver Therapy

28

Gaya Spolverato, Amy Robin Deipolyi, and Michael D'Angelica

Introduction

Every treatment has its own unique benefits and complications. Intra-arterial regional therapies for malignancy are no exception. In this chapter, we aim to summarize the most common complications resulting from transarterial chemoembolization (TACE), transarterial embolization (TAE), radioembolization, and hepatic artery infusion (HAI) chemotherapy. Various complications have been described after or during these treatments. These complications are caused either by the angiographic/surgical procedure itself, such as direct injury to the arterial system; by the embolic/treatment effect, such as post-embolization syndrome, injury to the liver or biliary system and tumor rupture; or by nontarget embolization/infusion to normal liver parenchyma, the unaffected biliary tree or to extrahepatic sites. In the case of HAI there are also issues related to durability and device-related complications. Understanding these complications, their etiology, and their incidence is critical for the clinician who makes decisions regarding the regional treatment of hepatic malignancy.

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Transarterial Chemoembolization (TACE) and Transarterial Embolization (TAE)

General Considerations

Transarterial embolization is a regional liver treatment consisting of selective embolization of the arterial blood supply of hepatic tumors. Conventional TACE (cTACE), involving injection of chemotherapeutic and other agents, such as gelatin (GelFoam), iodized oil (Lipiodol), and cytotoxic agents through the hepatic artery, has arisen as a primary modality for treating unresectable hepatocellular carcinoma (HCC), as the first transarterial treatment demonstrated to provide a survival advantage in randomized trials [1, 2]. Other methods include embolization with particles alone (TAE), with drug-eluting beads (DEB-TACE), or with Y90 loaded microspheres; however, none of these methods have been proven to be superior in terms of survival [3]. A recent randomized trial comparing TAE with DEB-TACE using doxorubicin in HCC patients showed that both modalities had similar outcomes [4]. Although ischemia plays the most important role in the treatment effect seen after embolization, the benefit of added chemotherapy in the embolization mixture is not well defined [4]. Adverse events are also similar between DEB-TACE and TAE, as evidenced by the trial by Brown et al. [4]. The most common complication in both groups (88% vs. 84%) was post-embolization

Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_28

syndrome, consisting of self-limited pain, fever, and/or nausea and vomiting. Twelve percent of patients in both groups experienced a major complication, such as cholecystitis, pancreatitis, liver abscess, transient liver failure, deep venous thrombosis (DVT), and pulmonary embolism (PE). Post-embolization syndrome was also reported as the most common adverse event in a previous randomized clinical trial by Lo et al. evaluating the efficacy of transarterial Lipiodol cTACE in patients with unresectable hepatocellular carcinoma [1], followed by gastrointestinal bleeding, bleeding from the arterial puncture site, transient liver failure, ruptured tumor, and liver abscesses. Also TAE was correlated with high rates (83%) of post-embolization syndrome in a randomized, controlled trial assessing the effect of TAE without associated chemotherapy on the survival of patients with unresectable HCC [5]. However, the occurrence of ascites, variceal bleeding, bacterial infection, hepatic encephalopathy or readmission was similar to best supportive care (BSC) [5]. Interestingly, DEB-TACE has been associated with increased hepatic toxicities compared to cTACE, in a retrospective study including 151 consecutive patients undergoing cTACE or DEB-TACE. Global hepatic damages overall biliary injuries, bile duct dilatation, intrahepatic biloma, and portal thrombosis were more frequent among patients treated with DEB-TACE compared to cTACE [6].

Specific Complications

Post-embolization syndrome First described over 20 years ago, the post-embolization syndrome consists of right upper quadrant abdominal pain, fever, malaise, and/or nausea and vomiting, and it occurs in about 90% of patients following TAE/TACE. It has been historically considered as the result of tumor necrosis, while other authors have postulated that it is a reflection of injury to the nontumorous liver parenchyma [7]. Gallbladder embolization and high doses of embolic agents at the time of TAE/TACE have been correlated with prolonged post-embolization syndrome [8].

Arterial injuries Arterial injuries can occur anywhere from the access site to visceral arteries. Relatively uncommon (<1%) and usually self-limiting, access site injuries include hematoma, arterial pseudoaneurysm, arterial dissection, and arteriovenous fistula [9]. Posttreatment arterial thrombosis, dissection, stenosis, or occlusion may occur up anywhere from the access site to the visceral branches [10]. Hepatic artery branch vasospasm or occlusion can also occur as a consequence of mechanical or chemical irritation and cause liver ischemia [10, 11].

Nontarget embolization Ischemic cholecystitis, acute pancreatitis, duodenal and gastric ulcers, and perforation are among the most common complications caused by nontarget embolization. They represent the most serious and devastating adverse events of TAE/TACE, but only occur in less than 1% of procedures [12]. Nontarget embolization is the consequence of reflux of embolic agents along the catheter or misidentification of the arterial anatomy. Since most embolization procedures use small particles, nontarget embolization results in terminal vessel blockade likely to cause ischemic damage. In particular, embolization of the cystic artery may lead to ischemic cholecystitis and even gangrene [13]. Embolization of the gastroduodenal artery or pancreaticoduodenal arteries may lead to duodenal ulcer and perforation, or acute pancreatitis. Reflux in the gastric or gastroepiploic arteries may lead to gastric ulcers and perforation [10].

Tumor rupture Tumor rupture is a rare but life-threatening complication, occurring in less than 1% of patients undergoing TACE/TAE, mostly for HCC [12]. It presents with sharp abdominal pain, bleeding, hemoperitoneum, and hypotension. The mechanism of rupture is unclear, but it can be due to tumor capsule necrosis, increased intratumoral pressure (due to edema or supra-infection) and/or mechanical or chemical vascular injury. Direct trauma, larger tumor size, exophytic and superficial tumor location, and large amounts of iodized oil plus polyvinyl alcohol particles are among the predictive factors of tumor rupture [14].

Biliary ischemia and bilomas Occurring in less than 1% of patients, biliary ischemia and bilomas are serious complications. Biliary ischemia is the consequence of embolization of terminal biliary arterial branches. TACE can also damage the peribiliary capillaries causing duct ischemia and necrosis [10]. The occurrence of biliary necrosis after TACE is more common in healthy livers, such as patients with metastatic disease, likely related to the fact that cirrhotic livers commonly have hypertrophy of the peribiliary capillary plexus [12]. Biliary ischemia causes disruption of the biliary ductal integrity, leading to formation of biliary disruption and bilomas. Biliary ischemia can also cause biliary strictures. Biliary ischemia can also cause biliary strictures. These biliary complications, while mostly occurring in the intrahepatic biliary tree, occasionally occur in the extrahepatic ducts as a consequence of non-target embolization, although such cases are very rare [9, 15].

Liver abscesses Hepatic abscesses occur in about 2% of patients undergoing TACE/TAE and can cause significant morbidity, prolonged hospital stay, and even mortality (Fig. 28.1). The most important predictors of abscess formation are biliary dilatation and biliary-enteric continuity (prior biliary stent or biliary-enteric anastomosis) resulting in biliary bacterial contamination [16]. While in retrospective analyses, the cefazolin- and metronidazole-based antibiotic prophylaxis was not associated with prevention of abscess formation in patients with previous bilioenteric anastomosis [17], prophylaxis with tazobactam/piperacillin and pre-procedural bowel-cleansing regimen was effective [18]. Most patients with hepatic abscess can be successfully treated with a combination of percutaneous drainage and long-term parenteral antibiotics; however, the abscesses tend to take a long time to resolve and if left untreated they can be lethal events [19, 20].

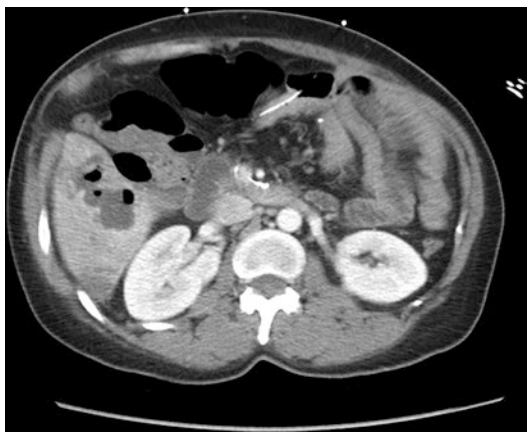

Fig. 28.1 Liver abscess after TAE: a collection containing both air and fluid, measuring 5.4 × 2.8 cm, suspicious for intrahepatic abscess, was found in hepatic segment 6 in a patient with metastatic pancreatic neuroendocrine tumor (status post Whipple procedure) treated with TAE

Pulmonary embolism Occurring in less than 1% of cases, embolization of chemoembolization agents to the lungs may occur through either arteriovenous or portovenous shunts [21]. Mild pulmonary embolization may be asymptomatic and discovered incidentally by computed tomography (CT). Large amounts of Lipiodol to the lung can produce a chemical pneumonitis, associated with high mortality rate [22]. The size threshold of the microsphere leading to PE is still unclear, but small particle diameters seem to be more likely to cause PE [9].

Radioembolization

General Considerations

Radioembolization therapy (RAE) involves image-guided delivery of microspheres laden with a β-emitting radioisotope, most commonly yttrium-90 (Y-90) [23]. RAE results in selective high dose radiotherapy, theoretically sparing the healthy liver, mostly supplied by the portal branches. The best quality data defining the complications related to this treatment derives from the FOXFIRE, SIRFLOX, and FOXFIRE-Global randomized studies [24–27] evaluating the efficacy of combining first-line chemotherapy with RAE using yttrium-90 resin microspheres in patients with metastatic colorectal cancer to the liver. In a combined analysis of the phase 3 trials, 411 (75%) deaths were recorded

in 549 patients in the FOLFOX alone group versus 433 (78%) in 554 patients in the FOLFOX plus RAE group and no difference in the overall survival was found. The most common grade 3–4 adverse event was neutropenia, which occurred in the 24% of patients receiving FOLFOX alone versus 37% of those receiving FOLFOX plus RAE. Serious adverse events of any grade were also more common (54%) in the FOLFOX plus RAE group compared to the FOLFOX alone group (43%). The serious adverse events reported for patients receiving RAE include ascites, hyperbilirubinemia, jaundice, encephalopathy, splenomegaly, and hepatic failure; radiation hepatitis; esophageal, gastric, and duodenal ulcers; esophagitis, gastritis, duodenitis, pancreatitis, and cholecystitis; perihepatic abscess; drug-induced pneumonitis; and off-target delivery of microspheres. In some cases, liver failure, drug-induced pneumonitis, and off-target delivery of microspheres were fatal [28].

Overall, the most worrisome RAE-related complications are gastrointestinal ulcers (3%), radiation pneumonitis (<1%), and radioembolization-induced liver disease (REILD) (5%) [29]. Post-embolization syndrome (90%) and liver abscess (<1%) are as common as after TACE/TAE. The post-radioembolization syndrome tends to present with more malaise and fatigue compared to the post-embolization syndrome after TAE/TACE that is more commonly characterized by abdominal pain [30]. Regarding liver abscesses, which occur in less than 1% of patients, there is no strong published evidence that patients history of biliary duct stenting, papillotomy, or surgical biliary bypass are at increased risk of infectious complications. However, RAE is not recommended in patients with a history of previous sepsis or biliary drainage without prophylactic antibiotics.

When evaluating quality of life (QoL) metrics in a small prospective study of patients undergoing Y-90 RAE or TACE for HCC, the data suggest that Y-90 RAE is better than TACE in maintaining health-related QoL [31], mostly due to social and functional well-being.

Specific Complications

Nontarget RAE Gastrointestinal ulcers and radiation cholecystitis are among the most common complications caused by nontarget RAE. Gastrointestinal ulceration normally occurs within 6 weeks of the procedure and can occur in up to 3% of patients (Fig. 28.2) [26]. The ulcers are usually multiple, measuring less than 2 cm and accompanied by gastritis or duodenitis [32, 33]. Patients typically experience acute epigastric pain, associated with nausea, vomiting, and dyspepsia that can occur weeks after the procedure. The ulcers can evolve into a stricture, bleeding, bilioenteric fistula, and death in rare situations (<1%) [32–35]. Radiation cholecystitis is a rare complication, occurring in less than 1% of patients after RAE, caused by the migration of the microspheres into the cystic artery. Usually, this complication is asymptomatic and diagnosed on follow-up imaging 20–30 days after treatment. Radiation cholecystitis may rarely present as typical acute cholecystitis. The most common symptoms are right upper quadrant abdominal pain, nausea or vomiting, malaise, and occasional fever [36]. Cholecystectomy should be considered only in patients at a high likelihood of future radioembolization.

Radioembolization-induced liver disease (REILD) Microsphere deposition in nontumorous parenchyma can result in radiation-induced liver injury, which in rare cases can result in death. First described by Sangro et al. in 2008 [37], REILD is defined as life-threatening liver damage characterized by jaundice and ascites developing 4–8 weeks after treatment, with pathologic changes consistent with veno-occlusive disease in the most severe cases. In a recent review by Manon et al. REILD was defined as "a symptomatic post-radioembolization deterioration in the ability of the liver to maintain its (normal or pre-procedural) synthetic, excretory, and detoxifying functions." Three grades of RAE-induced hepatotoxicity have been described by Braat and reported in Table 28.1: REILD manageable with noninvasive treatments such as diuretics, ursodeoxycholic acid, and steroids; REILD necessitating invasive medical treatment

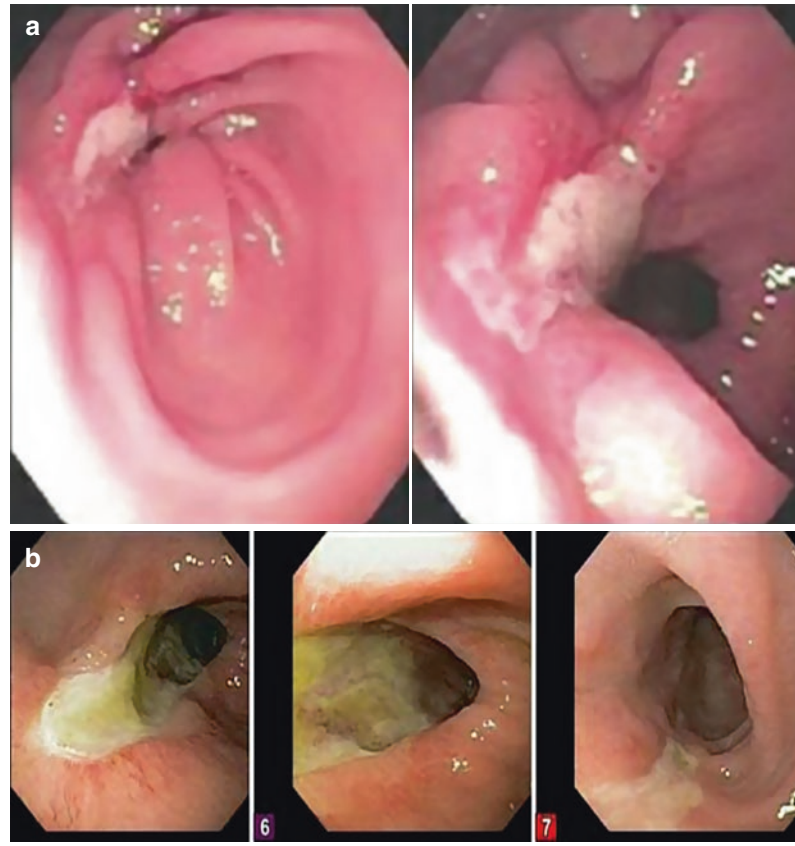

Fig. 28.2 Gastric ulcers after radioembolization: (**a**) A 4-cm nonbleeding cratered gastric ulcer with overlying exudate and without stigmata of bleeding was found in the pre-pyloric region of the stomach of a patient with metastatic breast cancer, 8 weeks after treatment with Y-90 embolization; the biopsy revealed Yttrium spheres. (**b**) A 4-cm cratered gastric ulcer without stigmata of bleeding was found in the gastric antrum extending through the pylorus into the duodenal bulb of a patient with metastatic breast cancer treated with Y-90 embolization

Table 28.1 Definition and grades of REILD by Braat et al. [29]

	Liver toxicity	Intervention
Grade 0	None	None
Grade 1	Minor (increased AST, ALT, ALP, GGT)	None
Grade 2	Moderate, self-limiting	None
Grade 3	REILD	Noninvasive treatments (diuretics, ursodeoxycholic acid, and steroids)
Grade 4	REILD	Invasive medical treatment (paracentesis, transfusions, hemodialysis, or TIPS)
Grade 5	Fatal REILD	

such as paracentesis, transfusions, hemodialysis, or a TIPS; and fatal REILD.

The incidence of REILD in large studies (>200 patients) ranges between 0% and 5.4% and the large variability is attributed to the different definitions of REILD and the time of onset [29]. Although the natural course of REILD is highly variable, ranging from self-limiting to fulminant hepatic failure, the majority of patients with REILD present with a grade 1–2 complications. The most widely accepted risk factors for hepatotoxicity and REILD include a reduced functional liver reserve (because of cirrhosis or previous treatments) and absorbed dose in nontumorous parenchyma [38].

Radiation pneumonitis Although rare, the devastating complication of radiation pneumonitis has been described in detail in only 6 patients after RAE. It can occur within 6 months from the treatment and is characterized by a restrictive ventilatory dysfunction with bilateral lung infiltrates, exertional dyspnea, and dry cough [39–41]. Arteriovenous channels allow the microsphere to reach the lung, thus lower doses are recommended in patients with lung shunt greater than 10% or 15%, while RAE is contraindicated if the lung shunt exceeds 20% [35].

Hepatic Artery Infusion (HAI)

General Considerations

Since the early 1960s, when the concept of administering chemotherapy directly into liver through the arterial supply was introduced [42]. Several trials have evaluated the feasibility and the safety of this procedure, using different catheters and drugs [42–50]. Mostly used for patients with metastatic colorectal liver disease, the hepatic artery infusion pump (HAIP) greatly facilitated the outpatient administration of hepatic intra-arterial chemotherapy. In the modern era, intrahepatic chemotherapy can be administered through a surgically implanted subcutaneous pump, or less frequently, through subcutaneous port connected with an external portable pump. Since variations in hepatic arterial anatomic features occur in approximately 45% of the population and can be associated with an increased rate of hepatic infusion pump misperfusion, preoperative CT angiography should be routinely used to define the vascular anatomy. An open or a minimally invasive approach can be adopted, based on the surgeon's preferences and experience. A cholecystectomy is required to prevent chemotherapy-induced cholecystitis. The common hepatic artery is dissected beyond the bifurcation to expose the right and left branches, the gastroduodenal artery is then isolated by dividing the right gastric artery and any small arteries that vascularize the first part of the stomach, duodenum or pancreas, are ligated. Selective ligation of the vessels originating distal to the point of insertion of the catheter tip is critical to prevent extrahepatic misperfusion. The gastroduodenal artery is then ligated distally, and a proximal arteriotomy allows the introduction of the catheter into the artery up to the junction of the gastroduodenal and common hepatic arteries. The catheter is then secured with nonabsorbable sutures (Fig. 28.3). A methylene blue dye test, consisting of injection of dye into the side port of

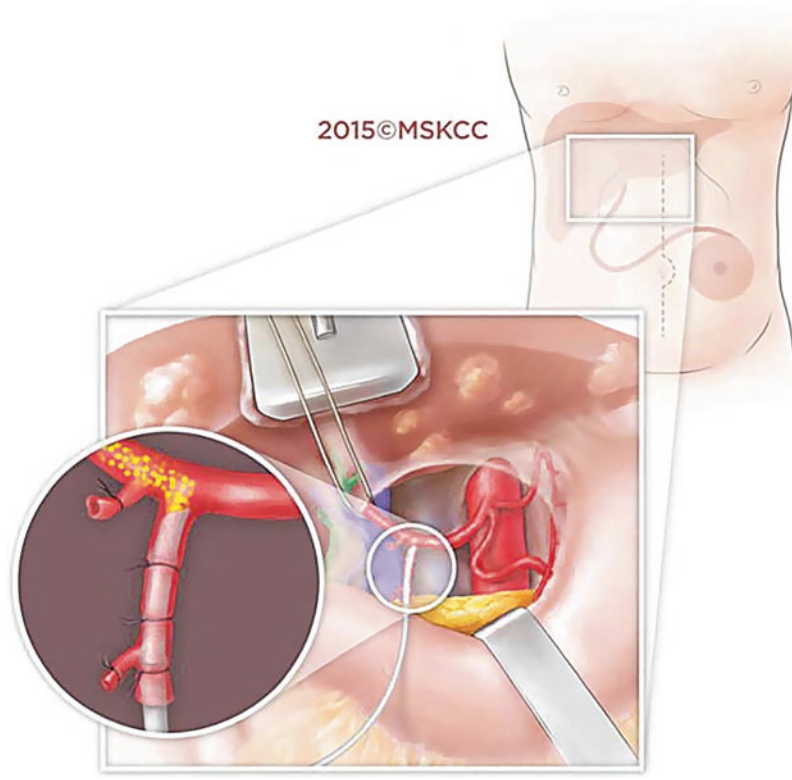

Fig. 28.3 HAIP placement: the catheter is secured to the gastroduodenal artery with nonabsorbable sutures. ©2015, Memorial Sloan Kettering Cancer Center

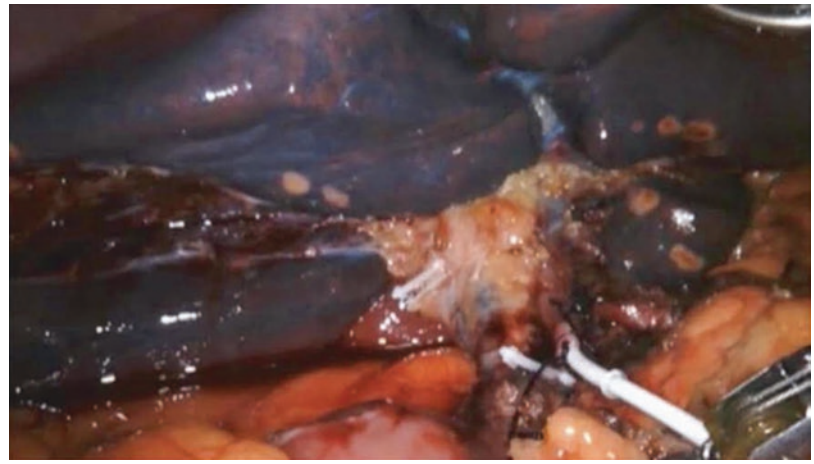

Fig. 28.4 HAIP placement: the methylene blue dye test is necessary to exclude misperfusion. (From Qadan et al. [72]. Epub 2017 Jan 26; used with permission)

the pump and watching for only the entire liver parenchyma to turn blue, is necessary to exclude misperfusion (Fig. 28.4). Redistribution of extrahepatic blood flow to collateral channels, after pump placement, can also contribute to misperfusion. A liver/spleen perfusion nuclear scan should be performed before starting chemotherapy, and extrahepatic collateral vessels, if found, should be treated with embolization. Interestingly, vessels ligated but not interrupted at the time of surgery can act as channels for misperfusion, thus not only ligation, but also division is essential to further minimize the risk of misperfusion [51].

Over the last half-century, different drugs have been tested, such as 5-fluorouracil, floxuridine (FUDR), and mitomycin, with FUDR being the most widely accepted regimen for metastatic colorectal cancer. Since the very first randomized studies, peptic ulceration, chemical hepatitis, and biliary sclerosis were described as the most common toxicities. It is important to note that HAI with FUDR alone is rarely associated with systemic side effects, such as myelosuppression, stomatitis, nausea, vomiting, or diarrhea, due to its high extraction rate by the liver. If diarrhea occurs, perfusion of the bowel should be suspected [42, 52]. Although biliary toxicity has been the most serious limitation of this treatment [42, 53], biliary stricture and jaundice usually can be averted through careful monitoring of liver enzymes and early dosage reduction or cessation. In the first trials on HAIP with FUDR, hepatic and gastrointestinal complications led to the transient interruption of HAI chemotherapy in 80% of patients [50], and in treatment discontinuation in the 30%. Over the years, attempts have been made to reduce the hepatic toxic effects of FUDR by adding dexamethasone. In a randomized study of FUDR with 20 mg of hepatic arterial dexamethasone for 14 of 28 days versus FUDR alone, patients receiving dexamethasone were less likely to have high bilirubin levels (9% vs. 30%) [46]. Although there was no overall difference for the total 6-month period in the amount of FUDR that could be administered in the two groups, the complete and partial response rates were greater in patients receiving dexamethasone and FUDR versus FUDR alone (8% and 63% versus 4% and 36%, respectively; $P = 0.03$), and there was a trend toward increased survival with the addition of dexamethasone (median, 23 months and 15 months, respectively; $P = 0.06$) [46]. The association of dexamethasone with FUDR is now widely accepted and routinely adopted. When Mitomycin C was added to FUDR and dexamethasone in patients with unresectable hepatic metastases from colorectal carcinoma, biliary toxicity was higher than expected. Major toxicities were liver bilomas (7.9%), elevation in bilirubin level >3 (22%), and biliary sclerosis (9.5%), which led to discontinuation of this combination of chemotherapeutics [48]. In a French trial, Irinotecan, Oxaliplatin, and 5-fluorouracil were delivered via an implanted HAI access port and combined with systemic Cetuximab every 14 days [44]. Three-quarters of the patients

received the full course treatment, but grade 3–4 toxicity of any type was recorded in 77%, consisting of neutropenia, abdominal pain, fatigue, and diarrhea. Also, catheter-related issues, such as hepatic artery thrombosis or arteritis, were common and occurred in more than the 50% of patients, who were then switched to IV chemotherapy. The median time to catheter occlusion was 3.3 months (2–4.8), while hepatic artery thrombosis or arteritis occurred in the 15% of patients each. In subsequent trials, other complications have been described when using HAIP such as pump pocket seroma or hematoma, infection, catheter obstruction or leakage [54]. Cholecystitis was also a complication of HAI chemotherapy in the past, occurring in up to 33% of patients; however, it is no longer a problem now that cholecystectomy is routinely performed at the time of pump placement [54].

In the most recent trial on combination hepatic artery infusion and systemic chemotherapy for unresectable colorectal liver metastases, the toxicity was more acceptable [43]. Elevated liver function tests was the most common toxicity with 20% of patients showing an increase in liver enzymes. Patients who received Bevacizumab with hepatic artery infusion and systemic chemotherapy regimens had unexpectedly significant biliary toxicity, with one-eighth of patients requiring biliary stenting. Among the remaining 40 patients treated without Bevacizumab, one required biliary stenting [55]. Bevacizumab is no longer recommended for use along with intra-arterial FUDR.

Specific Complications of FUDR Chemotherapy

Gastroduodenal toxicity Gastroduodenal toxicity includes inflammation/ulceration of the stomach or duodenum, due to inadvertent perfusion of branches of the hepatic artery supplying stomach and duodenum, with FUDR. Symptoms consistent with gastritis, duodenitis, or ulceration including epigastric pain, usually worsen after meals, upper gastrointestinal bleeding, nausea, and vomiting, should prompt holding of therapy and endoscopic evaluation. Persistent abdominal pain, melena, or diarrhea in patients on HAI therapy mandates prompt holding of therapy and endoscopic evaluation.

Chemical hepatitis Chemical hepatitis consists of an elevation in liver enzymes and/or bilirubin secondary to chemotherapy. It occurs in up to 42% of patients enrolled in randomized clinical trials and is the most common dose-limiting toxicity associated with HAI therapy with FUDR [56]. Biliary sclerosis is the pathologic mechanism of chemical hepatitis, and occurred in approximately 15% of patients enrolled in the first trials on HAI FUDR [56]. Dose reduction in patients with elevated liver function tests results in a normalization of liver enzyme levels in the majority of patients, whose enzyme should be monitored every 2 weeks (Table 28.2). In those who have persistently elevated liver enzymes, biliary sclerosis should be suspected, chemotherapy should be suspended and treatment with intra-arterial steroids should be continued [57].

Biliary sclerosis The first report on sclerosing cholangitis after continuous hepatic artery infusion of FUDR dates back to 1985, when Kemeny et al. described strictures of the extrahepatic and intrahepatic bile ducts in eight patients out of 46 treated with intra-arterial FUDR. The incidence of biliary sclerosis ranges from 0.9% to 26% in patients who receive FUDR [42, 50, 53, 54, 58–62]. As with idiopathic sclerosing cholangitis, the biliary stricture most commonly involves the common hepatic duct but also can involve the intrahepatic radicals or the entire biliary tree diffusely. Histologically, biliary sclerosis is characterized by diffuse fibrosis and scarring replacing the walls of the extrahepatic bile ducts, and by periportal fibrosis with increased bands of collagen around the intrahepatic ducts. The pathogenesis of biliary sclerosis is still unknown; however, a major contribution to this phenomenon could come from the direct infusion of chemotherapy into the biliary epithelium from the hepatic artery. Also, the ligation of all the collaterals of the hepatic artery could cause devascularization of the extrahepatic bile duct and in turn sclerosis.

Table 28.2 FUDR dose modification: MSKCC guidelines

AST			
Reference value	≤50 U/L	≥50 U/L	Dose
Current value	0 – <3 × ref	0 – <2 × ref	100%
	3 – <4 × ref	2 – <3 × ref	80%
	4 – <5 × ref	3 – <4 × ref	50%
	≥5	≥4	Hold
If held, restart when	<4	<3	50% of last dose given
ALP			
Reference value	≤90 U/L	≥90 U/L	
Current value	0 – <1.5 × ref	0 – <1.2 × ref	100%
	1.5 – >2 × ref	1.2 – <1.5 × ref	50%
	≥2 × ref	≥1.5 × ref	Hold
If held, restart when	<1.5 × ref	<1.2 × ref	25% of last dose given
Total bilirubin			
Reference value	≤1.2 mg/dL	>1.2 mg/dL	
Current value	0 – <1.5 × ref	0 – <1.2 × ref	100%
	1.5 – >2 × ref	1.2 – <1.5 × ref	50%
	≥2 × ref	≥1.5 × ref	Hold
If held, restart when	<1.5 × ref	<1.2 × ref	25% of last dose given

Courtesy of Dr. N. Kemeny
Reference value: value obtained at the time of the last dose of FUDR
Current value: value obtained at the time of pump emptying or on the day of planned treatment (whichever is higher)

However, this theory does not explain the intrahepatic biliary sclerosis. The association of a higher dosage of FUDR per cycle with biliary sclerosis suggests that dosing is also important; however, the true etiology of this complication remains unclear. The first sign of biliary sclerosis is an elevation in serum alkaline phosphatase (ALP) and/or total bilirubin; thus, routine monitoring of liver function tests (LFTs) is critical. If an elevation of ALP, alanine transaminase, or bilirubin occurred, dose reduction and administration of dexamethasone should be considered according to its severity [46]. Cholangiography is needed to confirm the presence of the stricture that can be typically be salvaged by stenting and/or dilation via endoscopic retrograde cholangiopancreatography. Interestingly, HAI FUDR combined with Bevacizumab is associated with a greater biliary toxicity [55]. The mechanism of the potentiation of bile duct toxicity resulting from Bevacizumab is unclear, but the effect on vascular permeability could lead to greater influx of chemotherapy and therefore greater biliary injury and stricture formations. Moreover, inhibition of angiogenesis by this monoclonal antibody that targets vascular endothelial growth factor (VEGF) impairs healing of injury and inflammation, leading to fibrosis.

Pump complications and durability Complications associated with the infusion pump range between 12% and 41% and consist of pump malfunction, pocket infection, catheter thrombosis or displacement, catheter erosion, arterial thrombosis or arterial dissection, and incomplete perfusion [63–65]. The strongest predictors of pump malfunction include variant arterial anatomy, cannulation of a vessel other than the gastroduodenal artery (GDA), and lack of surgeon experience [66, 67]. The difference in complications between experienced surgeons (more than 25 pump placement) and less experienced surgeon has been reported as high as 12% [68]. Other strong predictors of vascular complication include the infusion of intra-arterial Mitomycin C, which is correlated with arteritis and thrombosis [69, 70]. In general, the majority of complications is related to the hepatic arterial system and consists of arterial thrombosis, extrahepatic perfusion, incomplete hepatic perfusion, and hemorrhage [68]. Other types of complications include catheter-related complications, such as dislodgment, erosion, and occlusion; pocket complications, such as infection, hematoma, pump migration; and device-related complications. Pump complication rates can range from 40% to 60% in reports published in the 1990s [66, 71] to 22% in a recent study on patients undergoing pump placement at Memorial

Table 28.3 Types of complications, timing of occurrence, and ability to salvage pump function

	Early (<30 days)		Late (>30 days)	
Type of complications	*n*	% salvage	*n*	% salvage
Pump malfunction	6	100	–	–
Pocket				
Infection	4	50	10	40
Hematoma	1	100	–	–
Migration	1	100	3	33
Catheter				
Occlusion	–	–	11	36
Dislodgment	–	–	18	11
Erosion	–	–	4	0
Arterial				
Hemorrhage	1	100	–	–
Thrombosis	13	31	20	30
Extrahepatic perfusion	9	100	7	57
Incomplete perfusion	9	78	3	67
Overall	44	70	76	30

Modified with permission from Allen et al. [68]

Sloan Kettering Cancer Center for unresectable liver metastases [68]. Of note, 45% of all complications in the study from MSKCC could be salvaged, leaving 12% of patients with a pump-related complication that rendered the pump nonfunctional. The large majority of pump malfunctions are detected more than 30 days after surgery, when it is difficult to salvage them. In high volume centers, the salvage rate can be as high as 45% and occurs mostly when the malfunction is detected within 1 month from surgery (Table 28.3). Early complications are mostly misperfusions of the liver and can be corrected by operative or angiographic intervention. Late complications are usually catheter occlusions or arterial thrombosis. The incidence of pump failure with consequent HAI discontinuation is time-sensitive. The incidences of hepatic artery infusion pump failure at 6 months, 1 year, and 2 years after pump placement have been reported as 5%, 9%, and 16%, respectively.

Summary

In summary, intra-arterial regional liver treatments can be associated with angiographic/surgical procedure complications, embolic/infusion side effects, nontarget embolization/infusion to normal liver parenchyma, and with device malfunction in the case of intra-arterial infusion pump. The most common complications resulting from TACE and TAE are post-embolization syndrome, arterial injuries, nontarget embolization, biliary ischemia and bilomas, and liver abscesses. Radioembolization is associated with radioembolization-induced liver disease (REILD) and radiation pneumonitis. Finally, hepatic artery infusion (HAI) treatments are complicated by gastroduodenal toxicity, chemical hepatitis, biliary sclerosis, and pump/catheter malfunction.

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Part V

Limb Infusional and Perfusional Therapies

Infusion Technique

29

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Introduction and Historical Perspective

Patients diagnosed with melanoma or sarcoma can present with a bulky primary of the extremity, multifocal in-transit disease or unresectable masses limited to a single limb. Since we aim to provide limb-sparing treatment, these patients are generally not considered for surgical resection. High-dose regional therapy was first described in melanoma in the 1950s. Despite being considered a revolutionary technique with overall response rates as high as 90% [1], isolated limb perfusion (ILP) is a complex, costly, and invasive procedure. It is also a fairly morbid procedure, and the subsequent scarring and lymphedema preclude most patients from undergoing a repeat ILP [2].

In the early 1990s, the Melanoma Institute Australia (MIA, previously known as the Sydney Melanoma Unit) with Dr. John F. Thompson developed a technique of low-flow ILP via percutaneously placed arterial and venous catheters [3, 4]. The procedure, called isolated limb infusion (ILI) to differentiate it from its perfusion counterpart, is also performed under hypoxic conditions of the isolated limb. ILI offers a minimally invasive approach with outcomes comparable to ILP. Table 29.1 provides key comparative points between ILI and ILP [5, 6].

While high-dose regional therapy was first described in melanoma, it is now successfully used in other types of malignancies and even some benign conditions [6]. It can be used as a primary option, a second line of treatment, or in conjunction with other systemic therapies. This chapter reviews the technical and clinical aspects of ILI.

Patient Selection for Isolated Limb Infusion

ILI was first described in non-resectable in-transit melanoma disease; it has been reported in other advanced cancers such as extremity sarcoma, squamous cell carcinoma, Merkel cell carcinoma, and cutaneous T-cell lymphoma [7]. It is also a treatment option in refractory benign conditions such as hand warts [8, 9] and chromomycosis [6, 10]. The main criteria for consideration for ILI are disease in which proceeding with surgical excision would compromise the limb function or viability.

ILI is well-tolerated in a large variety of patients, including patients with multiple comorbidities, frail and elderly patients [11]. ILI is

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Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_29

Table 29.1 Differences between isolated limb perfusion and isolated limb infusion [5, 6, 18]

Isolated limb infusion	Isolated limb perfusion
Technically simple	Technically complex
Minimally invasive, percutaneously inserted vascular catheter	Open surgical cannulation of vessels for catheter insertion
Approximately 1 hour	4–6 hours duration
Easy to repeat procedure	Very challenging to repeat procedure
Equipment requirements modest	Complex and expensive equipment needed
Well tolerated by medically compromised, frail and elderly patients	Magnitude of procedure excludes patients
Can be performed selectively in occlusive vascular disease	Not possible in occlusive vascular disease
Systemic metastases not a contraindication	Systemic metastases normally a contraindication
Low flow rates of 80–120 mL/min, effective vascular isolation with tourniquet	High flow rates of 400–600 mL/min predispose to systemic leakage
Usually not possible to raise limb temperature above 40 °C	Hyperthermia (>41 °C can be achieved)
Anaerobic, ischemic, acidotic perfusate	Aerobic, oxygenated, mildly acidotic perfusate
Possible with regional anesthesia, general anesthesia (GA) preferred	GA required

generally better tolerated than ILP since it is a less invasive, shorter, and less morbid procedure (Table 29.1) [6]. Patients being considered for ILI need to be able to undergo general anesthesia. While ILI was first offered in patients with disease limited to a single limb, ILI is also considered as a palliative option in patients with metastatic disease who suffer from ulceration, bleeding, or severe pain in an affected limb. It is typically offered to patients who have a life expectancy of at least 3 months.

Preoperative Assessment

Routine preoperative evaluation is done based on the patient's age and comorbidities, as this procedure is virtually always performed under general anesthesia. It is technically possible to do it under a spinal anesthetic when the tap is atraumatic, but practitioners are reluctant to use this method due to the systemic heparinization required throughout the procedure. Preoperative assessment must include extremity pulse assessment, and antithrombin prophylaxis is recommended. Oral aspirin 325 mg daily is started on the day of the procedure and continued for 3 months after ILI. The patient also receives systemic anticoagulation during the procedure.

The limb volume needs to be measured to calculate the infusion dosage. Multiple techniques are described in the literature. *Water displacement volumetry* and serial circumferential measurements such as the *DISC model* are most commonly used [12]. *Water displacement volumetry*, first described by Wieberdink et al., is a simple method submerging the limb in water based on the well-known Archimedes' principle. In the context of limb infusion, several measures are done, and marks are left on the skin at every level it is done, to account for the location of the tourniquet. This method may seem obsolete in the context of modern imaging studies. However, Chromy et al. demonstrated in 2015 that it is still the most accurate method, followed by CT, MRI, and circumferential measurements [12]. The later can be extremely useful when a fast estimation is required or when the water displacement cannot be used. The *DISC model* is an example of this method. Circumferential measures are taken every 1 cm for fingers and toes and every 4 cm for the rest of the limb [12]. The proximal measurement is done at the anticipated lower level of the tourniquet, and final volume is calculated as a sum of all the cylinders created with this method. In our institution, we perform a hybrid of this method using 1–2 cm longitudinal intervals for increased accuracy.

Every patient should undergo appropriate staging and metastatic workup prior to be considered for ILI. As per NCCN guidelines, this includes an LDH level and a whole-body FDG PET/CT or chest/abdominal/pelvic CT with IV contrast, with or without brain MRI with IV contrast for melanoma, and a limb MRI +/− CT with IV contrast and a chest CT for extremity sarcomas [13, 14].

Catheter Insertion

Small caliber arterial and venous catheters are inserted in the Interventional Radiology (IR) Department just prior to the procedure under fluoroscopy. Upon arrival to the hospital, the patient is kept warm, and the limb is covered with a warming blanket to optimize treatment. Low body and limb temperature makes it more difficult to reach the target temperature goal at the time of chemotherapy infusion, increasing the failure rate [6, 15]. The surgeon marks the anticipated site of the distal catheters on the patient with a paper clip and tape for the radiologists. The patient is then transported to IR.

The contralateral groin is the preferred location for insertion. In a sterile fashion, under ultrasound guidance and fluoroscopy, a Seldinger technique is used to insert a 6-French straight arterial sheath in the femoral artery and an 8-French venous catheter in the femoral vein. The catheter will then be advanced as distally as possible, ideally bringing the tip to the level of the popliteal artery and vein just proximal to the knee joint in the lower limb and to the level of the brachial artery and basilic vein just above the elbow joint in the upper limb [6, 15]. The position of the tip of the catheter is confirmed by fluoroscopy. Angulation of the vessels and venous valves sometimes makes it challenging to achieve this goal, but various types of catheters and guidewires can be utilized to negotiate sharp turns and tight valves. Atherosclerosis and thrombosis can prevent the use of some vessels; however, if difficulty is encountered, the catheter can be inserted in the profunda femoral vessel when the superficial femoral vessel is occluded [15].

