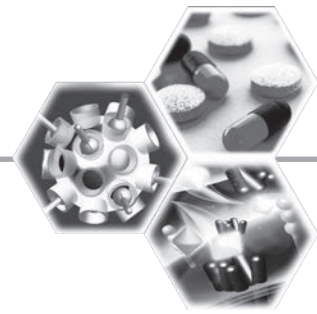

Development of regional chemotherapies: feasibility, safety and efficacy in clinical use and preclinical studies

Conventional oral and intravenous chemotherapies permeate throughout the body, exposing healthy tissues to similar cytotoxic drug levels as tumors. This leads to significant dose-limiting toxicities that may prevent patients from receiving sufficient treatment to overcome cancers. Therefore, a number of locoregional drug-delivery strategies have been evaluated and implemented in preclinical studies, clinical trials and in practice, in the past decades to minimize systemic toxicities from chemotherapeutic agents and to improve treatment outcomes. Localized treatment is beneficial because many cancers, such as melanoma, peritoneal cancer and breast cancer, advance locally adjacent to the site of the primary tumors prior to their circulatory invasion. In this article, we will review the feasibility, safety and efficacy of multiple localized chemotherapies in clinical use and preclinical development.

Shuang Cai[1], Taryn R Bagby[1] & M Laird Forrest[†1]

[1]Department of Pharmaceutical Chemistry, University of Kansas, 2095 Constant Ave, Lawrence, KS 66047 USA
[†]Author for correspondence:
Tel.: +1 785 864 4388
Fax: +1 785 864 5736
E-mail: mforrest@ku.edu

Localized chemotherapy

The most common types of cancer therapies include surgery, radiation, chemotherapy and their combinations. In the past decades, new treatment regimens have been discovered and implemented in the clinic, to concurrently or successively complement the standard procedures in cancer therapy, and provide patients with improved treatment outcomes with fewer side effects. Some of these clinical and investigational treatment methods include: anti-angiogenesis therapy [1–3], immunotherapy [4–6], gene therapy [7–9], bone marrow transplantation and peripheral blood stem-cell transplantation [10–12]. Owing to the complex nature of the molecular targets of these newer therapies and their relatively short history since clinical introduction, they are not as widely used as conventional chemotherapy and are substantially more expensive.

Most cancer patients will receive some type of chemotherapy during their treatments in the form of adjuvant, neoadjuvant or palliative therapy. Although the first-line chemotherapies have provided lifesaving treatments for numerous cancer patients, their potential life-threatening side effects should not be overlooked. The most severe side effects of chemotherapy are mainly caused by the systemic toxicities of the anticancer drugs. Since the conventional chemotherapy is administered intravenously via a catheter or via the oral route, the cytotoxic drug travels throughout the systemic circulation of the patient and accumulate in his or her healthy organs, such as the kidneys, heart and liver, which eventually causes organ toxicity over time.

One of the issues with infusion and oral chemotherapy is that the effective dose of conventional cytotoxic agents is often greater than or close to the maximum tolerable dose in the patient, depending on his or her disease stage and health condition. Therefore, to minimize the systemic exposure of the highly toxic chemotherapeutic agents, alternative locoregional drug-delivery routes have been explored in both preclinical investigations and clinical trials. To date, several localized chemotherapies have been adapted into clinical practices, providing cancer patients with additional options of therapy with fewer side effects. In this review, localized chemotherapy methodologies will be described, which include isolated limb perfusion (ILP), isolated limb infusion (ILI), heated intraperitoneal chemotherapy (HIPEC), intrapleural perfusion **hyperthermo-chemotherapy** (IPPHC), isolated hepatic perfusion chemotherapy (IHP), percutaneous hepatic perfusion (PHP), transarterial **chemoembolization** (TACE), brain chemowafers and **lymphatic chemotherapy**. All worldwide open trials of the aforementioned regional chemotherapies are summarized in **Table 1** [201]. This review article provides a basic introduction to a variety of regional chemotherapies. More detailed demonstrations of each procedure and results of the corresponding clinical trials are summarized in review articles elsewhere [13–26].

FUTURE SCIENCE part of fsg

Table 1. Worldwide open trials of regional chemotherapy.

Trial number	Official title	Phase	Recruiting period
NCT00873782	Safety and Feasibility of Transvenous Limb Perfusion with Normal Saline in Human Muscular Dystrophy	I	03/2009–05/2013
NCT01323517	A Phase II Trial of the Addition of Ipilimumab (MDX-010) to Isolated Limb Infusion (ILI) with Standard Melphalan and Dactinomycin in the Treatment of Advanced Unresectable Melanoma of the Extremity	II	02/2011–02/2015
NCT00565968	A Phase I Dose Escalation Trial to Evaluate Safety and Efficacy of Oral Sorafenib (Nexavar) with Regional Melphalan via Normothermic Isolated Limb Infusion (ILI) in Patients with Intransit Extremity Melanoma	I	10/2007–12/2014
NCT01127594	A Multi-Center Phase I Dose Escalation Trial to Evaluate Safety and Tolerability of Intra-Arterial Temozolomide for Patients with Advanced Extremity Melanoma Using Normothermic Isolated Limb Infusion	I	07/2010–12/2011
NCT01144442	WCC# 59: Pilot Study of Hyperthermic Intraperitoneal Chemotherapy Utilizing Carboplatin in First Recurrence		08/2010–09/2013
NCT01163552	Surgical Cytoreduction Followed by Intraoperative Intrathoracic Hyperthermic Chemotherapy Perfusion for the Management of Disseminated Pleural Malignancies	II	06/2010–06/2012
NCT00557557	A Phase I Trial of Isolated Hepatic Perfusion with Oxaliplatin and 5-fluorouracil (5-FU) Followed by Hepatic Arterial Infusion of FUDR for Patients with Unresectable Colorectal Liver Metastases	I	07/2007–07/2012
NCT01250158	First *In-vivo* Trial of the Liver Percutaneous Isolated Localized Perfusion (PILP) Set for the Treatment of Liver Metastases		09/2010–04/2012
NCT01348412	Phase II Randomized Study Comparing the Association of Intraarterial Perfusion of Raltitrexed and Oxaliplatin Versus Oral Capecitabine and Mitomycin Using Intravenous Perfusion for Colorectal Cancer Patient with Metastases Localized to Liver After Failure of Conventional Treatments.	II	12/2010–12/2012
NCT00557557	A Phase I Trial of Isolated Hepatic Perfusion with Oxaliplatin and 5-fluorouracil (5-FU) Followed by Hepatic Arterial Infusion of FUDR for Patients with Unresectable Colorectal Liver Metastases	I	07/2007–07/2012
NCT01348412	Phase II Randomized Study Comparing the Association of Intraarterial Perfusion of Raltitrexed and Oxaliplatin Versus Oral Capecitabine and Mitomycin Using Intravenous Perfusion for Colorectal Cancer Patient with Metastases Localized to Liver After Failure of Conventional Treatments.	II	12/2010–12/2012
NCT01236690	The Clinical Research of the Intermediate and Advanced Hepatoma Treated by Cinobufacin by Perfusion of Hepatic Artery Combining the Arterial Embolotherapy	II	11/2010–10/2013
NCT00857805	Randomized Controlled Trial of Transarterial Chemoembolization Versus Proton Beam Radiotherapy for the Treatment of Hepatocellular Carcinoma		01/2009–01/2012
NCT01360255	AFP – L3% and DCP as Tumor Markers in Patients with Hepatocellular Carcinoma (HCC) Treated with Transarterial Chemoembolisation (TACE)		05/2010–12/2011
NCT01009801	A Phase I Open Label/Phase II Randomized, Double-Blind, Multicenter Trial Investigating the Combination of Everolimus and TransArterial ChemoEmbolization (TACE) with Doxorubicin in Patients with Hepatocellular Carcinoma	I/II	02/2010–09/2012
NCT00844883	Phase II Trial of Sorafenib Combined with Doxorubicin Eluting Bead-Transarterial Chemoembolization (LC Bead-TACE) for Patients with Hepatocellular Carcinoma	II	02/2009–02/2012
NCT01229839	Chemoembolization of Unresectable Hepatocellular Carcinoma with or without Lipiodol: Effectiveness and Safety. A Prospective and Randomized Clinical Trial.	III	11/2010–11/2012
NCT01352728	A Phase II Study of Transarterial Chemoembolisation and Axitinib for the Treatment of Unresectable Hepatocellular Carcinoma	II	05/2011–05/2015
NCT01327521	International Randomized Study of Transarterial Chemoembolization Versus CyberKnife for Recurrent Hepatocellular Carcinoma	III	02/2011–02/2014
NCT00908752	A Randomized, Double-blind, Multicenter Phase III Study of Brivanib Versus Placebo as Adjuvant Therapy to Trans-Arterial Chemo-Embolization (TACE) in Patients with Unresectable Hepatocellular Carcinoma (The BRISK TA Study)	III	08/2009–02/2014

Data from [201].

Table 1. Worldwide open trials of regional chemotherapy (cont.).

Trial number	Official title	Phase	Recruiting period
NCT00960518	Combination Therapy with TACE and Adefovir Compared with TACE Alone for HBV-related Unresectable Hepatocellular Carcinoma	II	08/2009–08/2012
NCT01259414	Chemoembolization for Unresectable Hepatocellular Carcinoma: Comparison of Survival Rates with Different Methods of Combining Drugs. A Prospective and Randomized Clinical Trial	III	01/2011–01/2013
NCT01164202	A Double-Blind, Randomized, Phase II/III Study Comparing the Use of Chemoembolization Combined with Sunitinib Against Chemoembolization Combined with a Placebo in Patients with Hepatocellular Carcinoma (SATURNE)	II/III	07/2010–07/2013
NCT01011010	Phase Ib Clinical Trial of Sorafenib in Combination with Transarterial Chemoembolization (TACE) in Patients with Unresectable Hepatocellular Carcinoma (HCC)	I	07/2009–10/2011
NCT01004978	A Phase III Randomized, Double-Blind Trial of Chemoembolization with or without Sorafenib in Unresectable Hepatocellular Carcinoma (HCC) in Patients with and without Vascular Invasion	III	10/2009–09/2012
NCT01020812	Phase II Study of Combination Stereotactic Body Radiotherapy (SBRT) with Transarterial Chemoembolization (TACE) for Unresectable Hepatocellular Carcinoma	I/II	09/2009–09/2012
NCT01387932	Phase III Prospective, Randomized, Blinded, and Controlled Investigation of HepaSphere/QuadraSphere Microspheres for Delivery of Doxorubicin for the Treatment of Hepatocellular Carcinoma	III	04/2011–03/2013
NCT01236690	The Clinical Research of the Intermediate and Advanced Hepatoma Treated by Cinobufacin by Perfusion of Hepatic Artery Combining the Arterial Embolotherapy	II	11/2010–10/2013
NCT01350206	Hepatic Resection Versus Transcatheter Arterial Chemoembolization for Hepatocellular Carcinoma Complicated by Portal Vein Tumor Thrombosis. A Prospective and Randomized Clinical Trial	IV	04/2010–5/2012
NCT01040559	Chemoembolisation of Non Resectable, Non Metastatic Hepatocellular Carcinomas Combining DC Bead Microspheres Loaded with Idarubicin (Zavedos®): Phase I Trial	I	12/2009–12/2011
NCT00467974	A Randomized Controlled Trial of Transarterial Ethanol Ablation (TEA) with Lipiodol-Ethanol Mixture (LEM) Versus Transcatheter Arterial Chemoembolisation (TACE) for Unresectable Hepatocellular Carcinoma	III	06/2007–06/2012
NCT01186406	Phase II Trial for Patients with Newly Diagnosed Glioblastoma Multiforme (GBM) Treated with Gliadel Followed by Concurrent Radiation Therapy, Temodar and Avastin, then Followed by Avastin and Temodar Post-Radiation	II	03/2011–10/2011
NCT00814593	Randomized Phase II Trial of Intralesional Lymphokine Activated Killer Cells or Polifeprosan 20 with Carmustine Implant (Gliadel® Wafer) as Consolidation Therapy After Primary Treatment of Newly Diagnosed Resectable Glioblastoma	II	11/2008–07/2012
NCT01310868	An Evaluation of the Tolerability and Feasibility of Combining 5-Amino-Levulinic Acid (5-ALA) with Carmustine Wafers (Gliadel) in the Surgical Management of Primary Glioblastoma (GALA-5 Trial)	II	05/2011–05/2015

Data from [201].

Isolated limb perfusion chemotherapy

Isolated limb perfusion was initially introduced in the clinic in 1958 by the American surgeons, Creech and Krementz, using an extracorporeal circuit for regional chemotherapy of extremity melanoma [27]. Initially, the ILP procedure was performed at room temperature, but this procedure was later modified by Stehlin to be performed as a hyperthermic perfusion at 41–43°C [28], as hyperthermia may enhance the cytotoxicity of chemotherapeutics and further improve response rates. ILP works by temporarily isolating the arm or leg of the patient from the circulatory system using a tourniquet, and perfusing a highly concentrated anticancer agent, such as melphalan, for a short period of time. Typically, several temperature probes are inserted into the subcutaneous tissue of the patient to monitor his/her body temperature. For example, ILP of the leg is performed by perfusing the anticancer drug melphalan through a catheter inserted into the iliac artery of the leg. Another catheter in the draining vein collects the blood and the melphalan solution is allowed to circulate for 1–2 h. A tourniquet secured at the base of the leg prevents the highly concentrated anticancer agent from entering the systemic circulation. The ILP allows 10–20-fold higher

Key Term

Hyperthermo-chemotherapy: Chemotherapeutic agents are administered via a heated solution, usually at a temperature of 40–43°C. It is believed that cancer cells are more sensitive to heat compare to normal cells, thus, heat makes cancer cells more susceptible to drug treatment.

Key Terms

Chemoembolization: A combination of chemotherapy and embolization treatment, in which an anticancer drug is directly administered to the diseased organ, usually the liver, via the artery that supplies blood to the organ; meanwhile, embolic materials, such as biodegradable nanoparticles, are co-administered to the organ to partially block the blood supply so that cancer cells are deprived from sufficient nutrients.

Lymphatic chemotherapy: A locoregional treatment regimen for lymphatically metastatic cancers, in which an anticancer formulation is targeted to the lymphatic system.

regional drug concentrations to be administered compared with intravenous melphalan chemotherapy; therefore, it often leads to improved disease control, especially if the malignancy is confined to the limbs.

Koops and Vaglini reported the impact of ILP in a multicenter randomized Phase III clinical trial, as a preventive chemotherapy for melanoma patients who have a high risk of developing regional micrometastases [22]. A total of 832 patients were enrolled in the trial. At the end of the follow-up period (median duration of 6.4 years), it was found that patients who received ILP exhibited reduced occurrence of in-transit metastases (control: 6.6% vs ILP: 3.3%) and regional lymph node involvement (control: 16.7% vs ILP: 1.6%). However, the rate of the occurrence of distant metastasis or overall survival was not statistically altered.

Melphalan was the first and most effective anticancer agent utilized in ILP. Owing to the short half-life ($t_{degradation}$ = 50 min, pH 7.4 and 37°C) and the severe toxicity of melphalan in local limb tissues, there have been a number of clinical trials investigating alternative chemotherapeutic agents. One of the agents was cisplatin, which appeared to be effective for the treatment of melanoma in preclinical studies. Thompson and Gianoutsos conducted a cisplatin pilot trial in patients with recurrent melanoma [29]. Unfortunately, cisplatin ILP failed to demonstrate either disease inhibition or improved tissue toxicity, compared with melphalan therapy, in the majority of the patients. Another platinum-based cytotoxic agent, carboplatin, was also investigated in clinical trials. Although partial response was observed in some patients, severe local toxicities such as motor-sensory neuropathy and edema were reported in all patients. The pharmacokinetic data demonstrated extremely high drug concentration in the regional skin; hence, further evaluation of carboplatin-related treatment regimens was not warranted [30]. To date, melphalan remains to be the most successful anticancer drug for ILP in the treatment of unresectable extremity melanoma and other malignancies that recur in a localized fashion.