Once the location is confirmed, a single dose of 5000 IU of heparin is given, or a low-dose heparin infusion is started in the circuit and continued until the start of the ILI procedure [6, 15, 16]. The patient is then brought back to the preoperative area and the operating room is prepared. It is imperative to coordinate with the entire team to limit delays between catheter placement and transport to the operating room. Time is of the essence, since catheter migration can compromise the success of the procedure.

Chemotherapy Selection

Several chemotherapies have been investigated for use in regional therapy, but melphalan and actinomycin D are the most commonly used in ILI [17, 18]. Melphalan is an L-phenylalanine mustard, and its mechanism of action relies on alkylation of DNA bases to break the DNA molecules, resulting in severe cellular damage [19]. Melphalan has been the drug of choice for both ILP and ILI for several decades, but is a poor drug of choice for systemic treatment as myelosuppression occurs at a low systemic concentration [19]. When used in the regional setting, doses 10- to 100-fold higher than what can be tolerated systemically are infused, which can achieve therapeutic levels without causing systemic myelosuppression. Actinomycin D, an inhibitor of the DNA transcription, is commonly administered in addition to melphalan to increase the response rate, and its use has not been associated with increased limb toxicity [11].

The infusion dose of the melphalan and the actinomycin D are calculated based on the volume of the limb (see section "Preoperative Assessment"). The dose of melphalan is 7.5 mg/L for the lower extremity (to a maximum of 100 mg) and 10 mg/L for the upper extremity (to a maximum of 50 mg). The dose of actinomycin D is 75–100 mcg/L for the lower extremity and 100 mcg/L for the upper extremity. Some centers including ours correct the dosages for ideal body weight (IBW) in an attempt to decrease limb toxicity [11].

ILI Procedure

Prior to the patient's arrival, the operating room temperature is set around 28–30 °C. In the preoperative holding area, a liquid warming blanket such as the Kimberly-Clark Patient Warming System (Halyard, Alpharetta, GA, USA) or a Bair Hugger (Augustine Medical, Inc., Eden Prairie, MN, USA) is applied on the limb with a goal of approximately 41 °C. The patient is then transferred to the operating room, placed in supine position on the table, and the entire body is covered with a hot-air blanket. If the liquid warming

blanket is not available, a second hot-air blanket set to 41 °C is placed under and around the affected limb, forming a cocoon. Additional heat can also be provided from above using an overhead radiant heater if needed. It is imperative to take continuous measures to keep the patient and the limb warm. Initial subcutaneous temperatures can be as low as 34 °C if these precautions are overlooked.

Following induction of general anesthesia, a Foley catheter is inserted in the bladder. The patient is medicated with a single dose of a 5-HT3 antagonist (ondansetron, 8 mg IV), steroid (dexamethasone, 10 mg IV), proton-pump inhibitor (pantoprazole, 40 mg IV), and antibiotic (cefazolin, 1 g IV). Temperature needle probes are inserted in the limb, generally two in the lower extremity and one for the upper extremity to monitor subcutaneous and intramuscular limb temperatures. The affected limb must reach a temperature of at least 37.0 °C before the chemotherapy infusion can be initiated. The increased temperature increases vascular permeability making the tumors more sensitive to the chemotherapy. A pneumatic tourniquet is placed proximally on the limb. If disease extends more proximal or near the groin or axilla, an Esmarch tourniquet can be used to provide a larger infusion field. Distally, a second pneumatic or Esmarch tourniquet can be applied to exclude the foot or the hand if there is no disease at that level.

After a baseline-activated clotting time (ACT) level is drawn from the arterial line, the patient receives systemic heparin at a dose of 300 IU/kg IV. The ACT is checked every 5 minutes until the level reaches 400 seconds (s), and every 10 minutes throughout the procedure. The ILI circuit consists of an extracorporeal tubing circuit, a heat exchanger set at 41 °C and a wide-bore, high-flow, three-way tap (Level 1 Technologies, Inc., Rockland, MA, USA) (Fig. 29.1). The

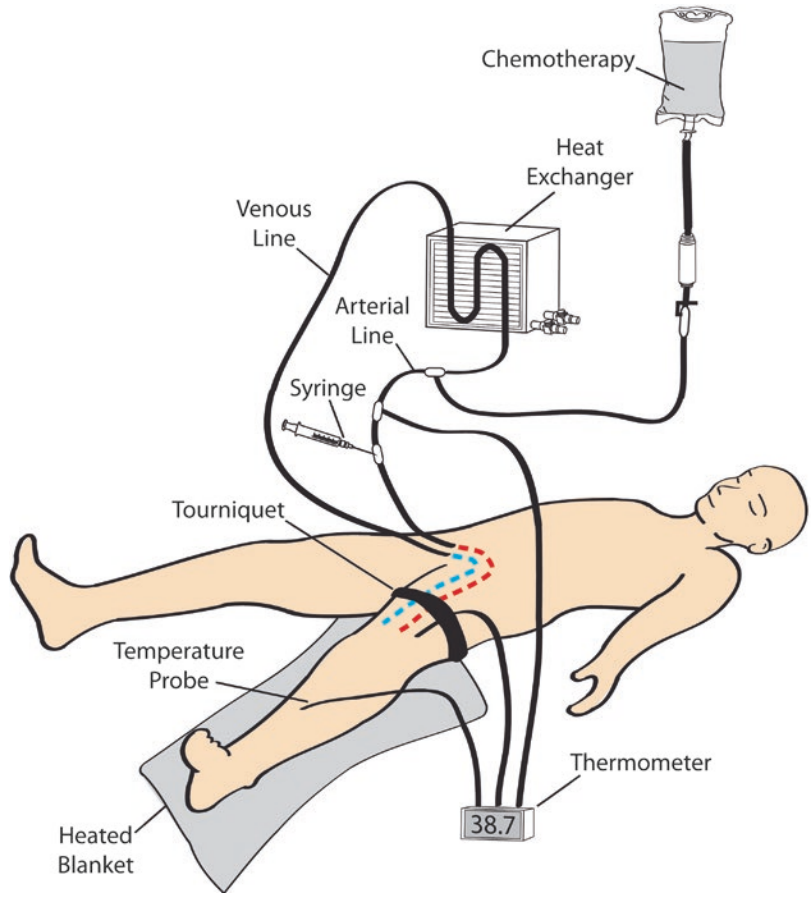

Fig. 29.1 Isolated limb infusion setup. Graciously provided by Fox Chase Cancer Center, https://www.foxchase.org/clinical-care/departments-programs/clinical-departments/surgical-oncology/surgical-techniques/isolated-limb-infusion

arterial catheters are connected to the circuit first, followed by the venous catheters via the 3-way stopcock.

Once the limb temperature reaches at least 37.0 °C and the ACT level is >400, the extracorporeal circuit is primed by manually drawing blood from the venous catheter and injecting it in the arterial catheter several times using a 20-cc syringe. Once the circulation is adequate, the proximal (and, if appropriate, distal) Esmarch bandage is tightly secured, or the pneumatic tourniquet is inflated to 300 mmHg for the lower extremity or 250 mmHg for the upper extremity. Manual circulation is continued as the tourniquet(s) are secured to maintain adequate flow in the extracorporeal circuit. A Doppler is used to confirm the absence of a distal pulse. At that point, papaverine (30–60 mg IV) is injected directly in the arterial catheter to maximize vasodilation.

Using the preoperative volume measurements marked on the skin as described in section "Catheter Insertion", the total dose of chemotherapy is calculated. The infusion consists of cytotoxic drugs diluted in 400 cc of heparinized normal saline solution. Given that the half-life of the chemotherapy is 1 hour, we work very closely with our Pharmacists to ensure appropriate timing. We generally call for the chemotherapy once the patient is heparinized. After confirming that the limb temperature is at least 37.0 °C and the ACT level is 400 s, the chemotherapy is infused over a period of 2–5 minutes through the arterial line using an intravenous pump fed from a pressurized infusion bag, using standard chemotherapy precautions. Some centers infuse 50% of the chemotherapy manually, circulate it 2–3 times, and then infuse the rest of the dose. Once the full dose is in the circuit, the chemotherapy infusate is circulated through the limb via the extracorporeal circuit for a total of 30 minutes. Alternatively, the entire procedure can be performed manually using two 60 cc syringes [6]. During the procedure, the limb will become mottled.

In order to maximize the effect of the chemotherapy, an attempt is made to increase the limb temperature to 39.0 °C during the 30 minutes circulation time which helps to increase vascular permeability. To ensure the procedure is performed safely and to assess for systemic leakage, blood gases, pH level, base excess, and chemotherapy drug levels are measured both in the systemic circulation and in the circuit at the start of the procedure, at 25 minutes and at 30 minutes. It is expected to see a certain degree of hypoxia and acidosis in the limb. A higher concentration of cytotoxic drug and an increase in the level of CO_2 in the circuit are associated with increased limb toxicity [11] (Table 29.2).

After 30 minutes of circulation, the heater is turned off. Using the arterial catheter, the limb is flushed with 500–1000 cc of normal saline or a Ringer's lactate solution at room temperature, until the venous effluent is clear. The venous flow is assisted with manual limb massage. Suction can be attached to the venous catheter to extract as much cytotoxic waste and blood as possible. The waste is disposed of in a cytotoxic waste disposal container. This process takes about 10 minutes and represents the estimated blood loss (EBL) for the case.

Intravenous protamine is used to reverse the heparin. The required dose is calculated based on the decay curve of the last ACT. Once the protamine is delivered, the tourniquet is released. ACT level is drawn at regular intervals until it normalizes, and then both catheters are withdrawn. Pressure on the exit site is maintained manually or with the use of an inflatable occluder for approximately 20 minutes. Additional devices such as Perclose™ (Abbott Vascular, Santa Clara,

Table 29.2 Median intraoperative values at 30 minutes; 185 patients treated with ILI at the Melanoma Institute in Australia [6, 11]

Variable	Median (IQR)
Tourniquet time (min)	55 (44–65)
Drug exposure time (min)	30 (21–32)
Peak T subcutaneous (°C)	38.1 (37.5–38.8)
Peak T intramuscular (°C)	38.1 (37.7–38.5)
pH	7.11
BE (mmol/L)	−10.8
PO_2 (mmHg)	8.4
SO_2 (%)	6.9
PCO_2 (mmHg)	54.3
CK (IU)	750 (173–2512)

IQR interquartile range, Δ difference between start and end of procedure, *CK* creatine kinase

CA, USA) or Angioseal™ (St. Jude Medical, St. Paul, MN, USA) can be used to prevent bleeding at the arterial exit site. Once hemostasis is achieved, the patient is extubated and brought to the recovery room or admitted directly to the intensive care unit (ICU).

Postoperative Care

Postoperatively, the patient is admitted to a monitored bed (either telemetry or ICU) and remains on strict bed rest overnight. Sequential compression devices are applied on both legs, and the treated limb is elevated at 30 degrees for a period of 48 hours. Neurovascular assessment of the treated limb is done every hour for the first 24 hours. Discomfort is usually mild. Oral and IV analgesia is administered as needed for pain control, but epidural analgesia and patient-controlled analgesia (PCA) are avoided to avoid masking signs and symptoms of compartment syndrome. Systemic side effects are rare; postoperative nausea and vomiting is usually due to the anesthetic rather than to the cytotoxic drug since the tourniquet and thorough flushing of the limb prevent systemic circulation of the cytotoxic drug [11].

Using the Wieberdink scale (Table 29.3) [20], the limb is assessed at least twice a day, and limb toxicity is recorded. Up to 56% of patients experience at least grade II toxicity (edema and erythema) [11], which develops over the first 24 hours and continues to worsen over the first 4–5 days, and then promptly subsides. The inflammation is usually more prominent on the skin overlying the tumor nodules, and toxicity is usually worse in the upper (vs lower) limbs. Grade III toxicity is seen in 27–39% of patients and consists of more severe edema and erythema associated with blistering and is usually associated with a good clinical response, but can take 2–3 weeks to resolve (Fig. 29.2) [11]. Up to 4% of patients develop grade IV toxicity and require a fasciotomy, but amputation is a very rare event reported in less than 1% of patients (grade V toxicity) [11]. Alternatively, toxicity can be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events [21]. Overall, short-term limb toxicity is usually worse with ILI than with ILP, but long-term morbidity is less frequent and less severe with ILI [11, 22, 23].

Table 29.3 Wieberdink toxicity grading [11, 20]

Grade I	No visible effect
Grade II	Slight erythema and/or edema
Grade III	Considerable erythema and/or edema with blistering
Grade IV	Extensive epidermolysis and/or obvious damage to deep tissues with a threatened or actual compartment syndrome
Grade V	Severe tissue damage necessitating amputation

Bloodwork is obtained in the recovery room and twice a day afterward. A multicenter study conducted in the USA demonstrated that a median peak CK level of >563 U/L is a significant predictor for developing severe acute regional toxicity ($p < .01$) [22, 23]. A high level of serum creatinine phosphokinase (CK) is considered a strong predictor of limb toxicity and is most frequently associated with grade III and IV toxicity rather than grade I and II toxicity [22, 23]. A multicenter study done in Australia reported a median level of 2553 IU/L (grade III/IV) versus 217 IU/L (grade I/II) ($p < .001$) [20, 21]. CK levels are measured every 12 hours, and patients with levels over 1000 IU/L are treated with a short course of corticosteroids (dexamethasone, 4 mg IV every 6 hours) until their clinical presentation have improved to less than a grade IV and their CK level have fallen below 1000 IU/L. Most patients are discharged around 5–7 days after the procedure. Prophylactic subcutaneous heparin is given throughout the hospital stay, and patients go home on a daily dose of ASA 325 mg orally for 3 months, as discussed in section "Preoperative Assessment" [6, 15, 16].

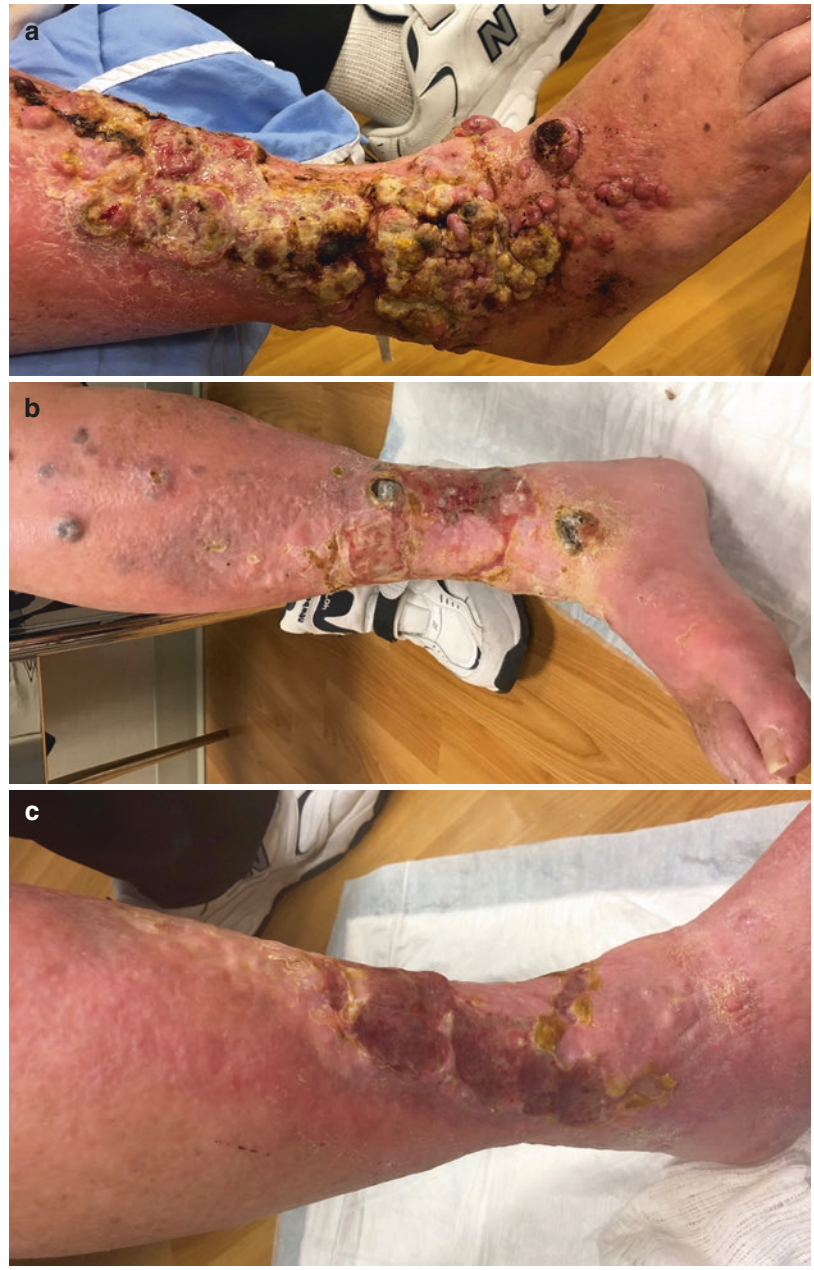

Fig. 29.2 Photographs of a clinical response. (**a**) Before ILI. (**b**) Six weeks post ILI. (**c**) Twelve weeks post ILI

Clinical Follow-Up

Following hospital discharge, the patient is followed every 1–2 weeks for the first 8 weeks, and every 3 months thereafter. Restaging PET/CT is done every 3 months. Clinical response is assessed and recorded using the World Health Organization criteria or the RECIST criteria (Response Evaluation Criteria in Solid Tumors) (Table 29.4) [24]. Two observations up to 4 weeks apart are necessary to confirm the clinical response. Based on RECIST criteria version 1.1,

a complete response is defined as the disappearance of all measurable disease, a partial response is characterized by a 30% decrease in total tumor size, stable disease is the absence of change that qualifies as a partial response or progressive disease, and progression is any increase in number of lesion or a 20% increase in tumor size with a minimum absolute increase of 5 mm [24]. In ILI, the overall response rate is as high as 73%, 40% of which have partial response, and 33% a complete response [6].

Table 29.4 RECISTv1.1: response evaluation criteria in solid tumors [24]

Complete response (CR)	The disappearance of all target lesions
Partial response (PR)	At least 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study
Progressive disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study), or the appearance of one or more new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm

Severe edema and erythema (grade III toxicity) can persist for 2–3 weeks. Superficial desquamation of the skin and hair loss is often seen around the same time. Hyperpigmentation of the limb can last for several months. Loss of nails or epidermis of the sole of the hand or the foot has been reported in rare cases, which also coincide with the absence of distal tourniquet during the procedure.

Repeat ILI procedures can be considered for recurrence after ILP or ILI (Fig. 29.3) [25]. However, repeating the procedure 2–8 weeks after the most recent ILI has been shown to increase toxicity without increasing efficacy [25].

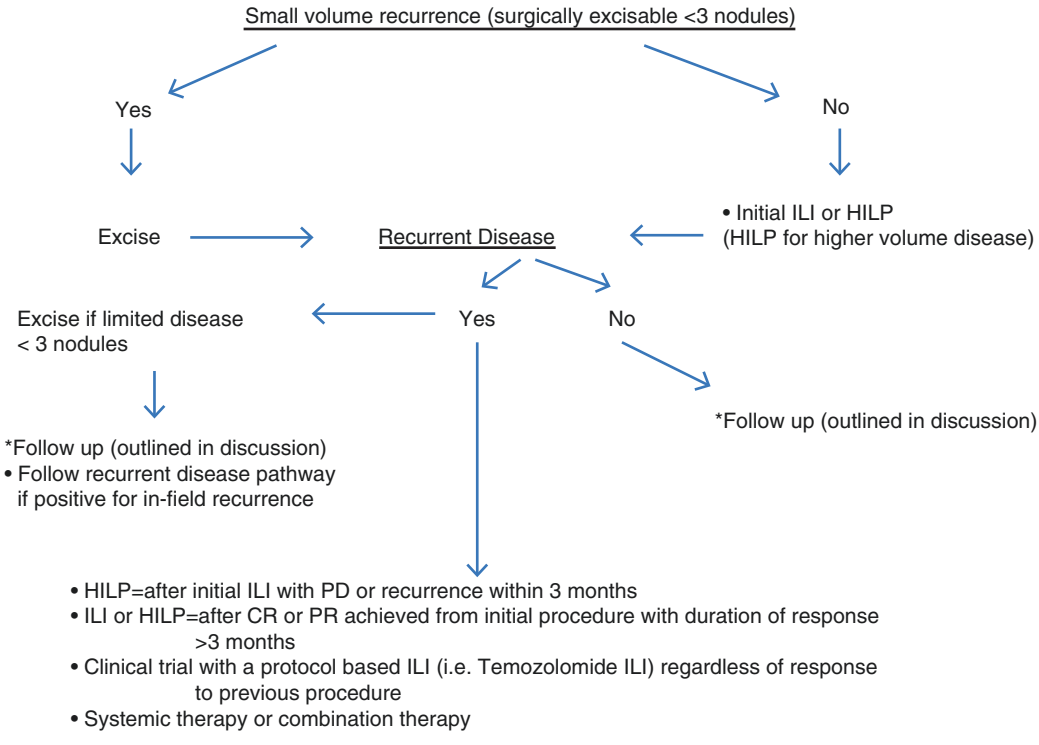

Fig. 29.3 Treatment algorithm for recurrent extremity melanoma after regional chemotherapy. (From Chai et al. [25]; used with permission)

Conclusion

Therapeutic options for patients with bulky primary, multifocal in-transit disease or unresectable masses limited to a single limb are evolving and expanding. Since its first introduction by Thompson et al. in the early 1990s as a minimally invasive alternative to ILP, ILI has been intensively applied in patients with in-transit melanoma confined to the limb, and its indication have largely expanded since then. In this chapter, we reviewed the technical and clinical aspects of ILI. Especially in melanoma, in which treatment options have significantly expanded in the past few years, patient selection is of utmost importance in deciding who will best benefit from the procedure, either as a primary therapeutic option, as a second-line treatment or in combination with systemic therapies.

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30 Hyperthermic Isolated Limb Perfusion for Melanoma

Kenneth K. Tanabe

In 1956, the Department of Surgery at University of Tulane embarked on regional perfusion studies with a goal of increasing intratumoral chemotherapy drug concentrations in tumors located where the vascular supply and drainage could be completely isolated [1]. The use of a heart-lung machine to support isolated hyperthermic perfusion of the tumor was evaluated an approach to increase the dose of nitrogen mustard and at the same time avoid systemic toxic effects [2]. Cannulation of both the arterial inflow and the venous drainage for connection to an extracorporeal circuit maintained by a heart-lung machine for blood oxygenation represented an improvement over the technique previously described by Kopp and colleagues in which the chemotherapy was administered into the artery, with the venous drainage left unaltered, or clamped [2].

In 1957, a patient with a very high burden of melanoma metastases to the extremity presented to Charity Hospital 2 years following treatment of a melanoma on the ankle. Amputation was recommended, as the patient had over 80 satellite lesions, but the patient refused this recommendation. The team performed an isolated chemotherapy perfusion using melphalan, a chemotherapy agent that was new and under evaluation at the time for metastatic melanoma. The patient experienced a complete clinical response and remained melanoma-free until his death at age 92, some 16 years later.

The following year Creech presented the results of isolated perfusion in 24 patients—6 with melanoma and another 18 with other advanced cancers—before the American Surgical Association in New York [3]. For pelvic tumors, the aorta and IVC were occluded below their renal branches and cannulated just above the bifurcation. For perfusion of lung tumors, two circuits and caval occlusion were used to prevent mixing between the systemic and pulmonic circuits. And a motor pump was used to create negative pressure in the venous return circuit to minimize systemic mixing in cases in which tourniquets could not be applied (e.g., breast). Creech reported gross or microscopic responses in 18 of 19 cases followed long enough for changes to be evident. By 1962 they had treated a sufficiently large number of patients to report results of 303 patients, 123 with melanomas [4].

Many hospitals followed suit and began performing isolated limb perfusion. Unfortunately, an opportunity for progress was lost during this interval because hypotheses were not prospectively addressed and data were not collected in a scientific manner. Studies were generally single arm, absent appropriate control groups, and involved heterogenous patient populations including patients with completely resected

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Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_30

tumors and unresectable tumors. Every study used a different types of patients and different doses of melphalan, perfusion duration, and temperature [5–13]. For example, in a report of 1139 perfusions performed over 35 years, the authors included patients with multiple indications: definitive treatment of in-transit metastases, unresectable recurrent or primary tumors, adjunctive therapy to surgical excision for regionally confined melanoma, conversion of advanced unresectable melanoma to resectable, and palliation in noncurable recurrent melanomas by maintaining a functional limb in the presence of systemic metastases [1]. Fortunately, clinical studies in the past two decades have been of significantly higher quality and with greater scientific rigor.

Equipment

The operation requires a standard heart-lung bypass device equipped with a roller pump, oxygenator with a gas source (95% oxygen 5% carbon dioxide), heater capable of reaching 42 °C, and venous reservoir (Fig. 30.1). Additional equipment necessary include an ultraviolet (black) light is used to evaluate for leakage of fluorescein from the extremity, access to a machine for activated clotting time measurements, a scintillation probe mounted over the chest (precordial) to monitor for I-131 or 99 m-Technetium labeled albumin or red cells as an indicator of leak from the circuit into the systemic circulation, a pulse volume recording machine to assess peripheral vasculature, and

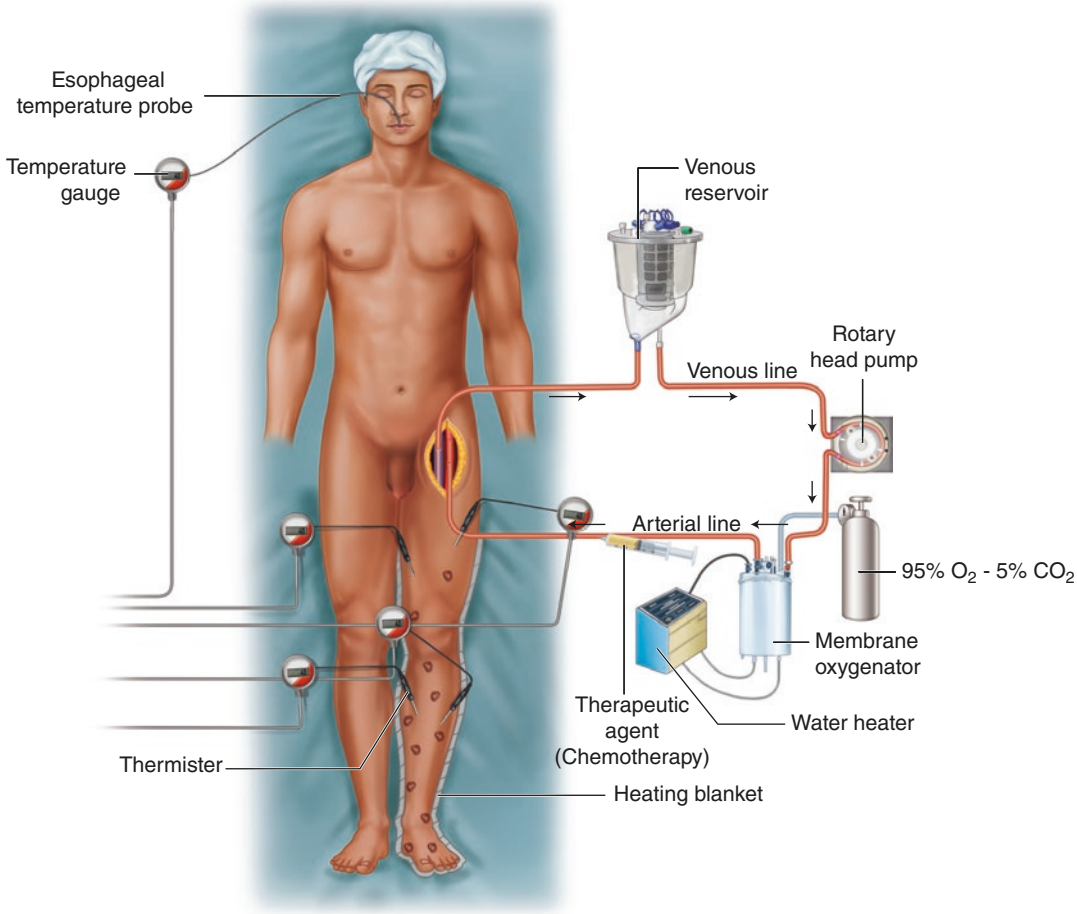

Fig. 30.1 Diagram showing typical set up for lower extremity hyperthermic isolated a limb perfusion

heating blankets for external warming of the extremity. Thermistors inserted under the skin are connected to digital temperature monitors to monitor temperature in different locations during the operation. A selection of different size arterial and venous cannulas should be on hand, as well as heparin-saline irrigation. A self-retaining retractor attached to the table is of significant help for approaching iliac vessels. Standard vascular instruments are used during the operation, as well as Rummel tourniquets, a hand drill for placement of Steinmann pins, and a Doppler probe.

Leak Monitoring

It is necessary during limb perfusion to assess for leakage from the circuit into the systemic circulation, or from the systemic circulation into the circuit. Leakage of melphalan into the systemic circulation can lead to acute nausea and delayed bone marrow suppression or hair loss. Leakage of even small amounts of tumor necrosis factor leads to proinflammatory cytokine storm responsible for sepsis-like side effects including intraoperative tachycardia, hypotension, and pulmonary edema [14].

A commonly used technique to measure leak involves mounting a shielded precordial scintillation detector over the precordium and injecting I-131 or Tm-99-labeled albumin or red cells into the perfusion circuit. A fraction of the total dose is administered into the systemic circulation to calibrate the system and allow for quantification of the leak, using the assumption that the volumes of the extracorporeal circuit and the systemic vasculature are in the proportion of 1:5. This technique allows quantification of the percent fractional leak over time.

A simpler but not quantitative approach involves administration of fluorescein into the circuit and then viewing different areas of the body with a Woods lamp. This technique reveals specific areas of skin outside the extremity that are receiving perfusate, thereby directing further dissection to identify and control specific collateral vessels. A disadvantage of this technique is that quantification is not possible, and once a significant systemic leak has occurred, it is not possible to confirm correction of the leak.

Another technique for leak detection that has been described but not used widely is administration of 3% desflurane into the bypass circuit using an anesthetic vaporizer. The expired breath is then monitored by standard gas analysis for desflurane as a sign of leakage [15].

Agents

Melphalan is the most widely used agent for HILP for melanoma. It is the agent that was used for the first patient treated with HILP and produced a clinical complete and durable response. Melphalan is a phenylalanine and a precursor for melanine biosynthesis and therefore taken up avidly by melanocytes and melanoma cells. The mechanism of action of melphalan is through its ability to interact directly with DNA and cause miscoding. A second mechanism by which alkylating agents cause DNA damage is by formation of cross-bridges in the DNA, thereby preventing strand replication or transcription.

Pharmacokinetic studies of melphalan in HILP demonstrate rapid uptake in tissue in the first 5—10 min, and continual reduction in drug concentration over 60 min to 10—20% of the starting concentration [16]. Dosing is calculated from limb volume or body weight, though notably, limb volume expressed as a percentage of total body weight results in as much as a twofold variation in the population for both lower and upper extremities. This could theoretically lead to double the amount of melphalan administered to the same volume of tissue in two different individuals when dosed by weight. When dosed by limb volume, optimal dosages of 10 mg/L limb volume in the leg and 13 mg/L limb volume in the arm have been determined as the highest dose with acceptable risk, and little variation in toxicity [11, 17, 18]. Melphalan is stable in sterile 0.9% sodium chloride for only 90 min at room temperature [19] and is therefore prepared immediately before administration. Melphalan is eliminated from plasma primarily by chemical

hydrolysis to inactive monohydroxymelphalan and dihydroxymelphalan. Renal excretion is extremely low. Identification of fluorescein in the urine from a leak test does not equate to a similar amount of melphalan in the urine. All discarded bodily fluids from an HILP case should be handled as chemotherapy biohazard waste. Side effects of melphalan administration as part of HILP are discussed below.

Tumor necrosis factor alpha TNFα gained considerable interest as an anti-cancer agent because it is a proinflammatory cytokine produced by multiple different immune cells and causes rapid and significant hemorrhagic necrosis of tumors. But humans are exquisitely sensitive to toxic effects of TNFα including a septic-like response with fevers, tachycardia, cardiovascular collapse, pulmonary edema, and shock. The maximum tolerated systemic dose has essentially no effect on tumors. With these observations in mind, TNFα is a logical choice of agent for isolated regional perfusion with a goal of achieving anti-tumor effects in the extremity without systemic side effects. TNFα alone has been used for isolated limb perfusion, with limited benefit observed [20]. Of six treated patients, partial response of less than 1 month duration was seen in two patients, and one patient had a complete response of only 7 months duration and then progressed. The observation that TNFα increases tumor neovascular permeability suggests that its best use is in combination with other agents. It has been combined most commonly with melphalan and interferon. Other agents used in the past for isolated limb perfusion either alone or in combination with other agents include cisplatin, dacarbazine, actinomycin D, and fotemusine [21].

Operative Technique

The operation involves the use of an extracorporeal circuit attached to a heart-lung machine (oxygenator and blood pump) to increase the oxygen tension and heat the circulating blood before delivery to the isolated limb and buffer with carbon dioxide. Anesthesia must be prepared for intraoperative fluid shifts between the vascular compartments of the limb and the remainder of the body, hypotension caused by low vascular tone, and sequela of ischemia reperfusion [22].

The operation typically lasts for 4–6 hours, depending on which vessels require isolation and whether a concomitant lymphadenectomy is indicated. Two large bore IVs are required, and anesthesia should be prepared for acute blood loss, particularly if surgical isolation of the vessels is anticipated to be difficult (e.g., iliac vessels and scarred vessels). Central venous pressure monitoring is not typically required. An arterial line is useful for repeated activated clotting time (ACT) measurements, and on occasion, close monitoring of blood pressure to enable manipulations necessary to manage leakage between the circuit and systemic circulation. A urinary catheter should be inserted. An epidural catheter for postoperative pain management is not typically used.

PVR is measured and saved for comparison after the operation. Similarly, peripheral pulses in the affected extremity are carefully assessed and recorded. Thermistors are placed in the proximal and distal extremity both medially and laterally (e.g., four thermistors) for real-time temperature monitoring during the operation. The extremity is wrapped in heating blankets, leaving the PVR cuff in place. It is necessary to place sterile surgical tubing (or Esmark bandage) around the root of the extremity for later use as a tourniquet.

A preoperative dose of antibiotic is administered. An incision is made over the vessels, with extension if needed for a lymphadenectomy. Axillary lymphadenectomy and iliac/hypogastric lymphadenectomy are performed as a matter of routine during isolated limb perfusion through the axillary or external iliac vessels, respectively. We do not perform superficial femoral lymphadenectomy at time of isolated limb perfusion unless there is clinical evidence of nodal metastases given that the incision used for this lymphadenectomy has high likelihood of infection or dehiscence, especially in a chemotherapy-treated field. Perfusion from an iliac approach does effectively perfuse lymph nodes in the femoral triangle [23]. The vessels are circumferentially

isolated, and small collateral vessels distal to the cannulation sites are tied off. A Steinmann pin is placed into the anterior superior iliac spine to serve as a cleat and prevent slippage of the tourniquet around the root of the extremity. Once the dissection is complete, 350 U/kg heparin is administered to achieve an ACT of over 450 s. The vessels are occluded proximally and distally with either vascular clamps or Rummel tourniquets. The vein and artery are cannulated through a transversely oriented incisions in the vessels, and each held in place with a Rummel tourniquet placed around the distal vessel and cannula, taking care to avoid fracturing any atherosclerotic plaque that is present. The tourniquet around the root of the limb is tightened to occlude superficial collateral vessels in the skin. After confirmation of a therapeutic ACT (longer than 450 s), the cannulas are connected to the extracorporeal circuit, and the roller pump is gradually brought up to the maximum flow rate at which the line pressure acceptable to avoid intimal injury and the reservoir volume does not diminish. Heparin resistance—defined by the inability to achieve therapeutic ACT with typical heparin doses—is typically successfully treated with additional heparin. However, antithrombin III deficiency should be suspected if this maneuver is unsuccessful, in which case use of argatroban instead, or transfusion of fresh frozen plasma or antithrombin is typically effective [24].

Once the extremity has reached the target temperature, melphalan is administered into the arterial side of the circuit based on the planned dose schedule. The heater for the heart-lung machine is adjusted based on the extremity temperatures registered by the thermistors. Isolated perfusion is conducted for the planned time, typically 60 or 90 min, during which time leak monitoring is employed to guide any necessary adjustments. Protocols for drug dosage, drug administration schedule, target temperature, and duration of perfusion differ among centers. After the perfusion is complete, the extremity is rinsed with crystalloid and/or colloid, with the drug-containing venous effluent discarded. The cannulas are removed, and the arteriotomy and venotomy are repaired with vascular sutures, meticulously avoiding narrowing of the vessels. PVR measurements in the distal extremity are obtained, and upon confirmation of a return to baseline, protamine is administered to reverse the effects of heparin. The wound is closed in multiple layers. A drain is left behind if a lymphadenectomy was performed.

In-transit metastases occur most commonly in the lower extremity, and therefore access for HILP is most commonly achieved via the iliac vessels or the femoral vessels. If in-transit metastases are located high in the extremity (e.g., within 6 inches of the inguinal crease), perfusion via the iliac vessels is required to achieve adequate perfusion of the proximal thigh. This operation involves an oblique incision in the lower abdominal wall, followed by incision of the external oblique fascia and splitting of the internal oblique musculature to reveal the transversalis fascia. This is incised, and the abdominal contents are retracted supero-medially to expose the iliac vessels. External iliac and obturator nodes are removed. Note is made of the quality and characteristics of the Doppler signals in the external iliac artery and vein. The hypogastric vein is ligated in situ or controlled with a bulldog vascular clip, and another bulldog clip is placed on the hypogastric artery. The external iliac vessels are followed under the inguinal ligament for as far as possible to allow for identification of small branches, which are clipped or tied off to prevent collateral flow. Removal of the clips on arterial branches at completion of the operation improves blood flow to portions of the healing wound. A drill is used to place a Steinmann pin in the anterior superior iliac spine to hold the tourniquet in place.

For approach to the axillary artery and vein, a generous incision is made in the axilla, and flaps are raised to allow a complete axillary lymphadenectomy. The pectoralis minor muscle is divided below its insertion onto the coracoid process. Level III axillary node are removed, which also provides additional exposure of the axillary vessels. Branches are tied off and divided. The brachial plexus trunks are carefully pushed aside to provide exposure to the artery with minimal disruption to the nerves. A

Table 30.1 Intraoprative leak identification and management

Precordial monitor (if used)	Circuit reservoir	Interpretation	Maneuver
Stable	Stable	Good isolation	None
Stable	Increasing	Systemic blood leaking into circuit	Tighten tourniquet, tilt table to place heart lower than limb (e.g., Trendelenberg position for leg perfusion), lower mean arterial pressure and venous pressure with nitroglycerin infusion, increase circuit flow rate
Increasing	Decreasing	Leakage from circuit into systemic circulation	Tighten tourniquet, tilt table to place heart higher than limb (e.g., reverse Trendelenberg position for leg perfusion), lower circuit flow rate, raise mean arterial pressure with pressor infusion, increase central venous pressure by infusing large amounts of intravenous fluid. If leakage persists, repeat flouresceine dye test to identify previously missed collateral vessels and guide dissection
Increasing	Stable	Two way leakage	Leakage in one direction is from venous collaterals, and leakage in the opposite direction is from arterial collaterals. First, stop leakage from circuit into systemic circulation, and once successful then stop leakage into the circuit. Tighten tourniquet and lower circuit flow rate. If this is unsuccessful, then raise mean arterial pressure with pressor infusion. If precordial monitor is still increasing, then lower mean arterial pressure back to baseline and instead increase central venous pressure by infusion large amounts of intravenous fluid. Once leakage from the circuit into the systemic circulation is stopped, the circuit reservoir should start increasing, in which case next lower the mean arterial pressure or the central venous pressure

Steinmann pin is placed to serve as a cleat for the tourniquet. An alternative approach is to use a retractor connected to the table to hold the tourniquet in place [25].

Specific maneuvers are employed to manage leakage between the circuit and systemic circulation during isolated limb perfusion (Table 30.1). Leakage from the circuit into the systemic circulation typically manifests as loss of volume in the venous reservoir. The route of leakage may be venous collaterals, arterial collaterals, or both. Leakage from the extracorporeal circuit that occurs after drug is administered results in systemic exposure to drug, and a lower concentration in the limb. The first step to manage leakage from the circuit to the systemic circulation is to lower the flow rate, which results in reduced pressure in collateral arteries and veins. The operating table can be tilted into reverse Trendelenberg position to lower the venous pressure in the leg relative to collateral veins. After infusion of fluorescein into the circuit, the skin should be examined with a Woods lamp to search for specific collateral vessels that were missed on initial dissection and can be tied off (e.g., inferior epigastric or circumflex iliac vessels). The systemic mean arterial pressure may be increased by infusion of pressor agents, and the central venous pressure may be increased by infusion of intravenous fluid.

Leakage from the systemic circulation into the isolated circuit manifests as an increase in reservoir volume over time. This results in unintended lowering of the drug concentration, as well as discarding more drug-contaminated blood at the end of the procedure. The first step is to increase the circuit flow rate, simultaneously monitoring outflow pressures to avoid intimal injury. The operating table can be tilted into Tredenlenberg position to raise the venous pressure in the lower limb relative to collateral veins. The central venous pressure and the systemic mean arterial pressure may be lowered by infusion of nitroglycerin.