Since melphalan became a commonly accepted treatment strategy, combination therapies using melphalan and other anticancer agents were extensively investigated in the 1990s, with the goal of further improving the rate of response and survival. Of these clinical investigations, the most successful regimen introduced TNF-α into the standard melphalan treatment. Eggermont and Lienard simultaneously reported the improved efficacy of melphalan and TNF-α combination chemotherapy in multicenter trials for the treatment of both melanoma and soft-tissue sarcoma [31,32]. To explore the underlying mechanism that leads to the synergistic effect between melphalan and TNF-α, a number of studies were conducted using animal xenograft models. Among the hypotheses of the synergism, de Wilt's explanation was widely accepted, in which he and his co-workers discovered that the addition of TNF-α resulted in a sixfold increase of melphalan tumor accumulation in a rat model. Hence, it was not surprising that the combination therapy increased the inhibition of tumor progression relative to melphalan treatment alone [33]. In an ILP trial with melphalan and TNF-α conducted by the US National Cancer Institute, 4 mg TNF-α was reported as a safe and effective dose for treating in-transit melanoma metastases of the extremities [34].

Strategies for localized chemotherapy, such as ILP, greatly reduce the systemic side effects of anticancer agents by confining the drug to the blood capillaries of the tumor-bearing limb. Systemic toxicities of melphalan ILP were only observed when systemic leakage had occurred due to the incomplete isolation of the perfused artery. A clinical study of 438 melphalan ILPs was conducted by Klaase *et al.* to determine the incidence of systemic leakage and the significant factors that caused the leakage [35]. Of all patients who received melphalan ILP, 12.6% exhibited systemic drug leakage of ≥1% of the administered drug; in addition, 6.2 and 1.4% of the patients had 5 and 10% systemic drug leakage, respectively. Since >90% of the melphalan was confined to the limb, the low amount of melphalan that leaked to the systemic circulation led to relatively mild side-effects compared with systemic regimens, for example, transient bone-marrow depression. The most significant factors associated with systemic leakage were determined to be the level of isolation, the diameter of the venous cannula and the extent of the ligation of the perfused iliac vein.

The emergence of the melphalan–TNF-α combination in ILP led to the clinical evaluation of the side effects caused by TNF-α systemic leakage. In a trial in the Netherlands, patients with recurrent melanoma received ILP with the combination of the two anticancer agents [36]. The pharmacokinetic data reported an 11.4- to 31.5-fold increase in the systemic TNF-α

concentration in patients who had drug leakage compared with patients without systemic leakage. Although the systemic concentration of TNF-α was greatly altered, only mild side effects manifested, including: fever, nausea and grade I/II hepatotoxicity, which represented the common toxicities of ILP using melphalan alone. Their findings suggested that the combination of melphalan and TNF-α did not cause increased systemic toxicities relative to melphalan treatment alone; thus, the combination regimen was recommended to patients as a standard ILP procedure in Europe considering its improved efficacy. However, a randomized multicenter ILP trial conducted by the American College of Surgeons Oncology Group (ACOSOG) suggested a conflicting finding; where two patients from the melphalan TNF-α combination cohort underwent a lower extremity amputation owing to the drug-induced side effects. The trial was terminated as a result of the lack of improvement of the melphalan–TNF-α therapy over standard melphalan therapy alone [37].

In addition to melanoma, ILP is also used as a regional therapy for soft-tissue sarcomas, which are malignancies of muscles. Wray *et al.* reported two Phase II trials of extremity sarcomas, in which doxorubicin– and melphalan–TNF-α combination therapy were compared using ILP. The results suggested that the latter regimen exhibited higher efficacy and lower toxicity [38]. Deroose *et al.* analyzed over 122 patients treated with ILPs to identify the role of adjuvant radiotherapy, in terms of recurrence rate of soft tissue sarcomas. All patients received surgical resection and ILP with melphalan TNF-α combination therapy, 70% of whom also received adjuvant radiotherapy. During the median follow-up of 31 months, a comparison of the recurrence rate was made between radiotherapy-treated and untreated patients; however, no significant benefits were observed with adjuvant radiotherapy [39]. In addition, Bonvalot *et al.* conducted a trial in patients with locally advanced soft tissue sarcoma, in which the toxicity of TNF-α was evaluated and a safe dose of 1 mg TNF-α was determined in the combination treatment with melphalan using hyperthermic ILP [40]. Besides melphalan, 1 mg TNF-α can also be used effectively in combination with doxorubicin for treating soft tissue sarcoma. Mild-to-moderate limb and systemic toxicities were observed, while no treatment-associated mortality was reported with the doxorubicin–TNF-α combination therapy [41].

Isolated limb infusion chemotherapy

Although ILP demonstrated improved efficacy and survival rate in patients with melanoma, it is still a complex and invasive procedure. To develop a simpler yet effective alternative, Thompson and co-workers at the Sydney Melanoma Unit introduced the ILI technique to the clinic in the 1990s [42]. ILI is a low-flow ILP, in which catheters are percutaneously inserted into the axial artery and vein of the diseased limb. The solution of a cytotoxic agent, such as melphalan, is infused and circulated for 15 to 60 min. A tourniquet is applied at the base of the limb to prevent systemic drug leakage **(FIGURE 1)** [43]. Unlike ILP, surgery is no longer necessary for this procedure; thus, the patient recovers quickly after the treatment.

A number of clinical trials were conducted to evaluate the feasibility and efficacy of this newer procedure and compared it to ILP [42,44–46]. Lindnér *et al.* reported a satisfactory response rate of 85% for patients with melanoma who were treated with ILI [47]. Of these patients, 41% had complete response and 44% had partial response. The response rate is comparable to the reported effectiveness of ILP. Another ILI trial conducted by Thompson *et al.* also demonstrated similar results, suggesting that ILI is a less invasive, but equivalently effective, alternative of ILP [42]. Fewer patients (32%) developed severe limb and systemic toxicities compared with the ones treated with ILP [48]. This is especially beneficial for elderly patients who cannot tolerate the surgery involved in ILP or its associated side effects. Several recent trials of ILI suggested a slightly lower response rate than the earlier trials; for instance, complete response rates of 31% and 24% were reported by Beasley *et al.* [49] and Barbour *et al.* [50], respectively, in 2009. In summary, ILI may be associated with less morbidity although it has been discovered to be slightly less effective in some patient populations compared with hyperthermic ILP. Another benefit of ILI may be the possibility to readily repeat the procedure over a relatively short period of time [51]. Further, similar to ILP, ILI could also be integrated with combination therapy, taking advantage of the improved effectiveness of newer chemotherapeutic agents [52,53].

Heated intraperitoneal chemotherapy

Intraperitoneal chemotherapy was developed by Sugarbaker *et al.* in the 1980s to treat peritoneal carcinomas, including gastric and colorectal cancers, as well as cancers that originated

Key Term

Cytoreduction: Also called debulking, which is an aggressive surgical procedure to remove a tumor mass as well as any surrounding tissues that may be susceptible to micro- and nano-metastases.