A complex situation may arise whereby the precordial scintillation monitor suggests ongoing leak, yet the reservoir volume is stable or increasing. This set of observations indicates bi-directional leak, with blood movement into the limb via one set of collateral vessels (i.e., venous) and out of the limb via different collateral vessels (i.e., arterial). The approach to this condition involves simultaneous management of both types of leak (Table 30.1).

Hyperthermia

In Creech's original report, hyperthermia was not used in the isolated limb perfusion circuit, and rather, the treatment was with chemotherapy alone [3]. Subsequent work demonstrated that the combination of chemotherapy with mild hyperthermia produced higher response rates [26]. Hyperthermia during HILP affects cancer cells and non-cancer cell populations within tumors including neovasculature and stromal cells, and normal tissues in the extremity. The addition of hyperthermia clearly increases side effects (e.g., effects on normal tissues). In one study, factors associated with a greater toxicity were tissue temperatures 40 °C or higher, female gender, low pH in the circuit, and perfusion at a proximal level of isolation [27]. However, it is equally clear that tumor cells are more susceptible to adverse effects of hyperthermia compared to normal cells. Results of animal model studies of isolated limb perfusion with versus without hyperthermia suggest added cytotoxicity and increased efficacy with the addition of the hyperthermia [28]. These studies implicated a mechanism of enhanced cytotoxicity of l-phenylalanine mustard with hyperthermia rather than improved drug delivery and uptake. There are no prospective randomized clinical trial results comparing isolated limb perfusion with versus without hyperthermia.

Patient Selection

The most common indication for limb perfusion is *in-transit* metastases. HILP is used for patients with unresectable metastatic melanoma confined to an extremity without evidence of distant metastases. The definition of unresectable is subjective but integrates the frequency of *in-transit* metastases recurrences as well as the number and distribution of metastases. Rapid recurrence of multiple in tumor nodules soon after excision of in-transit metastases indicates that further surgical resection is not warranted, despite being technically achievable. Full staging including PET-CT and head MRI to exclude other metastases should be performed. Patients with peripheral vascular disease are not good candidates for HILP because of a significantly higher risk for toxicity and complications. The presence of peripheral vascular disease is typically evident on preoperative evaluation. Patients with declining performance status or who are unable to ambulate because of comorbidities are poor candidates for HILP.

Prior to effective molecularly targeted and immunotherapies, HILP was recognized as the most effective and appropriate treatment for patients with melanoma recurrences confined to an extremity. However, with advent of effective systemic therapies, most patients are treated with systemic therapy before resorting to HILP. BRAF V600 mutant melanomas are sensitive to targeted therapy using a BRAF inhibitor combined with a MEK inhibitor, with a response rate of 63% and acceptable toxicity [29, 30]. And for patients without BRAF V600 mutations in their melanoma, immune checkpoint inhibitor therapy to block CTLA-4, PD1, or PDL1 is commonly used. Response rates range from 11% with ipilimumab to 61% with ipilimumab and nivolumab [31]. Combined BRAF and MEK inhibitor therapy is typically first-line treatment for unresectable *in-transit* metastases that are BRAF mutant. And immune checkpoint inhibitor immunotherapy is typically first-line treatment for unresectable *in-transit* metastases that are BRAF wild type. HILP is typically considered for patients who progress on these therapies. And it is a good approach for patients who have a contraindication to immunotherapy, such as liver transplant, active colitis, and/or unmanageable and severe toxicity to immunotherapy.

Adjuvant HILP was historically used as adjuvant therapy after resection of high-risk primary

melanomas. A small, prospective randomized control trial conducted at the University of Cologne randomized to excision alone or excision with HILP and demonstrated a remarkable reduction in recurrences in the HILP arm [32]. But subsequently conducted randomize control trials that are of higher quality and larger patient number have convincingly demonstrated lack of benefit of adjuvant HILP. The clinical trial considered definitive in this area was conducted by a consortium of EORTC, WHO, and the North American Perfusion Group (NAPG-1) [23]. Over a period of 10 years, 852 patients were randomized to wide excision alone or wide excision and HILP. HILP-treated patients experienced no benefit in overall survival or time to distant metastasis, though HILP-treated patients benefited from a reduction in incidence of in-transit metastases as first site of recurrence (reduced from 6.6% to 3.3%), and of regional lymph node metastases, with a reduction from 16.7% to 12.6%. Adjuvant HILP was also examined as adjuvant to excision of *in-transit* metastases, and similar to other adjuvant trial results, improvement in regional disease control could be demonstrated but not improvement in overall survival [33]. In summary, HILP is not beneficial as an adjuvant therapy.

Results

The primary agent used by nearly all centers for HILP has been melphalan. Administration schedules differ among centers in drug dose, temperature, and duration of perfusion. Accordingly, it is difficult to reach definitive conclusions about which techniques and schedules are optimal in efficacy and have the least toxicity. The complete response rate for HILP with melphalan alone is in the range of 40–60%, and the overall response rate (e.g., including partial responses) ranges from approximately 60–90% (Table 30.2). For leg perfusions, the melphalan dose varies from 6 mg/L to 10 mg/L of leg volume, or when dose by body weight 0.8 mg/kg to 2 mg/kg of body weight. The dose used for arm perfusions is lower and ranges from 0.45 mg/kg to 0.8 mg/kg. Target limb temperatures vary range from 37° (normothermia) to 42°. Perfusion times vary from 50 to 120 min. Because of heterogeneity in the reports, it is not possible to draw a conclusion about the relationship between dose schedule and response rates. An approach utilizing sequential perfusions via the external iliac and common femoral vessels staged 6 weeks apart has also been used [13]. While the complete response rate with this approach jumped up to 77%, no benefit in overall

Table 30.2 Perfusion schedules and response rates with melphalan alone

Authors	*n*	Melphalan dose leg	Melphalan dose arm	Perfusion duration	Target limb temperature	Complete response rate	Partial response rate	Overall response
Rosin [5]	80	2 mg/kg	N/A	50 min	39–40 °C	21 (26%)	29 (36%)	50 (62%)
Di Filippo [6]	69	1.5 mg/kg	0.8 mg/kg	60 min	41.5 °C	27 (39%)	30 (43%)	57 (82%)
Skene [9]	67	2 mg/kg	N/A	60 min	39–40 °C	N/A	N/A	52 (74%)
Knorr [41]	87	10 mg/L	13 mg/L	90 min	38.5–40 °C	58 (66%)	21 (25%)	79 (91%)
Cornett [40]	58	10 mg/L	13 mg/L	90 min	38.5–40 °C	14 (25%)	22 (38%)	38 (64%)
Klaase [12]	120	10 mg/L	13 mg/L	60 min	37–40 °C	65 (54%)	30 (25%)	95 (79%)
Kroon [13]	43	First: 6 mg/L Second: 9 mg/L	13 mg/L	60 min	37–38 °C	33 (77%)	1 (2%)	34 (79%)

survival was observed relative to patients undergoing a single perfusion.

The heterogeneity among reports in key technical aspects of the procedure makes evaluation of the contribution of hyperthermia challenging. One retrospective analysis compared 218 patients treated with mild hyperthermia (39–40 °C) to 116 patients perfused under normothermic conditions (37–38 °C), in which no benefit in recurrence-free or overall survival was observed [34]. Interpretation of these data are complicated by the observation that other factors varied besides treatment temperature, including differences in number of perfusions. In this study, many of the patients receiving normothermic perfusion received a double perfusion, and double perfusions were associated with a higher response rate than single perfusions [12]. Other factors associated with a higher response rate in this study were negative regional lymph nodes and leg as the site of disease rather than the arm or foot. Another study of 216 patients reported that prognostic factors for survival in order of significance were stage of disease, gender, age, Breslow thickness, Clark level of infiltration of the primary melanoma, and the number of metastases [35]. In a study from Tulane University on 174 patients treated with limb perfusion between 1957 and 1982 including adjuvant treatment, the factors associated with decreased survival rates in patients that also underwent elective lymph node dissection were increasing age, presence of subcutaneous or both subcutaneous and dermal metastases, treatment at normothermic temperatures, or earlier date of treatment [36].

The addition of other agents to melphalan can enhance response rates. Tumor necrosis factor alpha (TNFα) and interferon gamma (IFNγ) appear to be associated with an increased rate of response. In one series, preoperative subcutaneous interferon was combined with a perfusate containing IFNγ 0.2 mg and TNFα 4 mg and melphalan 10 mg/L limb volume for lower extremities, or INFγ 0.2 mg and TNF 3 mg and melphalan 13 mg/L limb volume for upper extremities. The total perfusion treatment time was 90 min, with the melphalan added 30 min into the perfusion. In this phase II study, 90% of melanoma patients treated experienced a complete response, with time to best response achieved in one-third of the time compared to that typically observed with melphalan alone [37]. As is observed in animal models, the tumors liquefied quickly. Toxicity was significant and included cardiovascular instability and ARDS despite the use of prophylactic dopamine infusion. This regimen was evaluated again in a successor phase III trial designed to evaluate the contribution of IFNγ, but the results did not reproduce the extremely high response rates even in the IFNγ-TNFα-melphalan arm [38]. Response rates in absence of IFNγ were lower though this did not reach statistical significance. The addition of TNFα to melphalan appeared to provide superior response rates compared to melphalan alone as observed in historical controls.

A phase III randomized control trial was performed at the National Cancer Institute (NCI) and compared the Lienard triple-drug combination [37] to melphalan alone. An interim analysis revealed a complete response rate of 80% in the triple-drug regimen compared to 61% for the melphalan-alone arm. In another NCI trial, TNFα was dose escalated in combination with the standard melphalan and IFNγ doses [39], and the complete response rate in the 26 patients that received 4-mg TNFα was 76%, with an overall objective response rate of 92%. The complete response rate in the 12 patients that received 6 mg TNFα was 36% with an overall objective response rate of 100%. In the TNFα 6 mg group, regional toxicity was dose-limiting and greater in the group that received TNFα 4 mg, particularly skin blistering, painful myopathy, and neuropathy. The investigators concluded that HILP with TNFα at 4 mg combined with IFN and melphalan was highly effective but considerably less toxic than TNFα at 6 mg.

Subsequent reports of HILP with TNF in a three-drug regimen have been associated a range of complete response and survival rates. With this as a backdrop, the American College of Surgeons Oncology Group conducted an important clinical trial evaluating the effects of TNFα in a two-drug regimen. Patients with in-transit metastases were randomized to melanoma combined with TNFα

or melphalan alone [40]. HILP was completed in 124 patients of the 133 enrolled. Patients in the arm randomized to also receive TNFα experienced significantly greater toxicity. Grade 4 adverse events were observed in 3 of 64 (4%) patients in the melphalan-alone arm compared to 11 of 65 (16%) patients in the melphalan-plus-TNF-alpha arm ($p = .04$). The complete response rate at 3 months were similar: 25% in the melphalan-alone arm and 26% in the melphalan-TNFα arm. The complete response rate at 6 months was higher in patients treated with the TNFα-containing regimen (42%) compared to the melphalan-alone regimen (20%), although this difference did not reach statistical significance. These clinical trial results do not support addition of TNFα to melphalan for treatment of in-transit metastases.

Specific Toxicities and Management

Normal tissues are sensitive to the high concentrations of therapeutic agents, hyperthermia, and mild acidemia. HILP produces toxicities in the form of lymphedema, skin blistering, painful neuralgia, or painful myopathy. The latter two conditions are managed conservatively with gabapentin and analgesics. Leg edema is managed with elevation and compression wraps. Skin blistering is self-limiting and managed conservatively. Muscle injury and swelling is a grave sign because it can lead to compartment syndrome (see below).

Post-operative hypotension resulting from "cytokine storm" may be observed even in the absence of TNFα in the perfusate and requires pressor agents for management. This condition is typically self-limiting and resolves with time. Systemic exposure to melphalan occurs either through leakage during HILP, or after limb vascularization is restored following HILP and melphalan in tissues gains access to the systemic circulation. Systemic melphalan typically causes acute postoperative nausea and emesis, and these symptoms can be effectively managed with ondansetron. Systemic melphalan may also lead to marrow suppression, manifest by neutropenia or pancytopenia 7–14 days after HILP.

HILP-treated limbs temporarily have poor capacity to heal wounds. Surgical wounds and incidental abrasions on an extremity treated with HILP do not heal well for the first 3 months. It is therefore important for the patient to assiduously avoid cuts or skin abrasions in the first few months following HILP. And HILP procedures combined with superficial inguinal lymphadenectomy are at very high risk for wound breakdown. And when wounds do develop on the treated extremity, surgical debridement should be very conservative. Debridement down to healthy tissue is not typically rewarded with subsequent granulation tissue and, rather, most commonly results in simply a larger wound. Surgical debridement should be limited to unroofing areas of purulence.

Post-operative acute vascular compromise is typically a result of technical problems with the vessels following cannulation and de-cannulation. Even a short period of unrecognized post-operative ischemia that results from vascular inflow compromise potentiates the toxicity of the HILP. Thus, diligence in monitoring distal extremity pulses and perfusion is of paramount importance in the immediate post-operative period. For example, technical problems encountered not infrequently are an atherosclerotic plaque that is cracked during the operation or creation of an intimal flap; both may result in post-operative vascular compromise. Unilateral loss of pulses, cool extremity, or evidence of reduced perfusion should be investigated immediately with noninvasive studies (PVR, Doppler) and angiography or CT angiography. Immediate repair of compromised inflow should be the goal. And following restoration of blood flow, careful monitoring for compartment syndrome should be performed by pressure measurements. A two-incision, four-compartment fasciotomy is performed immediately for signs or symptoms of compartment syndrome. Evidence for rhabdomyolysis should be sought by monitoring muscle tenderness, serum CK, and urine myoglobin. If found, maneuvers commonly employed include administration of large volumes of intravenous fluids, sodium bicarbonate, and potentially mannitol.

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31

Isolated Limb Perfusion and Infusion in the Management of In-Transit Melanoma of the Extremities: Modern Data Affecting Practice

Jacob S. Ankeny and Jonathan S. Zager

Introduction

Melanoma, an aggressive cutaneous malignancy, is the 5th most common cancer in men and 6th most common cancer in women in the USA [1]. In 2018, it is estimated that over 91,000 people, in the USA, will be diagnosed with melanoma, a rate that has more than doubled in the past 30 years [1]. Despite a very good overall prognosis secondary to most cases presenting at early stages, more than 9000 deaths from disease occur annually in the USA [1]. A somewhat common presentation of metastatic melanoma is that of locoregional spread including in-transit disease, satellitosis, and regional nodal disease. Satellitosis is defined as intralymphatic metastases that appear within 2 cm of the primary tumor, whereas in-transit disease is outside of 2 cm from the primary tumor and between the primary tumor and regional draining nodal basin [2]. These patterns of recurrence are seen in 2–11% of all patients with melanoma [2–6] and most commonly occur in the extremities. Both are considered stage III disease, regardless of regional nodal involvement, in the latest edition of the American Joint Committee on Cancer (AJCC 8th edition) staging manual and are associated with poor prognosis [2–6].

Management of patients with intralymphatic metastases of the extremities, particularly in-transit disease, can be challenging for physicians and also a significant source of physical and psychological morbidity for patients in regard to bulky lesions, number of lesions, limb threat, ulceration, bleeding, and pain [7, 8]. Fortunately, a number of therapies are available for in-transit disease, thus providing the physician with options for treatment depending on the burden and pattern of recurrence.

Systemic therapies have vastly improved over the past decade with the emergence of immunotherapy (CTLA-4 and PD-1 inhibitors) and targeted agents against BRAF and MEK. In addition to an improved side effect profile over systemic chemotherapy or IL-2, these agents have demonstrated dramatically improved response rates and disease-specific survival when used alone or in combination in a number of trials in patients with BRAF mutant and wild type, stage III, and/or IV melanoma [9–15].

Regardless of the vast improvements gained with immunotherapy and targeted therapy, there are still a significant number of patients that either fail to respond or recur after response to these agents. As a result, local, intralesional, and regional therapies continue to play an important role in the management of in-transit disease to the extremities. Surgery is most appropriate when a lesion or lesions can be completely excised

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Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_31

without the need for amputation, excessive skin grafting, or tissue transfer for wound closure. Radiation can occasionally act as an adjunct to surgery in select cases. Intralesional agents such as the FDA-approved oncolytic virus T-VEC or experimental agents such as PV-10 are more useful in cases of more widespread in-transit disease amenable to injection of each individual lesion. Several trials of T-VEC and PV-10, alone or in combination with immunotherapy, have demonstrated excellent efficacy in terms of response of in-transit disease [16–21].

Despite the above more recent therapies, the most studied methods of regional therapy for in-transit disease to the extremities are hyperthermic isolated limb perfusion (HILP) and isolated limb infusion (ILI). Described in the 1950s and 1990s, respectively, these methods were originally developed in a time when systemic agents led to very poor responses of in-transit disease in the extremities [22, 23]. The theoretical advantage to these methods is the ability to achieve chemotherapeutic drug levels 10–20 times higher than that attainable by systemic drug delivery given the treated extremity is isolated from the systemic vasculature and perfused or infused with high doses of chemotherapeutic agents. Both methods of regional therapy have shown historical benefits in regard to overall response and disease control within the effected extremity [24].

In cases of bulky, symptomatic, or limb-threatening disease, HILP or ILI may provide response and effective symptomatic relief in patients who have disease not amenable to treatment with surgery or intralesional therapies. HILP and ILI are also increasingly being used in combination with other therapies as part of a multimodality approach to improving patient outcomes and attempting to achieve no evidence of disease [25, 26]. As such, both methods still play an important role in the management of regional disease of the extremities.

While a large amount of data exists for the use of both HILP and ILI, most of the data is from retrospective review of prospectively collected databases at single and multiple institutions [27–30]. There are very few clinical trials addressing the use of either method. Thus, the current body of evidence suffers somewhat from heterogeneous patient populations and procedural methods that make comparison of data across the available studies difficult. Additionally, there are no available trials with uniform experimental groups directly comparing the results of HILP to ILI. With the advent of new immune agents and intralesional therapies, it will be important to design studies that better address the role that HILP and ILI should play in the multimodality management of complicated patients with regional disease of the extremities.

This chapter serves to review the available evidence driving clinical practice with HILP and ILI. We will begin with a brief discussion of history and important technical aspects. This will be followed by an in-depth discussion of the available data for both procedures in regard to the chemotherapeutic agents used, clinical outcomes from more recent and larger studies, and data regarding predictive factors, toxicity, and long-term morbidity. We will then address some available comparisons between HILP and ILI followed by discussion of some special clinical scenarios where these therapies may be successfully combined into multimodality treatment approaches.

Hyperthermic Isolated Limb Perfusion (HILP)

History, Technique, and Chemotherapeutic Agents

HILP was originally developed in the 1950s by Creech et al. to treat unresectable in-transit melanoma of the extremities [22]. At the time, response of advanced melanoma to available systemic agents was poor, and the main potentially curative treatment for unresectable melanoma of the extremities was amputation. Some long-term survival occurs with amputation, but at the cost of significant morbidity [31, 32]. Thus, the premise was based on the fact that chemotherapy concentrations in the blood/tissue that could be achieved with HILP were 20–25 times higher than could be achieved with typical systemic administration

[22]. Additionally, given the perfusion was conducted in an extremity isolated from the rest of the body, high systemic toxicity could be avoided. A detailed description of the HILP procedure is described in a separate chapter, but briefly, it involves surgical access to isolate the extremity vessels through incisions. Lymphadenectomy is often performed as part of the procedure. Collaterals are ligated, and the main vessels are cannulated to circulate the blood from the extremity through an extracorporeal circuit that both heats and provides oxygenation. Thus, the procedure is typically hyperthermic and aerobic. Perfusion pressures and flow rates are high, and leak rates are detected during surgery using radiolabeled albumin [33, 34]. The drug of choice for HILP is melphalan given its favorable clinical effect, toxicity profile, and pharmacokinetics. Of note, no single agent to date has shown greater efficacy than melphalan [35–37]. There is some disagreement about whether the addition of tumor necrosis factor-alpha (TNF-α) to the perfusion improves response, particularly in bulkier disease. This is commonly included in HILPs performed outside of the USA. Several historical trials and studies in melanoma HILP have demonstrated improved results with HILP when TNF-α and/or interferon-gamma (INF-γ) have been added to the regimen [38–42]. Two modern series from Italy and the Netherlands have shown improved overall response rate (ORR) and complete response (CR) when using HILP with melphalan and TNF-α compared to melphalan alone [43, 44]. One study showed a particularly strong advantage to using the combination in regard to response in patients with bulky disease defined as more than five in-transit metastases [44]. In contrast, a multicenter phase II randomized trial of HILP with melphalan and TNF-α versus melphalan alone did not show the same results [45]. This US-based study entitled ACOSOG Z0020 analyzed 124 patients randomized to one of the above regimens. Results showed equivalent ORR and CR between the two groups: 69% versus 64% ORR and 26% versus 25% CR, respectively. Unfortunately, patients treated with melphalan plus TNF-α experienced significantly higher toxicity with two patients undergoing toxicity-related amputations [45]. This has created debate as to the true utility of the combination. In addition, the exact dose of TNF-α, whether high or low, has also been debated in regard to which is most effective [46, 47]. As a result of the above findings, TNF-α has not been approved for use in HILP in melanoma in the USA.

HILP Outcomes in Clinical Trials and Modern Single and Multicenter Series

Despite some controversy over drugs used for the procedure, HILP for management of unresectable, in-transit melanoma of the extremities has been around for 60 years. In that time, numerous studies have been conducted at multiple institutions around the world that demonstrate the efficacy in treating advanced melanoma of the extremity [42, 48–51]: sometimes at high cost of morbidity such as lymph leak or lymphocele in almost 30%, and venous thrombosis, wound infection, or long-term edema/limb dysfunction in 1–17% [49, 50]. A systematic review published in 2010 reviewing 22 of the highest quality HILP studies, up to 2008, using mainly melphalan plus TNF-α or melphalan alone, showed ORR of 90% and CR of 58% in patients treated with HILP [52]. Additionally, patients treated with melphalan plus TNF-α had CR rates of 68.9% versus 46.5% in patients treated with melphalan alone [52]. Five-year overall survival (OS) was reported for the group as a whole and was 36%. Median overall survival was 36.7 months in all patients treated, with recurrence rates hovering around 41% [52]. Additionally, limb salvage was achieved in 95–100% of patients [52].

Randomized trials in outcomes of traditional HILP for known in-transit melanoma have been few and far between. The most recent was the phase II trial of melphalan plus TNF-α versus melphalan alone study described above. Other trials have been published, but these have either been small, in abstract form, or have looked at prophylactic HILP in the adjuvant setting and will be discussed in a separate section [39, 40, 53–55]. The remaining data guiding clinical use

Table 31.1 Summary of modern HILP studies and outcomes

Study	Patients (*n*)	Disease stages	Drugs	ORR (%)	CR (%)	PR (%)	Median survival
Moreno-Ramirez et al. [52] Sys. Rev.	2018 ILPs	II, III, IV	Melphalan/ melphalan + TNF	90	58	32	36.7 months
Sanki et al. [56]	111	II, III, IV	Melphalan/ melphalan + TNF	85	69	16	42.7 months
Rossi et al. [43]	112	III	Melphalan/ melphalan + TNF	90	51	39	34.8 months
Deroose et al. [47]	148	III, IV	Melphalan + TNF	89	61	28	24.0 months
Smith et al. [57]	93	III, IV	Melphalan + TNF	82	45	37	21.0 months
Alexander et al. [58]	91	III	Melphalan	95	69	26	47.4 months

HILP Hyperthermic isolated limb perfusion, *ORR* Overall response rate, *CR* Complete response, *PR* Partial response, *ILPs* Isolated limb perfusions, *TNF* Tumor necrosis factor-alpha

have derived from the numerous observational studies that have been conducted as described in the above systematic review. This section will focus on five, melphalan-based, large observational studies from different centers spanning the time since the above systematic review. Important response and survival statistics from these studies and the systematic review can be found in Table 31.1.

The Sydney Melanoma Unit (SMU), now Melanoma Institute Australia (MIA), published a large study looking at 111 patients who underwent HILP with mostly melphalan-based regimens over a 10-year period. They demonstrated outstanding ORR of 85% with 69% CR and 16% PR. Five-year survival was 40% overall in those that achieved an initial CR. Additionally, this study showed interesting results in regard to patients who were able to maintain a long-term CR. Nearly 34% of patients were able to maintain a long-term CR following initial HILP. An additional 22% were able to achieve long-term CR after multiple HILPs (56% total long-term CR). Of the patients who were able to maintain long-term CR, 63% survived 5 years and 49% survived 10 years, while 7% of patients with progressive disease survived 5 years, thus highlighting a biologically favorable group of patients who demonstrate true survival benefit with regional limb therapy, similar to limb amputation. Toxicity was not reported in this study [56].

A series from Italy in 2010 assessed 112 stage III patients who underwent HILP with melphalan ($n = 53$) or melphalan plus TNF-α ($n = 59$) using a 60–90 minute perfusion depending on the drugs used. Response of some kind was seen in 90% of patients with 51% achieving CR and 39% PR. Response rates were higher in patients receiving melphalan plus TNF-α, particularly in those with more than 15 extremity lesions or any lesion more than 3 cm. However, recurrence rate did not differ between groups (~46%) despite a trend toward longer time to progression (22.7 months versus 14.2 months) in patients receiving the two-drug combination. Overall survival was not different between groups (~29% at 5 years with median overall survival of 34.8 months), but patients who achieved a CR had improved survival compared to those who did not. In regard to toxicity, more than 93% of patients experienced Wieberdink grade I–II events with 1% developing compartment syndrome and 1% having treatment-related limb amputation. These more severe toxicities tended to occur in patients who received the two-drug combination [43].

Deroose and colleagues published a series out of the Netherlands in 2012 on 148 patients (stage III and IV) who underwent HILP with melphalan and TNF-α at varying doses for 90 minutes. Response rates were similar to prior series with ORR of 89% with 61% CR and 28% PR. Complete response was higher in patients treated with stage IIIb versus stage IIIc or IV disease, and in high-dose TNF-α compared to low dose. TNF dose did not affect rates of local progression or OS. Among all patients, there was 40% 3-year, 26% 5-year, and 13% 10-year OS with median overall survival of 24 months. Median overall survival improved to 44 months in those achieving CR. Grade IV or

higher toxicity developed in 3%, but there was not an insignificant amount of post-operative morbidity including loss of some limb function in 20% (3% severe) and complications leading to amputation in 2% [47].

The final international study that will be described came from London in 2015. This was a series of 129 patients with melanoma and sarcoma (93 with melanoma) who underwent HILP with melphalan and TNF-α for 60 minutes. Overall response rate was 82%, CR 45%, and PR 37%. The limb salvage rate was greater than 97%, progression-free survival (PFS) 11 months, median overall survival 21 months, and 2-year disease-specific survival was 43%. More than 90% of patients experienced grade II or better toxicity, but long-term outcomes and post-operative complications directly related to the surgical procedure were not reported [57].

Response rates in US studies have been similarly high. The National Cancer Institute (NCI) reviewed HILP with melphalan perfusion for 90 minutes in 91 stage III patients. Overall response rate was 95% with 69% of patients achieving CR and 26% PR. Median in-field progression-free survival was 12.4 months with median overall survival of 47.4 months with 43% and 34% of patients surviving 5 years and 10 years, respectively, thus demonstrating the possibility of long-term survival in this population comparable to what can be obtained with amputation. Response rates did not affect survival. Overall toxicity was relatively low, but post-operative complications and long-term morbidity were not reported [58].

Factors Associated with Response and Toxicity

Given the fair amount of morbidity and toxicity that can occur following HILP, most series attempt to describe factors that predict treatment response and toxicity so as to minimize toxicity, but also to potentially avoid treating those patients that have lower likelihood of response.

Disease burden is a common factor, in most studies, that predicts a CR. Patients with higher stage disease or burden of lesions tend to have lower response rates and OS. Regardless of stage, patients who achieve CR tend to have longer OS [42, 43, 47–51, 56–58]. Other factors that have been implicated to impact response in terms of achieving higher response are younger age, female sex, addition of TNF-α to melphalan-based regimens, and higher dose of TNF-α [42, 43, 47–51, 56–59].

In terms of toxicity, there is some evidence that supports the association of TNF-α with increased toxicity including severe limb dysfunction and limb loss [47, 58]. Peripheral vascular disease in the patient being treated is also a suggested predictor of toxicity in the form of vascular complications following cannulation [50]. Other factors that have been implicated to portend worse toxicity include elevated CK levels, no correction for melphalan dose based on ideal body weight, age less than 60, female sex, and the level of hyperthermia during perfusion, with temperatures more than 41 °C being associated with increased toxicity [33, 60].

Isolated Limb Infusion (ILI)

History, Technique, and Chemotherapeutic Agents

ILI was developed in Australia by Thompson and colleagues in the 1990s as a simple, yet effective alternative to HILP for treatment of in-transit extremity disease without the associated complexity, procedural duration, or risk of complications [23, 61–63]. HILP is a procedure that poses higher risk to patients directly related to the procedural access and open vascular cannulation, particularly in elderly patients and in the setting of repeat procedures for relapse [62–66].

In contrast to HILP, ILI is a minimally invasive technique that involves percutaneous access to the arteriovenous system of the extremities using fluoroscopy and angiography. It does not involve incisions or lymphadenectomy. Infusion is limited to the extremity via pneumatic tourniquet and is circulated with lower flow rates, and for shorter durations than HILP. Hyperthermia

is still used in most institutions, but one other major difference is that HILP is aerobic whereas ILI is hypoxic and acidotic as there is no re-oxygenation of blood via the extracorporeal circuit [23, 33].

Similar to HILP, standard ILI is a melphalan-based treatment due to melphalan's previously described efficacy, favorable toxicity profile, and drug pharmacokinetics. In the hypoxic environment of ILI, melphalan is believed to have enhanced activity against cancer cells based on prior animal models [67]. Additionally, many institutions incorporate actinomycin D into the infusion as it does not add appreciably to toxicity and may have additional benefit when compared to melphalan alone [68]. Other drugs are currently only being used in the setting of clinical trials [69]. As an example, Beasley and colleagues have completed a phase I dose escalation study on the use of temozolomide for ILI in melanoma [69]. Initial results from that study established a maximum tolerated dose that led to very low levels of toxicity with only 5% CR and 16% PR, but likely high ability to be used in multiple repeated infusions to obtain better responses [69]. This group also hopes to look at the role of methylguanine DNA methyltransferase (MGMT) expression levels in helping determine level or likelihood of response in future studies [69].

ILI Outcomes in Clinical Trials and Modern Single and Multicenter Series

Since the introduction of ILI, several retrospective series have demonstrated satisfactory results in terms of response rates and toxicity in patients with demonstrated in-transit disease of the extremities. A systematic review of ILI studies utilizing melphalan plus actinomycin D completed in 2014 showed an ORR of 73%, in 576 patients analyzed, with a CR in 33% and PR in 40% [70]. Even though response rates reported are on the lower end of those reported for HILP [33], they are still comparable, and the procedure is much less complicated for both patient and physician. As a result, there has been increasing adoption of this technique over HILP in multiple centers around the USA and other centers around the world [71].

To date, there has been one phase II clinical trial published on oncologic outcomes of the most common form of ILI with melphalan and actinomycin D [72]. Other clinical trials have been published, but using either different drugs or standard drugs simultaneously with systemic therapy [26, 69, 73, 74]. The remaining data that have guided the adoption of ILI for the treatment of in-transit disease to the extremities come from single-center and multicenter reviews of prospectively collected databases. Table 31.2 shows a

Table 31.2 Summary of modern ILI studies and outcomes

Study	Patients (*n*)	Disease stages	Drugs	ORR (%)	CR (%)	PR (%)	Median survival
Kroon et al. [70] Sys. Rev.	576	I, II, III, IV	Melphalan + actinomycin D	73	33	40	Not reported
Brady et al. [72]	22	III	Melphalan + actinomycin D	50	23	27	Not reported
Steinman et al. [75]	56	III	Melphalan + actinomycin D	45	25	20	36.0 months
Kroon et al. [76]	185	I, II, III, IV	Melphalan + actinomycin D	84	38	46	38.0 months
Coventry et al. [78]	131	III, IV	Melphalan/melphalan + actinomycin D	63	27	36	58.0 months
Kroon et al. [79]	316	I, II, III, IV	Melphalan/ melphalan + actinomycin D	75	33	42	44.0 months
Beasley et al. [80]	128	III, IV	Melphalan + actinomycin D	64	31	33	Not reported
O'Donoghue et al. [30]	148	III	Melphalan + actinomycin D	59	26	33	22.1 months
Miura et al. [82]	687		Melphalan + actinomycin D	64	29	35	38.2 months

ILI Isolated limb infusion, *ORR* Overall response rate, *CR* Complete response, *PR* Partial response

summary of the systematic review and some studies in outcomes of ILI using either melphalan alone or in combination with actinomycin D.

The loan phase II trial published on melphalan-based ILI for the treatment of melanoma was published in 2006 [72]. This trial enrolled 22 patients with stage IIIb or IIIc melanoma based on AJCC 6th Edition criteria. Patients underwent normothermic to mildly hyperthermic infusion with melphalan and actinomycin D for 20 minutes with response assessment occurring 3 months post-procedure. Dosages of the two drugs were somewhat variable during the study as they were initially dosed according to body weight over a range that would allow for dose adjustment based on observed toxicity. Later during the accrual process, an amendment was made that changed dosing to administration based on limb volume measurements. Results showed an ORR of 50%, with 23% of patients achieving CR, and 27% PR. Following CR, the median duration of response was 12 months. It is unclear how the dosing regimen used may have affected these results. In a retrospective follow-up to this trial in 2014, with an additional 34 patients with stage IIIb or IIIc in-transit disease of the extremities and dosing based on limb volume measurements, response rates were similar [75]. Overall response was 45%, with CR in 25%, and PR in 20%. Recurrence-free survival was similar at 11 months. Median overall survival was 36 months with 46% of all patients surviving 5 years. Of note, patients achieving CR showed 91% 5-year survival compared to 34% in patients with lesser responses, likely indicating a group of patients with more favorable tumor biology.

One of the earliest large, single-center studies came from Melanoma Institute Australia (MIA) in 2008 [76]. Similar to the above phase II trial and series, this study employed melphalan and actinomycin D ILI. However, the 185 patients treated in this study underwent hyperthermic ILI with infusion times varying between 20 and 30 minutes. Dosing of the two drugs was more consistent. There was also inclusion of patients with stage IV disease. Overall response rates seen in this study were significantly higher at 84% with 38% CR and 46% PR. In fact, response rates at the MIA are among the highest published in any series for ILI in melanoma. This may be partly related to procedural differences and experience [77], as well as the methods of assessing response as the MIA used World Health Organization criteria as opposed to a set time point. Despite differences in response rates, this series did not show improvements in survival as median response duration was 13 months with median overall survival of 38 months (53 months in those with CR).

A second Australian study published in 2014 [78] analyzed 131 patients in 4 major Australian centers outside of MIA. All institutions followed the MIA protocol for ILI, but one institution used melphalan alone, while the others used both melphalan and actinomycin D. Overall response was 63% with 27% CR and 36% PR. Median overall survival was 58 months, but again varied significantly depending on response (101 months CR, 41 months PR). 50% of all patients survived 5 years. Of note, the patients treated at Princess Alexander Hospital with melphalan alone have been published in a separate manuscript [61] and have response rates lower than those seen at the other hospitals. This difference between melphalan alone and melphalan plus actinomycin D trended toward significance in the combined multicenter analysis. However, this difference in response did not translate to a difference in 5-year survival.

A subsequent 2016 multicenter study examined the original MIA patient population from 2008 (185 patients) in addition to the 131 patients from the 2014 study. In all, there was 75% OR, 33% CR, 42% PR, and median overall survival of 44 months in patients treated at major melanoma centers in Australia [79].

Many series from the USA have also been reported in the literature as the use of ILI has increased [27, 30, 80]. Beasley et al. published the largest multicenter series in the USA in 2009 [80]. They reported on 128 patients, with stage IIIb, IIIc, or IV extremity disease. Patients underwent ILI using melphalan and actinomycin D for 30 minutes. Response outcomes were assessed at 3 months. Similar to one of the Australian multicenter reports, this series showed an ORR of 64% with 31% CR and 33% PR. Survival statistics were not calculated in this series, and, in general, the procedures used for ILI, assessments of response, and patient populations analyzed were variable between institutions. This likely resulted

in the highly variable response rates seen between institutions in the study.

The most recent single institution series was published on 148 patients from the Moffitt Cancer Center who underwent ILI with melphalan and actinomycin D for 30 minutes [30]. Again, response was assessed 3 months post-procedure using response evaluation criteria in solid tumors (RECIST) criteria [81]. Overall, 59% of patients had some response to the treatment with 26% achieving CR and 33% PR. The presence of response of any kind was associated with improved survival statistics. In field progression-free survival was 14.1 months for responders and 3.2 months for non-responders ($p < 0.0001$). Similarly, overall survival was 56 months in responders compared to 26.7 months in non-responders ($p = 0.004$). One interesting aspect of this study is that the patient population spanned 2007–2017 and is the only large study currently published that includes patients treated in the era of immunotherapy and targeted agents. Thus, it includes patients that have failed these highly effective systemic therapies and that may have increased burden of disease in comparison to other series. Analysis of various groups post-ILI was complicated and beyond the scope of the study, but it will be interesting to better understand the role of ILI in the current era of new and more effective systemic agents. In 2019 a multicenter ILI publication by Miura et al. was published looking at long-term outcomes after first time ILI for melanoma. This publication included patients from 9 centers in US and Australia. 687 patients were reveiwed (383 stage IIB and 304 stage IIIC). The overall response rate was 64.1% (complete response [CR], 28.9%; partial response [PR], 35.2%). Stable disease (SD) occurred in 14.5% and progressive disease (PD) in 19.8% of the patients. The median follow-up period was 47 months, with a median OS of 38.2 months. When stratified by response, the patients with a CR or PR had a significantly longer median In field PFS (21.9 vs 3.0 months; $p < 0.0001$), Distant PFS (53.6 vs 12.7 months; $p < 0.0001$), and OS (46.5 vs 24.4 months; $p < 0.0001$) than the nonresponders [82].

In comparing all above described series and the single clinical trial, reported response rates were fairly similar, and, importantly, toxicity and morbidity were generally low. The vast majority of patients experienced Wieberdink grade I–III toxicity, (from no effect to the presence of erythema, blistering, and swelling) and none experienced grade V toxicity requiring amputation [30, 61, 72, 75, 76, 78–80]. There were some studies that reported the need for fasciotomy due to compartment syndrome (grade IV), but only in a very small number of patients. In the Australian multicenter series, the procedure also proved to be safe for elderly patients with rates of toxicity even lower than patients under the age of 75 [83].

Factors Associated with Response and Toxicity

Despite the promise of ILI in relation to the relative simplicity of the procedure compared to HILP, reasonable response rates, and lower overall complication rate compared to HILP, toxicity can still be significant and several groups have analyzed outcomes to identify factors predictive of response and toxicity so as to better optimize the procedure moving forward.

Disease stage and whether or not the patient achieves CR are repeatedly predictive of survival in several studies as described above. In regard to response, several groups have demonstrated the relation of disease burden, whether Breslow depth, disease stage, or actual number/size of lesions, to response rates in that lower burden generally translates to better response [28, 61, 75, 78, 79]. As an example, Muilenburg et al. showed that patients who have more than 10 extremity lesions, or any single lesion more than 2 cm in size, both parameters considered to be high burden of disease (BOD), have worse CR rates of 24% versus 50% with low BOD, and worse progression-free survival of 3.8 months versus 6.9 months with low BOD, compared to patients who don't [28]. Overall survival was 38.4 months in patients with low BOD and 30.9 months in those with high BOD. This difference was not found to be significant between the 2 groups, but did trend toward significance ($p = 0.146$) [28]. Other factors that have been associated with increased response rates include limb volume >8 liters, limb temperature during the procedure >38.5 °C, increased toxicity grade

experienced, younger age, and lower extremity ILI [61, 78, 79, 83].

Dosage of chemotherapy has been shown in multiple studies to correlate with regional toxicity [84, 85]. In one of these studies, grade II toxicity occurred at mean doses of 34.7 mg and 337.1 μg of melphalan, respectively, while grade III and IV toxicity occurred at mean doses of 45.7 mg and 462.8 μg [84]. Beasley and colleagues have also demonstrated that toxicity rates vary depending on upper extremity or lower extremity infusion [86]. Grade III or greater toxicity occurred in 7% of upper extremity ILIs compared to 24% of lower extremity ILIs despite fairly similar rates of CR.

Other factors predictive of increased toxicity have been well described from a multicenter series by Santillan and colleagues [87]. This study looked at 171 patients who underwent ILI in 8 centers in the USA between 2001 and 2008. They subsequently analyzed factors predictive of Wieberdink limb toxicity, CK levels, and length of hospital stay. In regards to limb toxicity, multivariate predictors of grade III or higher toxicity included female sex, use of papaverine, and CK levels higher than 563 U/liter. While a melphalan dose adjusted for ideal body weight (aIBW) was not predictive of limb toxicity on multivariate analysis, failure to use this correction and having lower perfusate pO2s at 30 minutes did predict peak CK levels. In addition, in those patients that had CK levels above 1000, 78% had an unadjusted melphalan dose. Patients also tended to be younger. This adjusted dose of melphalan also predicted an earlier timing of peak CK level post procedure. Location of the ILI in the upper extremity and shorter ischemia times also predicted earlier peaking of the CK level. Finally, hospital length of stay was most influenced by time to peak CK level, absolute peak CK level, and lower extremity ILI [87]. Other series have shown some of these factors to be significant predictors as well [84, 85, 87].

Comparison of HILP and ILI

In looking at the overall comparison between HILP and ILI, it becomes very apparent from the series available that HILP appears to have improved efficacy in terms of response rates and durability of response over ILI, but no difference in overall survival [33, 52, 70]. In addition, it is apparent that both can be completed with reasonable regional toxicity related to the perfusion/infusion, but major differences in direct procedure-related morbidity given the complexity of HILP versus ILI [33, 45, 47, 50, 52, 70]. Unfortunately, no clinical trials exist directly comparing the two methods in equivalent patient populations, and, as a result, comparisons have mainly been made between heterogeneous studies.

Dossett and colleagues published perhaps the largest comparison series when they retrospectively analyzed 203 patients (HILP = 109, ILI = 94) undergoing HILP and ILI in two centers in two countries in 2016. The advantage with this study was that each institution only offered one procedure. Thus, all patients were treated the same in terms of the regional chemotherapy. While it did not eliminate selection bias, this helped to decrease it. They further categorized these patients into subgroups of low burden of disease (less than 10 lesions and no lesion more than 2 cm) and high burden of disease. Overall response rate for HILP was 80% and 53% for ILI. Median overall survival was not different between the 2 groups (46 months for ILI versus 40 months for HILP, $p = 0.31$). In fact, the only multivariate correlates of survival were low disease burden, N stage of disease, and presence of a response to therapy. Interestingly, burden of disease was higher in the ILI group (58% high burden of disease in ILI versus 44% in HILP, $p = 0.04$), and response was lower. Given the equivalence in survival between the two techniques, this may indicate differences in treatment of the patients at each center either before or after the HILP or ILI [29].

Advanced Clinical Uses of Regional Chemotherapy

Despite outstanding response rates and limb salvage rates due to HILP/ILI, effect on survival is questionable, and large numbers of patients still recur systemically. Additionally, multiple new regional and systemic therapies have become available. Thus, it is of increasing clinical importance to

Table 31.3 Summary of modern HILP and ILI studies and outcomes in multimodality settings

Study	Patients (*n*)	Clinical setting	Drugs	Study findings
Hafstrom et al. [53]	69	Routine adjuvant HILP	Melphalan	HILP following complete resection of recurrence did not improve survival ($p = 0.28$)
Koops et al. [55]	832	Routine adjuvant HILP	Melphalan	HILP following complete resection of primary did not improve survival ($p = 0.82$)
Noorda et al. [88]	43	Adjuvant HILP after multiple recurrences	Melphalan/melphalan + TNF/INF	HILP following surgery for 3 or more recurrences increased RFS 4.7 fold ($p < 0.001$)
Wong et al. [25]	176	ILI + surgical excision to obtain CR	Melphalan + actinomycin D	Complete resection after ILI with <CR has the same median survival as CR from ILI alone (not reached vs. 30.9 mo., $p = 0.304$)
Chai et al. [92]	44	Repeat regional CTx	Melphalan/melphalan + actinomycin D	Response rates following an initial procedure were similar. Survival was the same whether ILI or HILP, but HILP ORR higher
Kroon et al. [93]	37	Palliative ILI in metastatic setting	Melphalan + actinomycin D	ILI can be performed for palliative extremity therapy in metastatic patients with 76% ORR, 22% CR, and 86% limb salvage
Beasley et al. [73]	45	ILI + systemic therapy	Melphalan + systemic ADH-1	ORR 60%, CR 38%, PR 22%. These values not different than prior studies using melphalan ILI alone
Beasley et al. [74]	20	ILI + systemic therapy	Melphalan + systemic sorafenib	ORR 35%, CR 15%, PR 20%. Low response rates compared to historic series with significant toxicity
Ariyan et al. [26]	26	ILI + systemic therapy	Melphalan + actinomycin D + systemic ipilimumab	ORR 85%, CR 62%, PR 23%. 1 year PFS 58%. Encouraging results in comparison to ILI alone in most series

HILP Hyperthermic isolated limb perfusion, *ILI* Isolated limb infusion, *ORR* Overall response rate, *CR* Complete response, *PR* Partial response, *PFS* Progression-free survival, *RFS* Recurrence-free survival, *TNF* Tumor necrosis factor-alpha, *INF* Interferon gamma, *CTx* Chemotherapy

include regional intra-arterial chemotherapy as an option in the multimodality approach to melanoma patients with advanced disease of the extremities. As such, several studies have looked at ways to integrate HILP and/or ILI into multimodality treatment plans to improve outcomes in terms of palliation, response, and survival. A summary of the studies in this section, and outcomes in regards to response, etc., can be found in Table 31.3.

Regional Chemotherapy in Combination with Surgery

Multiple groups have conducted trials showing weak results for the use of adjuvant regional chemotherapy following complete resection of isolated extremity disease. Trials by Hafstrom and Koops, in 1991 and 1998, respectively, looked at patients undergoing HILP following surgery in slightly different patient populations [53, 55]. The 1991 trial compared patients with recurrent extremity melanoma that underwent complete resection followed by HILP with melphalan versus those who underwent complete resection alone and failed to demonstrate survival difference despite decrease in time to locoregional recurrence in those who did not undergo perfusion [53]. The authors thus concluded that there was a questionable role for HILP in the adjuvant setting of recurrent extremity melanoma. The 1998 trial compared groups

with primary, intermediate thickness melanoma who underwent either surgery or surgery plus HILP with melphalan. Again, adjuvant HILP improved locoregional recurrence statistics, but failed to improve survival [55]. The authors similarly concluded that there was no role for HILP in the adjuvant setting of those with primary melanoma undergoing complete resection. As such, the use of regional chemotherapy in adjuvant settings following complete resection is not recommended.

However, in the case of patients who have multiple in-limb recurrences of melanoma with shortening of disease-free intervals over time and without distant recurrence, Noorda et al. demonstrated that addition of HILP to these multiple excisions can lengthen the limb recurrence-free interval and potentially provide benefit in these patients in the form of decreased burden of disease with the next in-limb recurrence [88]. In summary, they looked at 43 patients who underwent initial HILP following the 3rd or 4th in-limb recurrence following surgical excision. With each recurrence, they noted that local recurrence-free survival decreased and that addition of HILP increased the subsequent local recurrence-free survival by a factor of 4.7 over the last recurrence-free interval. If lesions were completely resected prior to HILP, the factor of the last recurrence-free interval increased to 5.9. In addition, patients who had HILP following multiply recurrent disease experienced recurrence with 2.6-fold fewer lesions [88].

There is also some evidence for additional clinical benefit of adding surgical excision in patients with recurrent extremity melanoma who have undergone regional chemotherapy with less than complete response. Wong et al. looked at a group of 176 patients with recurrent extremity melanoma who either underwent ILI alone or ILI plus subsequent surgical resection to render the patient no evidence of disease (NED). They found that DFS and median overall survival were similar between patients who experienced a CR with ILI alone versus those who experienced less than CR but subsequently underwent complete resection to NED (i.e., ILI plus surgery) (Median overall survival 30.9 months versus not reached; DFS 9.6 months versus 12.4 months) [25]. This suggests a role for the use of this combination of therapies when needed to achieve an equivalent outcome.

Repeat Regional Chemotherapy

Given patients with recurrent extremity melanoma often have multiple in-limb recurrences, the efficacy of repeat regional chemotherapy and its effects also become of interest. Multiple groups have looked at this in the past and have shown promising results [89–91]. A multicenter experience looking at repeat procedures for both HILP and ILI, and the combination of the two methods, was published in the USA in 2012 [92]. This study again demonstrated increased overall response rates for HILP compared to ILI. More interestingly, they found that repeat ILI after an initial ILI or repeat HILP after an initial HILP carried similar response rates and toxicity risks compared to the initial procedure. Additionally, they found that ILI tended to have very low response rates in recurrences treated with an initial HILP. In contrast, HILP tended to have very high response rates in recurrences treated with an initial ILI. Despite the exact sequence of treatments and differences in response, overall survival was the same [92].

ILI for Palliation in Patients with Systemic Disease

Even in patients with systemic disease, regional chemotherapy can be of benefit. A study from the MIA in 2009 studied 37 patients with metastatic melanoma who underwent ILI with melphalan and actinomycin D for advanced extremity disease. They observed an overall response rate of 76% with 22% CR and 28-month duration of response in those patients achieving complete response. Overall limb salvage rate was 86% [93]. Despite being conducted in an era with poor systemic treatment options, this still supports a palliative role in patients with incurable systemic melanoma and one or more limbs affected by advanced disease.

Melphalan-Based ILIS Combined with Systemic Therapy

With the increasing availability of new and more effective systemic agents, there have been several studies looking at the concurrent use of systemic agents with regional chemotherapy in hopes of augmenting response and improving outcomes. Some of these studies have shown mixed results [73, 74, 94]. A prospective multicenter phase II trial, published in 2011, examined the use of ADH-1, a systemic disruptor of N-cadherin complexes, in combination with melphalan ILI [73]. ADH-1 was given on day 1, ILI completed on day 2, and a second dose of ADH-1 was given on day 8 in 45 patients enrolled from 4 institutions. Overall response rate was 60% with 38% CR and 22% PR, and was not different from prior series with melphalan alone. Tumor response also did not vary depending on tumor N-cadherin expression [73].

A year later, Beasley and colleagues also published a phase I study using systemic sorafenib in combination with melphalan ILI in 20 patients [74]. Overall response rates were low at 35% with 15% CR and 20% PR. In addition, significant toxicity occurred in 4 patients including some cases of compartment syndrome [74].

A phase II clinical trial from 2018 showed more encouraging results in patients who underwent concurrent treatment with systemic ipilimumab in combination with regional chemotherapy in the form of ILI with melphalan and actinomycin D [26]. This study enrolled 26 patients with in-transit extremity disease (stages IIIb, IIIc, and IV). Patients first underwent ILI then were subsequently started on ipilimumab 7–21 days following ILI. Response rates were among the highest ever shown in the USA with OR of 85%, CR of 62%, and PR of 23%. The study is too young to comment on overall survival, but 1 year PFS has been 58% [26].

The above results are indeed exciting and may be the first steps in demonstrating a new multimodality method for improving outcomes in patients with advanced melanoma of the extremities.

Chapter Summary

Advanced extremity melanoma in the form of in-transit disease is a challenging problem for both patient and clinician. It presents issues with both morbidity, associated with locoregional control, and also survival in terms of the large number of patients that ultimately recur systemically.

HILP and ILI are two highly effective regional therapies that have both been around for more than 20 years. They can be used repeatedly, in combination with surgery, and in cases of palliation in patients with more advanced stage IV disease that have high risk of morbidity related to a component of advanced extremity disease. Limb salvage rates approach 90% for both procedures, and there are some long-term survivors, as with amputations, in patients with in-transit disease truly limited to the extremity. Despite this fact, important differences between the two methods exist.

HILP is a much more complex procedure in terms of procedural sequence, resources, and time required. Although its regional toxicity profile is generally well tolerated, it does carry procedure-related risks including lymph leak, lymphocele, wound infection, extremity swelling, and potentially permanent limb dysfunction that can range from mild to severe. Regardless of these pitfalls, it shows very high response rates of over 80% in most series and a high proportion of complete responses. Although more difficult and associated with a high rate of complications, it has been shown to be efficacious with repeated use in patients with in-limb recurrences following prior regional chemotherapy.

ILI is a more simplified procedure that is easier to execute and absorbs less overall time and resources. Its toxicity profile is excellent and generally favorable to HILP. Despite the lower overall response rates and complete response rates documented in the literature, the procedure has equivalent overall survival and also presents some advantages over HILP. It is a simpler procedure to learn, and results have less variation across institutions with variable experience and in both single institution and multicenter studies, possibly due to this fact. It is easier to perform in

repeat fashion, is associated with lower morbidity in older patients, and can easily be used to test new regional perfusion or potentially even new systemic agents [69, 95]. Additionally, the recent development of new agents shows promise with regard to increasing the efficacy of this treatment as described in the previous section [26].

Due to these facts, ILI has become increasingly popular among multiple centers and is currently the first procedure of choice over HILP in many locations. However, HILP should not fall entirely out of favor as it continues to show excellent response rates when administered following either a failed HILP or ILI, and thus represents a potentially important terminal therapy with the goal of limb salvage in patients with advanced melanoma of the extremities.

Future clinical trials of regional chemotherapy alone or in combination with other therapies, particularly new systemic agents, will be an exciting endeavor in the journey to improve outcomes in complicated melanoma of the extremities.

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Trial Data for Sarcoma

32

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Introduction

Soft tissue sarcomas (STS) represent a heterogeneous group of neoplasms that account for about 1% of malignancies in adults [1, 2]. Approximately 50–60% of STS involve the extremities [1]. Historically, patients with high-grade, deep-seated tumors of the extremities underwent amputation, but studies have failed to show improved survival after amputation compared to limb-sparing surgery with radiation [3–5]. The lack of survival benefit with amputation has led to increased interest in limb-preserving therapies. One of the strategies for limb preservation utilizes regional chemotherapy, which includes isolated limb perfusion (ILP) and isolated limb infusion (ILI). Over the last 60 years, these regional therapies have undergone several transformations. Although multi-institutional trials and large cohort patient series are limited, ILP and ILI have been used with some success for regional tumor control in locally advanced STS, palliation of symptoms in the metastatic setting, and to improve feasibility of function-preserving limb salvage surgery in the borderline primary tumor setting.

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Isolated Limb Perfusion

Early ILP Studies

ILP was first described in the 1950s by Creech et al. [6] The initial series of 24 patients treated at Tulane University included nine who were diagnosed with STS, including rhabdomyosarcoma, osteogenic sarcomas, chondrosarcoma, and synovial sarcoma among others. While the technique has evolved in the last 60 years, the basic principles have remained the same. Large cannulas are placed by open surgical technique in the involved extremity's main artery and vein, such as the external iliac, common femoral, and axillary or brachial vessels, and connected to an oxygenated extracorporeal perfusion circuit. A tourniquet is then applied proximal to the site of drug administration to isolate the limb and limit systemic circulation of the drug. Creech et al. used nitrogen or phenylalanine mustard as the chemotherapy agents of choice; other agents have included doxorubicin, actinomycin D, cisplatin, and tumor necrosis factor α (TNFα). Systemic leakage of perfusate has been monitored with radiolabeled albumin. The initial experience with regional chemotherapy showed that it was technically feasible

Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_32

to isolate the limbs from the systemic circulation for targeted drug administration [6].

Despite successful use in melanoma, early experiences with ILP for STS in the 1970s and 1980s were disappointing. In 1977, Krementz et al. published their experience with a large series of STS patients treated at Tulane between 1957 and 1975 [7]. The series included 113 patients diagnosed with more than 20 different histologic subtypes. The application of ILP fell into three categories: 73 patients underwent ILP and surgery, including amputation, for curative intent; 17 patients to convert an otherwise unresectable tumor to one that could be resected in a limb-preserving fashion; and 39 patients with known metastatic disease for palliative therapy and local tumor control. A combination of melphalan, a nitrogen mustard, and actinomycin D were used as the drugs of choice. After the introduction of hyperthermia in the late 1960s [8, 9], perfusion temperature was raised up to 41 °C to potentiate the effects of chemotherapy. Unfortunately, results remained fairly disappointing. Among patients who underwent ILP and surgery for curative intent, 27% developed a local recurrence, and 32% died during the follow-up period [7]. Only 10 of the 17 patients who received ILP for limb preservation were able to avoid amputation, resulting in a limb salvage rate (LSR) of 59%. Among patients with metastatic STS who underwent palliative ILP, the overall response (OR) rate was 33%, although the authors reported amelioration in pain symptoms in a portion of patients.

Early experience with ILP using melphalan and doxorubicin in the Netherlands had similarly poor outcomes [10]. In a cohort of 26 patients diagnosed with various STS histologies, indications for treatment included both adjuvant therapy after surgical resection in 9 patients and locoregional control for tumors that would otherwise require amputation in 17 patients. Among patients who underwent adjuvant ILP, 56% experienced a local recurrence. Although the LSR was not reported, only 23% of patients who underwent ILP for unresectability demonstrated any clinical response. Additionally, local toxicity from ILP was severe: three patients required an amputation due to treatment complications, two suffered chronic stiffness, two had severe blistering, and two experienced limb shortening. Because of the poor outcomes and toxicities observed, the authors reported that the use of ILP was not justifiable until safer and more effective agents could be identified.

Interest in ILP was renewed when Lienard et al. introduced the addition of recombinant TNFα to the standard melphalan regimen in a phase II clinical trial in the early 1990s [11]. TNFα is a cytokine produced primarily by macrophages. Its systemic use was severely limited by fevers and hypotension, and lower doses showed only marginal clinical efficacy [12–16]. The study by Lienard et al. included 23 patients, 4 of whom were diagnosed with STS and the others with melanoma. Short-term outcomes were encouraging. Clinical complete response (CR) was observed in 89% of patients and partial response (PR) in another 11% of patients, resulting in an OR rate of 100%. At 12 months of follow-up, the disease-free survival (DFS) rate was 70%. Local toxicity, as graded by the Wieberdink system (Table 32.1) [17], was less severe than previous reports, with a majority of patients experiencing only mild transient erythema and/or edema and 13% of patients with Grade III toxicity. Systemic side effects, however, were common. Almost all patients experienced fevers and chills post-operatively, and despite prophylactic intraoperative infusion of dopamine, 13% of patients experienced hypotension. Another 48%

Table 32.1 Wieberdink classification of local toxicity [17]

Grade	Reaction
Grade I	No subjective or objective evidence of reaction
Grade II	Slight erythema and/or edema
Grade III	Considerable erythema and/or edema with some blistering; slightly disturbed motility permissible
Grade IV	Extensive epidermolysis and/or obvious damage to the deep tissues causing definite functional disturbances; threatening or manifest compartmental disorders
Grade V	Reaction which may necessitate amputation

of patients had bone marrow failure with neutropenia and thrombocytopenia. The high rate of systemic toxicity correlated with a high systemic leak rate, which was ˃10% in 43% of patients.

Following the encouraging results demonstrated by Lienard et al., a multicenter European study was conducted in 186 patients diagnosed with STS that led to the approval of the use of TNFα in ILP in Europe [18] (Table 32.2). Indications for ILP were better defined than in previous studies. Because the primary treatment goal was limb preservation, only patients judged to have unresectable tumors were included. Unresectability was defined as tumors that would otherwise require amputation or mutilating surgery, such as multifocal primary or multiple recurrent tumors, fixation to and/or invasion of a neurovascular bundle or bone, recurrence in a previously irradiated field, and very large tumors that would be unresectable without amputation or functionally mutilating surgery. Patients with synchronous metastases were also included for local tumor control. Exclusion criteria were debilitating cardiopulmonary disease, coagulopathy, severe peripheral arterial disease, severe lymphedema of the involved extremity, and concurrent immunosuppressive therapy, chemotherapy, or radiotherapy. ILP was performed using melphalan and 3 mg TNFα for upper extremities and 4 mg for lower extremities. IFNγ was also added to the circuit for the first 55 patients in the series. Two to four months after ILP, patients underwent delayed radical resection of the tumor.

In the multicenter study, clinical CR and OR rates were 18% and 75%, respectively, and pathologic CR (100% tumor necrosis) and OR rates were 29% and 82%, respectively. Thirty-four patients required an amputation, resulting in a LSR of 82% after a median follow-up of 2 years. Although a majority of patients suffered Grade II or III local toxicity, the rates of Grade IV and V toxicities were relatively rare at 7.5% and 0.5%, respectively. Severe systemic toxicities were less common than reported by Lienard et al. [11] and included significant hypotension (3.2% of patients), adult respiratory distress syndrome (0.5%), severe renal toxicity (0.5%), severe liver toxicity (9.1%), leukopenia (3.2%), and thrombocytopenia (4.3%).

ILP with Standard-Dose TNFα

Following the multicenter European study, several institutions reported their own experiences with ILP for extremity STS using melphalan and 3/4 mg TNFα [19–26]. Clinical CR rates ranged from 18% [20, 22] to 37% [19] and PR rates from 42% [23] to 64% [20]. In studies that reported pathologic tumor responses, CR rates ranged from 18% [24] to 26% [22], and PR rates (>50–99% tumor necrosis) were 49% [22] to 58% [24]. Jakob et al. categorized pathologic response as >90% and <90% tumor necrosis and reported rates of 37% and 53%, respectively [25]. Of note, the retrospective study by Noorda et al. had particularly low response rates (clinical CR and PR rates of 2% and 47%, respectively; pathologic CR and PR rates of 8% and 29%, respectively) compared to other similar studies [22].

Reported LSR ranged widely from 57% [22] to 93% [20], with most studies reporting rates in mid-70% to mid-80% range [19, 21, 23–25]. The term "limb salvage" is not well defined, and there are likely differences in how this rate is reported. LSR also differs with length of follow-up, decreasing over time as more patients experience local recurrences. In the study by Noorda et al., 73% of patients did not undergo amputation, but the reason for this was progressive metastatic disease in eight patients, and therefore the LSR was only 57% among patients with localized disease [22]. Jakob et al. reported an exceptionally high percentage of patients (96%) who were able to undergo limb-sparing surgeries following ILP, but an additional four patients underwent amputations for post-ILP complications, resulting in a more accurate LSR of 91% [26]. Among patients who underwent limb-sparing surgeries, the local recurrence rate ranged from 14% to 35% [19, 21, 23–25]. Patients who died early in the follow-up period were typically excluded from these calculations. Five-year local recurrence-free survival (LRFS) ranged from 78% to 83% [22, 26].

Table 32.2 Summary of selected ILP and ILI Studies for STS

Study	Year	Country/region	Cohort size[a]	Study type[b]	ILP/ ILI	Time (min)	Agents	CR	OR	LSR
ILP with standard-dose TNFα										
Eggermont et al. [18]	1996	Europe, multicenter	186	T	ILP	90	Melphalan + TNFα 3/4 mg	18%	75%	82%
Gutman et al. [19]	1997	Israel	35	R	ILP		Melphalan + TNFα 3/4 mg	37%	91%	85%
Olieman et al. [20]	1998	Netherlands	34	T	ILP	90	Melphalan + TNFα 3/4 mg w/ radiation	7%[c]	93%	93%
							w/o radiation	58%[c]	95%	79%
Lejeune et al. [21]	2000	Switzerland	22	T	ILP	90	Melphalan + TNFα 3/4 mg	18%	82%	86%
Noorda et al. [22]	2003	Netherlands	49	R	ILP	90	Melphalan + TNFα 3/4 mg	2%	49%	57%
Grunhagen et al. [23]	2006	Netherlands	197	P	ILP	90	Melphalan + TNFα 3/4 mg	18%	69%	87%
Cherix et al. [24]	2008	Netherlands	51	R	ILP		Melphalan + TNFα	25%	67%	76%
Olofsson et al. [25]	2012	Sweden	54	P	ILP	90	Melphalan + TNFα 3/4 mg	21%	71%	76%
Jakob et al. [26]	2014	Germany	90	P	ILP	90	Melphalan + TNFα 3–4 mg lower extremity or 1–2 mg upper extremity	37%[d]	90%	91%
ILP with reduced-dose TNFα										
Di Filippo et al. [28]	1999	Italy	18	T	ILP	60	Doxorubicin + TNFα 0.5–3.3 mg	22%	72%	75%
Grunhagen et al. [29]	2005	Netherlands	48	P	ILP	90	Melphalan + TNFα <3/4 mg	38%	69%	NR
Bonvalot et al. [30]	2005	France	100	T	ILP	60	Melphalan + TNFα 0.5 mg	32%	68%	88%
							TNF 1 mg	40%	56%	80%
							TNF 2 mg	32%	72%	88%
							TNF 3/4 mg	40%	64%	92%
Bonvalot et al. [31]	2009	France	100	P	ILP	60	Melphalan + TNFα 1 mg	30%	79%	87%
Nachmany et al. [32]	2009	Israel	42	R	ILP		Melphalan + TNFα 3/4 mg	22%	65%	76%
							TNFα 1 mg	8%	31%	53%
Hoven-Gondrie et al. [35]	2011	Netherlands	98	R	ILP	90	Melphalan + TNFα 3/4 mg	32%	83%	76%
						60	TNFα 3/4 mg	0%	81%	62%
						60	TNFα 1/2 mg	11%	59%	86%
Deroose et al. [33]	2014	Netherlands	275	P	ILP	90	Melphalan + TNFα 3/4 mg	NR	70%	79%
							TNFα 1/2 mg	NR	69%	
Hayes et al. [36]	2006	United Kingdom	16	P	ILP	60	Melphalan + TNFα 1/2 mg	20%	53%	NR
Smith et al. [37]	2015	United Kingdom	36	P	ILP	60	Melphalan + TNFα 1/2 mg	22%	61%	62%

ILP with non-TNFα regimens										
Rossi et al. [38]	1994	Italy	23	T	ILP	60	Doxorubicin	43%[e]	69%	91%
Eroglu et al. [39]	2000	Turkey	37	R	ILP	60	Doxorubicin + cisplatin	14%	79%	79%
Pennacchioli et al. [40]	2007	Italy	88	R	ILP	60	Melphalan + TNFα 1 mg	41%	96%	67%
						60	Doxorubicin + TNFα 1 mg			
						90	Melphalan	19%	84%	51%
						90	Doxorubicin			
Wray et al. [41]	2011	United States	29	T	ILP	90	Melphalan + TNFα	6%	70%	41%
							Doxorubicin	0%	0%	20%
Rastrelli et al. [42]	2016	Italy	117	R	ILP	90	Doxorubicin	NR	72%	78%
						90	Doxorubicin + TNFα 3/4 mg	NR	79%	
						60	Melphalan + TNFα 3/4 mg	NR	75%	
ILI studies										
Hegazy et al. [53]	2006	Egypt	40	P	ILI	15–25	Doxorubicin	38%[d]	80%[f]	82%
Moncrieff et al. [50]	2008	Australia	21	P	ILI	20–30	Melphalan + actinomycin D[g]	57%	90%	76%
Turaga et al. [46]	2011	United States, multicenter	14	R	ILI	30	Melphalan + actinomycin D	17%	75%	78%
Wong et al. [51]	2013	United States	24	P	ILI	30	Melphalan + actinomycin D	16%	63%	NR
Mullinax et al. [52]	2017	United States, Australia, multicenter	77	R	ILI	30	Melphalan + actinomycin D	30%	58%	78%

ILP isolated limb perfusion, *ILI* isolated limb infusion, *CR* complete response, *OR* overall response, *LSR* limb salvage rate, *TNFα* tumor necrosis factor alpha, *NR* not reported

[a]Number of patients with soft tissue sarcomas included in the study

[b]T = trial, R = retrospective study, P = retrospective review of prospectively collected database

[c]Patients selected for adjuvant radiation based on extent of tumor necrosis seen on histopathologic evaluation

[d]Defined as >90% tumor necrosis

[e]Defined as >75% tumor necrosis

[f]Defined as >60% tumor necrosis

[g]Melphalan and actinomycin D were the primary agents used, but three patients received mitomycin C and one received mitomycin C, doxorubicin, and cisplatin

Survival after ILP has been inconsistently reported. Three studies found 5-year overall survival (OS) rates to be 44–49% with a large proportion of patients succumbing to metastatic progression of disease [23–25]. Five-year disease-specific survival (DSS) rates fell into a similar range of 48–69% [22, 26]. Median DFS was only a little over 1 year: 12.5 months in the study by Lejeune et al. [21] and 14.9 months in the study by Cherix et al. [24] Jakob et al. found 2- and 5-year metastasis-free survival (MFS) rates of 63% and 55%, respectively [26].

Local toxicity has been well characterized according to the Wieberdink system [17]. Grade II toxicity was common and ranged from 63% to all patients [19, 21–26]. Grade IV and V toxicity were generally rare, ranging from 0% [21] to 7.8% [25] of patients. Reasons for complication-related amputations were typically liquefactive necrosis and subsequent sepsis [19, 26] or severe compartment syndrome [24, 26]. Systemic complications after ILP were less consistently characterized. Most studies reported at least transient fevers, hypotension, mild elevations in liver enzymes or creatinine, and leukopenia and thrombocytopenia in a majority of patients [19, 21, 24, 25]. Gutman et al. found that high flow rates in their early perfusions correlated with leak rates >10% and more severe systemic symptoms [19].

ILP with Low-Dose TNFα

After the initial success with TNFα-based ILP, attention was turned toward determining the optimal TNFα dose. The original doses of 3 mg and 4 mg TNFα for upper and lower extremities, respectively, were arbitrarily selected based on ten times the maximum tolerated dose in humans [27]. An Italian phase I trial of 18 patients with unresectable STS underwent ILP with doxorubicin and 0.5 mg, 1.0 mg, 1.6 mg, 2.4 mg, and 3.3 mg TNFα [28]. Four patients achieved 100% tumor necrosis, three with 90–95%, four with 80%, and two with 70%. There was no difference in pathologic tumor response by TNFα dose, and 100% tumor necrosis was found in one of the five patients who had received 0.5 mg TNFα and two of the four patients who received 1.0 mg TNFα. The overall LSR was 75%, with two patients from the 0.5 mg TNFα group and all four patients in the 1.0 mg TNFα group able to undergo limb-preserving surgery. In addition to providing equivalent short-term outcomes, low-dose TNFα also seemed to cause less severe local toxicity. While six (66.6%) of the nine patients receiving >1.0 mg TNFα suffered a Grade III-IV reaction, only four (44.4%) of the nine patients in the 0.5–1.0 mg TNFα group had a severe reaction.

In 2005, a study was published evaluating melphalan with reduced (defined as <3/4 mg) versus standard-dose (3/4 mg) TNFα in patients with melanoma and non-melanoma soft tissue malignancies [29]. Among the 240 patients with non-melanoma soft tissue malignancies treated at the Netherlands institution, 48 underwent ILP with reduced-dose TNFα. Patients received lower doses of TNFα in a non-randomized manner for leakage problems and after a change in practice at the institution. The study found no difference in systemic toxicity between the reduced and standard-dose TNFα cohorts (P = 0.62) and a trend toward decreased local toxicity in the reduced-dose group (P = 0.14). Among non-melanoma patients in particular, there was also no significant difference in clinical OR rates between reduced and standard-dose TNFα (69% versus 74%, P = 0.47), 5-year local progression rates (44% versus 59%, P = 0.27), 5-year systemic progression rates (45% versus 50%, P = 0.58), and 5-year OS rates (36% versus 47%, P = 0.69).

Efficacy of lower doses of TNFα was further validated in a phase II trial that randomized 100 patients with unresectable STS to 4 different doses of TNFα (0.5 mg, 1 mg, 2 mg, and 3/4 mg) with 25 patients in each cohort [30]. The groups did not differ in clinical CR rates (32%, 40%, 32%, and 40% for 0.5 mg, 1 mg, 2 mg, and 3/4 mg, respectively, P = 0.71) or clinical OR rates (68%, 56%, 72%, and 64%, P = 0.93). The study also found similar LSRs (88%, 80%, 88%, and 92% for 0.5 mg, 1 mg, 2 mg, and 3/4 mg, respectively), 2-year local recurrence rates (27%, 95% Confidence Interval (CI) 18–38%), 2-year

DFS rates (49%, 95% CI 39–59%), and 2-year OS rates (82%, 95% CI 73–89%) by TNFα dose. Local toxicity rates also did not differ by TNFα dose, tumor location, or irradiation prior to ILP. However, only patients who received higher doses experienced systemic side effects, such as low blood pressure requiring fluid resuscitation (five patients receiving 2 and 3/4 mg TNFα) or pressor support (one patient receiving 3/4 mg TNFα). In a subsequent analysis of a prospectively maintained database from the same group consisting of 100 patients with advanced STS, the efficacy of 1 mg TNFα was further confirmed [31]. Clinical CR rate was 30%, and OR rate was 79%; the LSR was 87%; and 3-year DFS rate was 67%, and OS rate was 89%, comparable to studies using standard-dose TNFα [19, 21, 23–26].

Several retrospective studies have also compared outcomes between low- and standard-dose TNFα. In a retrospective study of 26 patients who underwent ILP with 3/4 mg TNFα (1997–1999) and 17 patients who received 1 mg TNFα (2000–2006), Nachmany et al. found a higher pathologic OR rate in the high-dose than the low-dose group (65.2% versus 30.7%, $P < 0.05$), but this did not translate into a significantly higher LSR (76.0% in high-dose versus 53.3% in low-dose group, $P = NS$) [32]. However, time to local recurrence was significantly shorter in the low-dose than high-dose group (8.18 versus 28 months, $P < 0.05$). Expanding upon their previous experience [29], the Netherlands group published their results with high- and low-dose TNFα in 2014 [33]. Two hundred seventy-five patients with unresectable STS underwent ILP with 3/4 mg TNFα between 1991 and 2003 and 1/2 mg TNFα between 2003 and 2012. Similar to their previous findings, there was a trend toward decreased local toxicity in the low-dose group that did not reach statistical significance (23% versus 14% Grade III-V toxicity, $P = 0.086$). Although there was no difference in the clinical OR rate (70% high dose versus 69% low dose, $P = 0.873$), there was a significantly higher rate of pathologic response in the high-dose cohort (51% versus 26% with ≥50% tumor necrosis, $P = 0.007$). However, the difference in the pathologic response rates did not translate into differences in local recurrence rate (66% high dose versus 70% low dose, $P = 0.949$) or OS (HR 0.99, $P = 0.978$).

In addition to reduced TNFα dose, studies have assessed the effect of decreasing perfusion time from 90 minutes to 60 minutes. Decreased perfusion time was based on the fact that, although TNFα concentrations remained stable throughout the perfusion period, melphalan effect decreased significantly in the last 30 minutes [34]. Perfusion duration of 60 minutes with 1 mg TNFα showed good short-term outcomes [28, 31]. In a retrospective study with median follow-up time of 76 months (range 4–203 months), Hoven-Gondrie et al. compared 102 perfusions divided into three groups: (A) 90-minute perfusion with 3/4 mg TNFα ($N = 59$), (B) 60-minute perfusion with 3/4 mg TNFα ($N = 16$), and (C) 60-minute perfusion with 1/2 mg TNFα ($N = 27$) [35]. Although longer perfusion time with 3/4 mg TNFα resulted in higher response rates, especially with respect to CR rates (32.2% versus 0.0% versus 11.1% for groups A, B, and C, $P = 0.05$), there was no difference in the ability to perform an R0 resection (82.7% versus 62.5% versus 79.2%, $P = 0.3$) or in LSR (76.3% versus 62.5% versus 85.2%, $P = 0.2$). In a multivariate analysis, reduction in duration and TNFα dose had no effect on 5-year LRFS ($P = 0.1$). Five-year MFS (56.1% versus 47.1% versus 36.4%, $P = 0.9$) and DSS (55.4% versus 52.2% versus 57.3%, $P = 0.9$) were also not significantly different. While reduction in duration and dose had no impact on outcome, it also did not decrease leak rates ($P = 0.7$) or toxicities.

ILP for Palliation

While the long-term results of ILP as induction prior to limb-sparing surgery has been favorable, its use for palliation without subsequent surgery has been less promising. In a small study from the United Kingdom, 16 patients diagnosed with STS underwent ILP with 1/2 mg TNFα between 2000 and 2004 [36]. Although the clinical CR rate of 20% and OR rate of 53% were comparable to findings from other studies [18, 22, 24, 29, 30, 32, 33, 35], the results were not durable.

Seventy-one percent of patients experienced local progression after a median time of only 5 months (range 1–17 months), and 27% of patients underwent an amputation following ILP. In a subsequent study of 36 STS patients treated between 2005 and 2015 at the same institution, the results were similar [37]. The CR rate was 22.2%, and OR rate was 61.1%. Twelve of 36 patients developed disease progression and required an amputation, resulting in a LSR of 62%. The 2-year local PFS was 16.6%, and the median PFS time was only 12 months.

ILP with Non-TNFα Regimens

Since the introduction of ILP with TNFα [11], several European and American centers have continued to perform ILP with non-TNFα regimens. While early studies of ILP performed without TNFα showed poor results [7, 10], more recent studies have shown greater success, especially in combination with higher degrees of hyperthermia. In a phase II trial of 23 patients with advanced STS, Rossi et al. used doxorubicin as a single agent for hyperthermic ILP performed at 40.5–42 °C [38]. Clinical tumor response ≥50% was achieved in 69% of patients. While limb-preserving surgery was able to be performed in 91% of patients, 27.3% (6 patients) developed a local recurrence after a short follow-up period, and two of three patients who did not have concurrent distant disease progression underwent an amputation for local tumor control.

Eroglu et al. performed ILP with cisplatin and doxorubicin in 37 patients with unresectable Grade 2–3 STS at a perfusion temperature of 41–42 °C [39]. Combining clinical and pathologic responses, the objective OR rate was 78.6%. Among 14 patients who received ILP for induction, 11 (78.6%) were able to undergo limb-preserving surgery, comparable to the LSRs reported for TNFα-based ILP [18, 24, 25, 28, 32, 33, 35]. The five-year OS rate was 62% and DFS rate was 54%.

Several single-center studies have compared their experiences with TNFα and non-TNFα-based ILP. While some studies found that TNFα-based regimens were associated with improved clinical outcomes, others did not. An Italian retrospective study compared outcomes for patients undergoing ILP with four different chemotherapy regimens [40]. Among 88 patients with unresectable STS, 33 underwent ILP with melphalan and 1 mg TNFα, 18 received doxorubicin and 1 mg TNFα, 18 received melphalan alone, and 19 received doxorubicin alone. The TNFα-based regimens were performed at 38–40 °C and the non-TNFα regimens at 40–41 °C. Patients who received TNFα achieved higher CR (41% versus 19%, $P < 0.05$) and OR rates (96% versus 84%, $P < 0.05$) compared to non-TNFα regimens. Improved responses also translated into better local tumor control and limb preservation in the TNFα group: unadjusted LSR was 67% in the TNFα group versus 51% in the non-TNFα group. In a multivariate Cox regression model, while there was a trend toward improved local DFS with TNFα, this was not statistically significant (HR 0.8, 95% CI 0.4–1.8).

While the overall outcomes were poor in the phase I/II trials of ILP performed at MD Anderson Cancer Center, patients who underwent ILP with melphalan and TNFα seemed to have better outcomes than those who received doxorubicin monotherapy [41]. The study included 17 patients who received melphalan and TNFα in a phase II trial between 1995 and 1997 and 12 patients who received doxorubicin in a phase I trial between 2001 and 2003. The inclusion (diagnosis of unresectable STS as previously defined [18], age >16 years, ECOG 0 or 1, and normal cardiac function) and exclusion (synchronous metastasis) criteria were the same in both trials. Among patients who received melphalan and TNFα, the clinical OR rate was 70%. None of the patients in the doxorubicin trial achieved clinical CR or PR, with only 17% of patients experiencing a minor treatment response. While the LSR was low in both trials, it was higher in the TNFα (41%) than the doxorubicin (20%) trial. Patients who received doxorubicin also had a shorter DFS of 2.7 months (95% CI 0.83–4.6 months) compared to 4 months (95% CI 3.9–4.1 months) for the TNFα group. The authors hypothesized that the relatively high proportion of patients with

recurrent STS treated at the center may explain the poor outcomes compared to other studies. Of note, a lesser degree of hyperthermia (38–40 °C) was used in this study compared to others utilizing non-TNFα agents [38–40, 42].

In an update to the Italian phase II trial of doxorubicin-based ILP [38], Rastrelli et al. did not find significantly different outcomes in ILP performed with or without TNFα [42]. However, because treatment strategy at the institution differed over time and patients were not randomized to treatment groups, direct comparisons between treatment groups are difficult to make. The study included 117 patients who underwent ILP between 1989 and 2013. Over time, three different regimens were used: doxorubicin monotherapy for 90-minute perfusion between 1989 and 1998 ($N = 47$ patients), doxorubicin and 3/4 mg TNFα for 90-minute perfusion between 1999 and 2003 ($N = 30$), and finally, melphalan and 1 mg TNFα for 60-minute perfusion since 2004 ($N = 40$). Among 115 evaluable patients, the clinical OR rate was 81.7%, of which the CR rate was only 1.7%. All three regimens had similar OR rates: 72.3% for doxorubicin alone, 78.6% for doxorubicin and TNFα, and 75.0% for melphalan and TNFα. Pathologic OR rate was 76.5% with no significant difference by treatment strategy ($P = 0.501$). Limb salvage was achieved in 77.8% of patients. Five-year local PFS rates were also similar: 78.4% for doxorubicin alone, 84.0% for doxorubicin and TNFα, and 79.5% for melphalan and TNFα ($P = 0.47$). Local and systemic toxicity were rare in all cohorts, with one patient in the doxorubicin and TNFα group requiring amputation on post-perfusion day three for Grade V toxicity and one patient in the melphalan and TNFα group who died within 30 days with refractory bone marrow aplasia.

In a meta-analysis of 19 contemporary studies of ILP and ILI for STS published since the year 2000, Neuwirth et al. also found no difference in outcome by treatment regimen [43]. The OR rates did not differ between TNFα-based treatments and others (73.5% versus 72.5%, $P = 0.74$). The overall LSR for TNFα-based regimens was 71.0% (95% CI 69.1–74.8%) and did not differ from regimens using melphalan with or without actinomycin (77.7%, 95% CI 68.8–85.0%, $P = 0.14$) or doxorubicin (80.5%, 95% CI 70.6–88.2%, $P = 0.06$).