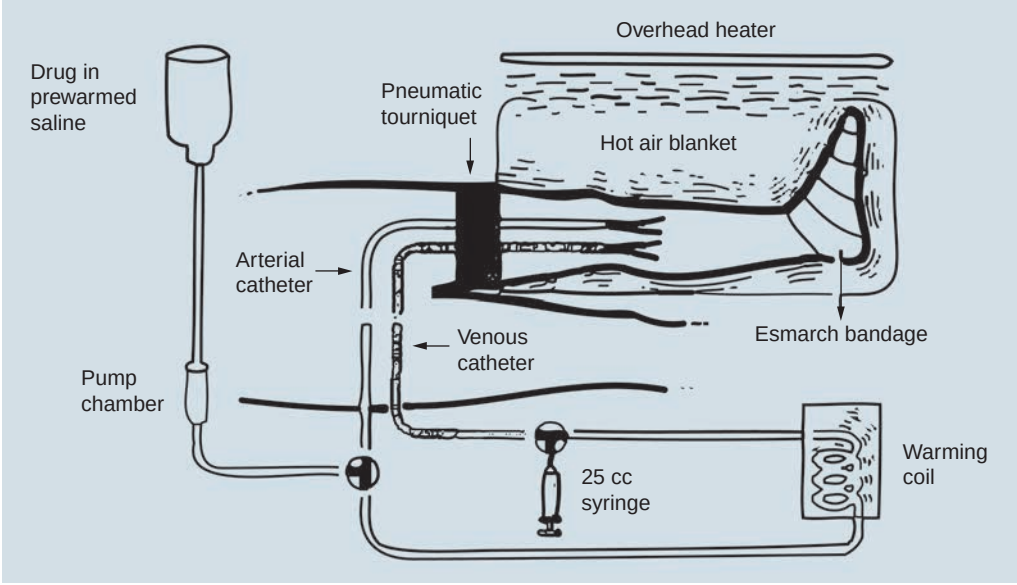

Figure 1. Schematic representation of isolated limb perfusion.
Reproduced with permission from [43].

elsewhere in the body, but have metastasized to the surface or interior of the peritoneal cavity [54]. In HIPEC, a heated, high dose of an anticancer drug is circulated for a short period of time through the peritoneal cavity **(Figure 2)**. HIPEC is often used as an adjuvant therapy after complete resection of the primary malignancies, to eradicate the residual disease at the site of the tumor. Some commonly used chemotherapeutics, their dosages and durations of perfusion are summarized in **Table 2** [23,55–63].

A clinical trial of patients with GI carcinoma reported the advantageous pharmacokinetics of HIPEC, in which the median AUC ratios

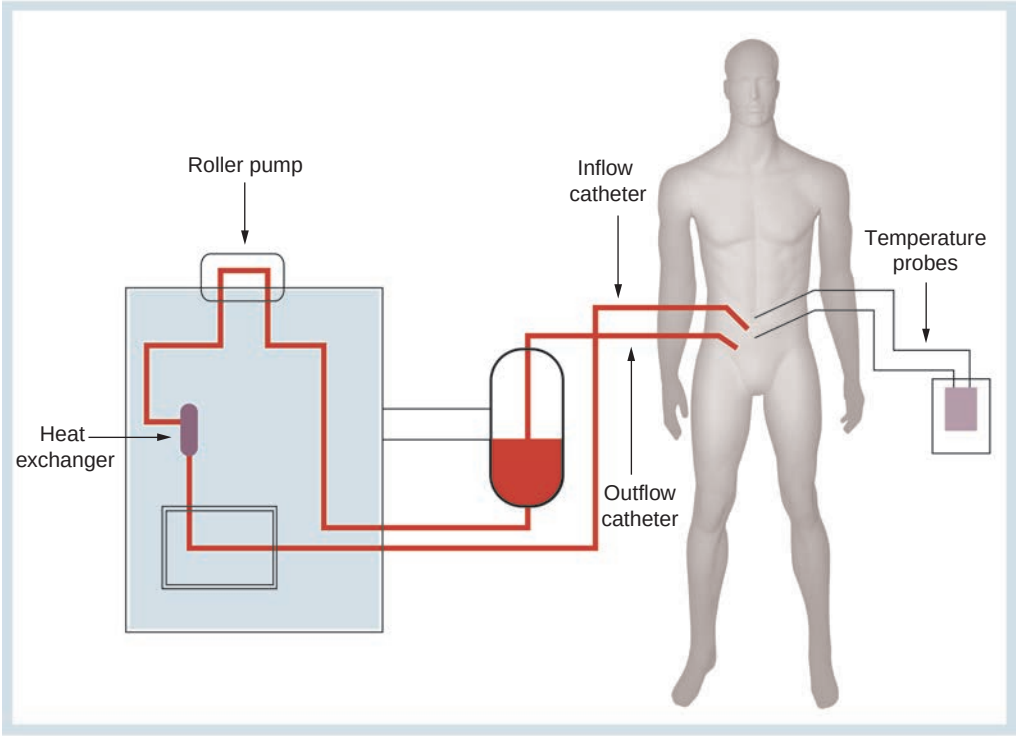

Figure 2. Schematic representation of heated intraperitoneal chemotherapy.

Table 2. Recent trials of colorectal, mesothelioma and gastric cancers using heated intraperitoneal chemotherapy.

Cancer type	Drug and dosage	Duration (min)	Ref.
Colorectal	Cisplatin (25 mg/m²/l) and mitomycin C (3.3 mg/m²/l)	60–90	[54]
	Oxaliplatin (460 mg/m²)	30	[55]
	Mitomycin C (35 mg/m²)	90	[56]
Mesothelioma	Cisplatin (25 mg/m²/l) and mitomycin C (3.3 mg/m²/l)	60	[57]
	Cisplatin (45 mg/l) and doxorubicin (15 mg/l), 3.4–6 l	60–90	[58]
	Cisplatin (50 mg/m²) and doxorubicin (15 mg/m²)	90	[59]
Gastric	Cisplatin (120 mg) and mitomycin C (30 mg)	60–90	[23]
	Oxaliplatin (360–460 mg/m²) and irinotecan (100–200 mg/m²)	30	[60]
	Mitomycin (30–50 mg/m²) and cisplatin (50–100 mg/m²)	60–120	[61]
	Cisplatin (75 mg/m²) and doxorubicin (15 mg/m²)	60	[62]

of intraperitoneal/intravenous were determined to be 117 and 22 for 5-fluorouracil (FU) and mitomycin C chemotherapy, respectively [54]. To justify the addition of HIPEC to the standard procedures of peritoneal cancer therapy, clinical trials were conducted to compare the treatment outcome of surgery alone to the combination regimen of HIPEC and complete resection in patients with advanced gastric carcinomas. In a clinical trial in Japan, 141 patients with advanced gastric cancer along with invasion were registered, 71 were treated with HIPEC using 5-FU after complete gastric resection, and the remainder received surgery alone [64]. The results revealed a greatly reduced peritoneal recurrence rate over the 7-year follow-up period (27 vs 47%, p = 0.0000847), and improved 2-, 4- and 8-year survival rates in the HIPEC cohort.

Besides 5-FU and mitomycin C, other anticancer agents have also been investigated for HIPEC. One of these investigational candidates for HIPEC is oxaliplatin, which is a platinum-based anticancer agent often used in the intravenous treatment of colorectal cancer. Elias *et al.* conducted a Phase II study of oxaliplatin in patients with advanced colorectal cancer in France [65]. They reported a prolonged 3-year survival rate of 65%, with 68% of the living patients being free of peritoneal recurrence at the conclusion of the follow-up period (18.3–49.6 months).

Many late-stage cancer patients with unresectable tumors that cannot be effectively treated with available therapies receive palliative surgery preceding systemic chemotherapy to relieve disease-associated pain and improve their quality-of-life. Verwaal *et al.* conducted a randomized trial in the Netherlands to compare HIPEC of 5-FU-leucovorin in combination with aggressive **cytoreduction** surgery to the standard treatment regimen of palliative surgery followed by systemic chemotherapy, in patients with peritoneal carcinomatosis from colorectal cancer [66]. Aggressive cytoreduction is the surgical removal of any detectable microscopic tumors or metastases, often by debriding of the intestine and other tissue surfaces within the peritoneal cavity, after the complete excision of the primary tumor. Verwaal *et al.* reported a prolonged median survival period of 22.3 months for patients who received the experimental therapy with HIPEC, compared with 12.6 months for patients who received the standard treatment. Further, a significant improvement in survival was observed for patients with five or less metastatic lesions in the peritoneal cavity, relative to patients who had seven or more metastases at the time of the surgery. According to a consensus statement published by Esquivel *et al.* in 2007, HIPEC is usually recommended to patients who are eligible for complete cytoreduction, therefore patient selection may play a critical role in the outcome of the HIPEC procedure [67].