Isolated Limb Infusion

ILI: A Simpler Alternative to ILP?

Thompson et al. at the Sydney Melanoma Unit first introduced ILI in the 1990s as a minimally invasive alternative to ILP [44]. Preoperatively, limb volumes are measured by a water displacement method [45] or calculated based on serial circumferential limb measurements [46]. Arterial and venous catheters are inserted by Seldinger technique. A tourniquet is then placed proximally to isolate the limb and avoid systemic leakage. Patients receive prophylactic anti-thrombotic therapy preoperatively and are fully heparinized in the operating room. The chemotherapeutic drugs are added to the infusate and injected via the arterial catheter. Manual recirculation of the infusate is performed using a syringe with a three-way stopcock or one-way valves to ensure unidirectional flow. Blood is withdrawn repeatedly from the venous catheter and reinjected into the arterial catheter to maintain circulation.

Several important differences exist between ILP and ILI techniques (Table 32.3). First, ILI is less invasive as the relevant arteries and veins of the extremity are accessed percutaneously rather than by open surgical technique. This facilitates vascular access in patients with peripheral vascular disease and after prior lymph node dissection, conditions that could make vascular access in ILP challenging, and allows for repeated sequential treatment [45]. Because infusion is delivered manually rather than via an extracorporeal perfusion circuit, flow is significantly reduced, and risk of leakage into the systemic circuit is small. In fact, there is less direct monitoring of potential leakage in ILI as in ILP, so TNFα is generally not used [47, 48]. Additionally, the infusion in ILI is not performed using an oxygenating chamber, necessitating shorter treatment times under progressively ischemic conditions [45]. The resulting progressively hypoxic and acidotic conditions

Table 32.3 Comparison of ILP and ILI [45, 47, 48]

	ILP	ILI
Vascular access	Open surgical technique	Percutaneous technique
Circulation	Extracorporeal perfusion circuit	Manually with syringe
Oxygenated circuit	Yes	No
Flow rate	High	Low
Leak monitoring	Yes	No
Perfusion/infusion time	60–90 minutes	15–30 minutes
Common chemotherapy agents	Melphalan ± TNFα Doxorubicin	Melphalan + actinomycin D doxorubicin

may increase response to chemotherapy [49], but can also potentiate ischemia and tissue damage, limiting duration of treatment [45]. The infusion time of 15–30 minutes is much shorter compared to 60–90 minutes used for ILP. Significant hyperthermia is also not achieved as the external warming coil is limited by the relatively small arterial and venous catheters [45].

Thompson et al. reported their initial experience with ILI performed with melphalan and actinomycin D in nine patients diagnosed with STS [45]. Clinical CR was achieved in one (11%), and PR was achieved in four (44%) patients, resulting in an OR rate of 55%. While temporary limb erythema and edema were common, systemic side effects, such as bone marrow suppression, were rare. In this small cohort of patients, full evaluation of clinical outcomes was difficult to perform.

ILI Outcomes

The Sydney Melanoma Unit published an updated report of their experience with ILI in 2008 [50]. The study included 21 patients with unresectable STS who underwent ILI between 1994 and 2007: 14 as an induction therapy prior to tumor resection and 7 for palliation. Different chemotherapeutic agents were used over time. The majority of patients received melphalan and actinomycin D, three received melphalan and mitomycin C, and one received mitomycin C, doxorubicin, and cisplatin. Tumor responses were encouraging: clinical CR was seen in 57% and PR in 33% of patients, resulting in an OR rate of 90%. Among those patients who underwent ILI as induction therapy, clinical CR and OR rates were 65% and 100%, respectively. The overall LSR was 76%, within the range of 57–91% reported for ILP [18–26, 28, 31–33, 35, 37, 38, 40]. While the overall local recurrence rate was 42%, when combined with post-ILI tumor resection, this decreased to 21%, comparable to the experience with ILP combined with surgical resection (11–37%) [7, 18–21, 23–26, 28, 31, 33, 35, 38, 40]. Complete tumor excision was significantly associated with a lower local recurrence rate (HR 0.20, $P = 0.013$). With a median follow-up time of 28 months, the DSS rate was 62%.

A five-center retrospective study was published in 2011 of the ILI experience in the United States [46]. The study included 26 infusions performed with melphalan and actinomycin D for 22 patients, 14 of whom were diagnosed with STS and 8 with non-melanoma cutaneous malignancies, including Merkel cell carcinoma and squamous cell carcinoma. The clinical OR rate for STS patients was 75%. A subsequent study of 24 STS patients from one of the centers, Moffitt Cancer Center, demonstrated OR in 63% of patients [51]. While these response rates were lower than that achieved in the Sydney cohort [50], the LSR was similar at 78%. Unlike the Sydney cohort, the majority of patients in the American studies underwent ILI as primary therapy without subsequent tumor resection. Despite this, very few patients required amputation, and many had at least short-term stable disease. The Moffitt study also demonstrated that repeat ILI was feasible after disease progression and achieved similar response rates as initial ILI ($P = 0.9$) [51]. Finally, there was less severe local

toxicity experienced in the American study compared to the Sydney study: no patients had Grade IV to V toxicity in the American reports [46, 51] compared to 14% in the study by Moncrieff et al. [50] The difference in local toxicity may be due to adjustment of chemotherapy dosing by ideal body weight rather than the observed weight.

The combined American and Australian experience with melphalan/actinomycin D ILI was reported in a multicenter retrospective study consisting of 77 patients with locally advanced STS [52]. Local toxicity was Grade I-II in 60% of patients and Grade III-V in 40% of patients. Clinical OR rate was 58.4%, significantly lower for ILI performed in upper than lower extremities (36.8% versus 65.5%, $P = 0.0277$). There was no significant difference in OR between patients who experience high-grade versus low-grade toxicity (66.7% versus 54.4%, $P = 0.2855$). The overall LSR was 77.9% with a large proportion of patients undergoing ILI without post-procedure tumor resection. Patients who experienced treatment response had significantly longer median LRFS (16.9 versus 2.7 months, $P < 0.001$), distant MFS (not reached versus 13.6 months, $P = 0.02$), and DSS (not reached versus 32.2 months, $P = 0.2$), but no difference in median OS (44.3 versus 32.2 months, $P = 0.9$). A contemporary cohort of 71 patients treated with amputation for STS at Moffitt was also evaluated for comparison. In the amputation group, survival outcomes were similar with median distant MFS of 6.4 months and OS not reached.

ILI has also been performed with doxorubicin in a series of 40 STS patients in Egypt [53]. Unlike the American and Australian studies, all patients underwent ILI followed by radiation and tumor resection. Grade II to III local toxicity was experienced by 30% of patients; there were no Grade IV or V toxicities. Although there was no clinical CR, PR was apparent in 30% of patients. On histopathologic assessment, >90% tumor necrosis was present in 37.5% of patients. Despite the relatively low response rates, the LSR of 82.5% and local recurrence rate of 13.3% (median follow-up 15 months) are comparable to ILP studies [7, 18–22, 24–26, 28, 31–33, 35, 37, 38, 40, 47].

No randomized trial of ILP and ILI has been or is likely to ever be performed, so it is difficult to directly compare the outcomes of these two regional chemotherapy techniques. In a meta-analysis of ILP and ILI for STS, Neuwirth et al. found that ILI resulted in higher unadjusted LSRs than ILP (78.9% versus 71.0%, $P = 0.03$) among patients who did not receive TNFα [43]. Additionally, unadjusted for patient and tumor factors, ILI was associated with higher CR rates than non-TNFα-based ILP (40.2% versus 10.1%, $P < 0.001$), although the OR rates were similar (71.8% for ILI versus 73.3% for ILP, $P = 0.77$). To what extent these differences reflect patient or tumor factors versus differences in technique is difficult to discern.

Radiation Following Regional Chemotherapy

The role of adjuvant radiation following regional chemotherapy for STS remains controversial. No randomized controlled trial has been performed to address this question. In a non-randomized phase II trial, Olieman et al. compared the outcomes of those who received TNFα-based ILP with adjuvant radiation versus ILP alone [20]. Fifteen patients who underwent ILP with curative intent received adjuvant 60–70 Gray external beam radiotherapy if histopathologic assessment of their tumor resection showed incomplete tumor necrosis. Patients who had distant metastases ($N = 5$) or those who had pathologic CR ($N = 14$) did not receive adjuvant radiation. Uncontrolled for differences in patient and tumor factors, the resulting LSR was higher in the radiation than the no radiation group (93% versus 79%). The unadjusted rate of local recurrence after a median follow-up of 34 months was also significantly lower in patients who received radiation (0% versus 21%, $P < 0.05$).

Radiotherapy has additionally been associated with better outcomes in several retrospective studies. Eroglu et al. found that patients who received adjuvant radiation had improved rates of 5-year OS (82% versus 21%, $P = 0.0013$) and DFS (82% versus 17%, $P = 0.0002$) in univariate analyses

[39]. In a multivariable Cox proportional hazards model, radiotherapy remained an independent predictor of improved 5-year DFS (HR 5.5, 95% CI 1.7–17.3, $P = 0.0014$). Pennacchioli et al. also found increased 5-year local DFS rate of 79.3% in the radiation group compared to 55.4% in the non-radiation group, but this difference was not statistically significant in multivariable analysis (HR 0.5, 95% CI 0.1–1.6) [40].

While these results suggest that radiation may potentiate the effect of regional chemotherapy in maintaining local tumor control, its routine use in this setting may not be justified. Deroose et al. found similar local outcomes in patients who had >50% tumor necrosis after ILP and were able to undergo R0 resection with (0%) or without radiation (3.6%) [33]. Among patients who underwent ILI, Moncrieff et al. did not identify radiotherapy as an independent predictor of improved OS, DFS, or local recurrence rate [50].

Outcomes by Histology

Diverse STS histologies are included in every study with regional chemotherapy, and rarely are outcomes stratified by histology as most studies are too small to achieve sufficient numbers of patients in each cohort. The most common subtypes reported in studies of ILP and ILI are malignant fibrous histiocytoma (more recently classified as undifferentiated pleomorphic sarcoma or UPS), liposarcoma, synovial sarcoma, and leiomyosarcoma [43]. Several studies have reported on comparison of outcomes following ILP or ILI stratified by histology. Among patients who underwent ILI, Moncrieff et al. reported that the UPS subtype, which represented 48% of histologies in the study, was associated with significantly lower chance of local recurrence compared to other histologic subtypes (HR 8.38 (95% CI 1.41–24.15), $P = 0.015$) [50]. Using a multivariable Cox proportional hazards model, the UPS subtype was also an independent predictor of decreased local recurrence and increased DFS. In a study of histopathologic regression after TNFα-based ILP, Grabellus et al. also identified UPS, leiomyosarcomas, and clear cell sarcomas as subtypes that demonstrated high levels of tumor regression [54]. On the other hand, liposarcomas, sarcomas not otherwise specified, synovial sarcomas, and malignant peripheral nerve sheath tumors showed little regression. On the contrary, Rastrelli et al. identified clear cell sarcomas among the histologies that uniformly demonstrated no clinical response and <50% tumor necrosis after ILP [42]. This group of poor responders also included epithelioid sarcoma, osteogenic sarcoma, and extraskeletal myxoid chondrosarcoma. All seven patients with lymphangiosarcoma, on the other hand, achieved pathologic CR. Similarly, Pennacchioli et al. found poor local control in patients with multifocal epithelioid and clear cell sarcomas after ILP [40]. In a multivariable analysis, patients with multifocal epithelioid and clear cell sarcomas had more than double the rate of local recurrence compared to other histologies (HR 2.2, 95% CI 1.02–4.9). Moreover, their 5-year local DFS rate was 49.9% compared to 67.3% for other groups.

Future Directions

While no large trials of ILP and ILI have been performed, data from small phase I/II trials, retrospective studies, and meta-analyses support the selective use of regional chemotherapy for local tumor control in STS. A number of different ILP regimens have been employed over time, but the most common agents currently in use are melphalan and 1 mg TNFα. In the United States, where TNFα is no longer approved for regional chemotherapy, non-TNFα-based ILI is more commonly used. Although no randomized trial has been performed comparing the two regional chemotherapy strategies (ILP versus ILI), no difference in oncologic outcomes was demonstrated in a meta-analysis of ILI and non-TNFα ILP. Across institutions performing ILP and ILI, there have been significant variations in patient selection, tumor histology, and the use of adjunctive therapies, such as adjuvant radiation and systemic therapy. Further studies are needed to better define the patient populations most likely to benefit from treatment and to stratify outcomes

by STS subtypes. Moreover, studies combining regional and systemic delivery of drugs may help to achieve more durable local and distant control of disease. Finally, systems of regional drug delivery provide an optimal setting for the study and discovery of new drugs to treat STS, for which there is an urgent need.

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Part VI

Other Regional Therapies

Regional Therapy of Bladder Tumors

33

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Introduction

Bladder cancer is a one of the more commonly treated malignancies treated by urologists. In 2018, an estimated 81,190 new cases of bladder cancer (62,380 in men and 18,810 in women) were diagnosed with approximately 17,240 deaths (12,520 men and 4720 women) [1]. Bladder cancer is the fourth most common cancer in men and 11th most common cancer in women in the United States. The male to female ratio is 4:1, with approximately 1 in 26 males and 1 in 87 females developing bladder cancer over the course of their lifetime [1]. Of these cases, approximately 70% were diagnosed as non-muscle-invasive bladder cancer [2, 3]. The staple of management of localized bladder cancer remains transurethral resection of bladder tumor (TURBT) in order to stage patients and remove all visible tumor to the depth of the muscularis propria [4–6]. Further management involves intravesical chemotherapy and immunotherapy, extirpative surgery, or chemoradiation depending on the clinical stage, grade, and underlying histological features of the cancer. In this chapter, we will review the presentation, diagnosis, and management of localized bladder cancer specifically focusing on intravesical therapies when clinically appropriate.

Etiology

Bladder cancer has several multiple risk factors. The most well-known and important acquired risk factor is smoking, with current smokers having double the relative risk for developing bladder cancer [7]. The precise mechanism by which smoking leads to bladder cancer is postulated to be due to exposure of carcinogens to the urothelium. Occupational exposures to chemicals such as aromatic amines, aromatic hydrocarbons, and other carcinogens contribute to roughly 20% of all bladder cancers [8–10]. Radiation therapy to the pelvis for other malignancies also is an important risk factors for bladder cancer, with a hazard ratio of 1.7 [11]. Though uncommon in the United States, infection by the parasite *S. haematobium* is associated with an increased risk of squamous cell carcinoma of the bladder [12]. Further acquired risk factors are related to occupational exposures [13].

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Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_33

Clinical Presentation and Diagnostic Assessment

Hematuria is the most common presenting symptom in patients with bladder cancer, both visible and nonvisible (NVH). Any incidence of gross hematuria as well as microscopic hematuria after ruling out benign causes should prompt a urologic evaluation [14]. In the adult population, bladder cancer is found on initial evaluation in 13–34.5% of patients with gross (macroscopic) hematuria and 0.5–10.5% of patients with microscopic hematuria [15, 16] For NVH, reported rates of bladder cancer range from 0.5% to 10.5% [17–19]. For any patient in whom urothelial cancer is suspected, workup includes assessment of the upper and lower urinary tract.

Lower Tract

Cystoscopy, which is the endoscopic evaluation of the bladder and urethra, remains the standard examination for the evaluation of the lower urinary tract. Cystoscopy is indicated for any patient with visible hematuria and on all patients with NVH aged 35 years and older per current American Urologic Association guidelines (AUA) [5, 20]. Conventional cystoscopy is a valuable technique to visualize tumors in the lower urinary tract; however, small tumor and flat lesions can be difficult to visualize completely on conventional white light cystoscopy, especially as at presentation most patients present with a solitary lesion less than 15 mm [21].

Newer technologies have been incorporated to aid in the detection of small and flat lesions such as enhanced cystoscopy using either narrow band imaging (NBI) or blue-light cystoscopy (known as photodynamic diagnosis). Photoactive porphyrins accumulate preferentially in neoplastic tissue; blue-light cystoscopy is performed by injecting hexaminolevulinate hydrochloride prior to cystoscopy. Under blue light, these accumulated porphyrins emit red fluorescence which can help diagnosing smaller lesions. A recent meta-analysis showed that blue-light cystoscopy can improve the rate of detection of Ta (non-invasive papillary) tumors (odds ratio [OR] 4.90, 95% CI 1.94–12.39) and carcinoma in situ lesions (OR 12.3, 6.34–24.13) and was associated with lower recurrence rates from up to 12 months in patients with T2 or CIS lesions (relative risk[RR] 0.70, 85% CI 048–1.00; $p = 0.05$) and Ta tumors (RR 0.80, 0.65–0.99; $p = 0.040$) [22].

Another imaging technology is narrow band imaging, which filters white light into two bands in the blue and green spectrums. These penetrate tissue superficially but are absorbed by hemoglobin, highlighting areas of increased vascularity. One meta-analysis showed that the pooled sensitivity and specificity for diagnosing bladder cancer were 0.943 and 0.847 with an AUC of 0.98 [23]. A further meta-analysis examining outcomes of RCT showed no difference between recurrence rate of cancer using blue light compared to NBI (OR 1.11, 95% CI [0.26–2.1]) with resection occurring at a lower rate than using conventional white light cystoscopy [24]. This suggests that enhanced cystoscopy plays an important role in the diagnosis, treatment, and surveillance of bladder cancer.

Upper Tract

In cases of hematuria and possible bladder cancer, investigation of upper tracts is recommended. Multiphase CT scan of abdomen/pelvis (known as CT urogram) to include an excretory phase is the recommended investigation to fully evaluate for other causes of hematuria such as urolithiasis, renal mass, and infection [25]. CT urography allows for visualization of collecting system and ureter with a sensitivity of 0.87, specificity of 0.99, positive predictive value of 0.91, and a negative predictive value of 0.98 [26]. If kidney function precludes contrast-enhanced imaging, MRI [27] and retrograde pyelography are acceptable alternative options.

Urinary Markers

Several urinary markers are available as adjuncts for the diagnosis and follow-up of bladder cancer.

Table 33.1 Urine biomarkers

Marker	Method for detection	Sensitivity (%)	Specificity (%)
NMP22	ELISA	56	86
UroVysion	FISH	69–87	89–96
MicroRNA	RT-PCR	75	75
Epigenetic marker	Methylation-specific PCR	79–92	87–90
Mutation	NGS	70	97
Cytology	Pathology	48	94

The most common of which is urine cytology in order to detect neoplastic cells in the urine. However, currently it is not recommended by the AUA for an initial hematuria workup due to poor specificity and cost.

Other markers used include nuclear matrix protein 22, UroVysion fluorescence in situ hybridization, microRNAs, and epigenetic markers (Table 33.1). None have supplanted cytology and play a limited role in the diagnosis and monitoring of bladder cancer [28].

Grade and Stage of Urothelial Carcinoma

As noted previously, roughly 70% of patients who initially present with bladder cancer have non-muscle-invasive bladder cancer with the remaining 30% with muscle-invasive or metastatic disease. Furthermore, about 50% of non-muscle-invasive bladder cancer is diagnosed as low grade [29].

Grading

For NMIBC, grading remains an important prognostic factor. The original grading system for urothelial carcinoma was introduced in 1973 by the WHO [30]. Currently, the 2016 WHO grading system categorizes urothelial carcinoma into three categories: papillary urothelial neoplasm of low malignant potential (PUNLMP), low grade or high grade based on cellular architecture, and cytological atypia [31–33].

Staging

The most important prognostic factor for bladder cancer is the stage, which is based on tumor depth and metastasis [34]. Clinical staging is based on bimanual examination at time of TURBT, cystoscopy, and cross-sectional imaging. Accurate pathologic staging requires sampling of urothelium, tumor, as well as detrusor muscle in order to determine depth of invasion. The diagnosis of pT2 disease differentiates non-muscle-invasive bladder carcinoma (T1 and below) from muscle-invasive bladder carcinoma (T2 and above), which has implications for further treatment. Clinical stage T3 is defined as a palpable mass on bimanual examination after complete TURBT or clear extravesical extension on cross-sectional imaging. Likewise, diagnosis of T3 is another important step in staging as this indicates upstaging from organ-confined to non-organ-confined disease [35] (Table 33.2) [36].

Histological Variants/Histology

Urothelial carcinoma is the predominant histology of bladder cancer [36]. Urothelial cancer arises from the uroepithelial cells lining the bladder (previously known as transitional cells). Other histologies are squamous cell carcinoma (3–7% of bladder cancers in the United States.), adenocarcinoma (<2% of bladder cancers in the United States). It is important to note that histological variants are not limited to the bladder and therefore can be present in other sites. Therefore, metastasis from other organs should be considered and immunohistochemistry can be helpful to confirm a urothelial origin [37–42]. Histological variants tend to be aggressive and diagnosed at an advanced stage with extravesical disease and metastasis. Therefore, it is a recommendation from the 2017 AUA guidelines that an experienced genitourinary pathologist reviews the pathology when variant histology is suspected or if muscle invasion is equivocal [20].

Table 33.2 AJCC bladder cancer staging

Stage		Characteristics
Primary tumor		
Tx		Primary tumor unknown
T0		No evidence of primary tumor
Ta		Noninvasive primary tumor
Tis		Carcinoma in situ (CIS)
T1		Invades lamina propria
T2	T2a	Invades detrusor muscle superficially
	T2b	Invades detrusor muscle deeply
T3	T3a	Invades peri-vesical fat microscopically
	T3b	Invades peri-vesical fat macroscopically
T4	T4a	Invades prostate or vagina/uterus
	T4b	Invades pelvic side wall or abdominal wall
Regional lymph nodes		
Nx		Lymph nodes unknown
N0		No cancer in nodes
N1		1 positive pelvic node
N2		≥ 2 positive pelvic nodes
N3		Positive common iliac nodes
Distant metastasis		
Mx		Unknown metastasis
M0		No metastasis
M1		Distant organ or non-regional metastasis

From Amin, M. B., American Joint Committee on Cancer & American Cancer Society. *AJCC Cancer Staging Manual*. Eight edition/editor-in-chief, Mahul B. Amin, MD, FCAP; editors, Stephen B. Edge, MD, FACS and 16 others; Donna M. Gress, RHIT, CTR—Technical editor; Laura R. Meyer, CAPM—Managing editor. Edn, (American Joint Committee on Cancer, Springer, 2017); used with permission

Management of NMIBC

Risk Stratification

The management of bladder cancer is determined by stratifying based on risk of recurrence and progression. Reported overall 5-year rates of recurrence for NMIBC ranges from 50% to 70%, with 5-year rates of progression ranging from 10% to 30% [43]. In order to help stratify patients risk of recurrence, two calculators have been used, the European Organization for Research and Treatment of Cancer (EORTC) risk calculator and the Spanish Urological Club for Oncological Treatment/Club Urologico Espanol de Tratamiento Oncologico (CUETO) [44, 45]. Features at risk for recurrence taken into consideration by these calculators are tumor size, number of tumors, grade, stage, presence of CIS, and prior recurrence. The AUA non-muscle-invasive guideline uses these factors but also adding the presence of lymphovascular invasion, prostatic urethral involvement, presence of variant histology, and poor response to BCG [20]. These factors are used to classify patients into low, intermediate, or high risk for recurrence and progression and help guide further management [44, 46–48] (Table 33.3).

Transurethral Resection of Bladder Tumor (TURBT)

The first step in managing bladder cancer is to remove all visible and suspected tumors. Transurethral resection of bladder tumor (TURBT) is performed endoscopically using a resectoscope with a cutting loop either uni- or bipolar energy. The patient is positioned in lithotomy, and general or spinal anesthesia is typically used. TURBT can be done using either a monopolar or bipolar energy source. The bladder is distended and careful, systemic resection is performed with the goal removal of all visible tumor

Table 33.3 Risk stratification

Low risk	Low-grade solitary Ta ≤3 cm
	Papillary urothelial neoplasm of low malignant potential
Intermediate risk	Recurrence within 1 year, low-grade Ta
	Solitary low-grade Ta >3 cm
	Low-grade Ta, multifocal
	High-grade Ta ≤3 cm
	Low-grade T1
High risk	High-grade T1
	Any recurrent, high-grade Ta
	High-grade Ta, >3 cm (or multifocal)
	Any carcinoma in situ
	Any BCG failure in high-grade patient
	Any variant histology
	Any lymphovascular invasion
	Any high-grade prostatic urethral involvement

Adapted from Chang et al. [20]; used with permission

with adequate depth of resection to include the muscularis propria. Care must be taken to avoid the obturator reflex, which can lead to sudden leg adduction and risk of perforation. This can be ameliorated by using paralysis, decreasing current and avoiding resection while bladder is over distended. Deep biopsies and resections can be sent separately. For small resections, a urethral catheter can be avoided, but for larger resections a catheter is typically left in place for maximal drainage. It is important to perform bimanual examination of the bladder at this time, as presence of a fixed or persistent palpable mass after resection suggests non-organ-confined disease.

In patients found to have high-risk, high-grade Ta tumors, evidence suggests that a repeat resection should be performed within 6 weeks of initial TURBT as residual tumor can be found in up to 50% of patients with up to 15% of tumors being upstaged [49–51]. Furthermore, patients found to have T1 disease should undergo repeat TURBT as well as upstaging rates have been reported to be as high as 30–40% [49].

First-Line Intravesical Chemotherapy and Intravesical Immunotherapy

Intravesical Immunotherapy: BCG

The Bacillus Calmette-Guérin (BCG) vaccine is a live attenuated strain of *Mycobacterium bovis*. Initially studied as possible immunotherapy the landmark study by Morales et al. in 1976, it has become a mainstay for intravesical treatment of bladder cancer [52] and was approved by the US Food and Drug Administration for use in 1990. The postulated mechanism of action is a local immune response, with an influx of immunogenic cells followed by induced cytokines which result in antitumor activity [53]. The most successful and recommended regimen remains the one detailed in the Southwest Oncology Group 8507 study, which consisted of an induction course of 6 weeks of intravesical BCG, followed three weekly instillations at 3 and 6 months, and every 6 months for a total of 3 years [54]. This regimen lead to a reduction in disease progression by 37% and has been validated by other randomized controlled trials which show reduction in progression by 23–27% [55–57].

Because BCG is a live bacteria, it is important to minimize risk of intravasation of live bacteria by performing a urinalysis prior to instillation, avoiding instillation traumatic catheterization, and avoid treatment while an active urinary tract infection is present. Due to the immune response, BCG treatment does have side effects to monitor. The most common is adverse effect is BCG cystitis, with some studies noting rates as high as 53.8% [58]. In a study by Brausi et al., in a total of 1316 patients started on BCG, 62.8% experienced local side effects vs 30.6% systemic side effects. Of the systemic side effects, malaise was reported in 15.5% and fever in 8.1%, with sepsis occurring in 0.3%. For local side effects, BCG can be held until symptoms resolve. For fevers >38.5 °C for 12–24 hours, treatment should be isoniazid 300 mg for 3 months and can resume BCG once asymptomatic. If patients experience severe fever >39 °C, they should undergo combination therapy for tuberculosis with INH, rifampin, and ethambutol with no further BCG treatment. If experiencing above with signs of sepsis, it is imperative to start antituberculosis antibiotics immediately along with steroid therapy and inpatient admission [59].

Postoperative Intravesical Therapy for Low-Risk NMIBC

Current guidelines recommendation from the AUA and EAU for low-risk patients with NMIBC is for a single, immediate instillation of intravesical chemotherapy (mitomycin, epirubicin, or gemcitabine) within 6 hours of TURBT. A meta-analysis of randomized trials showed benefit for patients with low- and intermediate-risk disease (hazard ratio [HR] 0.65, 95% CI 0.48–0.74) but not in patients with high-risk disease or more than one previous recurrence per year [60] Overall estimates for recurrence for TURBT alone compared to TURBT and perioperative intravesical chemotherapy are 20 vs 10% at 12 months, and 25 vs 15% at 24 months [61].

Current use of intravesical chemotherapy after TURBT in the United States is limited [62]. Recently, clinical trial data suggests that

intravesical gemcitabine following TURBT reduces the risk of recurrence in patients with low-risk NMIBC. In the United States., mitomycin is the most common chemotherapeutic agent, but there are concerns of drug availability, side effects, and cost [62–65]. Intravesical gemcitabine is well tolerated and less expensive than mitomycin [66]. Though no head-to-head comparison exists between the two agents, gemcitabine has the potential to become an option for NMIBC.

Intermediate-Risk NMIBC

The intermediate-risk group is more heterogeneous. In addition to an immediate postoperative dose of intravesical therapy, additional intravesical therapy can be considered based on patient's recurrence risk, symptomology, and toxicity of therapy. Meta-analyses of BCG, mitomycin, doxorubicin, and epirubicin all decrease risk of recurrence [67]. One of the most recent meta-analyses showed a 32% reduction in recurrence risk for BCG vs mitomycin maintenance therapy [68]. A large RCT was performed to answer the question of duration for BCG in both intermediate- and high-risk NMIBC. For the intermediate-risk group, no further improvement of outcome was noted in 3 vs 1 year of maintenance therapy [69].

High-Risk NMIBC

For high-risk disease, guidelines recommend induction intravesical BCG followed by maintenance therapy [4, 20]. All experts currently recommend maintenance therapy, with EAU guidelines recommending at least 1 year of maintenance therapy. The best results have been obtained by the Southwest Oncology Group (SWOG) 8507 schedule [6, 54]. Randomized clinical trial data support the use of maintenance BCG delivered for a full 3 years compared to intravesical chemotherapy for improved recurrence-free survival (HR 1.61; 95% CI, 1.13–2.3) [68]. However, the added benefit of 3 years of BCG maintenance therapy must be weighed with toxicity of treatment [69].

Unresponsive or Relapsing After BCG

Intravesical immunotherapy failure can be divided into three categories: no response to BCG (BCG-refractory disease), relapse after BCG, and BCG intolerance [61, 70]. To facilitate selection for clinical trial enrollment, the "BCG unresponsive" category has been adopted by the International Bladder Cancer Group and the American Society of Clinical Oncology GU Cancers group [61, 71, 72]. This category contains BCG-refractory disease (as noted above) and patients with relapsing BCG within 6 months of last exposure to BCG. This category of patients is at highest risk of progression and recurrence and does not benefit from any continued BCG, and should be recommended for radical cystectomy. Patients with late BCG relapse can undergo a trial of salvage intravesical treatment with repeat induction course of BCG, BCG with interferon, gemcitabine, or valrubicin [73].

Second-Line, Salvage, and Rescue Intravesical Therapy Options

Conventional Intravesical Chemotherapy (Mitomycin, Valrubicin)

The role of conventional intravesical chemotherapy in BCG-failure patients is limited. Valrubicin is the only FDA-approved intravesical medication for BCG-refractory CIS. Response rates are low, with only a 21% complete response rate at 3 and 6 months, and only 9% remain disease free at 2 years [74]. This agent is not commonly used in practice and is not currently recommended.

Chemohyperthermia

The use of hyperthermia in combination with intravesical mitomycin is referred to as chemohyperthermia. The rationale for its use is that enhanced mitomycin absorption is possible when the bladder is warmed to 42 °C [75]. One working group examined 51 patients with CIS who underwent weekly chemohyperthermia treatments for 6–8 weeks, followed by 4–6 treatments every 6–8 weeks. Complete response rate was 92% and remained 50% at 2 years [76]. In a recent systematic review, a 59% relative reduction by chemohyperthermia was seen compared to mitomycin alone, with an overall bladder preservation rate of 87.6% [77]. Although chemohyper-

thermia has shown promising results, further studies are needed.

Alternative Single Agent Chemotherapy (Gemcitabine, Docetaxel)

Randomized studies of BCG-failure patients have compared the efficacy and toxicity of intravesical gemcitabine vs mitomycin and a second cycle of BCG [78, 79]. At 36 months after a 6-week course of gemcitabine, 72% patients were recurrence free and had a lower rate of chemical cystitis compared to 61% of patients who received mitomcyin [78]. A phase II study comparing gemcitabine to a second cycle of BCG showed 52% of patients treated with gemcitabine had disease recurrence compared to 88% of patients treated with a second course of BCG [79].

Intravesical docetaxel has also been investigated for BCG-failure NMIBC. A small phase I trial of 18 patients with BCG failure underwent a 6-week course of intravesical docetaxel and had a complete response of 56% and a 4-year durable response rate of 22% [80]. A further extension of this study included an additional 36 patients plus monthly maintenance for 1 year. Response rates at 1 and 3 years were 40% and 25%, respectively [81].

Combination Chemotherapies (Gemcitabine + Mitomycin and Gemcitabine + Docetaxel)

Another modality being investigated in the management of BCG failure is intravesical multiagent chemotherapy. One study showed that a combination of sequential mitomycin followed by gemcitabine in 10 patients showed 6 patients without recurrence at a median time of 14 months [82]. Another multi-institutional study of 47 patients treated with sequential therapy had a 1- and 2-year recurrence-free survival of 48% and 38%, with the finding that only 10 patients required cystectomy [83]. Another study of 27 patients who received 6–8 weeks induction course of gemcitabine and mitomycin resulted with 10 patients (37%) found to have no evidence of disease at a median follow-up of 22 months [84].

Sequential gemcitabine and docetaxel are another combination that has been investigated in BCG-failure patients. One study enrolled a total of 45 patients (of whom 41 had prior BCG) and was treated with a 6-week induction course of intravesical sequential gemcitabine and docetaxel, followed with monthly maintenance therapy for 2 years. Overall response rates were 66% at 3 months, 54% at 1 year, and 34% at 2 years [85]. Another study similar results for high-risk NMIBC patients treated with combination gemcitabine and docetaxel, with a 1- and 2-year recurrence-free survival rate of 56% and 42% [85]. Results with combination gemcitabine and docetaxel show promise, but the optimal sequence or agents have yet to be determined. Table 33.4 highlights different intravesical agents and reported response rates in the literature. Figure 33.1 highlights flow diagram on the treatment of bladder cancer.

Management of Muscle-Invasive Bladder Cancer

Radical cystectomy and bilateral pelvic lymphadenectomy preceded by neoadjuvant cisplatin-based chemotherapy is the gold standard treatment for MIBC. Options for urinary diversion range from an ileal conduit to an orthotopic neobladder. To determine if orthotopic diversion is possible, it is imperative that intraoperative frozen sections of bladder neck and prostatic urethra to rule out cancer at the apical urethral margin.

As lymphatic drainage from the bladder proceeds in a bilateral manner, a bilateral pelvic lymphadenectomy is necessary. A complete pelvic lymphadenectomy should be performed [86].

Radical cystectomy, as noted before, has high rates of morbidity, with a reported 90-day mortality rate as high as 9% in some series [87, 88]. Radical cystectomy can be performed via an open or minimally invasive approach. Several randomized controlled trials have shown no differences in morbidity or length of hospital stay for open vs robotic-assisted cystectomy [89, 90].

Table 33.4 Response rates of conventional and investigational salvage intravesical therapies

Agent	Indication	Risk group	Estimated decrease in recurrence	Standard (S)/ investigational (I)
Intravesical immunotherapy				
BCG	Induction and maintenance	Intermediate risk High risk	46% [67] 44% [67]	S
Intravesical chemotherapy				
Mitomycin	Post TURBT	Low risk	10–15% [94]	S
Epirubicin	Post TURBT	Low risk	10–15% [94]	S
Thiotepa	Post TURBT	Low risk	10–15% [94]	S
Gemcitabine	Post TURBT	Low risk	47% [66]	I
Valrubicin	BCG failure	BCG failure (CIS only)	4% [95]	S
Mitomycin (chemohyperthermia)	Post TURBT	BCG failure	59% (vs MMC) disease-free survival [77]	I
Docetaxel	Salvage	BCG failure	25% (disease-free survival) [81]	I
Gemcitabine	Salvage	BCG failure	21% (disease-free survival) [96]	I
Combination therapy				
Mitomycin + gemcitabine	Salvage	BCG failure	37% (disease-free survival) [84]	I
Gemcitabine + docetaxel	Salvage	BCG failure	34% (disease-free survival) [85]	I

Bladder-Sparing Trimodal Therapy

Select patients with muscle-invasive bladder cancer who wish to spare their bladder are possible candidates for trimodal therapy. This consists of complete TURBT of all gross disease followed by concurrent radiotherapy and radiosensitizing chemotherapy [91]. A key concept in a bladder-sparing approach is that decision to remove bladder can be deferred until the response to organ-sparing therapy is assessed. Patient selection criteria are important, and the ideal patient should have conventional urothelial histology, minimally invasive T2 disease, complete resection of tumor, absence of tumor-associated hydronephrosis, no carcinoma in situ, and good pretreatment bladder function [92].

For appropriately selected patients, outcomes of trimodal therapy can be successful. Data from trials show that up to 70% of patients who undergo trimodal therapy can achieve a complete response and retain their native bladder [92, 93]. Five-year disease-specific survival rates range from 65% to 70% [92, 93].

After receiving systemic therapy, lifelong cystoscopy surveillance is imperative [93]. Serial cytological examinations and cystoscopies are required, in addition to imaging and laboratory studies. Local recurrences are treated on extent of disease at time of relapse. Tis, Ta, T1 tumors can be managed with resection and intravesical BCG or cystectomy.

Follow-Up

Surveillance remains an important aspect of management of bladder cancer, as both non-muscle-invasive and muscle-invasive bladder cancers tend to have high rates of recurrence. In non-muscle-invasive bladder cancer, overall risk of recurrence after 5 years remains 50–90%, whereas risk of progression is 10–30%, with low-grade lesions having lower rates than high-grade and CIS

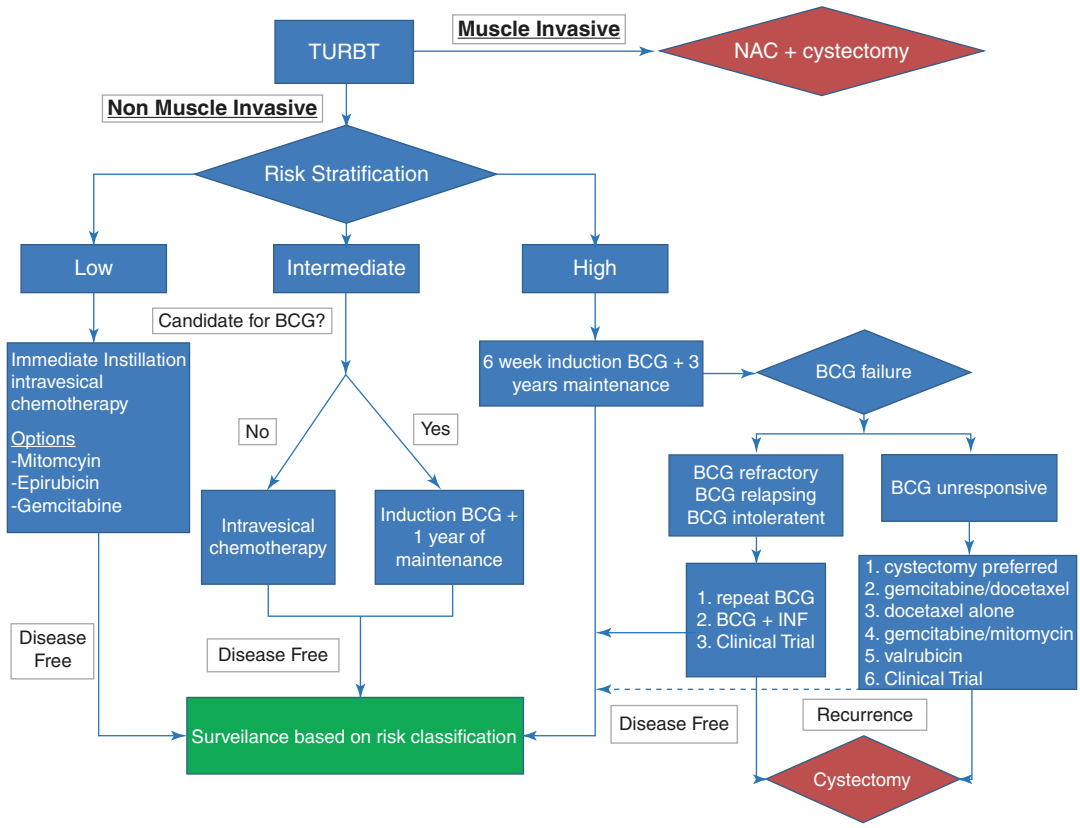

Fig. 33.1 Flow diagram of treatment of bladder cancer

lesions [44]. For low-risk disease, NCCN guidelines recommend cystoscopy at 3 and 12 months after treatment in 1st year of diagnosis, followed by annually up till 5 years, with no role of urine biomarkers. Conversely, the cystoscopic surveillance follow-up schedule is at 3, 6, and 12 months after treatment in 1st year of diagnosis, followed by every 6 months in 2nd year, and annually thereafter up till 5 years. For intermediate-risk patients, urine biomarkers are recommended same time as cystoscopic surveillance.

High-risk NMIBC has the strictest surveillance schedule as these patients are at highest risk for recurrence and progression. For the first 2 years, patients undergo cystoscopy and urinary urothelial markers every 3 months, followed by every 6 months for 3–5 years. Furthermore, surveillance of upper tract with cross-sectional imaging is recommended at 1 year, followed by every 1–2 years for up to 10 years.

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Delivery of Antineoplastic Therapeutics to the Central Nervous System

Lisa Feldman and Mike Chen

Introduction

Cancer involving the central nervous system (CNS) is a tremendous challenge in oncology. High-grade gliomas, including glioblastoma multiforme (GBM), are the most commonly diagnosed primary brain tumors in adults with an incidence range of 4.67–5.73 per 100,000 people [1, 2]. Moreover, brain metastases, which most commonly include lung, breast, and melanoma [3], develop in 10–20% of adult cancer patients and are diagnosed 10-times more frequently than primary brain tumors [4]. Leptomeningeal metastasis, which requires demonstration of malignant cells in patients' cerebrospinal fluid (CSF) for diagnosis, carries an especially poor prognosis with median survival of 2–4 months [5, 6] and, if not diagnosed early, results in irreversible neurological deficits [7]. Altogether, these tumors pose a phenomenal challenge in oncology as they are extraordinarily difficult to treat, with GBM patients carrying 5-year survival of approximately 5% [8]. The infiltrative nature of high-grade gliomas render complete surgical resection impossible, and therefore treatments including chemotherapies and radiation are necessary adjuvants. Although novel pharmaceuticals to treat diseases of the CNS are developing at an astoundingly high rate, these medications prove to be among the least efficacious [9, 10]. Among many challenges to developing therapies for brain tumors, drug delivery remains a major problem.

Physical and Physiological Barriers to the CNS

The blood-brain barrier (BBB) is a major limitation to these medications, by both preventing the penetration of drugs to the CNS and by not allowing these medications to reach an efficacious concentration. The BBB is comprised of microvascular endothelial cells that line the brain's blood vessels, are bound together through tight junctions and astrocytic end feet, and respond to signals primarily initiated by astrocytes [11, 12]. These endothelial tight junctions, in addition to a wide array of enzymes, receptors, transporters [13], significantly limit access of intravascular molecules to the brain. While this complex system successful blocks out toxins to the brain, it also excludes 100% large-molecule drugs, 98% of small-molecule drugs [14]. Indeed, it is so restrictive that only small molecules and proteins less than 400 daltons successfully diffuse across the BBB [9]. Moreover, inter-endothelial junctions lock endothelial cells into a solid, resistant barrier that strongly reduces penetration of water-soluble substances in the

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Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_34

CNS [9]. Lipid-soluble molecules, however, are able to cross the BBB, but because of diffusion, they are restricted in terms of distribution throughout the brain.

The majority of chemotherapies are bound to plasma proteins with molecular weights far surpassing the BBB's 400 dalton limit [15]. Furthermore, the BBB expresses high concentrations of active efflux transmembrane pumps, such as P-glycoprotein, which actively eliminate chemotherapies from the brain [16, 17]. An interesting strategy to improve the delivery of chemotherapeutic agents to the CNS involves blocking transmembrane protein transporters [18]. A number of new and innovative delivery techniques have also been developed to either weaken or bypass the BBB to augment CNS drug delivery.

Because brain tumors often have increased number of abnormal microvessels [19] which include distended capillaries with sluggish flow and leaky walls and ultimately are more permeable than healthy brain vessels [20]. Therefore, tumors have a unique blood-tumor barrier (BTB). This BTB allows tumors to be visualized with contrast agents on computed tomography or magnetic resonance imaging and might lead to inconsistent or reduced diffusion of therapeutics to tumors [21]. Furthermore, highly abnormal blood flow in these vessels results in areas of intratumoral hypoxia, which leads to further resistance of chemotherapies and radiation therapies [22]. Altogether, the BTB presents an additional, formidable challenge to optimized delivery of therapeutics to CNS tumors [23].

Blood-Brain Barrier Disruption Strategies

Many approaches to circumvent the BBB have been developed over time with the gross aim of improving drug delivery to the CNS through manipulating either therapeutics or capillary permeability, or by delivering the medication directly to CSF and bypass the BBB altogether. The older methods include intra-arterial injections of medications, such as hyperosmolar therapy; however, newer strategies include developing sophisticated novel pharmaceuticals that chemically pass the BBB or utilization of technology that injects therapeutics directly into tumor or tumor cavity [20] (see Table 34.1, [24]). Overall, direct delivery to the CSF, either via intracerebro-

Table 34.1 Various methods to circumvent BBB for therapeutic delivery to CNS

Method	Advantages	Disadvantages
Drugs engineered to utilize BBB transport mechanisms	Noninvasive administration, delivered throughout CNS	Expensive drug development, manufacturing. Requires systemic administration, ongoing clinical development
Trans-nasal delivery	Noninvasive, easy to administer outside clinical setting, repeatable	Small volume of drug delivered, relatively restricted delivery, interindividual variability
Arterial injection of osmotic solutions or other agents	Effectively delivers targeted drugs throughout CNS, strong clinical experience	Invasive, requires general anesthesia, inconsistent results, may result in local neurotoxicity
Intrathecal, intraventricular injection	Effectively delivers drugs within CSF and to brain surface	Little drug penetration beyond brain surface, invasive, risk of infection with implanted catheter/system
Focused ultrasound, with or without microbubbles	Noninvasive, repeatable, allows target drug to reach high concentrations of drug in CNS, can be improved with use of microbubbles or magnetic particles for additional targeting	Requires systemic administration, risk of infection, technically challenging, ongoing clinical development

Modified from: Aryal et al. [24]; used with permission

ventricular, intracisternal, or intrathecal injection, is the most common method of administration of therapeutics to bypass the BBB.

Chemical Disruption of BBB

A number of endogenous physiological substances, including neurotransmitters, inflammatory markers, a variety of hormones [11], as well as physiological states of hypertension and hypercapnia, have all been noted to transiently open the BBB [25]. Unfortunately, the transient disruption to the BBB by these factors resulted in inconsistent barrier opening and duration of disruption. This placed subjects at risk of permanent structural damage, thus rendering this method a less favorable means of drug delivery [26]. Ideally, BBB disruption for therapeutic purposes should be transient and reversible. Hypertonic solutions, particularly by the use of intra-arterial mannitol, but also lactamide, saline, urea, and radiographic contrast agents have been used for this purpose with success [25]. The intra-arterial injection of mannitol results in dramatic diffusion of fluid out of cells, dehydration, and shrinking of endothelial cells, ultimately opening the BBB tight junction for at least a number of hours [27]. The delivery of chemotherapeutic agents following the disruption of BBB shows significant increase in medial survival time in patients with CNS lymphoma [28], as well as in patients with other chemo-responsive tumors [29]. Intra-arterial injection of osmotic agents, however, comes with inherent risks that patients must be prepared to give informed consent. The procedure (1) requires general anesthesia, (2) is considered an invasive procedure, and (3) results in inconsistent delivery of goal medications to the CNS [24].

A major limitation of disrupting BBB prior to chemotherapeutic agent delivery is neurotoxicity. For example, although doxorubicin and cisplatin are well-tolerated systemically, they can result in significant neurotoxicity when administrated with BBB disruption in canine and rodent models [30, 31]. Moreover, alternative systemic toxic risks associated with mannitol-induced BBB disruption, including hyperkalemic ventricular tachycardia [32], seizures [33], and vasovagal episodes with bradycardia and hypotension [34], further limit this clinical application.

Mechanical BBB Disruption

To circumvent the toxic side effects of using osmotic agents, scientists and physicians developed focused ultrasound (FUS) methods to disrupt BBB. During FUS, transcranially directed low-frequency ultrasound waves transiently open the tight junctions in BBB endothelial cells [35]. One of the earliest uses of this technique was to successfully deliver liposome-encapsulated doxorubicin across an FUS-disrupted membrane in a rat glioma model [36]. Because FUS generated excessive heat on the skull, this technique required a craniotomy [37] and therefore was largely restricted to animal studies.

Newer FUS ablation systems, however, have been developed to overcome this problem by reducing skull heating through active cooling of the scalp, as well as utilizing transducers with large apertures to distribute ultrasound energy over a large skull surface [38]. When used in conjunction with acoustic simulation calculated by skull CT scans to optimize phase and amplitude corrections for optimal FUS delivery, as well as MR temperature imaging to measure heat, these systems are able to achieve high intensities of energy to deliver thermal ablation through the human skull for clinical use [24]. FUS results in transient BBB opening, which can close within 6 hours of the procedure [39], and once closed resumes normal physiological function [40, 41].

More recently, the FUS technique has been enhanced to include the use of circulating microbubbles. Intravenous administration of microbubble contrast agent allows the BBB to remain consistently open, without resulting harm to underlying brain [42]. The oscillation of microbubbles during FUS leads to greater disruption of the BBB with lower frequencies of ultrasound [24], hence resulting in significantly

less heat damage to skull or underlying brain [43]. This combination allowed a novel way to disrupt the BBB in a targeted, repeatable fashion that ultimately can be delivered noninvasively [24].

Direct Delivery

Intranasal Delivery

Intranasal application is an alternative method to bypass the BBB and deliver medications to the brain and spinal cord noninvasively and within minutes. A number of therapeutic delivery pathways involved in intranasal delivery have been described. The olfactory pathway involves drug absorption throughout the olfactory epithelium, traveling to the olfactory bulb, where it is dispersed through the brain parenchyma and into the cerebrospinal fluid (CSF) [44]. Although it was originally assumed that the olfactory nerve was the exclusive conduit for intranasal delivery to the brain [45], it is now understood that the trigeminal nerve and pathway also are involved, particularly in the delivery to the brain stem and spinal cord [46]. Because the olfactory and trigeminal nerves serve as specialized connections between the outside environment and the central nervous system, this direct delivery method does not result in side effects seen in systemic delivery [47]. The nasal mucosa presents as an ideal therapeutic conduit due to its large surface area, high blood flow, porous endothelial membrane, and circumvention of hepatic first-pass metabolism [48]. A vast majority of therapeutics, including but not limited to micro- and macromolecules, growth factors, viral vectors, and stem cells [49], have been delivered intranasally to the central nervous system to treat Alzheimer's disease, stroke, neurodegenerative diseases, and cognitive functions such as memory, attention, and mood in both animal and human models [47].

Benefits of intranasal delivery include a painless, noninvasive, self-delivery of therapeutics with a fast onset of action because of the high vascularization and large absorptive surface area of the nasal mucosa and avoidance of chemical/enzymatic degradation which may occur in the gastrointestinal tract [48]. Limitations to this delivery, however, include limited clearance of drug by mucociliary clearance, enzymatic degradation, and relatively low permeability for some drugs through the nasal epithelium [49] including hydrophilic molecules, peptides, proteins, and nucleotides [50, 51].

Intracerebroventricular and Intracisternal Delivery

In this direct mode of therapeutic delivery, medication directly bypasses the BBB and is released into CSF in lateral ventricles or cisterna magna. This mode of administration has been used for decades to deliver treatments for a broad range of diseases including infectious meningitis, intractable pain, and a wide variety of cancers in pediatric and adult patients [52]. Please refer to Table 34.2 for antineoplastic agents currently administered via CSF delivery [53–74].

Similar to intranasal delivery, this mode of administration also generally requires less medication and causes fewer side effects as compared to oral drug administration. Drug administration may be delivered in a trial, short-term, or long-term schedule. For intraventricular administration, an extraventricular drain (EVD) may be placed for short-term administration of medication, such as antibiotics or antivirals to treat meningitis or encephalitis. An EVD also provides added benefits of allowing intracranial pressure measurements, as well as allowing CSF draining to reduce ICP or to sample CSF regularly to assess therapeutic benefit over time. EVDs are typically placed at ICU bedside, or intraoperatively, and are temporary conduits to the ventricles. Delivery of medications into the cisterna magna involves the placement of a catheter between the first and second cervical vertebrae (C1–C2 interspace) under radiographic guidance.

Patients are evaluated as good candidates for this type of delivery through use of preoperative scans such as computed tomography (CT) or

Table 34.2 Neoplastic agents delivered into CSF

Therapeutic agent	Neoplasms treated	Adverse effects
Methotrexate (MTX)	First-line treatment for lymphoma and meningeal leukemia; breast, lung, osteosarcoma [53]	Bone marrow, hepatic, pulmonary or renal toxicities [53]; neurotoxicity [54], aseptic meningitis or chemical arachnoiditis [55]
Cytarabine (Ara-C)	CNS prophylaxis for acute lymphocytic leukemia (ALL), lymphoma, neoplastic meningitis [56]. Also administered in liposomal formula for slow release [55]	Neurotoxicity [56], bone marrow, febrile neutropenia, cardiomyopathy [57], transverse myelopathy, aseptic meningitis, chemical arachnoiditis [55]
Hydrocortisone	Given in conjunction with MTX and/or Ara-C for CNS prophylaxis for B-progenitor acute lymphoblastic leukemia [58], non-Hodgkin lymphoma [59]. Coadministered to reduce chemotherapy side effects	Toxicity has not been well-documented in controlled studies; otherwise psychiatric adverse effects [55], headache, nausea, and confusion have been described [60]
Thiotepa (Thioplex)	Monoclonal anti-CD20 antibody to treat leptomeningeal carcinomatosis related to B-cell non-Hodgkin lymphoma, primary CNS lymphoma	Typically, well-tolerated. Myelosuppression, aseptic meningitis [61], polyneuropathy [62]
Rituximab (Rituxan)	Monoclonal anti-CD20 antibody to treat leptomeningeal carcinomatosis related to B-cell non-Hodgkin lymphoma, primary CNS lymphoma	Hypertension, nausea, vomiting, and double vision [63].
Trastuzumab (Herceptin)	Monoclonal antibody to treat leptomeningeal carcinomatosis from human epidermal growth factor receptor 2 positive (HER2+) breast brain metastasis	Very well-tolerated with few side effects [64, 65]; aseptic meningitis [66]
Oncolytic viral therapy	Wide variety including high-grade glioma, melanoma, squamous cell carcinoma, breast (review [67]. Utilizes viruses that selectively target and induce lysis of tumor cells (review [68, 69]); also sensitizes tumor cells to chemotherapy and radiotherapy [70]	Wide variety specific to viral therapy, includes flu-like symptoms [67], nausea, vomiting, fever, chills, asthenia, leukopenia [69]
Immunotherapies	Wide variety including GBM, pediatric high-grade glioma, melanoma, breast, lymphoma, lung. Includes the use of immunostimulants (cytokines, interferons, pathogen-associated molecular pattern (PAMPs) receptors), chimeric antigen receptor (CAR) T-cell [71] T- and B-cell-based immunotherapies and vaccines; checkpoint inhibitors (review [72])	Wide variety specific to immunotherapy, includes CNS-related immune toxicity (hypophysitis [73], hypothyroidism [74], encephalitis, demyelinating polyneuropathy, encephalomyelitis [72]

magnetic resonance imaging (MRI). Typically, patients undergo a trial process involving either of these temporary catheter placements, whereby patients are monitored in an intensive care unit for adverse reactions including cognitive changes, hallucinations, seizures, respiratory depression, or coma [75]. Moreover, patients are monitored as medication dosing and schedule are optimized for each individual [76].

If the trial is successful for a patient, he or she may be brought to the operating room for placement of a permanent implanted drug-delivery device under general anesthesia. Drug reservoir devices, such as an Ommaya reservoir or Rickham reservoir, are implanted under the skin and contain a catheter that terminates in the lateral ventricle. Neurosurgeons may wish to utilize intraoperative neuro-navigation to improve accuracy of placement of reservoir catheter. Patients are then able to receive delivery of therapeutics via small gauge needle administration through the skin, directly into the device reservoir. Frequent drug administration through these types of reservoirs is convenient and well-tolerated by patients. This method is so successful that a number of clinical trials have been designed to deliver medications for late-infantile neuronal ceroid lipofuscinosis type 2 disease, mucopolysaccharidosis II, amyotrophic lateral sclerosis, and Parkinson's disease [52].

Risks associated with placement of reservoirs include intracerebral hemorrhage, infection, poor positioning of catheter, CSF leak, device malfunction (i.e. clotting), and risks associated with undergoing general anesthesia. A meta-analysis reported risks associated with reservoir placement and use from 35 published papers and noted an overall infection rates between 0% and 27% and noninfectious complication rates ranging from 1% to 33%, with CSF leak, hemorrhage, catheter malposition, and catheter obstruction being the most common [52]. An additional theoretical risk is increasing intracranial pressure (ICP) particularly with administration of large volumes of drug [77]. To avoid this potential risk, most medical care providers withdraw CSF volumes equal to that being delivered prior to administration [78, 79]. While the vast majority of patients retain their intraventricular reservoirs far beyond the duration of their therapies [52], neurosurgeons must be readily available to repair or remove a device should a complication arise or should the patient wish to have it removed.

Lumbar Intrathecal Delivery

The first well-known reported use of spinal intrathecal medication delivery was written in 1899 by Dr. August Bier, a German surgeon, who injected cocaine into his own intrathecal space, as well as in that of six other patients, to assess a novel anesthetic technique [80]. Subsequently, physicians added morphine to cocaine for intrathecal anesthetic to counteract adverse side effects of cocaine [81]. Since then, a wide variety of medications have been used for analgesia including ziconotide, morphine, fentanyl, bupivacaine, and sufentanil, all of which with or without clonidine for intractable pain, and baclofen for spasticity [82].

Major advantages of intrathecal is delivery of smaller doses of medications, with significant reduction in systemic side effects, such as respiratory depression and constipation with narcotics and delirium, coma, and seizures with baclofen. Unlike oral medications, patients are much less likely to overdose from medication delivered intrathecally. Furthermore, patients with implanted pumps only require intermittent visits with medical care providers for pump refill, making this a convenient option for many patients.

Intrathecal infusion pumps were developed in the 1970s to improve delivery of opiates in patients [83], and since then, pumps have only become smaller and more sophisticated. Currently, there are two general methods to continuously deliver therapeutics intrathecally and involve either an external pump or a fully implanted device. A percutaneous catheter with an external pump is less invasive to place, may be beneficial in patients with a short life expectancy, and may be used in patients for an extended drug trial [82]. Implanted pumps currently on the market are complex and allow substantial adjustments per individual patient's needs. For example, pumps might delivery drug in a fixed-rate or a variable-rate fashion, may allow the patient to self-delivery bolus as needed, may have a battery or be re-chargeable, and come in different reservoir chamber size to accommodate different volumes of medications. Many of these pumps are interrogated or deactivated noninvasively with a hand-held wand and are now MRI-compatible.

Although there are no established guidelines for selecting patients for intrathecal pain pump placement, most physicians consider this option for patients with either cancer or non-cancer pain, or intractable spasticity which do not respond to maximum oral medications doses. Most physicians advocate for a trial period of intrathecal medication administration. A single or few injections of therapeutics into the lumbar intrathecal space may be performed for a drug trial, or as initiating intrathecal delivery prior to a permanent version, such as an intraventricular reservoir, or a pain pump.

Device implantation requires general anesthesia and involved two separate incisions: one on the lower back at midline, typically between the lumbar fourth and fifth vertebral bodies, and the second on the abdomen, with the side preoperatively selected by the patient. The posterior incision is used to deliver the pump catheter in

between the spinous processes, into the dura, and is tunneled rostrally well into the thecal space. The distal catheter is tunneled under the skin from the posterior incision to the anterior incision, where a subcutaneous pocket is created to hold the drug reservoir chamber. Risks associated with this procedure include bleeding; infection, reported at about 2–5% [84, 85]; CSF leak; seroma or granuloma formation [82]; long-term risk of pump malfunction or obstruction; and risk from general anesthesia.

Convection-Enhanced Delivery

Convection-enhanced delivery (CED), otherwise referred to as high-flow microinfusion, is a form of highly controlled local drug delivery. This technique was developed in the 1990s by Dr. Edward Oldfield and his team at the National Institute of Health [86, 87] and allows for the delivery of highly concentrated solutions, including nanoparticles, to exquisitely accurate target brain regions. This delivery system is targeted such that healthy surrounding brain tissue is exposed to little drug, while the BBB restricts the infused agent from entering the systemic circulation. CED plays an important theoretical role in treating malignant gliomas, which have a high propensity to recur in, or within centimeters of the first tumor [88], and it also has applications in treating Parkinson's disease and Alzheimer's disease [89].

CED consists of an external, automated pump that continuously drives the flow of the desired therapeutic agent through a delivery device. The delivered agent exits through a cannula or catheter that is stereotactically placed directly into the brain or tumor parenchyma, or just adjacent to the target region of infusion [86, 87]. The inner cannula can then be delivered through the outer cannula such that its tip ends at the desired infusion point. In doing so, this two-cannula technique maintains the integrity of the predetermined trajectory of the cannula placement [90]. Once the pump is activated, the pressure gradient at the tip of the catheter generates bulk flow of drug, rather than diffusion, through the interstitial space. Diffusive flow as described by Fick's law is dependent on tissue diffusivity, as well as drug concentration, gradient, and molecular weight [89]. Essentially, this law describes why large molecular weight pharmaceuticals take longer to diffuse in brain tissue and require dangerous concentrations to deliver them to target.

With the use of improved technology, such as MRI and sonograms, which allow for real-time tracking of infused material, more complex models of intraparenchymal flow pattern have been developed. For example, an incredibly accurate computer-generated CED system was developed to use both anatomical and diffusion tensor magnetic resonance imaging as a source for data input. These data points are supplemented with a description of infusate movement using a stochastic differential equation that assesses both advective and diffusive terms. Predication of drug concentration at particular times and locations relative to the delivery site are either confirmed or manipulated using feedback from the imaging device. By following the movement of traceable material in the targeted region of the brain, these researchers were able to collect an array of information pertaining to varying concentration gradients at neighboring points in the tissue. Not only does this model allow for anisotropic variations, but it also incorporates potential sinks for medication such as leakage into the subarachnoid space, drainage into cavities, and fluctuations in tissue clearance rates [91]. Further human trials conducted by these researchers have shown that treatment plans can be altered while the administration of the traceable material is in progress due to real-time feedback [92]. With sufficient intraoperative time, deviations from the predicted flow pattern and desired distribution can be immediately adjusted by manipulating delivery parameters such as injection site and infusion rate.

By controlling the variables that govern the efficacy of delivery, including drug particle size, surface area of particles, and fluid carrying the particles, CED enables a slow, controlled infusion of the desired agent in a manner that expands

the extracellular space, similar to that seen in vasogenic edema, while preserving the integrity of the surrounding tissue. Indeed, these variables have been manipulated to successfully deliver nanoparticles, particularly virus-sized particles as would be utilized in gene therapy to the brain [93]. Altogether, CED offers a unique and innovative method of direct intraparenchymal delivery, achieving therapeutic concentrations of compounds in a targeted and restricted area of the CNS [94].

To date, numerous human clinical trials have successfully demonstrated the delivery of nanoparticles using CED. Though a variety of particles including enzymes, antibodies, and viruses have been convected, the vast majority of trials have examined the delivery of receptor-directed toxins. Receptor-directed toxins consist of one protein that targets a particular feature on the cell surface and another protein that causes cytotoxicity [93]. The first reported clinical trial using CED was performed by Oldfield and utilized a chemotherapeutic agent selective for transferrin receptor Tf-CR107, a transferrin conjugate bound to a point-mutated diphtheria toxin, to treat malignant brain tumors [95].

In a phase I study, the delivery of Tf-CRM107 was well-tolerated, reduced tumor volume by more than 50% in nine out of ten patients, and resulted in a median survival of 75 weeks in comparison to 36 weeks in nonresponders [95]. In a phase II study, complete and partial tumor response without severe toxicity occurred in 35% of patients treated with Tf-CRM107 [96]. Another immunotoxin clinical trial used cintredekin besudotox, a recombinant protein consisting of interleukin-13 (IL-13) and a truncated form of Pseudomonas exotoxin, PE38QQR. The initial phase I trial showed promising clinical results for the treatment of recurrent glioblastoma multiforme [97]; however, a phase III study (PRECISE) of 296 participants who received either CED of cintredekin besudotox postoperatively or a gliadel wafer implanted at the time of surgery demonstrated no survival benefit [98] . Interestingly, it was found that only about 50% catheters were properly placed for this study, suggesting that proper catheter placement might have improved this clinical trial's final outcome [99].

Viral particles for treatment of Parkinson's disease have also been successfully delivered through CED [100, 101]. AAV2 encoding human aromatic L-amino acid decarboxylase (hAADC) was convected into the putamens of 10 humans and 3 nonhuman primates [101]. MRI with T2 hyperintensity and associated increased uptake on PET scans appeared similar in both groups. Nonhuman primates also had immunohistochemical studies demonstrating that hAADC expression occurred in these regions. This result strongly supports the feasibility of using CED of nanoparticles such as virus for clinical gene therapy.

In summary, CED, which has been described as molecular neurosurgery, is a technique that can be used to deliver nanoparticles to target areas in the CNS. With advancements in imaging technology, researchers have been able to optimize the parameters to facilitate a greater variety and volume of therapeutics to treat neurological diseases.

Conclusion

In summary, despite much effort to improve adjuvant therapies for the treatment of CNS tumors, such as radiation therapy and chemotherapy, there is considerable effort in designing creative ways to deliver high concentrations of novel targeted therapies directly to tumors. Not only would this strategy avoid unwanted side effects often seen in systemic delivery of therapeutic agents, but delivery of higher concentration of medication would likely result in more efficacious treatment. A major limitation to the development of new treatments involves circumventing the BBB. As unique ways of bypassing the BBB are developed such as via physical or chemical disruption, or new development of new pharmaceuticals that utilize the barrier's endogenous transporters, exciting new agents are expected in the near future.

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Intralesional Therapies: Oncolytic Viral Therapies, Immunostimulants

35

John T. Miura and Jonathan S. Zager

Introduction

The overall effectiveness of regional therapies is centered on the unique distribution of a disease, enabling the delivery of concentrated treatments to a specific site or area of the body, while minimizing the systemic side effects. Most regional therapies for cancer can be classified into two broad categories that include arterial-delivery-based treatments or intracavitary treatments. However, an additional modality not to be excluded from the discussion surrounding regional therapies includes the application of intralesional therapies. As its name implies, intralesional therapies involve the direct injection of an agent into the target lesion. In recent years, there has been growing enthusiasm for intralesional-based therapies after studies in melanoma demonstrated favorable responses with minimal toxicities.

However, intralesional therapy is not a new concept. The origins of intralesional therapies can be traced backed to over a century ago, when Dr. William B Coley, a New York surgeon, first proposed the concept of introducing a bacterial toxin into a tumor to promote regression [1]. In 1893, Dr. Coley described a patient with unresectable sarcoma who underwent a series of injections using "Coley's toxin" (a mixture of killed *Serratia marcescens* and *Streptococcus pyogenes*), which ultimately led to regression of the tumor over several months [2–4]. Despite his ongoing success in subsequent cases, the inability to reliably manufacture the toxin coupled with a lack of prospective clinical trials resulted in heavy skepticism [1]. Moreover, occurring around the same period was the introduction of novel therapies that included radiation and chemotherapy that prevented the concept of intralesional therapy from gaining traction.

It was not until 1975, after a case report by Dr. Donald L. Morton was published in cancer, that intralesional therapies were put back on the map. While at the National Cancer Institute, Dr. Morton was presented with a patient with metastatic melanoma that had numerous intracutaneous metastasis along with a pulmonary metastatic deposit [1]. Over a period of 8 months, the patient underwent a series of injections using Bacille Calmette-Guerin (BCG) into the dermal and subcutaneous deposits. Treatment response was significant with a 100% complete response rate among injected lesions along with partial regression of the pulmonary metastasis [5]. Around the same period, Dr. Morton also reported his seven-year experience with BCG intralesional therapy for malignant melanoma and reported regression among 91% of injected lesions, but interestingly, 21% of nonin-

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Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_35

jected lesions regressed as well [6]. These initial findings by Dr. Morton highlighted the potential for intralesional therapies, but also suggested a possible secondary immunologic effect.

Since the early work by Dr. Morton, multiple intralesional agents have been investigated with only a few that demonstrated durable outcomes in the clinical setting, while maintaining an appropriate safety profile. To date, the majority of studies involving intralesional agents have been conducted in melanoma as the disease in advanced states can present with locoregional metastasis, where cutaneous or subcutaneous tumor deposits develop proximal to the draining nodal basin [7, 8]. Typically, these lesions are too numerous or bulky to be amendable to surgical resection, but remain attractive targets for intralesional therapies as they are easily accessible for direct injection. While the original impetus behind intralesional therapy for melanoma was to promote local tumor destruction, the finding that the disease is closely linked with the immune system has given rise to newer intralesional agents with enhanced immune activation [9, 10]. As such, agents such as talimogene laherparepvec, PV-10, HL10, and Allovectin-7 have demonstrated the ability to not only exert its treatment effect locally but also initiate a systemic immune response, termed a "bystander effect," whereby distant disease might respond as well (Fig. 35.1) [11, 12].

In this chapter, the varying intralesional therapies that have been evaluated or are currently undergoing evaluation will be reviewed, with specific emphasis placed on immunotherapy-based intralesional agents (Table 35.1). Topics including mechanism of action, outcomes, side effects, and combination therapies will be supported through studies conducted for melanoma, as this remains the primary cancer type that has derived the greatest benefit from this treatment strategy.

Bacille Calmette-Guerin

Following early reports that saw a dramatic response to BCG therapy among injected in-transit melanoma lesions, contemporary studies have failed to achieve similar success rates. BCG is a live, attenuated strain of Mycobacterium bovis that, when initially studied in animal models, triggered an immune reaction against transplanted murine tumors [13, 14].

At present, BCG therapy remains more of a historical intralesional agent following reports of severe toxicity along with the inability to demonstrate a survival benefit when applied on a larger scale. Several smaller studies using intralesional BCG reported toxicities of anaphylaxis, disseminated intravascular coagulation, and death [15–17].

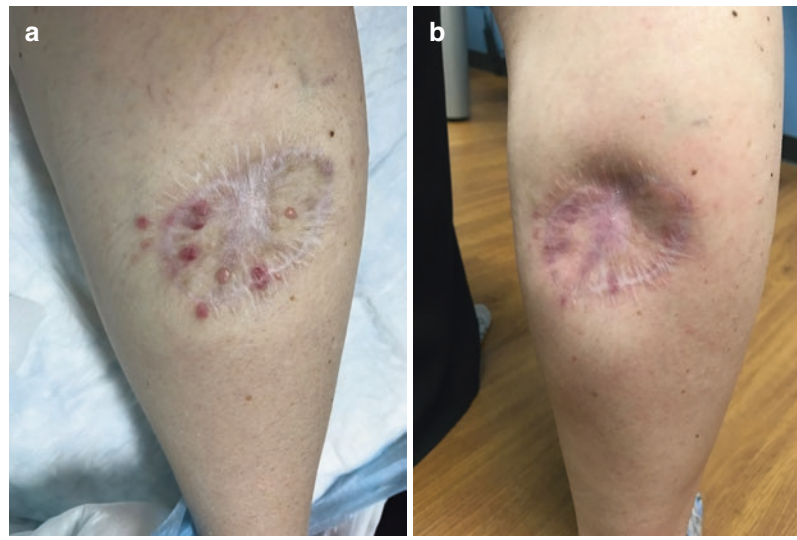

Fig. 35.1 (**a**) Melanoma recurrence at the original primary resection site. (**b**) Objective response at 2.5 months following T-VEC therapy

Table 35.1 Select studies of intralesional therapy in melanoma

Injection agent	Author	Study design	No. of participants	Injected lesions				Uninjected lesions
				CR (%)	PR (%)	SD (%)	PD (%)	
BCG	Karakousis [14]	Observational	8	75	0	0	25	No response
BCG	Storm [59]	Prospective	27	74 (CR/PR)		NR	26	No response
IL-2	Weide [23]	Phase II	48	79	0.7	16.3	4.3	No response
IL-2	Radny [24]	Phase II	24	85	6	6	3	No response
IL-2	Byers [25]	Systematic review	140	78	2.5	19.6 (SD/PD)	NR	No response
Allovectin-7	Bedikian [37]	Phase II	127	3	9	25	63	Response in 21% of patients with stage IV disease
Allovectin-7	Gonzalez [60]	Phase II	77	3	7	23	68	No response
GM-CSF/IL-2	Ridolfi [61]	Phase I/II	16	0	13	69	19	No response
PV-10	Thompson [45]	Phase I	11	36	12	28	24	Response in 27% of lesions
PV-10	Thompson [46]	Phase II	80	26	25	18	31	Response in 33% of lesions
T-VEC	Senzer [30]	Phase II	50	16	10	24	50	Response
T-VEC Vs GM-CSF	Andtbacka [50]	Phase III	295 vs. 141	11 1	16 5	73 (SD/PD) 94 (SD/PD)		T-VEC: Response in 34% nonvisceral and 15% visceral
HF10	Ferris [54]	Phase I	9	0	11	44	44	No comment
CVA21	Andtbacka [56]	Phase II	57	14	14	72 (SD/PD)		Response

CR complete response, *PR* partial response, *SD* stabile disease, *PD* progression of disease, *BCG* Bacille Calmette-Guerin, *IL-2* Interleukin-2, *TNF* tumor necrosis factor, *ECT* electrochemotherapy, *Bleo* bleomycin, *GM-CSF* granulocyte macrophage colony-stimulating factor, *T-VEC* talimogene laherparepvec, *CVA21* coxsackievirus A21

While very high doses of BCG were used in these studies, which likely contributed to the increased risk of developing severe toxicity, the poor outcomes were enough to temper enthusiasm for the agent. Additionally, there has been a lack of compelling evidence supporting the clinical benefit following BCG therapy. In a large phase III randomized trail (E1673) conducted in 2004 by the Eastern Cooperative Oncology Group (ECOG), intralesional BCG failed to demonstrate a significant benefit in disease-free or overall survival [18]. The trial tested the adjuvant use of BCG with or without dacarbazine in 734 patients with stage I–III melanoma. Patients were treated between 19,741 and 978 with outcomes projected out to a median of 30 years. While toxicity was generally mild, over two-thirds developed punctate abscesses during the course of therapy. The study concluded that BCG could not be recommended due to the lack of efficacy and potential problematic side effects.

Despite the lack of studies supporting its efficacy and cases reporting significant adverse events, BCG must be credited for the revival of intralesional therapies and likely served as the impetus for the development of alternative agents.

Interleukin-2

Interleukin-2 (IL-2) has a long history in melanoma therapeutics. Following its discovery in 1976, early studies investigating IL-2 activity reported a heightened immune response following treatment by the agent as demonstrated by

expansion of clonal T cells, maturation of T regulatory cells, and increase in natural killer cell activity [19, 20]. The application of IL-2 as a potential therapy for melanoma came at a time when there were limited systemic treatment options to treat advanced stages of disease. Despite suboptimal response rates of 10–15% along with high-treatment-related toxicities, IL-2 obtained FDA approval in 1998 [21, 22]. Fortunately, advances in immunotherapy and targeted therapies have given rise to newer and more effective systemic agents for melanoma, making it now a dated therapy.

However, when applied intralesionally, IL-2 has generated more promising results. In early clinical work, intralesional IL-2 resulted in complete response (CR) rates as high as 70% [23, 24]. In a phase II trial by Weide et al., 48 patients with clinical stage III/IV melanoma were injected with 0.3 to 6 million international units (MIU) of IL-2 three times weekly [23]. CR was achieved in 33 patients (69%) with the treatment effect lasting greater than 6 months in 70% of injected lesions. Moreover, toxicity was minimal with only grade 1/2 events being reported.

Limited by small study cohorts, a follow-up systematic review assessing intralesional IL-2 efficacy was conducted, which included six studies, that captured a total of 2182 injected lesions [25]. Despite a lower CR rate of 50% being reported, intralesional IL-2 was still able to achieve a significant response and treatment was overall well tolerated. Only three grade 3 events were experienced in the analysis.

While intralesional IL-2 appeared to achieve high response rate, widespread adoption of this therapy was tempered by several major drawbacks. Treatment schemes were laborious, requiring multiple injections per week, and overall cost of therapy was high. Moreover, IL-2 did not generate a bystander effect unlike some of the newer intralesional agents. Therefore its application as a monotherapy has remained limited, especially among patients with extensive locoregional or metastatic disease. Instead, if IL-2 is to remain a viable intralesional agent, it will likely come from combination strategies with one of the new systemic immunotherapy options.

Granulocyte Macrophage Colony-Stimulating Factor

Granulocyte macrophage colony-stimulating factor (GM-CSF) is an additional intralesional agent of mostly historical interest. It is a cytokine first identified as a factor leading to the expansion and activation of granulocytes, macrophages, and T cells, which ultimately resulted in increased antitumor responsiveness [26, 27]. Preclinical studies found that expression of GM-CSF resulted in durable antitumor immunity when injected into immune competent hosts [28]. However, when applied in the clinical setting, intralesional GM-CSF has been met with inconsistent results.

In early phase I studies, a common observation among patients that responded to intralesional GM-CSF was a marked increase of T-cell infiltrate into the tumor. Unfortunately, in the study conducted by Si et al., of the 13 patients with advanced melanoma treated with GM-CSF, only three patients experienced a partial response and there were no complete responders [29]. A similar overall response rate (ORR: complete response + partial response) was reported in the phase II trial by Senzer et al. [30]. Fifty patients with stage IIIc/IV melanoma were injected with intratumoral GM-CSF every 2 weeks for up to 24 treatments. The ORR was 26% (CR: 8 patients, PR: 5 patients), and adverse effects were limited to flu-like symptoms. Unfortunately, as a monotherapy, intralesional GM-CSF has not led to robust responses and, as a result, has fallen out of favor.

Velimogene Aliplasmid

Velimogene aliplasmid (Allovectin-7), a plasmid/lipid complex, containing DNA sequences encoding human leukocyte antigen (HLA)-B7 and ß2 microglobulin, components of MHC-I, received significant attention following its FDA approval for orphan drug designation in 1999 [9]. During cancer progression, it is believed that alteration of MHC-I was one such mechanism that enabled tumor cells to evade the immune system [31]. In early studies, Allovectin-7 was found to increase HLA-B7 cytotoxic T-cell frequency fivefold,

along with upregulate MHC-I molecules, resulting in a pro-inflammatory response, which led to augmentation of the immune system [32].

In the clinical setting, Allovectin-7 showed great promise in both phase I/II trials. Four different phase I trials reported response rates up to 50% [33–36]. In phase II results, VCL-1005–208 was a dose escalation study that enrolled a total of 133 patients with stage IIIB/C and IV M1a/b melanoma [37]. Patients received six weekly injections ranging from 0.5 to 2 mg of Allovectin-7. An ORR of 11.8% was reported (CR: 3%, PR: 9%), with a median duration of response lasting 13.8 months. Additionally, of the patients with stage IV disease, response in uninjected lesions was observed in 21% (9 of 42 patients). Toxicity was also negligible and included paresthesias, myalgias, fatigue, and flu-like symptoms. However, these positive findings were unable to be reproduced in two subsequent phase III trials [38, 39]. The Allovectin immunotherapy for metastatic melanoma trial (AIMM, NCT00395070) randomized 390 patients with stage III/IV melanoma 2:1 to Allovectin-7 or intravenous dacarbazine or oral temozolomide [38]. The primary end point of response at ≥24 weeks found the Allovectin-7 group to be lower compared with the dacarbazine/temozolomide arm (4.6% vs 12.35, respectively, $p = 0.010$). OS, albeit not statistically significant, also favored the chemotherapy group versus those injected with Allovectin-7 (24.1 months vs 18.8 months, $p = 0.491$). The second phase III trial by Richards et al. randomized 202 metastatic melanoma patients to receive either dacarbazine alone or dacarbazine plus Allovectin-7 [39]. The study failed to reach its end point after demonstrating no difference in response rates or survival with the addition of Allovectin-7. After a disappointing performance at the phase III level, further research involving Allovectin-7 was discontinued.

PV-10

First described in the 1920s as an intravenous diagnostic agent to assess liver function, PV-10 (rose bengal disodium 10%) continues to be used by ophthalmologists as a diagnostic aid [40–42]. Early preclinical in vitro and in vivo studies using PV-10 found the small-molecule fluorescein derivative to be preferentially taken up by the lysosomes of cancer cells while sparing normal cells, triggering lysosomal release and cell autophagy [43]. The local destruction of tumor cells led to the acute exposure of tumor antigens, which resulted in an increase in tumor infiltrating lymphocytes and the activation of a tumor-specific host immune response [44]. The end result was the observation of a bystander effect where uninjected tumors also regressed (Fig. 35.2).

When applied in the clinical setting, similar responses to intralesional PV-10 were reported. The first phase I study enrolled 11 patients with local/regionally recurrent melanoma (stage IIIB/C) [45]. Tumors were injected with PV-10 at a dose of 0.5 mL/cc of measure lesion volume. Both injected and uninjected lesions were monitored for response to PV-10 injection. In total, 26 lesions were injected and an ORR of 48% (CR: 36%, PR: 12%) was observed. A bystander effect was also noted with 33% of untreated lesions experiencing a decrease in size. Capitalizing on their initial success, a phase II trial was conducted by the same group. In this study, 80 patients with stage III/IV melanoma were enrolled and injected with PV-10 in up to 20 target lesions, up to four times over a 16-week period and followed for 52 weeks [46]. An additional 1–2 bystander lesions per patient were also identified. The ORR was 51% for target lesions with 26%, achieving a CR. Regression in untreated bystander lesions that included both visceral and cutaneous lesions was also noted in 40% of 35 evaluable patients. Overall, the treatment was well tolerated with the vast majority of patients experiencing either grade 1 or grade 2 toxicities. Pain and edema at the injection site was the most common side effect, but was transient in duration.