Cytoreduction, also known as debulking, may reduce the rate of recurrence for some patient populations. It is not always recommended, because the aggressive resection may result in the removal of surrounding noncancerous tissues, causing severe complications and increased mortality. A clinical trial, conducted by Jacquet *et al.* evaluated the post-treatment complications and the major risk factors of the HIPEC–cytoreduction combination procedure in patients with peritoneal carcinomatosis from adenocarcinoma of the colon or appendix [68]. The major complications included: anastomotic

leaks, bowel perforations, bile leaks and pancreatitis, which resulted in a 35% morbidity rate and 5% mortality rate. The complications were believed to be associated with the extent of the surgery, the length of the operation and the temperature of the perfused chemotherapeutic agents [68,69]. To investigate the role of hyperthermia in localized chemotherapy a trial was conducted in patients with colon cancer. The authors reported that both normothermic and hyperthermic intraperitoneal chemotherapies were clinically safe and feasible. Although the patients who received the heated chemotherapy showed a higher incidence of anastomotic leakage, it was caused by the extensive resection of the colon, as opposed to the hyperthermic conditions of the perfusate [70].

Intrapleural perfusion hyperthermo-chemotherapy

Since the clinical success of melphalan ILP was recognized, other localized treatment strategies have been investigated over the past decades. Intrapleural perfusion chemotherapy, a localized therapy for the treatment of pleural disseminated malignancies in the body cavity that surrounds the lungs, is one of these newer therapies developed in the 1990s. Pre-surgery, several temperature probes are inserted into the intercostal pleura to monitor the temperature of the pleural cavity. During the IPPHC procedure, the primary malignancy is first excised; subsequently, an irrigation inlet catheter and a drainage outlet catheter are inserted into the pulmonary artery and the pulmonary vein, respectively, and a highly concentrated anticancer drug, such as cisplatin, is perfused for 1–2 h.

To determine the efficacy of IPPHC, a number of clinical trials were undertaken in patients with metastatic cancers that had spread to the pleura [71–74]. Matsuzaki *et al.* reported a trial conducted in Japan in which one cohort of patients received intrapleural perfusion of cisplatin after the removal of the malignancies, and the other cohort was treated with surgery alone [71]. The median survival of the experimental group was 2.3-fold longer than the standard surgery-treated group (20 vs 6 months). In addition, advantageous pharmacokinetic profiles were seen, demonstrated by the increased local concentration of cisplatin in the pleural cavity, along with minimal observed clinical complications. A similar clinical study was conducted a few years later by the same institution to compare the apoptotic status of the tumor tissue, pre- and post-IPPHC with cisplatin. An eightfold increase in the number of the apoptotic cancer cells was detected immunochemically in the post-perfusion tissues compared with the tumor tissues pretreatment [72].

Although intrapleural perfusion is often utilized as adjuvant chemotherapy after tumor excision, there is a possibility that a new modality consisting of presurgical IPPHC may provide better control of the tumor progression before the surgery is performed. Shigemura and co-workers evaluated this new modality in a 2003 pilot study for the treatment of lung cancer with carcinomatous pleuritis. A mean survival time of 19 months was reported for patients in the IPPHC and panpleuropneumonectomy combination arm [73]. No severe complications were observed in the study. Future trials with more patients and a longer follow-up time may be warranted to determine whether the new modality is superior to the previous regimen.

Cisplatin is the most commonly used anticancer agent for IPPHC, but mitomycin C is also a candidate for this procedure. To evaluate the effectiveness of IPPHC using a cisplatin and mitomycin C combination treatment, a clinical trial was undertaken in patients with malignant pleural disease in France in 2003 [74]. The 1- and 5-year survival rates of 74 and 27%, respectively, were reported, over a follow-up period of approximately 7.5 years. This combination regimen appeared to be especially effective for patients with T1 ("Tumor involves same-side pleura of the chest wall, with or without focal involvement of the pleura on the outer side of lung.") or T2 ("Tumor involves same-side pleura of the chest wall with at least one of the following features: confluent tumor on the outer surface of the lung, involvement of the muscles of the diaphragm, or involvement of the lung tissue deeper to the mesothum covering the lung.") mesothelioma [202], indicated by a median survival of 41.3 months. Therefore, patient staging and selection play a significant role in the design of a successful clinical trial for locoregional therapy.

Isolated hepatic perfusion chemotherapy

Locoregional chemotherapy for the treatment of unresectable liver cancers was first developed by Ausman in 1961 as an isolated hepatic perfusion technique [75]; which isolates the hepatic blood flow from the systemic circulation, and directs anticancer drugs through the hepatic artery and vein. Unresectable liver carcinoma and hepatic

metastases disseminated from colorectal cancer and ocular melanoma are especially lethal diseases with an average survival time of only several months despite aggressive treatment. IHP offers the advantage of circulating a highly concentrated anticancer drug solution through the tumor-bearing liver. Since the maximum delivered dose is limited by the tolerance of only the liver, as opposed to the whole body, usually a much higher concentration of perfusate can be administered compared with intravenous chemotherapy. The most commonly used anticancer drugs for IHP consist of mitomycin C, melphalan alone or a melphalan–TNF-α combination. At the beginning of an IHP procedure, a laparotomy is performed to locate the hepatic artery and vein for the insertion of the irrigation inlet catheter and the drainage outlet catheter. The gastroduodenal artery is cannulated for the insertion of the inlet catheter, and the retrohepatic inferior vena cava is dissected to position the outlet catheter. A perfusion circuit with a roller pump, a heat exchanger and an oxygenator, is secured to perfuse the anticancer drug through the liver for an hour [76].

To examine the efficacy of this new procedure, Alexander *et al.* conducted a clinical trial of IHP using the melphalan and TNF-α combination in patients with unresectable primary or metastatic secondary liver cancers [77]. The patients received a 1 h hyperthermic perfusion of the melphalan and TNF-α combination. Post treatment, 75% of the patients developed reversible hepatic toxicities. At the end of the median follow-up period of 15 months, 3% of the patients showed a complete response to the therapy, and 72% of the patients exhibited a partial response. The findings suggested that the melphalan and TNF-α combination therapy might be an effective and safe treatment regimen for patients with unresectable liver cancers.

Percutaneous hepatic perfusion

Whereas ILP requires only a small incision in the tumor-bearing limb, IHP requires a laparotomy for veinal and arterial access, thus it is a highly invasive and risky procedure despite the other advantages offered. To minimize the surgical invasion and reduce complications, the IHP technique was modified and adapted to a nonsurgical procedure known as PHP. PHP is a relatively non-invasive alternative to IHP, which delivers an anticancer drug to the liver at dramatically increased concentrations, with minimum systemic side effects. Owing to the greatly reduced side effects and elimination of surgery, this procedure can be performed four-to-six times at 1 month intervals. During a PHP, an infusion catheter is inserted through the skin into the femoral artery and guided to the hepatic artery, and then a second catheter is inserted into the femoral vein on the other leg and guided to the inferior vena cava **(FIGURE 3)** [78]. After insertion, double balloons on each catheter are inflated to block the normal blood flow to complete the organ isolation. Subsequently, an anticancer drug is perfused through the liver for 30 min. At the end of the procedure, the balloons are deflated and the catheters are removed. To evaluate the feasibility and procedure-associated side effects of PHP, Ravikumar *et al.* carried out a pilot study in patients with advanced primary or metastatic liver cancers [79]. Patients were treated with PHP of either doxorubicin or 5-FU. In the dose-escalation study, the dose-limiting toxicity was determined to be leucopenia in patients who received the highest dosage of doxorubicin or 5-FU. One of the benefits of PHP is that the procedure only requires an overnight hospital stay, and patients recovered quickly after the perfusion. A significant tumor