Currently, PV-10 is being studied in a phase III trial (NCT02288897) for locally advanced cutaneous melanoma, where the intralesional agent will be compared to systemic chemotherapy (dacarbazine or temozolomide) or an

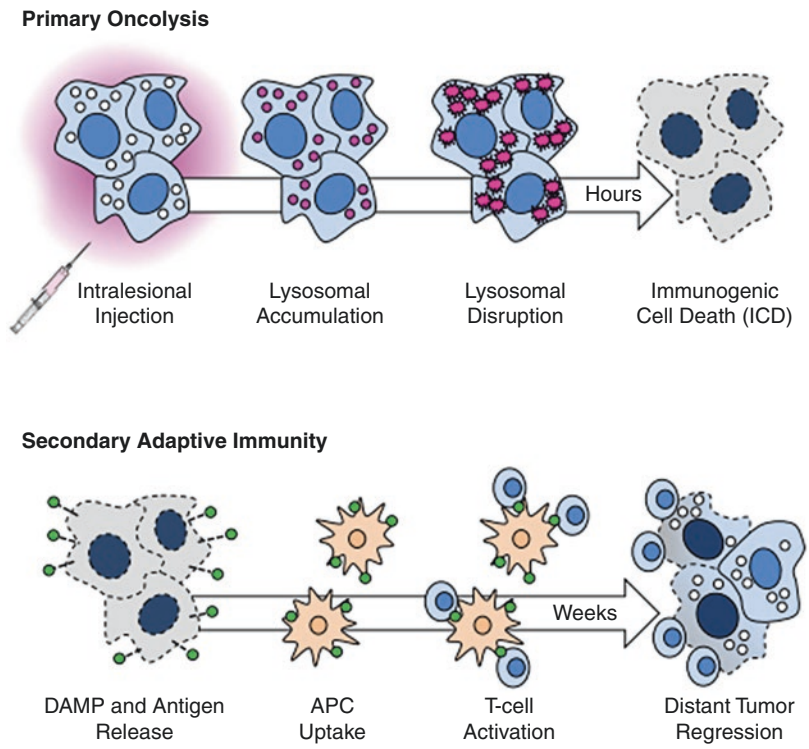

Fig. 35.2 PV-10 is an oncolytic intralesional therapy designed to produce both local and systemic effects resulting in tumor lysis and cell death. Reproduced with permission from Provectus

additional intralesional oncolytic therapy, talimogene laherparepvec (T-VEC), which will be discussed later. The study is currently accruing patients with a target completion date in the fall of 2018. Nonetheless, the compelling results surrounding the treatment effect of PV-10 cannot be ignored and will likely become a vital treatment added to the armamentarium of melanoma therapeutics.

Talimogene Laherparepvec (T-VEC)

To date, talimogene laherparepvec (T-VEC) is the only FDA-approved intralesional therapy for unresectable stage IIIB through IV melanoma. The agent was derived from the herpes simplex virus type I (HSV-1) and has since been altered by removing the ICP34.5 loci, which eliminated the pathogenic properties of the virus [47, 48]. Additional modifications to the virus included the capacity to express GM-CSF [27]. The final result was the creation of T-VEC, whose mechanism of action was twofold: preferentially replication in cancer cells leading to cell lysis and enhancement of a tumor-specific immune response mediated through the release of virally derived GM-CSF and increased presentation of tumor antigens and activation of the antigen-presenting cells (Fig. 35.3).

Early clinical work proved T-VEC to be safe with minimal side effects that included local inflammation, erythema, and febrile responses. Initial observations in phase I trials also confirmed viral replication within tumor cells with resultant treatment-related tumor necrosis [49]. Promising findings led to the execution of a single-arm phase II trial that enrolled patients with stage IIIC/IV melanoma [30]. In total, 50 patients were treated with intralesional T-VEC. The treatment protocol included an initial injection of target lesion up to a maximum cumulative dose of 4 mL of 10^6 pfu/mL, followed 3 weeks later by 4 mL of 10^8 pfu/mL, that was delivered every 2 weeks, for up to 24 treatments. The median number of injection sets was six with the overall treatment cohort experiencing an ORR of 26% (CR: 16%, PR: 10%). Regression of

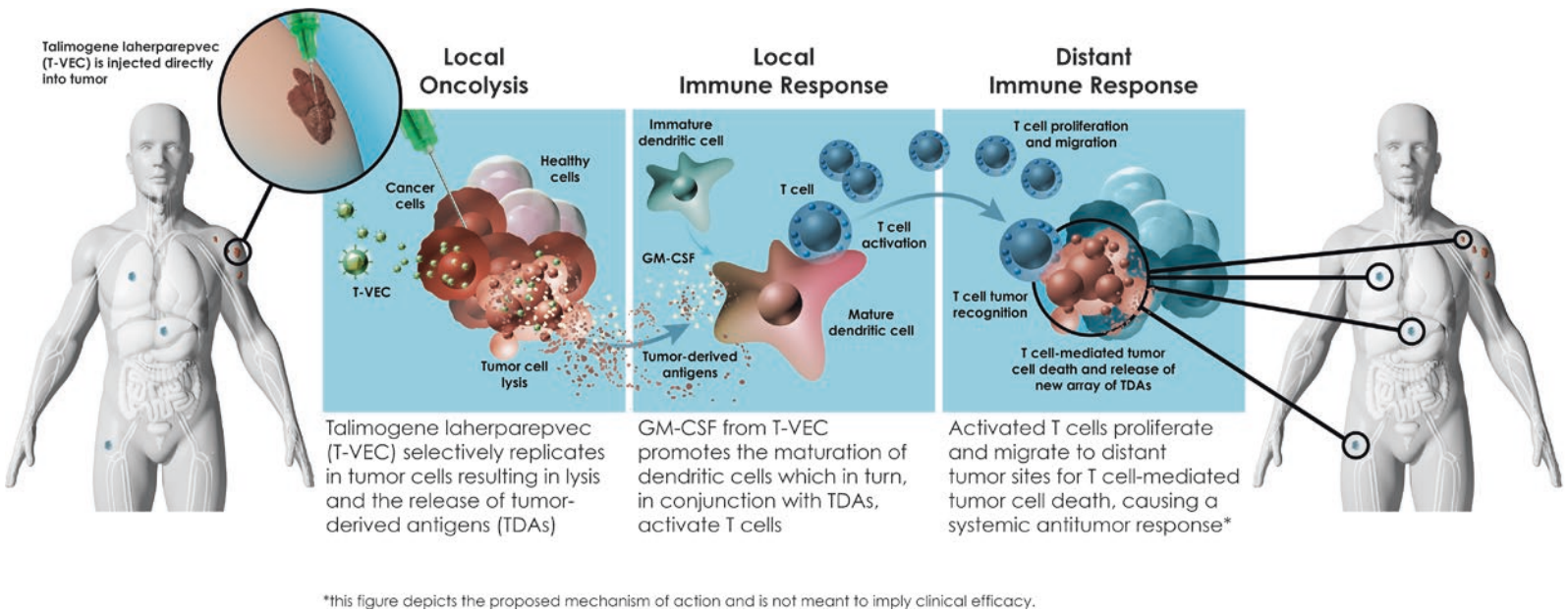

Fig. 35.3 Talimogene laherparepvec (T-VEC) mechanism of action. GM-CSF: granulocyte macrophage colony-stimulating factor. Reproduced with permission from Amgen

uninjected lesions was also observed. Overall survival at 1 and 2 years were 58% and 52%, respectively.

In 2015, results from the phase III randomized clinical trial, OPTIM (Oncovex GM-CSF Pivotal Trial in Melanoma), was reported [50]. T-VEC was compared with GM-CSF in 436 patients with stage IIIB/C and IV melanoma. The primary and secondary end points were durable response rate (DRR: partial or complete response that lasted ≥6 months during the first 12 months of treatment), OS, and ORR. In the intention to treat analysis, the DRR was 16.3% in the T-VEC arm compared to 2.1% in the GM-CSF arm, a treatment difference of 14.1% ($p < 0.001$). Furthermore, in subgroup analysis, patients with only stage IIIB/C and IVa disease derived a significant improvement in OS with T-VEC therapy versus GM-CSF (T-VEC: 41.1 months vs GM-CSF: 21.5 months, $p < 0.001$). Adverse events were mild with fatigue and chills occurring in 50.3% and 48.6% of patients treated with T-VEC. The only grade 3/4 toxicity that occurred in 2.1% of patients was cellulitis.

Additional lesion-level response analysis by the OPTIM investigators also reported that of the 2116 lesions injected with T-VEC, a greater than 50% size reduction was observed in 64% of the cohort, 34% of uninjected nonvisceral and 15% of visceral lesions experienced a similar size reduction, underscoring the ability of T-VEC to mediate a bystander effect [51].

The high response rate coupled with durable treatment effect has made T-VEC an attractive agent for locoregionally metastatic melanoma. Its treatment characteristics, notably its ability to exert its effect both locally and distantly along with a favorable safety profile, serves as the core characteristics of an effective intralesional agent. Until newer agents are developed, T-VEC will likely serve a major role in melanoma therapeutics.

HF10

While T-VEC has garnered most of the attention for viral-based intralesional therapies, there are several additional agents actively being studied that have also demonstrated promising results. HF10 and coxsackievirus A21 are two additional oncolytic viral-based intralesional agents currently undergoing clinical investigation. Similar to T-VEC, HF10 is also derived from a strain of HSV-1. However, the genetic modification of HF10 involves the removal of the UL56 gene, which causes a reduction of the neuroinvasiveness of the virus, without affecting replication [52]. In in vivo melanoma mouse models, inoculation of subcutaneous tumor deposits resulted in cytolytic effects, which ultimately led to reduced tumor growth [53]. A systemic antitumor immune response was also observed as non-inoculated tumors also demonstrated a response to treatment. When applied in the clinical setting, intralesional HF10 has been well tolerated with the majority of adverse events being limited to flu-like symptoms [54]. At the phase I level, HF10 was first investigated in a dose escalation trial where patients with refractory head and neck cancers or other solid tumors with cutaneous or subcutaneous deposits were enrolled [54]. Of the 26 patients treated with HF10, nine patients had melanoma. Stable disease was reported in 31% of the overall treatment cohort. However, in the subgroup analysis, melanoma patients demonstrated the greatest frequency of PR+ SD (56%). Recently, HF10 was studied in a phase II trial where the agent was administered in combination with ipilimumab, a CTLA-4 systemic immunotherapy, in patients with advanced melanoma (Stages IIIB, IIIC, IV). Results of this study will be discussed in the next section [55].

Coxsackievirus A21 (CVA21)

Coxsackievirus A21 (CVA21) is another example of a genetically modified intralesional oncolytic viral-based therapy. Commonly known to cause "colds" in its native state, CVA21 has been engineered to selectively target intercellular adhesion molecule-1 (ICAM-1), a protein upregulated in melanoma [9]. In the phase II CALM trial (CAVATAK in late stage melanoma), 57 patients with unresectable stage IIIC-IVM1c melanoma were enrolled. The overall response rate was 28%

(CR: 14%, PR:14%) with no grade 3 or 4 drug-related adverse events being reported [56].

With similar mechanisms of action to T-VEC coupled with encouraging clinical results in early studies, it is very likely that in the near future, multiple additional intralesional oncolytic viral-based therapies will become available for the treatment of advanced melanoma.

Combination Therapies

A major limitation in melanoma therapeutics, even among the most effective treatments, is the large cohort of patients deemed nonresponders. At best, for intralesional agents that have demonstrated efficacy at the phase II/III level, approximately half of patients will have stable, if not progressive, disease. Seeing that treatment response is not universal, and disease presentation for locoregional metastatic melanoma is heterogenous, a logical progression in treatment strategy would be combination therapies.

Currently ongoing are multiple trials assessing whether the addition of immunotherapies with intralesional agents could lead to a synergistic affect that would improve response rates and ultimately prolong survival (Table 35.2). The rationale behind combination approaches lies in the understanding of the distinct mechanisms of action between two treatments. Unlike the programmed cell death produced by checkpoint inhibitors, intralesional agents lead to tumor rupture, release of antigens with subsequent influx of T cells, resulting in an antitumor systemic immune response.

Ipilimumab, an anti-CTLA4 immunotherapy approved for advanced stage melanoma, recently completed a phase II trial where T-VEC was combined with the immunotherapy agent [57]. The final result of the study demonstrated a significant improvement in ORR when T-VEC was combined with ipilimumab compared to ipilimumab alone (39% vs 18% respectively, $p = 0.002$). Similarly, when ipilimumab was combined with HF10 in a phase II trial, patients with stage IIIB/C or IV unresectable melanoma achieved an ORR of 41% (CR: 16%, PR: 25%) [55].

An additional trial investigated the combination strategy of T-VEC with the immune checkpoint inhibitor, pembrolizumab [58]. At the phase I level, the study reported an ORR of 57% with a CR of 24%. The promising results led to the execution of the randomized phase 3 trial of T-VEC + pembrolizumab versus placebo + pembrolizumab (NCT02263508) with an estimated completion date of December 2018. Lastly, PV-10 is also being investigated in combination trials. NCT02557321 is a phase Ib/II trial, comparing PV-10 in combination with pembrolizumab

Table 35.2 Combination trials of intralesional therapy in melanoma

Injection agent	Author	Study design	No. of participants	Injected lesions				Uninjected lesions
				CR (%)	PR (%)	SD (%)	PD (%)	
T-VEC + Ipi Vs Ipi	Chesney [57]	Phase II	98 vs 100	13 7	25 11	19 24	31 33	Response in 57% nonvisceral and 52% visceral lesion in the T-VEC + Ipi Arm
HF10 + Ipi	Andtbacka [55]	Phase II	46	16	25	27	32	No comment
T-VEC + Pembro	Long [58]	Phase Ib	21	24	33	NR	NR	No comment
T-VEC+ Pembro Vs Pembro	NCT02263508	Phase III	Ongoing					
PV-10 + Pembro	NCT 02557321	Phase Ib/II	Ongoing					

CR complete response, *PR* partial response, *SD* stabile disease, *PD* progression of disease, *T-VEC* talimogene laherparepvec, *Ipi* Ipilimumab, *Pembro* Pembrolizumab

versus pembrolizumab alone in patients with stage IV metastatic melanoma with at least one injectable cutaneous or subcutaneous lesion. Primary outcomes include safety and progression free survival. Target completion date is November 2023.

If the ongoing clinical trials confirm initial trends of improved response rates without an increase in treatment-related toxicity, these results will likely solidify the role of combination therapies for metastatic melanoma. Whether intralesional therapies will every gain an expanded role in treating other cancers remains unclear. Additional studies are needed, which investigate new routes of administration of intralesional therapies, aside for its common application for dermal, subcutaneous, or lymph node metastasis. Active areas of research include the injection of T-VEC into visceral lesions to determine if a similar treatment effect can be achieved. As newer studies continue to support the expanding role of immunotherapy in cancer therapeutics, the additive effects achieved with intralesional combination strategies seen in melanoma will likely serve as the impetus to broaden its usage for other cancer types.

Conclusion

The evolution of intralesional therapies has come full circle. From its original description as an injectable toxin, to its revival by Dr. Morton and his work with BCG, to its current state as an oncolytic virus, the premise behind intralesional therapies has remained the same over this period: to promote local tumor destruction following injection of an agent. The theoretical advantage of intralesional therapies has been the direct application of a concentrated agent to the tumor, while limiting systemic exposure. Moreover, with the integration of immunotherapies into intralesional agents, treatment effects are now occurring distantly as well. While multiple intralesional agents have been studied in melanoma, the few that have successfully completed rigorous clinical testing with promising results have helped to expand the therapeutic armamentarium for cancer. Additional studies are still needed to help define whether intralesional therapies can be applied in other cancer types. Until a single agent is able to effectively treat all sites of disease, multimodal treatment strategies will continue to exist, and intralesional therapies will continue to occupy a place for the management of locoregionally metastatic disease.

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36 Ongoing Clinical Trials and Rationale in Regional and Oligometastatic Disease

Oliver S. Eng and Yuman Fong

Introduction

As the development of systemic and local treatment approaches to malignancies has improved over time, the concept of metastasectomy has been shown to be associated with improved survival in certain cancers [1]. Thus, our approach to management of malignancies is not simply a decision point based on metastatic versus non-metastatic. Patients with metastatic disease are evaluated based on the disease burden, sites involved, and primary tumor characteristics, both grossly and at a molecular level [2]. As such, patients with regional or oligometastatic disease are a unique subset to which therapies are targeted.

Although the burgeoning possibilities for regional therapies have revolutionized the field of regional and oligometastatic disease, this is a constantly evolving field of medicine. As demonstrated in previous chapters, there are a plethora of clinical trials currently ongoing in regional cancer therapies. Here in this chapter, we highlight other currently registered novel clinical trials which are active, recruiting, or enrolling. A detailed search including terms such as "regional," "infusion," "therapy," and "cancer" was performed. Rationale and trial descriptions are described in the following sections.

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Hyperthermia

The molecular basis of the effects of hyperthermia in the treatment of malignancies has been reported extensively in preclinical studies [3, 4]. Localized hyperthermia by high-energy radiofrequency waves was demonstrated to be effective in causing necrosis of both normal and cancer tissue in animals above 45 °C [3]. Other studies have demonstrated that malignant cells in vivo are selectively destroyed by hyperthermia in the temperature range of 41–43 °C [4]. Hyperthermic intraperitoneal chemotherapy (HIPEC) remains a modality for regional treatment of peritoneal carcinomatosis in conjunction with cytoreductive surgery (CRS) [5]. In this section, we discuss ongoing clinical trials involving hyperthermia, summarized in Table 36.1.

While the use of CRS/HIPEC has been shown to provide a survival benefit in some cancers, its use in gastric cancer with peritoneal carcinomatosis remains an area of investigation [5]. In a phase III trial by Yang et al. comparing CRS alone versus CRS/HIPEC in patients with peritoneal carcinomatosis from gastric cancer, the authors found median overall survival (OS) to be 6.5 months in the CRS-alone group versus 11.0 months in the CRS/HIPEC group [6]. However, this trial was subject to a variety of

Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_36

Table 36.1 Ongoing clinical trials involving hyperthermia

Trial	Official title	Sponsor/institution	Status
NCT01882933 [8]	GASTRICHIP: D2 Resection and HIPEC in Locally Advanced Gastric Carcinoma: A Randomized and Multicentric Phase III Study	Hospices Civils de Lyon	Recruiting
NCT02240524 [9]	A Phase III Study of HIPEC in the Treatment of Locally Advanced Gastric Cancer After radical Gastrectomy With D2 Lymphadenectomy	Affiliated Cancer Hospital & Institute of Guangzhou Medical University	Recruiting
NCT02359474 [13]	Trabectedin Combined With Regional Hyperthermia as Second Line Treatment for Adult Patients With Advanced Soft-tissue Sarcoma	Ludwig-Maximilians—University of Munich	Recruiting
NCT02655913 [18]	Phase I–II Study of Vitamin C Infusion in Combination With Local modulated electro-hyperthermia (mEHT) on Non-Small Cell Lung Cancer Patients	Clifford Hospital, Guangzhou	Recruiting

criticisms, including the lack of information regarding systemic chemotherapy regimens reported. In addition, the REGATTA study demonstrated a 16.6-month median OS in patients with metastatic gastric cancer treated with chemotherapy alone [7]. The GASTRICHIP trial (NCT01882933) is an ongoing phase III trial examining the role of HIPEC in patients with advanced gastric adenocarcinoma (T3/4 and/or N+ and/or positive peritoneal cytology). In this study, patients are randomized to curative gastrectomy with D1/2 lymph node dissection with or without HIPEC with Oxaliplatin [8]. Another study, NCT02240524, A Phase III Study of Hyperthermic Intraperitoneal Chemotherapy in the Treatment of Locally Advanced Gastric Cancer After Radical Gastrectomy With D2 Lymphadenectomy, is randomizing patients to surgical management with or without HIPEC, followed by 8 cycles of systemic chemotherapy (XELOX) [9]. What is noteworthy about this trial is that HIPEC is administered twice—once intraoperatively and another postoperatively (within 48 hours of indexed operation) with paclitaxel, 75 mg/m^2, at 43 °C, for 60 minutes [9].

Regional hyperthermia has been utilized in the management of soft-tissue sarcoma as well. In the EORTC 62961 study, 341 patients with locally recurrent, incompletely resected, or resected with margin <1 cm were randomized to chemotherapy (etoposide, ifosfamide, doxorubicin) either alone or combined with regional hyperthermia (between 40 and 43 °C) followed by local therapy [10]. Patients who received regional hyperthermia experienced a greater treatment response rate (28.8% vs. 12.7%) [10]. On long-term follow-up, regional hyperthermia patients experienced a greater 10-year overall survival (52.6% vs. 42.7%) [11]. Trabectedin is a newer treatment modality (mechanism is via blocking DNA repair) for metastatic soft-tissue sarcoma approved as second-line therapy based on a phase II study demonstrating improved progression-free survival (PFS) versus best supportive care [12]. As such, the study NCT02359474 in Germany, *"Trabectedin Combined with Regional Hyperthermia as Second Line Treatment for Adult Patients with Advanced Soft-tissue Sarcoma,"* is recruiting, randomizing patients with to Trabectedin with or without regional hyperthermia. The regional hyperthermia will be administered at 41–44 °C to the tumor area and surrounding tissue for 60 minutes at the end of the Trabectedin infusion [13].

Locoregional electro-hyperthermia is a sophisticated modality utilized in the treatment of malignancies [14]. It is noninvasive and combines both thermal and electromagnetic effects and shown to be safe in patients with relapsed high-grade gliomas by Wismeth et al. [14] In this study, electro-hyperthermia was performed via transcranial capacitive coupled with conductive radiofrequency heating, providing a synergistic effect. This combined modality has been investigated in non-small cell lung cancer (NSCLC) and shown to be safe with individual reports of

effectiveness [15]. High-dose intravenous ascorbic acid, or Vitamin C, has shown to be effective in decreasing cell proliferation in lung cancer cell lines and, in vitro, demonstrates synergistic effects with hyperthermia in carcinostatic effects [16, 17]. Thus, NCT02655913 is a Phase I-II Study of Vitamin C Infusion in Combination With Local Modulated Electro-hyperthermia (mEHT) on Non-Small Cell Lung Cancer Patients which is currently recruiting patients [18].

Hepatic Infusion

Management of hepatic metastases from colorectal cancer has evolved over time. Long-term survival is now possible in patients who undergo surgical resection [1]. Hepatic intra-arterial chemotherapy is a treatment modality utilized in a multidisciplinary fashion, which has been shown to be associated with improved survival in some studies [19, 20]. As such, regional therapies targeted to treating hepatic disease now are being performed in a variety of malignancies [19, 21]. Here, we discuss several ongoing trials involving hepatic infusion, shown in Table 36.2.

Infusion of floxuridine (FUDR) into the portal vein has been investigated as an alternative to hepatic arterial infusion. In fact, phase II trials have demonstrated portal vein infusion of FUDR to be associated with a low drug-induced hepatic toxicity rate [22]. However, DFS/OS were inferior compared to hepatic arterial infusion [19]. A recent single-institution randomized trial of patients with stage II and III colon cancer randomizing patients to intraportal chemotherapy plus adjuvant chemotherapy (mFOLFOX6) versus adjuvant chemotherapy alone found a reduction in distant metastases and improved DFS in the intraportal chemotherapy arm, but no difference in 3-year OS [23]. As a result of the findings of this study, NCT02402972, A Multi-center Randomized Controlled Trial: Intraportal Chemotherapy Combined With Adjuvant Chemotherapy (mFOLFOX6) for Stage II and III Colon Cancer, is ongoing and recruiting, with an estimated enrollment of 700 patients [24].

Isolated hepatic infusion is a technique involving temporary surgical isolation of the hepatic circulation and has been shown to be effective in the management of unresectable and/or small multifocal hepatic metastases from uveal melanoma [25]. However, due to the complexity and associated morbidity of this technique, percutaneous hepatic perfusion (PHP) was developed to allow an endovascular alternative. Reports have been encouraging, as PHP has demonstrated improved progression-free survival compared to best supportive care [26]. A phase III multicenter international trial is underway, using melphalan and with a primary endpoint of objective response rate [27]. PHP has garnered interest in the use of other malignancies as well. Currently, a prospective trial is underway, randomizing patients with intrahepatic cholangiocarcinoma who have received induction systemic therapy with gemcitabine/cisplatin for four cycles to either PHP or continued systemic gemcitabine/cisplatin, with a primary endpoint of overall survival [28].

As immunotherapy has been garnering more traction in the management of cancers, the use of oncolytic viruses is one modality that can alter

Table 36.2 Ongoing clinical trials involving hepatic infusion

Trial	Official title	Sponsor/institution	Status
NCT02402972 [24]	A Multi-center Randomized Controlled Trial: Intraportal Chemotherapy Combined With Adjuvant Chemotherapy (mFOLFOX6) for Stage II and III Colon Cancer	Zhongshan Hospital, Fudan University	Recruiting
NCT02678572 [27]	Percutaneous Hepatic Perfusion in Patients With Hepatic-dominant Ocular Melanoma (FOCUS)	Delcath Systems Inc.	Recruiting
NCT03086993 [28]	Percutaneous Hepatic Perfusion vs. Cisplatin/Gemcitabine in Patients With Intrahepatic Cholangiocarcinoma	Delcath Systems Inc.	Recruiting
NCT02749331 [31]	Study of Recombinant Adenovirus (AdVince) in Patients With Neuroendocrine Tumors: Safety and Efficacy	Uppsala University	Recruiting

the immune microenvironment and promote antitumor immunity [29]. Several other ongoing clinical trials utilizing oncolytic viruses are discussed in the respective section below. The oncolytic virus AdVince has been developed to target liver metastases from neuroendocrine tumors (NETs) [30]. It has been evaluated in a preclinical setting and found to selectively replicate and kill NET cells [30]. As such, NCT02749331, *"Study of Recombinant Adenovirus (AdVince) in Patients with Neuroendocrine Tumors: Safety and Efficacy,"* is recruiting. This study is a single-center phase I/IIa study to evaluate the safety of hepatic artery infusions of AdVince in patients with metastatic NETs [31].

Regional Perfusion

Table 36.3 illustrates ongoing novel clinical trials involving regional perfusion. Isolated limb infusion and perfusion for regional management of unresectable sarcoma limited to the extremity is associated with a limb salvage rate of 73.8% [32]. It is also safe and effective in locally advanced melanoma as well [33]. Please refer to earlier chapters regarding isolated limb infusion and perfusion. Metastatic spinal disease is often difficult to manage, as many available treatments are aimed at symptomatic control, such as pain management and glucocorticoid administration. Prognosis in metastatic spinal disease is largely dependent on tumor type and patient-related factors [34]. However, sometimes systemic chemotherapy is variable in its effectiveness, and thus other modalities for delivery of chemotherapy to sensitive tumors are being explored [35]. Thus, NCT01637766, Selective Intra-arterial Chemotherapy in the Treatment Strategy of Metastatic Spinal Disease, is recruiting currently. Patients in this phase I study will receive melphalan injected intra-arterially into artery branches feeding the spinal tumor via access from the femoral artery, for three treatments at 3–6 week intervals [36].

Leptomeningeal metastases from breast cancer similarly remain a challenging disease process to treat. As HER2 + -targeted therapy has evolved, outcomes in this subset of patients with metastatic breast cancer have dramatically improved [37]. However, metastases to the central nervous system remain prevalent due to the lack of significant penetration of HER2-targeted therapy to this area [38]. As such, Lu et al. described a case report of a patient who received intrathecal Trastuzumab for leptomeningeal metastases, which resulted in clinical remission with stable disease 46 months after diagnosis of leptomeningeal metastases [39]. Currently, NCT01325207, "*Phase I/II Dose Escalation Trial to Assess Safety of Intrathecal Trastuzumab for the Treatment of Leptomeningeal Metastases in HER2 Positive Breast Cancer,"* remains active [40].For additional discussion on ILI/ILP for melanoma and sarcoma, please refer to previous chapters.

Oncolytic Viruses

As discussed in the preceding section, oncolytic viruses are one modality that can alter the immune microenvironment and promote antitumor immunity [29]. The first agent to be approved by the Food and Drug Administration (FDA) vas talimogene laherparepvec (T-VEC), an attenuated

Table 36.3 Ongoing clinical trials involving regional perfusion

Trial	Official title	Sponsor/institution	Status
NCT01637766 [36]	Selective Intra-arterial Chemotherapy in the Treatment Strategy of Metastatic Spinal Disease	Weill Medical College of Cornell University	Recruiting
NCT01325207 [40]	Phase I/II Dose Escalation Trial to Assess Safety of Intrathecal Trastuzumab for the Treatment of Leptomeningeal Metastases in HER2 Positive Breast Cancer	Northwestern University	Active, not recruiting

herpes simplex 1 virus, after results of a phase III trial in advanced melanoma showed improved durable response rates and overall survival compared to granulocyte macrophage colony-stimulating factor (GM-CSF) [41]. A variety of oncolytic viruses are undergoing investigation; for example, oncolytic herpes simplex virus has shown to be cytotoxic in stemlike tumor-initiating human colon cancer cells [42]. Furthermore, in combination with checkpoint inhibition, oncolytic viruses have shown to improve response rates than with checkpoint inhibition alone [43, 44]. Table 36.4 outlines ongoing clinical trials involving oncolytic viruses.

Currently, the clinical trial NCT03294486, *"Safety and Efficacy of the ONCOlytic VIRus Armed for Local Chemotherapy, TG6002/5-FC, in Recurrent Glioblastoma Patients,"* is recruiting [45]. This study is a phase I dose-escalation trial in patients with recurrent glioblastoma multiforme (GBM), which builds upon preclinical data presented in 2017 [46]. TG6002 expresses the gene *FCU1*, which encodes enzymes that transform flucytosine (5-FC) into 5-FU. Antitumor activity of the combination of TG6002 and 5-FC in GBM cell lines both in vitro and in xenografted mice demonstrated a survival benefit from the combination compared to TG6002 alone [46]. Of note, phase IIa of this study will include patients treated intravenously at the recommended phase II dosage [45].

Another oncolytic virus, GL-ONC1, is a vaccinia virus and is currently being investigated in use in patients with ovarian cancer. This trial, NCT02759588, Phase 1b/2 Study With GL-ONC1 Oncolytic Immunotherapy in Patients With Recurrent Ovarian Cancer (VIRO-15), reported on its phase I results recently [47, 48]. 55% of patients experienced either a partial response or had stable disease for 15 weeks or more with intraperitoneal infusion of GL-ONC1 monotherapy, while more than doubling of progression-free survival compared to the previous chemotherapy regimen was seen in 36% of patients [48]. A similar phase I study was recently published on a cohort of patients with advanced peritoneal carcinomatosis or advanced peritoneal mesothelioma, showing GL-ONC1 to be well-tolerated [49].

Immunotherapy/ Immunomodulating/Intralesional

Various approaches to immunotherapy have been developed and resulted in therapeutic advances in the treatment of malignancies [50]. In this section, we report on a spectrum of ongoing clinical trials involving different approaches with immunotherapy, shown in Table 36.5.

Chimeric antigen receptor (CAR) T cells are genetically modified autologous T cells in which T cells are designed to target a variety of cell surface molecules independent of HLA restriction [51]. Many targets for CAR-modified T cells remain targets under investigation. For example, one of the more-studied targets is CD19, which is expressed by most B-cell leukemias and lymphomas [52]. Patients with advanced hepatocellular carcinoma (HCC) remain a challenge, as systemic and locoregional interventions are not curative for patients who are not surgical candidates [53, 54]. CAR-modified natural killer (NK) cells targeting glypican-3 (GPC3) have

Table 36.4 Ongoing clinical trials involving oncolytic viruses

Trial	Official title	Sponsor/institution	Status
NCT02263508 [44]	Pembrolizumab With or Without Talimogene Laherparepvec or Talimogene Laherparepvec Placebo in Unresected Melanoma (KEYNOTE-034)	Amgen Merck Sharp & Dohme Corp.	Active, not recruiting
NCT03294486 [45]	Safety and Efficacy of the ONCOlytic VIRus Armed for Local Chemotherapy, TG6002/5-FC, in Recurrent Glioblastoma Patients	Assistance Publique—Hôpitaux de Paris	Recruiting
NCT02759588 [47]	Phase 1b/2 Study With GL-ONC1 Oncolytic Immunotherapy in Patients With Recurrent Ovarian Cancer (VIRO-15)	Genelux Corporation	Recruiting

Table 36.5 Ongoing clinical trials involving immunotherapy

Trial	Official title	Sponsor/tnstitution	Status
NCT03130712 [57]	An Open-label, Uncontrolled, Single-arm Pilot Study to Evaluate Intratumor Injection Mediated GPC3-targeted Chimeric Antigen Receptor T Cells in Advanced Hepatocellular Carcinoma	Shanghai GeneChem Col, Ltd.	Recruiting
NCT03500991 [60]	Phase 1 Study of HER2-Specific CAR T Cell Locoregional Immunotherapy for HER2 Positive Recurrent/Refractory Pediatric Central Nervous System Tumors	Seattle Children's Hospital	Recruiting
NCT01570036 [63]	Combination Immunotherapy With Herceptin and the HER2 Vaccine E75 in Low and Intermediate HER2-expressing Breast Cancer Patients to Prevent Recurrence	Cancer insight, LLC	Active, not recruiting
NCT02151448 [64]	A Phase 1/2 Trial Evaluating αDC1 Vaccines Combined With Tumor-Selective Chemokine Modulation as Adjuvant Therapy After Surgical Resection of Peritoneal Surface Malignancies	University of Pittsburgh	Recruiting
NCT02557321 [69]	PV-10 In Combination with Pembrolizumab for Treatment of Metastatic Melanoma	Provectus Biopharmaceuticals, Inc.	Recruiting
NCT03233152 [71]	Phase I Clinical Trial on Intra-tumoral Ipilimumab Plus Intravenous Nivolumab Following the Resection of Recurrent Glioblastoma	Universitair Ziekenhuis Brussel	Recruiting
NCT02806687 [74]	Phase 2 Gene Therapy Trial of Locally Advanced Pancreatic Adenocarcinoma Using Intra-tumoral Injection of CYL-02 in Combination With Gemcitabine	University Hospital, Toulouse	Recruiting

been shown to increase tumor apoptosis and decrease tumor proliferation in preclinical studies [55]. GPC3 CAR T cells have been shown in a phase I study to be safe and feasible in patients with GPC3+ HCC [56]. The clinical trial, NCT03130712, An Open-label, Uncontrolled, Single-arm Pilot Study to Evaluate Intratumor Injection Mediated GPC3-targeted Chimeric Antigen Receptor T Cells in Advanced Hepatocellular Carcinoma, is recruiting patients with advanced HCC [57]. This phase I study is evaluating the safety of a one-time intratumoral injection of GPC3-targeted CAR T cells [57]. CAR T cells have also demonstrated effectiveness in recurrent multifocal GBM [58]. HER2-specific CAR T cells have been developed for brain metastases from breast cancer [59]. As such, study NCT03500991, entitled Phase 1 Study of HER2-Specific CAR T Cell Locoregional Immunotherapy for HER2 Positive Recurrent/Refractory Pediatric Central Nervous System Tumors, involves delivering CAR T cells into the tumor resection cavity or ventricular system in this patient population [60].

As discussed previously, HER2-expressing breast cancers remain a subset of breast cancers in which receptor-targeted therapy via monoclonal antibodies has shown to improve survival [37]. Immunotherapy is an emerging area of research in the treatment of breast cancers. An immunogenic peptide called E75 is derived from HER2 protein, and multiple early phase trials have investigated the safety and efficacy of E75 mixed with GM-CSF in a vaccine form (NeuVax™) in preventing breast cancer recurrence [61]. Results from these early trials have demonstrated improved 5-year DFS in patients who received NeuVax™ versus controls in an adjuvant setting, and are the basis for the PRESENT trial (NCT01479244), which has completed enrollment [61, 62]. Another trial, NCT01570036, Combination Immunotherapy With Herceptin and the HER2 Vaccine E75 in Low and Intermediate HER2-expressing Breast Cancer Patients to Prevent Recurrence, is active [63]. This will be a multicenter, prospective randomized phase II trial for patients with HER2 1+ and 2+ expressing tumors after receiving stan-

dard of care therapy. Patients will be randomized to either Herceptin + NeuVax™ or Herceptin + GM-CSF alone, with the primary endpoint being DFS [63].

Another vaccine-based trial is currently recruiting patients with peritoneal surface malignancies who have undergone surgical resection. This is trial NCT02151448 [64], A Phase 1/2 Trial Evaluating αDC1 Vaccines Combined With Tumor-Selective Chemokine Modulation as Adjuvant Therapy After Surgical Resection of Peritoneal Surface Malignancies [64]. The background for this trial is based on the concept that dendritic cells (DCs) are antigen-presenting cells involved in primary immune responses. DC-based vaccines have subsequently been developed and examined in various clinical trials [65]. The immune microenvironment has also been found to be altered in favor of promoting oncolytic viral therapy with the addition of immune modulation with chemokines [66]. Given the need for more novel therapies in the treatment of peritoneal surface malignancies, this trial will evaluate the safety and efficacy of αDC1 vaccines in combination with a systemic chemokine modulation regimen as adjuvant therapy after CRS/HIPEC.

Both ipilimumab and nivolumab are immune checkpoint inhibitors administered systemically in the management of advanced melanoma [67]. Intratumoral injection of ipilimumab has been shown to be effective and with little toxicity in patients with melanoma [68]. A phase Ib/II trial investigating the effects of intralesional PV-10, a non-pyrogenic 10% solution of rose bengal, in combination with pembrolizumab is ongoing (NCT02557321) [69].

Recent results from the CheckMate 143 trial, in which patients with recurrent GBM were randomized to either nivolumab monotherapy or nivolumab and ipilimumab, reported on the safety and efficacy of both arms [70]. NCT03233152, entitled *"Phase I Clinical Trial on Intra-tumoral Ipilimumab plus Intravenous Nivolumab Following the Resection of Recurrent Glioblastoma,"* is recruiting patients. In this study, nivolumab will be injected intravenously 24 hours prior to surgical resection, with ipilimumab injected within the brain tissue lining the resection cavity post-resection [71].

As outcomes in patients with pancreatic adenocarcinoma overall remain dismal, novel agents in the locoregional management of disease in this patient population are being explored [72]. The concept of introducing a therapeutic gene transfer (gene therapy) to restore somatostatin receptor type 2 (SSTR2) expression in pancreatic ductal adenocarcinoma tumors in combination with genes to counteract the pathway responsible for gemcitabine resistance was explored by a French collaborative and reported in 2015 [73]. This combination product, CYL-02, was injected intratumorally via endoscopic ultrasound in a phase I study, with nine patients having stable disease up to 6 months following treatment [73]. NCT02806687, entitled *"Phase 2 Gene Therapy Trial of Locally Advanced Pancreatic Adenocarcinoma Using Intra-tumoral Injection of CYL-02 in Combination with Gemcitabine,"* is actively recruiting. The objective of this study is to compare the efficacy of gemcitabine plus CYL-02 versus gemcitabine alone in patients with locally advanced pancreatic ductal adenocarcinoma, with the primary objective of progression-free survival [74].

Conclusion

In conclusion, the field of regional therapies is constantly evolving, and this is reflected by the many ongoing clinical trials available today. Innovation and science in medicine will continue to provide more novel therapeutic approaches to malignancies, and these approaches will only increase over time. We look forward to the possibilities available for patients in generations to come.

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Radiation Therapy

37

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Radiation Therapy

Radiation therapy is an important modality for local, regional, and metastatic oncologic management. Since the discovery of the X-ray in 1895 by Wilhelm Roentgen and the early clinical applications, innovation and technology have fueled improvements in the field of radiation oncology [1]. Dating back to the field's inception, practitioners have sought to maximize the tumoricidal effect of radiation while minimizing injury to surrounding tissues. Through a better understanding of cell biology and rapid technological advances, radiation therapy has become more precise and less toxic.

Radiation Intent

Radiation can be delivered with definitive curative intent or for symptomatic palliation of both local and metastatic disease [2]. The difference in these two paradigms is typically the radiation dose, the complexity of the plan, the number of treatments, and the desired outcome. Definitive radiation generally consists of higher total doses delivered in small daily fractions over several weeks with twin goals of tumor ablation and limiting damage to normal structures. Palliative radiation differs in that the focus is decreasing symptoms as rapidly and effectively as possible, typically using simple plans with larger doses per treatment for a limited number of treatments [3]. Treatment intent guides planning decisions with many possible dose schemes. The biological effect of radiation differs based on the size of the daily doses and total dose received. To account for these differences, the concept of a biological effective dose (BED) was developed. BED can be calculated for any fractionation schema and provides a way to evaluate the effectiveness of different radiation regimens [4]. Higher BED treatments are typically associated with a higher likelihood of both tumor ablation and toxicity. The manifestation of radiation toxicity can present acutely during treatment or in the months to years following the completion of therapy and is related to the dose that was delivered, the size of the daily fraction, the volume of the structure receiving radiation, and the radiosensitivity of the irradiated tissue [5].

Radiobiology

Ionizing X-ray radiation kills cancer cells by direct and indirect actions. Photon radiation causes direct DNA injury and indirect damage

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Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4_37

through the generation of hydroxyl radicals that cause DNA breaks. As unrepaired DNA breaks accumulate, the cell becomes nonviable due to loss of genetic information [5]. This process preferentially affects cancer cells because they have aberrant DNA repair and checkpoint mechanisms. Exploitation of these biological differences allows for radiation to be delivered in doses sufficient for tumor control with acceptable toxicity.