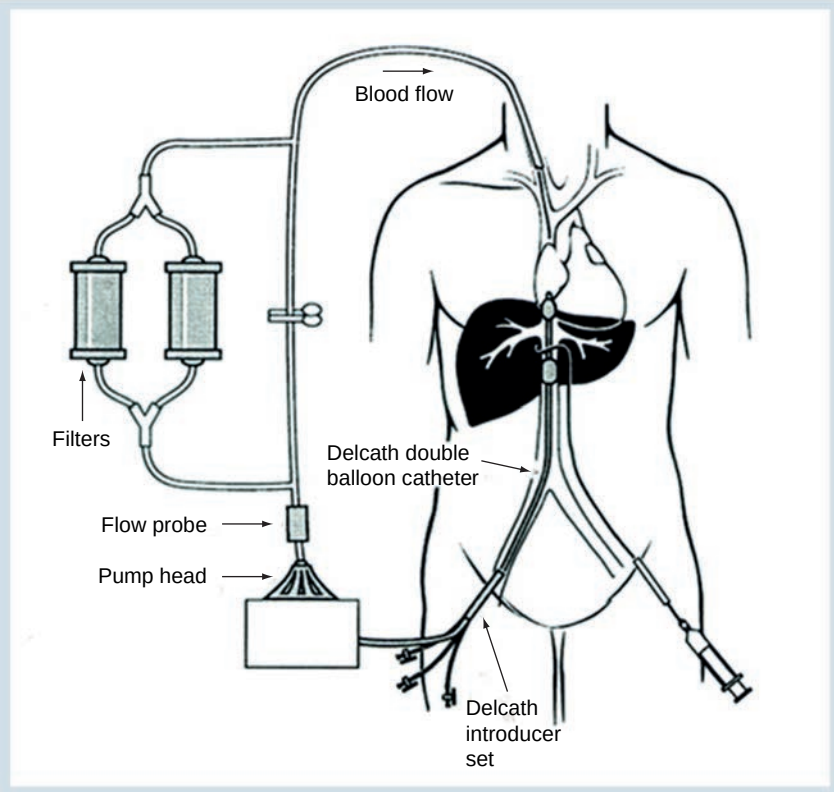

Figure 3. Schematic representation of percutaneous hepatic perfusion.
Reproduced with permission from [78].

response (>95% reduction of tumor size) was observed in 9.5% of the patients. Since the size of the patient population was small (23 patients), further randomized trials will have to be conducted to evaluate the efficacy and safety of PHP compared with IHP. Pingpank *et al.* evaluated the safety of melphalan PHP and determined the maximum tolerated dose to be 3 mg/kg in patients with unresectable liver cancers. The results indicated that melphalan PHP had limited toxicity and improved anti-tumor efficacy compared with hepatic arterial infusion of the drug in a Phase I trial [80]. The same group also conducted a Phase III randomized trial in 2010 to compare the hepatic progression-free survival and the overall response rate in patients with liver cancers originated from metastatic melanoma, who were treated with either melphalan PHP or the best standard of care. The results demonstrated a fourfold extension in the hepatic progression-free survival of patients treated by PHP relative to patients treated with standard of care (245 vs 49 days; $p<0.001$). In addition, PHP significantly improved the overall response rate compared with standard of care (34.1% for PHP vs 2% for standard of care; $p<0.001$) [81].

Transarterial chemoembolization

Transarterial chemoembolization is a localized chemotherapy strategy used for the treatment of unresectable primary or metastatic liver carcinomas. It was developed by French surgeons Doyon and co-workers in 1974 [82]. Similar to PHP, TACE is another nonsurgical approach to deliver anticancer agents to the liver via catheters that are inserted into the femoral artery. Unlike PHP, a TACE procedure does not require the double-balloon catheters. In the TACE procedure, drug-encapsulated degradable starch microspheres, liposomes, or other drug–particle matrices are administered to the liver to deliver the anticancer drug in a sustained-release pattern. These particulates embolize the branches of the hepatic artery; thus, tumor deposits are deprived of nutrients and oxygen **(Figure 4)** [83]. Similar to the other locoregional therapies, TACE is confined to the tumor-bearing liver; hence, the systemic toxicities of the anticancer drug may be greatly reduced.

A nationwide clinical trial of TACE was undertaken in Japan to elucidate the impact of TACE on the survival of patients with unresectable hepatocellular carcinoma, which is the most common type of liver malignancy [84]. A total of 8510 patients were enrolled in the study, who received an emulsion of Lipiodol®, a contrast agent for *in vivo* imaging, and chemotherapeutic agents, such as cisplatin and doxorubicin, preceding the administration of gelatin sponge particles. Gelatin sponge particles are resorbable materials first introduced to the clinic in the mid 1960s in interventional radiology. The optimal size of the gelatin sponge particles is believed to be 500–1000 μm. After administration, they induce the formation of thrombus, causing occlusion of the small end arteries. In this trial, the median survival, 1-year and 3-year survival rates were determined to be 34 months, 82% and 47%, respectively. The mortality rate of treatment-related complications was determined to be 0.5%. Their results suggested that TACE may be a safe and feasible treatment modality, laying the foundation for further developments to improve treatment effectiveness. However, the superiority of TACE over conventional intravenous chemotherapy remains controversial due to the mixed clinical results of its efficacy in treating liver cancers [85–87].

Although TACE is an independent procedure, it can be performed in combination with other procedures, such as a percutaneous ethanol injection (PEI), to improve the treatment efficacy and overall survival. Allgaier *et al.* conducted a trial of TACE and PEI combination therapy, and they compared it with TACE or PEI alone in patients with inoperable hepatocellular carcinoma [88]. The TACE and PEI combination cohort had a median survival of 25 months; whereas, TACE and PEI monotherapy cohorts had median survival times of 8 and 18 months, respectively. Although TACE-involved treatment modalities have shown some advantages over standard intravenous chemotherapy, the procedure-related morbidity and mortality rates, remain major issues. A clinical trial conducted by Poon *et al.* revealed overall treatment morbidities and mortalities of 23 and 4.3%, respectively, for patients with inoperable hepatocellular carcinoma [89]. The mortality rate was as high as 20% for patients with tumors greater than 10 cm at the time of the procedure or serum albumin concentrations ≤35 g/l before the TACE. Therefore, careful evaluation of prognostic factors and patient selection are key factors in the design of successful TACE protocols.

In 2002, Camma *et al.* conducted a computerized meta-analysis of randomized controlled trials of TACE conducted between 1980 and 2000 for unresectable hepatocellular carcinomas, to evaluate whether the previously reported superiority of TACE is significant relative to other conservative

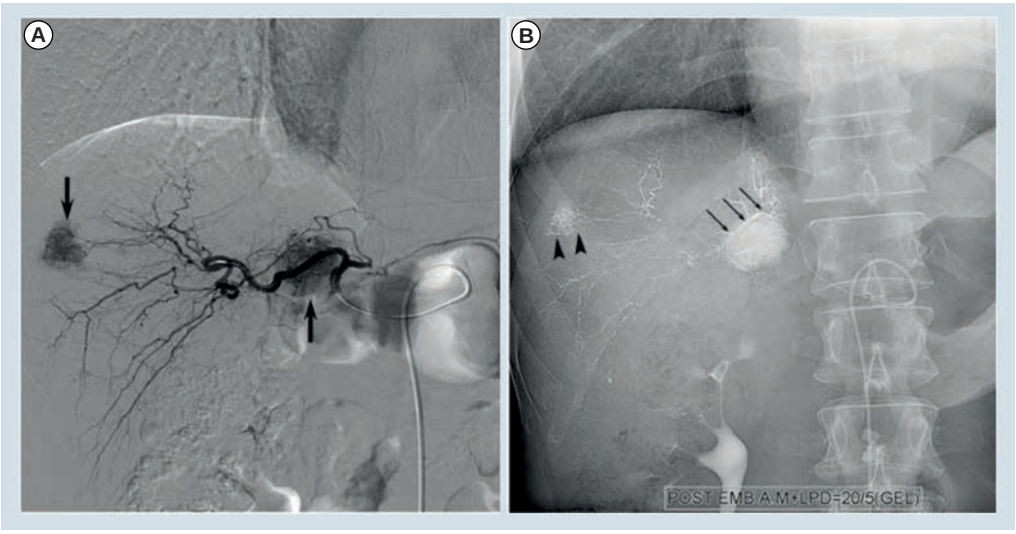

Figure 4. A 56-year-old man with hepatocellular carcinoma. (A) Hepatic arteriogram shows two hypervascular tumor nodules (arrows) in corresponding segments. Segmental transarterial chemoembolization was performed with a mixture of 5 ml of Lipiodol® and 20 mg of doxorubicin followed by gelfoam embolization. **(B)** Post-transarterial chemoembolization plain radiograph shows better deposition of Lipiodol in portal vein around tumor in segment 7 (arrows) when compared with tumor in segment 8 (arrowheads).
Reproduced with permission from [83].

modalities [90]. The survival data from the following trials involving intrahepatic procedures: TACE, TAC (transarterial chemotherapy), and TAE (transarterial embolization) were compared with the conventional intravenous chemotherapies. TAC and TAE are modified TACE procedures. With TAC, chemotherapeutic agents are administered without embolizing particles; whereas with TAE, particle-based artery-blocking materials are given without chemotherapeutic agents. The authors reported that TACE significantly prolonged the 2-year survival rate compared with standard intravenous chemotherapy for patients with unresectable hepatocellular carcinoma. However, TACE did not demonstrate significant benefits, in terms of efficacy, relative to TAE. Their findings were consistent with the controversial role of using chemotherapeutic agents in TACE, owing to the additional side effects that were caused by an anticancer drug. The data involved in the meta-analysis was generated from the trials of TACE using 5-FU as the anticancer drug. Further analysis using data from trials involving other chemotherapeutic agents may be informative in elucidating the impact of TACE over other therapy modalities.

Brain chemo-wafers

Glioma is the most common type of brain cancer, affecting approximately 10,000–20,000 Americans annually. Depending on the status of disease progression, gliomas can be classified into low-grade gliomas (non-anaplastic, good prognosis) and high-grade gliomas (anaplastic, poor prognosis). Conventional chemotherapy usually offers limited benefits for patients with high-grade gliomas; most patients still have a short survival period of less than a year. To improve the efficacy of chemotherapy, drug-releasing wafer implants have been developed as a regional treatment strategy to treat residual brain malignancy after excision of the primary tumor **(FIGURE 5)**. These biodegradable wafers are made of polymers, such as polyanhydrides, coated with chemotherapeutic agents, including carmustine, and placed in the resection cavity during surgery.

Westphal and co-workers reported a multicenter controlled trial of carmustine-releasing wafers (Gliadel® Wafer, Guilford Pharmaceuticals) in patients with malignant gliomas [91]. Of the 240 post-surgery patients, 50% received carmustine wafers and 50% received placebo wafers. Following the wafer implantation, all patients were given radiotherapy. During a long-term follow-up study, the 1-, 2- and 3-year survival rates of patients in the carmustine group were 59, 16 and 9%, respectively. In comparison, the 1-, 2- and 3-year survival rates of patients in the placebo group were 49, 8 and 2%, respectively. Thus, an improvement in the survival rate was observed for the carmustine wafer cohort.

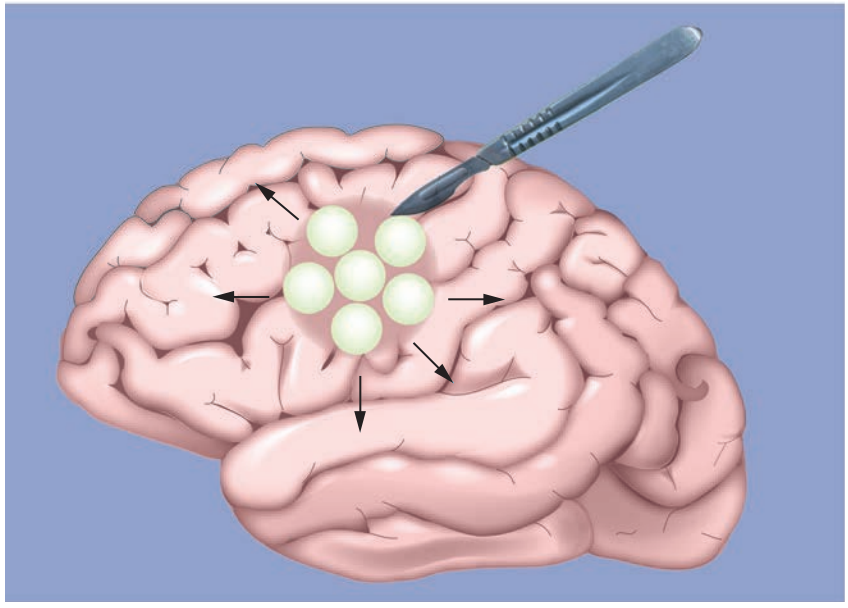

Figure 5. Schematic representation of brain chemo-wafer.

To evaluate the benefit of Gliadel wafers for local disease control, a clinical trial was conducted in patients with a single brain metastasis. The brain metastases resulted from the metastasis of the following primary cancers: lung cancer (52%), melanoma (16%), breast cancer (12%) or renal carcinomas (12%). After craniotomy, all patients were implanted with a Gliadel wafer and underwent postoperative radiation therapy. During a follow-up study of 9 months, no patients had relapsed at the site of wafer implantation; 16% of patients developed recurrent disease elsewhere in the brain; and 8% of patients developed distant metastasis in the spinal cord. The results suggested that carmustine polymer wafers may be a promising strategy for providing local disease control and increasing survival rate [92].

Since the approval of the Gliadel wafer, it has become a favorable approach for delivering chemotherapy to the brain. To assess its safety and identify wafer-associated morbidities, a large clinical trial spanning 10 years and involving 1013 patients with gliomas was reported by Attenello *et al.* Of all the patients, 288 received a Gliadel wafer and the remainder did not receive any implant. Morbidities were observed post surgery, they included: pulmonary embolism, deep-vein thrombosis, surgical site infection, cerebrospinal fluid leak, seizure, symptomatic malignant edema and meningitis. None of the aforementioned side effects were specific to the wafer implantation, suggesting Gliadel may be a safe approach for local delivery of carmustine chemotherapy [93].

Key Term

Nonhematological spread: Cancer cells may disseminate from a primary tumor to other healthy organs via a noncirculatory route, such as a lymphatic route, in their initial metastasis.

Lymphatic chemotherapy

The lymphatic system is a part of our immune system. The immune system is responsible for collecting and removing interstitial fluid from tissues; transporting fatty acids and vitamins to the circulatory system; and carrying antigen-presenting cells to the lymph nodes via the lymph fluid, when an immune response is simulated by an invading microorganism. The lymphatic system is a unidirectional network that is comprised of lymph fluid (lymph), lymphatic capillaries that carry the lymph and connecting lymph nodes. The lymph originates from the interstitial fluid, travels through the lymph vessels and is filtered by the lymph nodes, before it ultimately returns to the circulatory system via the right or the left subclavian veins. Unlike the circulatory system, the lymphatic system is unidirectional and is regulated by a valve mechanism **(Figure 6)**. The one-way valves are located in both afferent and efferent lymph vessels, and they move the lymph from one segment to another segment of a lymph vessel due to segmental contractions. In addition, lymph flows slowly, because the lymphatic system lacks a 'pump', such as the heart, to force the fluids to circulate. Similar to blood capillaries, lymph capillaries branch into every part of our body except for the brain; therefore, tumor cells may use the lymphatic system in their initial **nonhematological spread**.

When a primary tumor mass develops, it secretes lymphangiogenic cytokines that induce the formation of new lymph vessels [94]. The tumor cells invade the new lymph vessels and follow the lymph until entering the nearest draining lymph node, the sentinel lymph node, via the subcapsular sinus. The sentinel lymph node can trap the cancer cells, but if it does not successfully destroy the cancer cells, it may become the site of a secondary tumor and pass the tumor cells to the next draining lymph node. Ultimately, tumor cells may travel to the circulatory system and deposit in healthy organs resulting in the formation of distant metastases **(Figure 7)** [95]. Since the lymphatic system plays a critical role in cancer metastasis, it has been recognized as a target for localized approaches to treat cancers that spread via the lymphatics, such as breast cancer, lung cancer and ovarian cancer, as well as head and neck cancer.