Radiation Techniques

Since the 1950s, most external beam radiation therapy has been delivered by medical linear accelerators (linacs). Linacs generate high energy, penetrating electrons and photon X-rays that are therapeutic [6]. Prior to the advent of more precise imaging technology, radiation therapy was delivered by a 2D technique. Simple radiation field arrangements were designed on X-rays using bony anatomic landmarks. The development of computed tomography (CT) and magnetic resonance imaging (MRI) provided a three-dimensional rendering of tumor and patient anatomy. This enabled the development of three-dimensional conformal radiation (3DCRT), which used multiple radiation fields to better shape the target, increase accuracy, and limit OAR exposure [7]. This increasing conformality of targets spurred the International Commission on Radiation Units (ICRU) to develop the following nomenclature and definitions of treatment volumes [8, 9]:

- Gross tumor volume (GTV): extent of malignant tumor based on palpation, direct visualization, and/or imaging studies.
- Clinical target volume (CTV): expansion of the GTV that accounts for microscopic tumor extension.
- Planning target volume (PTV): expansion of the CTV to account for patient movement, inaccuracies in beam and patient setup, and other uncertainties.

Advances in computing and the multileaf collimator led to the development of intensity-modulated radiation therapy (IMRT), which uses multiple beamlets of varying intensity to optimally shape radiation dose around concave and convex targets and avoid organs at risk (OAR). IMRT achieves similar efficacy and decreased toxicity as compared to 3DCRT across multiple disease sites [10]. Refer to Fig. 37.1 for a comparison of the different techniques (2D, 3D, IMRT).

Stereotactic radiosurgery (SRS) uses precise 3D imaging to deliver high-dose radiation to highly conformal, small volume benign and malignant CNS targets. SRS treatment is most often delivered in one fraction but can be delivered in up to 5 fractions [11] and can be administered by Gamma Knife (Elekta Inc., Norcross, GA), LINAC radiosurgery systems, or proton beam systems [12].

Stereotactic body radiation therapy (SBRT) is a technique that delivers image-guided, high-dose, highly conformal radiation in 5 or fewer treatments to body sites outside of the CNS [13]. The daily dose for SBRT is typically 5–10 times higher than conventional radiotherapy and is a promising treatment paradigm. Refer to Table 37.1 for selected studies of definitive management of primary site disease with SBRT [14–25].

General Overview of the Logistics of Radiation

Potential candidates for radiation therapy are typically referred by other oncologic, medical, or surgical services and are first seen in consultation to complete staging, define the intent of treatment (e.g., curative vs palliative, preoperative or adjuvant vs definitive), and discuss the benefits and risks of therapy. Prior to starting radiation, patients first undergo a CT simulation to establish treatment position and customize immobilization and setup, and acquire a CT scan with thin slices (1–5 mm) for planning. Physician placed radiopaque markers, as well as intravenous, oral, rectal, and/or vaginal contrast can be utilized to better delineate both the target and anatomy. 4DCT scans can be obtained to account for organ motion with respiration. CT images are then transferred

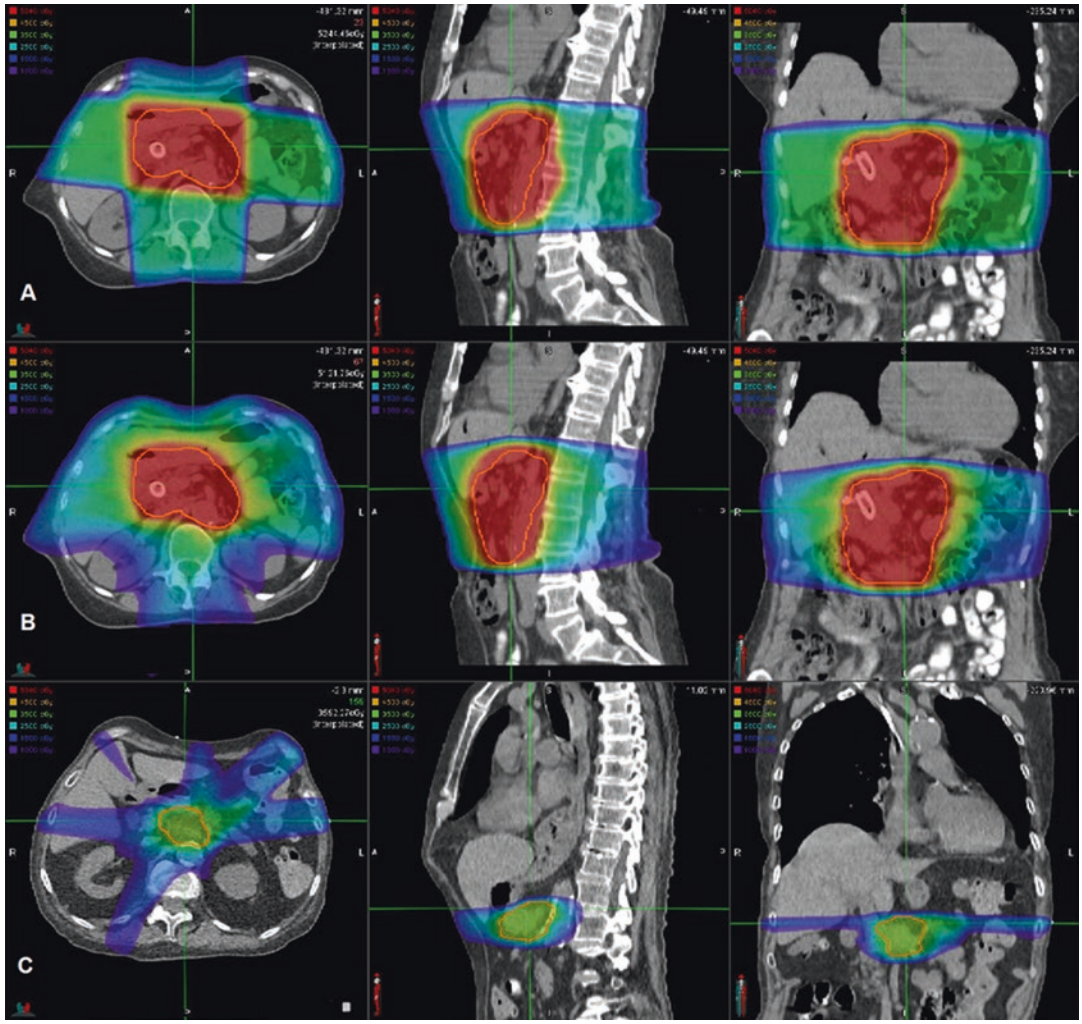

Fig. 37.1 Comparison of 3D conformal, IMRT, and SBRT plans for pancreatic cancer. Color wash of radiation dose distribution in axial, sagittal, and coronal planes. The PTV is outlined in orange. Different colors represent dose: red (5040 cGy), yellow (4500 cGy), green (3500 cGy), light blue (2500 cGy), royal blue (1500 cGy), purple (1000 cGy). (**a**) 3D conformal technique for resectable, T1N0M0, adenocarcinoma of the pancreatic head treated with preoperative chemoradiation to 5040 cGy in 28 fractions. (**b**) IMRT technique for the same patient in A. (**c**) Patient with a locally advanced, unresectable, T4N1M0, adenocarcinoma of the pancreatic head with encasement of the celiac artery and enlarged periportal lymph nodes treated to 3500 cGy in 5 fractions using SBRT

to a computer planning system, where radiation oncologist will contour or outline the tumor or tumor bed, at-risk nodal or soft tissue regions, and OARs. Doses will be assigned to PTVs and dose limitations will be applied to OARs. Using this information, the radiation planning team, dosimetrists, physicists, and radiation oncologists, will create a 3DCRT or IMRT plan which will then undergo thorough evaluation and modification before obtaining physician approval. Rigorous quality assurance (QA) is performed prior to treatment delivery to ensure that the teletherapy machine can effectively and safely administer the radiation plan as designed. In most clinical settings, radiation therapy is delivered in an outpatient clinic setting daily, Monday–Friday, for the prescribed number of treatments, ranging from a one-time treatment to greater than 9 weeks.

Table 37.1 Selected studies stereotactic body radiation therapy for primary sites

Primary site	Median follow-up (m)	# of patients	Median dose	Median tumor size	Local control	Overall survival	Toxicity	Comments
Lung								
Timmerman [14]	34.4 m	59	18 Gy × 3 fx	20% T2	3-yr: 97.6% primary, 90.6% lobe, 87.2% regional	3-yr: 55.8%	Grade 3: 12.7% Grade 4: 3.6%	RTOG 0236
Ricardi [15]	28 m	62	15 Gy × 3 fx	30% T2	3-yr: 87.8%	3-yr:57.1%	Minimal in 10%	
Nagata [16]	47 m inoperable 67 m operable	104 65	12 Gy × 4 fx	Median 2.1 cm both groups	3-yr: 87.3% inoperable 85.4% operable	3-yr: 59.9% 3-yr: 76.5%	Grade 3: 9.8% inoperable, 7.7% operable Grade 4: <2% inoperable	JCOG 0403
Liver (HCC)								
Bujold [17]	31 (2–36)	102	36 Gy in 6 fx (24–54 Gy)	117 cc/7.2 cm	1-year 97%	Median 17 m 1-year 55%	30% Grade ≥ 3	55% with PVT 61% with multiple lesions
Lasley [18]	CPA: 33 CPB: 46	59 CPA: 39 CPB: 21	CPA: 48 Gy (36–48 Gy/3 fx) CPB: 40 Gy/5 fx	34 cc	1 year CPA: 91% CPB: 82%	Median /3 yr. CPA: 44.8 m/61% CPB: 17.0 m/26%	Grade ≥ 3 CPA: 11% CPB: 38%	20% with PVT
Scorsetti [19]	8 month	43	<3 cm:48–75 Gy in 3 fx 3–6 cm: 36–60 Gy in 6 fx	4.8 cm	1-year All patients: 86% BED>100: 100% BED<100: 52%	Median/1-year 18 months/78%	16% Grade ≥ 3	47% CPB, 20% PVT

Pancreas								
Herman [20]	13.9 m	49	33 Gy in 5 fractions	Median PTV was 71.4 cc (31.9-225 cc)	1 year was 78%	Median 13.9 m	≥2 toxicity: Acute = 2% Late = 11%	Unresectable 84% panc head
Tozzi [21]	11 m	30	7.5 Gy × 6 fx, reduced to 6 Gy × 6 fx OARs to high	25.6 cc	85% at 11 m all patients 96% at 2 yrs. for 45 Gy	1-yr: 47%	No ≥3 toxicity	Unresectable/ recurrent
Didolkar [22]		85	25.5 Gy in 3 fx (5–10 Gy/fx)	60 cc	1-yr: 92%	Median 18.6 m	Grade ≥ 3: 22%	Unresectable
Prostate								
Pham [23]	60 m	40	6.7 Gy × 5 fx	NA	93% PSA RFS at 5 yr	5-yr: 75%	No ≥3 toxicity	
Katz [24]	30/17	50/254	7 Gy in 5 fx/7.25 Gy in 5 fx	NA	PSA: 88% <1 ng/ml at 30 m 81% <1 ng/ml at 24 m	94% at 30 m 99% at 17 m	No ≥3 late or acute toxicity	
Mantz [25]	60 m	102	8 Gy × 5 fx	NA	6-yr 99% PSA RFS at 6 yr	NR	No ≥2 toxicity	

Select Disease Sites

Head and Neck

Definitive radiation therapy with or without chemotherapy is the standard of care for many head and neck tumors, particularly squamous cell carcinoma of the oropharynx, nasopharynx, supraglottis, larynx, and hypopharynx. This paradigm preserves function and spares the morbidity of extensive surgical resections without compromising survival [26, 27]. Due to the high risk of lymphatic spread, radiation targets the primary tumor site and at-risk regional nodal regions in a risk-dependent manner with gross disease receiving a higher dose and low-risk areas receiving a lower dose.

Radiation can be delivered after surgical resection for large tumors (T3, T4), positive or close margins, multiple positive lymph nodes, large positive lymph nodes (>3 cm), lymphovascular space invasion, perineural invasion, and extracapsular nodal extension [28]. Postoperative RT improves local-regional control, relapse-free survival, and disease-specific survival [29, 30]. Chemoradiation improves local-regional control and disease-free survival in the setting of positive margins or extracapsular nodal extension [31]. Advances in radiation delivery with IMRT improves tumor coverage and reduce toxicity [32].

Lung Cancer

Radiation plays an important part in the multidisciplinary management of lung cancer at all stages. Improvements in treatment delivery and new technologies, such as the development and widespread adoption of stereotactic body radiation therapy (SBRT), have expanded the indications for radiation therapy both in early and metastatic disease.

Although the gold standard for medically fit patients with early stage NSCLC remains surgical resection, SBRT has emerged as a highly effective treatment for peripheral lesions. Using a 3-fraction schema, SBRT achieved local control at 5 years of 93%, lobar control of 80% and regional control of 62% [14]. In comparison to conventional RT, SBRT was equally effective with less toxicity, thus making SBRT the preferred radiation technique for solitary peripheral tumors [33]. For more central lung lesions, early reports showed higher risk of toxicity compared to peripheral lesions, so protracted dose fractionation schemes were developed, which allowed for safe treatment of central lesions with both convenience and efficacy [34–36].

More controversial is whether SBRT may be an acceptable alternative for patients suitable for surgical resection. Early phase I/II studies have been promising [37]. A combined analysis of two trials that randomized patients to lobectomy and mediastinal lymph node dissection versus SBRT demonstrated a 3-year survival advantage for SBRT (95% vs 79%) with no difference in recurrence-free survival, and a higher rate of grade 4–5 toxicity in the surgical arm [38]. This combined analysis has limitations, and the question continues to be addressed in additional trials: VALOR trial through Veterans Affairs, multi-institutional STABLEMATES trial [39]. The results of these randomized controlled trials may establish a role for SBRT in operable early stage lung cancer.

The role and benefit of radiation therapy in operable stage II and III disease is less well defined. Postoperative radiation is often recommended for positive margins not amenable to re-resection and for positive mediastinal nodes. This is supported by data as postoperative radiation improves survival with involved mediastinal lymph nodes, but decreased survival in cases without mediastinal adenopathy [40, 41]. Unfortunately, radiation was not randomized in the major studies and techniques from that era are associated with higher rates of toxicity. An ongoing trial, LungART, will assess the benefit of modern and uniform RT delivery in mediastinal node-positive patients following surgery [42].

The role of radiotherapy in locally advanced NSCLC, stage IIIA/B, has been investigated as both definitive and preoperative treatment. Preoperative chemoradiation has been compared to both definitive chemoradiation [43] and induction chemotherapy followed by postoperative

radiation [44]. In both instances, pathological complete response and local control were superior with preoperative radiation, but without an overall survival benefit. In these studies patients receiving radiation and pneumonectomy had decreased survival [45]. For inoperable stage III patients, definitive chemoradiation remains the standard of care. Attempts to improve outcomes with increased radiation dose or adjuvant targeted EGFR inhibition failed to show improvement, but secondary analyses revealed similar efficacy with less severe toxicity using modern IMRT techniques compared to 3D conformal approaches, despite larger and more advanced stage disease in the IMRT patients [46]. Figure 37.2 shows a typical IMRT plan for lung cancer with isodose lines and a dose-volume histogram showing the dose to targets and surrounding organs.

Gynecologic Malignancies

The mainstay of most gynecologic malignancies remains surgery. While often utilized in the adjuvant setting to decrease the risk of locoregional

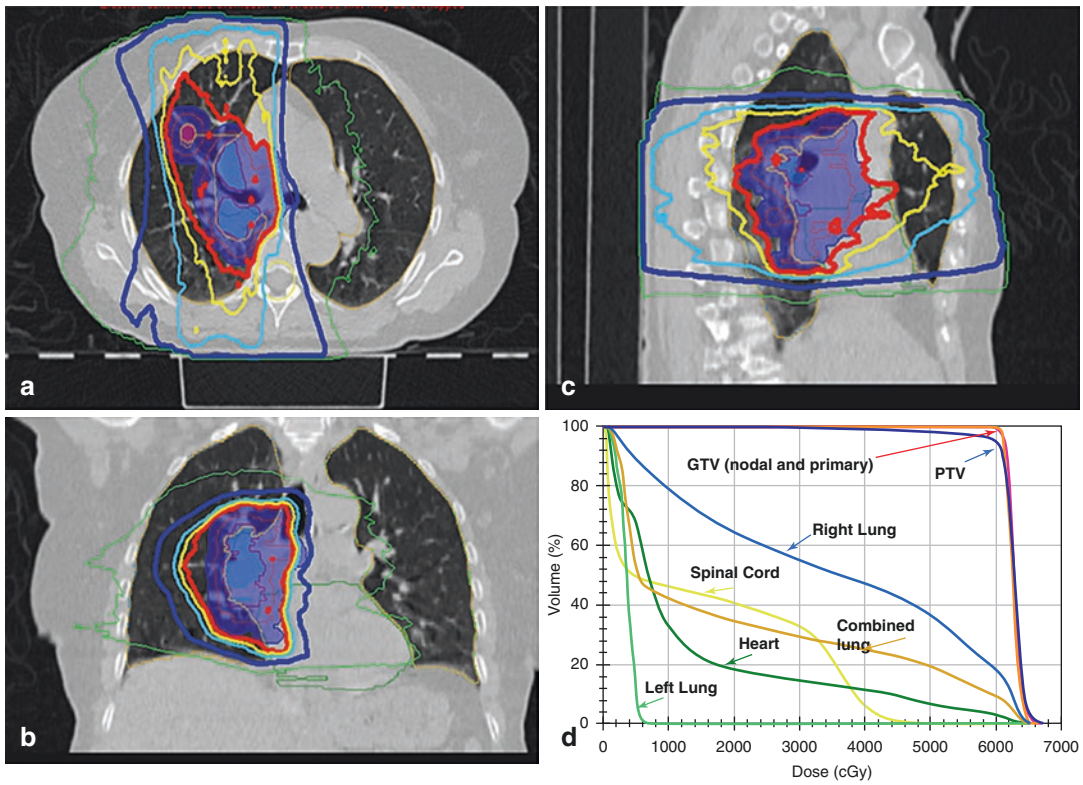

Fig. 37.2 Lung IMRT plan. A 76-year-old woman with T1 N1 adenocarcinoma of the right lung. Medically inoperable because of recent stroke and need for pneumonectomy due to bulky hilar disease. (**a**) Axial, (**b**) coronal, and(**c**) sagittal slices of planning CT with radiation isodose lines (60Gy red, 54Gy yellow, 45Gy light blue, 20Gy blue and 5Gy green, which are used to spatially evaluate the radiation dose distribution. Both the PET-positive primary tumor (solid red) and nodal disease (solid light blue) are delineated. They are then expanded by 5–7 mm and then manually edited by the physician to create a CTV (dark orange) which encompasses areas at high risk for microscopic spread of disease. This is again expanded by 5–7 mm to create the PTV, which accounts for daily variance in anatomy and patient position. The organs at risk are also drawn including the heart (dark green), spinal cord (yellow), and lungs (dark yellow). The uninvolved lung, best seen in the coronal section, is largely spared any significant radiation dose. A dose-volume histogram is generated (**d**) and utilized to quantitatively assess parameters determined as adequate and safe by the physician for target coverage and doses to organs at risk

recurrence, radiation therapy does provide effective definitive therapy in specific settings.

Cervical Cancer

The cervix has a rich lymphovascular supply which influences patterns of spread and treatment. Deep stromal invasion, lymphovascular space invasion, and tumor size predict for pelvic and para-aortic lymph node involvement [47]. Adjuvant pelvic radiation leads to lower rates of recurrence in patients with deep stromal invasion, large tumor size, and LVSI whereas adjuvant pelvic RT with concurrent chemotherapy increases PFS and OS in patients with positive margins, parametrial invasion, and lymphadenopathy [48].

Nonoperative treatment consisting of external beam radiotherapy (EBRT) and brachytherapy with concurrent cisplatin-based chemotherapy is the preferred treatment for stage IB2, II, III, and IVA cervical cancer [49]. EBRT is administered utilizing 3DCRT or IMRT and encompasses gross disease, the entire cervix, uterus, parametria, internal and external iliac lymph nodes, and, depending upon nodal involvement, the common iliac and the para-aortic lymph nodes [50, 51]. In the era of image-guided EBRT and adaptive brachytherapy, the rates of local control range from 96% for IB2 disease to between 73% and 6% for stage III/IV disease with limited severe morbidity [52, 53].

Uterine Cancer

Surgical staging, including total hysterectomy, bilateral salpingo-oopherectomy, and lymph node assessment through either lymph node dissection or sentinel lymph node biopsy, is both diagnostic and therapeutic. The role of adjuvant pelvic and regional nodal irradiation is somewhat controversial. In general, adjuvant EBRT recommended is considered for woman with grade 3 disease and greater than or equal to 50% myometrial invasion or cervical stromal involvement. Pelvic radiation, pelvic radiation and chemotherapy, and chemotherapy alone are treatment options considered in the setting of positive lymph nodes [54]. Women who are not surgical candidates can be treated with definitive radiation therapy delivered via brachytherapy alone for woman without imaging evidence of deep myometrial invasion or extrauterine disease or a combination of EBRT and brachytherapy [55].

Vular/Vaginal

Local and regional radiation is an important modality in the adjuvant setting for high-risk vulvar cancers and can be used for preoperative down staging or as definitive therapy for locally advanced or inoperable patients [56]. External beam radiation and brachytherapy with or without concurrent chemotherapy form the backbone of treatment of primary vaginal squamous cell carcinomas [57].

Breast Cancer

Evaluation of the axilla has historically been important for both diagnosis and outcomes. In the last two decades, surgical management of the axilla has progressively evolved from more radical surgery to a more modest axillary lymph node dissection (ALND) [58, 59] and finally arriving at the use of sentinel lymph node biopsy (SLNB) as sufficient and less toxic in most early stage node-positive patients [60–62]. Selective ALND is now only recommended for patients with significant disease burden, inflammatory breast cancer, clinically positive nodes at presentation, or are otherwise unsuitable for SLNB [63].

The use of radiotherapy has mirrored these changes over the same period. In early stage disease radiation therapy is delivered with the intent of addressing microscopic disease, both in the breast and regional lymph nodes, and contributes to excellent control and survival [64, 65]. Analysis of multiple randomized trials showing disease-free and overall survival benefits when delivered after mastectomy [66]. Axillary radiotherapy has also been shown to be non-inferior with less toxicity than axillary dissection in sentinel node-positive patients in two randomized trials [67, 68]. Studies have also evaluated regional nodal irradiation (RNI), including the internal mammary chain, in high-risk node-negative and node-positive patients after ALND. These trials demonstrated that in early

stage breast cancer, RNI improved local-regional control, disease-free and metastasis-free survival, with trends toward improved overall survival [69, 70]. Outcomes in the treatment of early stage lymph node-positive patients in the modern era have been excellent with isolated locoregional failure at 4.2% at 10 years, with disease-free survival at 82% and overall survival at 82.8% [70].

The benefits of RNI must be weighed with the potential for toxicity. Inclusion of the internal mammary chain, in particular, raises concerns for possible cardiovascular toxicity, which would reduce any clinical benefit [71, 72]. Advances in technology and treatment techniques have allowed for reduced radiation dose to heart and the associated toxicity, including deep inspiration breath hold [73, 74], intensity-modulated radiation therapy [75–77], and proton therapy [78, 79]. Figure 37.3 shows an IMRT plan covering the breast and regional lymphatics. These improvements also allow for better coverage of the target while at the same time reducing exposure to surrounding normal tissues and improve therapeutic ratio. Further improvements in patient selection using molecular and genetic profiling [23] as well as the outcomes of multiple current clinical trials investigating management of the axilla after neoadjuvant chemotherapy will further clarify radiation's role in the management of the axilla in the modern era [80].

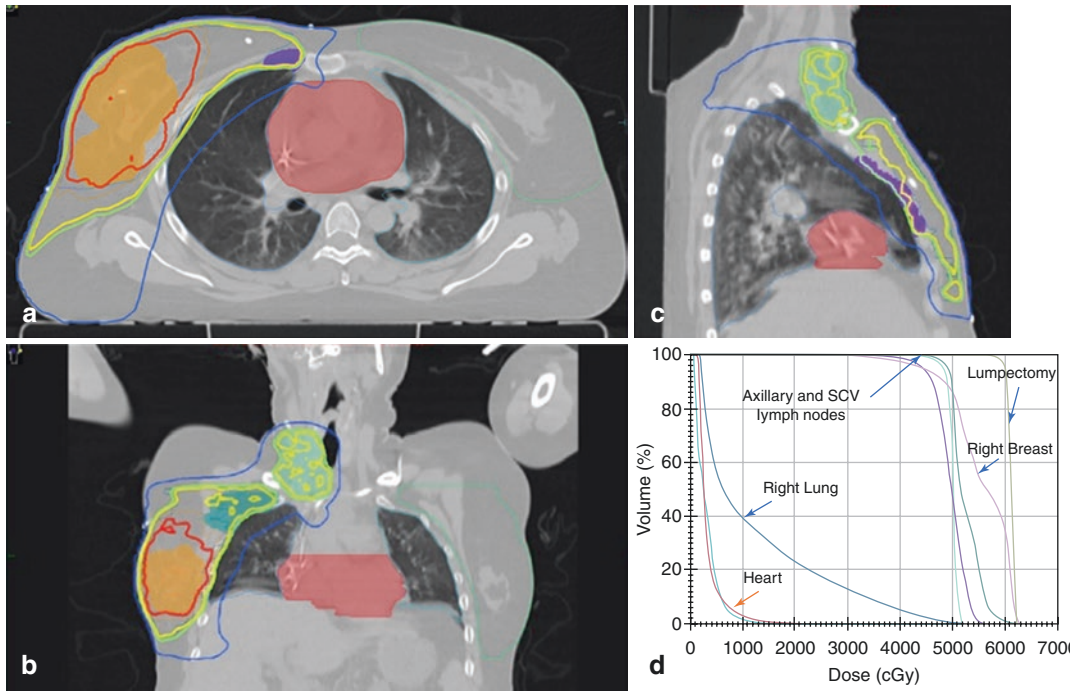

Fig. 37.3 Breast IMRT plan for a 30-year-old woman with clinical T3 N0 estrogen receptor-positive, HER2-positive invasive ductal carcinoma treated with neoadjuvant chemotherapy followed by lumpectomy and SLNB, ypT2N1. She declined axillary lymph node dissection and received 50Gy to the whole breast, supraclavicular, internal mammary, and axillary lymph nodes, followed by a 10Gy boost the lumpectomy cavity plus a margin. (**a**) Axial, (**b**) coronal, and(**c**) sagittal slices of planning CT with radiation isodose lines (60Gy red, 50Gy yellow, 47.5Gy green, 20Gy blue) are used to evaluate the radiation dose distribution. The right breast is contoured in pink, the IM nodes in purple, the supraclavicular nodes in light green, the axillary nodes in dark green, and the lumpectomy PTV in orange. Organs at risk including the heart (red) and right lung (light blue) are also delineated and their radiation exposure assessed. The shaping of the higher dose radiation away from the heart and lungs can be seen in all three planes. A dose-volume histogram is generated (**d**) and utilized to quantitatively assess parameters determined as adequate and safe by the physician for target coverage and doses to organs at risk. It can measure how much of a target, either expressed as percentage or absolute volume, is receiving a given dose of radiation

Gastrointestinal Malignancies

Pancreas

Pancreatic primary tumors are staged based on their surgical resectability: resectable, borderline resectable, locally advanced unresectable, and metastatic. However, due to the high risk of local, regional, and distant recurrence, chemotherapy and radiation are often utilized in a neoadjuvant, adjuvant, or definitive manner.

Preoperative radiation can sterilize vessel margins, address micrometastatic disease, and facilitate margin-negative oncologic resections [81]. The role of elective nodal irradiation is controversial. At the Medical College of Wisconsin, preoperative and definitive radiation fields generally include the major trunks of the celiac and SMA axes and suspicious peripancreatic lymph nodes. A retrospective review of 108 locally advanced unresectable patients treated with chemotherapy followed by chemoradiation demonstrated that 40 patients were ultimately able to undergo successful resection [82].

For patients undergoing upfront surgical resection in pancreas, adjuvant radiation therapy is often administered for risk features for locoregional and distant recurrence. Consensus guidelines for adjuvant pancreas chemoradiation not only describe recreating and including the preoperative tumor volume using imaging but also recommend coverage of the surgical anastomoses and at-risk nodal areas [83].

The use of SBRT for pancreas is increasingly studied as a promising way to deliver high-dose radiation while minimizing surrounding organ exposure and limiting the overall number of treatments. As with fractionated radiation, SBRT can be utilized as definitive local therapy or to potentially downstage patient and facilitate surgery [20, 84].

Anal

Prior to the 1970s, patients with anal canal carcinoma underwent abdominal perineal resection (APR) which was associated with sub-optimal disease control and morbidity [85]. Nigro et al. reported the efficacy of radiation with combined 5-fluorouracil (5-FU) and mitomycin-C (MMC) chemotherapy in the absence of surgical resection [86]. Sphincter-preserving chemoradiation was validated by multiple randomized studies, becoming the standard of care for the management of localized anal canal carcinoma [87–90]. While reported outcomes, such as local control, colostomy-free survival, and overall survival, have been excellent, chemoradiation for anal canal carcinoma is associated with significant hematologic, gastrointestinal, and dermatologic toxicity. IMRT has been shown to minimize treatment-related toxicity and achieve acceptable disease control [91, 92]. RTOG 0529, a multi-institutional phase II study of dose-painted IMRT with 5-FU and MMC demonstrated decreased toxicities as compared to historical standards with similar rates of 5-year DFS and OS, 68% and 76%, respectively [93, 94]. With the increased precision of IMRT, atlases guide radiation oncologists to ensure coverage of primary and gross nodal disease and at-risk lymph node regions, including the inguinal, mesorectal, presacral space, and the internal and external iliac [95].

Rectal

Multimodality therapy is the standard for rectal primary tumors with invasion through the muscularis propria or nodal positivity. The German Rectal Cancer Group compared preoperative to postoperative chemoradiation, demonstrating a significant reduction in local recurrence and treatment-related toxicity with preoperative chemoradiation [96, 97]. The standard for locally advanced resectable rectal cancer is preoperative chemoradiation followed by surgical resection followed by adjuvant chemotherapy. Unlike many other disease sites, IMRT has not demonstrated improved toxicity as compared to 3DCRT [98]. 3D conformal fields encompass the gross tumor, entire mesorectum, presacral space, internal iliacs, and external iliacs for T4 lesions.

There is an increasing body of evidence supporting the use of total neoadjuvant therapy to facilitate the administration of all systemic therapy and, in some settings, enable omission of surgical resection [99]. NRG-GI002 is a phase II trial assessing FOLFOX × 4 months followed by preoperative radiation with capecitabine followed

by surgical resection. There is retrospective and growing prospective data demonstrating that a "wait and see approach" with total neoadjuvant therapy with close clinical observation rather than surgical resection may be a viable, nonsurgical management option for patients with locally advanced rectal cancer [100, 101].

Liver

Traditionally radiation therapy had a limited role in hepatic malignancies due to the relatively low radiation tolerance of the liver, but with modern radiotherapy techniques (IMRT, SBRT), high-quality image guidance, and improved motion management, ablative doses can be delivered safely with good efficacy [102]. Although radiation therapy is often used when other options are exhausted, it can be offered as a definitive standalone treatment [17, 18, 103], as a bridge to transplant [104–106], or in combination with other therapies [107, 108]. SBRT can offer excellent long-term control with minimal toxicity. Prospective longitudinal assessment of quality of life metrics shows good tolerance with only minimal temporary worsening of appetite and fatigue without overall change in quality of life after SBRT [109].

Hepatocellular Carcinoma

Several prospective trials [17–19] have shown safety, good overall survival, and excellent local control for unresectable HCC (overall local control of 75–91% with >90% for small tumors (<3 cm) treated with ablative doses). Additionally, SBRT has been shown to be effective for patients with portal vein invasion [17, 110]. Although there are no randomized trials comparing outcomes between various modalities, retrospective studies suggest SBRT is equivalent to other liver-directed modalities like radiofrequency ablation, transarterial chemoembolization, transarterial radioembolization [111–115].

Cholangiocarcinoma Limited prospective data is available for guiding management of cholangiocarcinoma, but retrospective reviews show good response and limited toxicity with ablative radiation doses which improve outcomes [116–118]. Patients receiving a BED dose greater than 80.5 Gy had improved outcomes compared to those receiving less dose (3-year overall survival (73% vs 38%) and local control (78% vs 45%) [119].

Metastases Although radiation was once only considered a palliative option, the advent of SBRT allowed for radiation dose escalation for definitive ablative treatments. Several early phase clinical trials investigating dose escalation showed excellent local control and limited toxicity. The University of Colorado trial reported overall 2-year actuarial local control of 92% for patients receiving 60 Gy in 3 fractions with tumors less than 3 cm having local control of 100% [120]. Similarly, a trial from UT-Southwestern using a 5-fraction scheme reported 2-year actuarial control rates of 56%, 89%, and 100% for 30 Gy, 50 Gy, and 60 Gy cohorts, respectively, which highlights the role of dose and tumor control [121]. Even large tumors can be safely treated if the dose is personalized to match normal tissue tolerance. A study from Princess Margaret Hospital using a 6 fraction regimen that was adjusted according to the probability of normal tissue tolerance showed a 1-year local control of 71% for a cohort with a median volume of 75 cc with minimal toxicity [122].

Cutaneous Malignancies

Melanoma

Radiation therapy can be used as local and regional therapy for melanoma. As a local therapy, RT significantly improves local control for patients with nonmetastatic desmoplastic melanoma treated with negative margin resections, who have traditionally high-risk features, including a Breslow depth > 4 mm, Clark level V tumor, or a head and neck tumor location and also reduces the local failure rate from 54% to 14% for patients with positive margins [123]. Additional primary site RT can be used as definitive treatment for unresectable melanomas or those who are medically inoperable and as an adjuvant therapy for those with close or positive

margin that cannot be re-excised and those with extensive neurotropism [124].

After resection of advanced melanomas, radiation therapy to the regional lymph node basins reduces the risk of regional failure [125–128]. For patients in high-risk subgroups, regional RT lowers the 5-year risk of regional recurrence from 30% to 6% for clinically detected lymph nodes and from 38% to 3% for patients with extracapsular extension [128]. Relative indications for covering regional lymphatics include positive lymph nodes (≥1 parotid node, ≥2 cervical or axillary nodes, ≥3 inguinofemoral nodes), large tumor size (≥3 cervical/axillary, ≥4 cm inguinofemoral), and extranodal extension. In these cases, adjuvant radiotherapy improves locoregional control, but not overall survival or relapse-free survival [125].

With the advent of immunotherapy, the role of adjuvant radiation therapy is less clear, but several reports suggest synergy between radiation and immunotherapy in the metastatic setting. These studies showed that melanoma patients treated with Ipilimumab plus radiation therapy had longer overall survival and better response rates than those on Ipilimumab monotherapy [129–131]. This synergistic relationship is possibility due to the release of tumor antigens because of the local radiation, which helps the immune system generate a more robust response and potentially abscopal effects.

Merkel Cell Carcinoma

Merkel cell carcinoma is a rare aggressive cutaneous neuroendocrine neoplasia that is radiosensitive. Due to its rarity, most of the evidence regarding management is limited to retrospective and population-based studies with limited prospective or randomized evidence [132, 133]. As such surgery is the mainstay of local and regional management, with radiation being used as a definitive modality in the surgically or medically inoperable patients or as adjuvant treatment after surgery to both primary and regional sites.

A meta-analysis of patients treated with definitive radiation showed good control rates of 92.4% at primary sites and a 83.7% at regional sites [134]. Likewise, one of the largest retrospective series showed 5-year local relapse-free survival of 90% for patients treated with RT alone [135]. Prophylactic regional radiation decreases the risk of regional relapse for stage I resected Merkel cell carcinoma from 16% to 0% [136].

Adjuvantly radiation is typically recommended to the primary site after excision except in those with small tumors <2 cm without adverse pathological features or the immunocompromised [137]. Regional radiation is recommended for multiple positive nodes or extracapsular extension, or as a prophylactic measure in instances when sentinel lymph node or surgical nodal evaluation is not recommended or impractical [132]. Adjuvant RT has been associated with improved outcomes for both patients with stage I–II [138] and node-positive disease [139].

Oligometastatic Disease

One of the fastest growing applications of advanced radiation therapy with IMRT and SBRT is in the oligometastatic setting when patients have a limited number of metastatic sites, typically one to three, and ablative radiation is used to control the sites of visible disease [140–142]. The concept of the oligometastatic state was proposed by Hellman and Weichselbaum in 1995 [143]. This theory suggested that prior to widespread metastases that cancer existed in a limited number of metastatic sites. The philosophy of this new paradigm is that ablating all known disease will improve progression-free survival and possibly even overall survival in properly selected patients. This shift is a significant deviation from the days when radiation was only given to metastatic sites as a means of symptomatic palliation and comes as a direct result of improve techniques and ability to give high radiation doses with rapid fall off and sparing of normal tissues. A recent phase II randomized trial of de novo metastatic lung cancer patients supports this paradigm. In this trial patients who responded to first-line chemotherapy were randomized to consolidative local therapy at metastatic sites or maintenance therapy alone, which tripled the

median progression-free survival with limited toxicity in patients receiving consolidative therapy [144]. Patients with a long-disease-free interval, breast histology, one to three small metastases, and disease sites amenable to higher radiation doses (biologic effective dose 90–100 Gy) are the best candidates for SBRT for oligometastatic disease [140]. Table 37.2 highlights some select studies showing results for using SBRT for various metastatic sites [120, 121, 145–156].

Table 37.2 Selected trials of stereotactic radiosurgery and stereotactic body radiation therapy for metastatic sites

Primary site	Median follow-up months	# of patients	Median dose	Local control	Overall survival	Toxicity
Brain						
Andrews [145]	NR	167 164	WBRT WBRT+SRS	71% 81%	4.9 m 6.5 m	<5% grade 3–4 toxicity in both arms
Aoyama [146]	7.8 m	65 67	WBRT+SRS SRS alone	1-yr local control 88.7% (WB + SRS) vs 72.5% (SRS)	7.5 m 8.0 m	<5% grade 3–4 toxicity in both arms
Kocher [147]	Survivors 49 m WBRT 40 m Obs	81 81 90 95	Surgery Surgery+WBRT SRS SRS + WBRT	Initial site relapse-rate 59% 27% 31% 19%	median 10.9 (WBRT) vs 10.7 (OBS)	Slightly more acute toxicity for WBRT, WBRT may impair learning and memory
Liver (mets)						
Rustoven [120]	15.4 m	38	60 Gy in 3 fx	2-yr: 96%	2-yr 39%	8% grade 3, no 4–5
Hoyer [148]	4.3 yrs	44	45 Gy in 3 fx	86%	2-yr: 38%	NR
Rule [121]	20 m	27	30–60 Gy in 5 fx	2-yr: 100% for 60 Gy, 89% for 50 Gy, 56% for 30 Gy	NA	No grade ≥ 3 toxicities
Lung						
Rustoven [149]	15.4 m (6–48)	38	60 Gy in 3 fx	2-yr: 96%	2-yr 39%	8% grade 3, no 4–5
Ricardi [150]	20.4 m (3–77)	61	45 Gy in 3 or 26 Gy in 1 fx	2-yr: 89%	2-yr: 66.5%	1.6% grade 3
Norihisa [151]	27 m (10–80)	34	48 Gy or 60 Gy in 4 fraction	2-yr: 90%	2-yr: 84%	3% grade 3
Spine						
Gerstzen [152]	21 m (3–53)	393	Mean dose 20 Gy in 1 fx	88% at 21 m	NA	No neurological effects
Yamada [153]	15 m (2–45)	93	18–24 Gy in 1 fx	90% at 15 m	Median 15 m	1% grade ≥ 3
Wang [154]	15.9 m	149	27–30 Gy in 3 fx	72% control	Median 23 m	7% grade ≥ 3
Abdominal nodes						
Choi [155]	15 m (2–65)	30	33–45 Gy in 3 fx	4-yr: 67%	4-yr: 50%	3% grade 3–4 toxicity
Jereczek-Fossa [156]	16.9 m	95	Median 24 Gy in 3 fx	3-yr: 68%	3-yr-31%	rare

Abbreviations: *m* months, *yr* year, *NA* not applicable, *NR* not reported, Gray, *fx* fraction, *WBRT* whole brain radiation therapy, *SRS* stereotactic radiosurgery

Conclusion

Over the past 120 years, radiation has become central to multimodality cancer management. Better understanding of cell biology and technological advances have enabled more targeted, effective therapy, enhancing damage to cancer cells and minimizing injury to adjacent nonmalignant cells. The development and refinement of image-guided IMRT, SRS, and SBRT, in particular, have led to dose escalation and improved conformality, maximizing the therapeutic ratio across multiple disease sites. Radiation plays an important role in locoregional therapy alongside surgery, chemotherapy, and other treatment techniques. In a growing number of clinical scenarios, radiation serves as an effective definitive treatment option.

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Y. Fong et al. (eds.), *Cancer Regional Therapy*, https://doi.org/10.1007/978-3-030-28891-4