The subcutaneous tissues contain a rich supply of lymph capillaries, and so subcutaneous injections have become the most widely used route for delivering lymphatic-targeted chemotherapeutic agents in preclinical trials. The fate

of subcutaneously injected materials depends on a variety of factors, including: size, charge and hydrophobicity. The optimal size range for lymphatic drainage is believed to be 10–100 nm. Molecules smaller than 10 nm mainly enter the systemic circulation through blood capillaries via diffusion; whereas, molecules larger than 100 nm have substantial local retention at the injection site. Therefore, molecules of 10–100 nm may be good candidates for subcutaneous injections for lymphatic drug delivery. Furthermore, neutral or anionic materials were shown to demonstrate better lymphatic uptake compared with cationic materials [96]. This is likely due to the enhanced macrophage uptake and the subsequent lymphatic drainage of the neutrally or negatively charged particles. The interior wall of the lymphatic lumen bears negative charges; thus, the charge repulsion between the wall of the lymph vessel and the surface of the

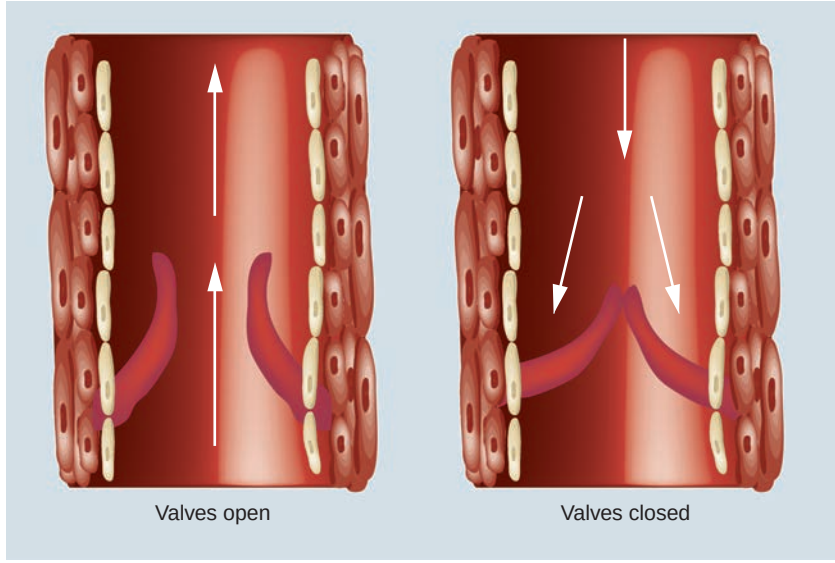

Figure 6. Open and closed valves of a lymphatic vessel.

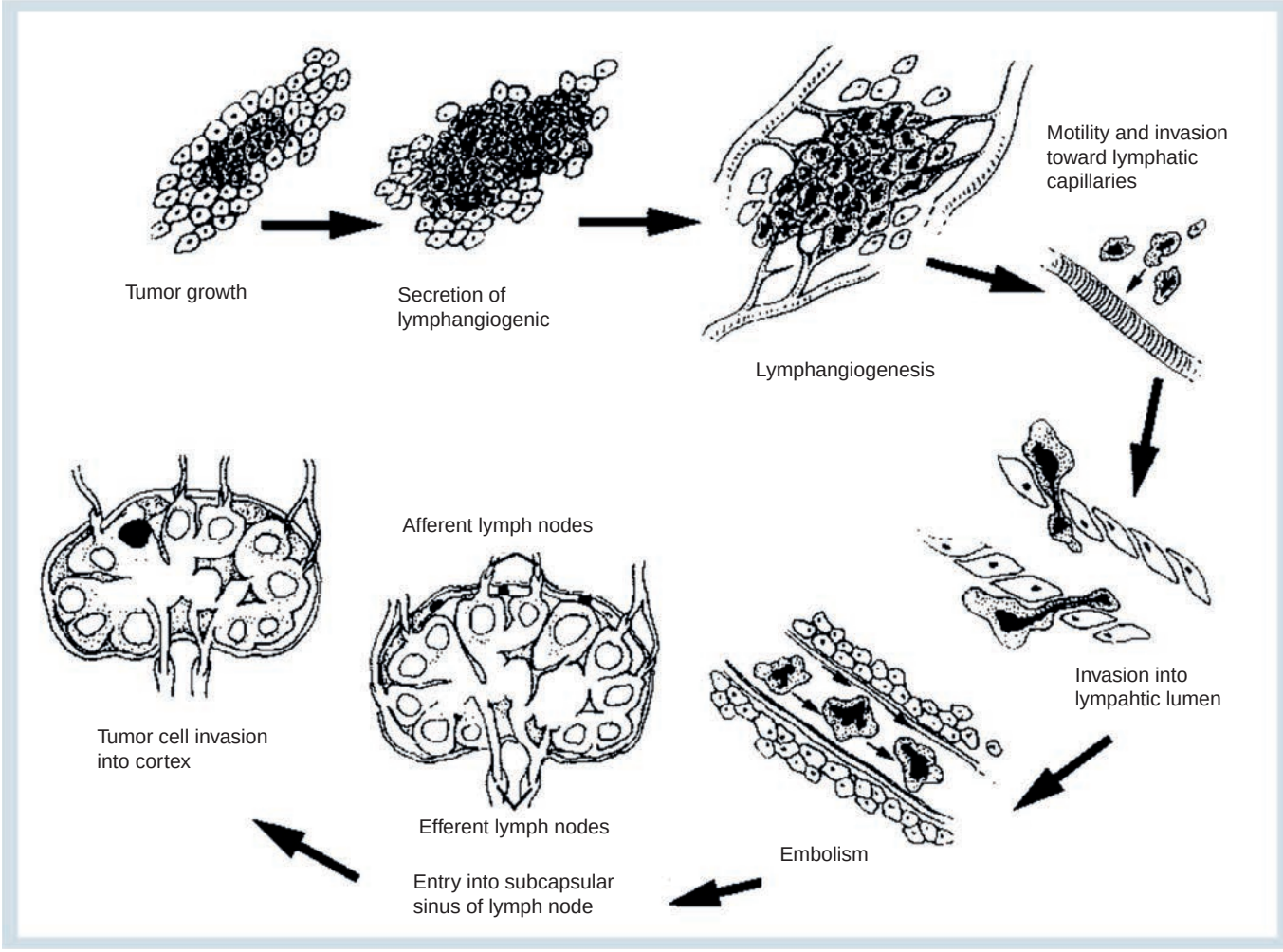

Figure 7. Cancer spread from primary tumor to draining lymph nodes.
Reproduced with permission from [95].

subcutaneously injected materials causes them to move faster towards the draining lymph nodes. Since most first-line cytotoxic drugs are small molecules, carriers that can deliver small-molecule drug cargo to target the lymphatics are of great interest to drug-delivery scientists. The candidates in this category include a variety of biodegradable polymers [97–99], liposomes [100–102], micelles [103,104] and nanoparticles [96,105]. The therapeutic and imaging applications of these lymphatic platforms have been reviewed in detail by Xie *et al.* [106].

Subcutaneous administration of these drug-loaded nanoformulations usually leads to enhanced accumulation and retention of the drug in the draining lymph nodes, in preclinical animal models. These conjugates also take advantage of their controlled drug release properties to alter the pharmacokinetics of the anticancer drugs, by reducing the peak plasma concentration, as well as prolonging systemic retention. The modified pharmacokinetics may further translate into an improved safety profile, by reducing the C_{max}-associated systemic side effects of the drug. In addition, a number of xenograft models suggest that subcutaneously injected carrier-based drug conjugates resulted in better treatment efficacy and survival compared with the conventional intravenous chemotherapy. Although no lymphatic chemotherapies have yet entered the clinic, a number of intralymphatically delivered imaging agents have been used in the clinic for cancer staging and identification of the sentinel lymph node [107–111].

Future perspective

Since the introduction of isolated limb perfusion chemotherapy into the clinic in the mid-1950s for the treatment of melanoma, a variety of locoregional chemotherapy strategies have been developed and adapted into clinical practices in past decades, including HIPEC, IHP and brain wafer chemotherapy, which are discussed in this article. These procedures have now become the standard-of-care for patients with peritoneal cancer, unresectable liver cancer and gliomas. Such localized chemotherapy regimens usually offer improved local disease control and reduced systemic toxicity, compared with conventional chemotherapy, therefore, they hold great promise for cancer patients. Other less widely used regional chemotherapies that are not reviewed in this article include administration of chemotherapeutics via pancreatic perfusion (pancreatic cancer) [112,113], celiac axis infusion (pancreatic cancer) [114,115], hypoxic abdominal stop-flow perfusion (gastric cancers) [116,117] and pelvic perfusion (advanced colorectal cancers) [118,119]. Nevertheless, the absolute superiority of some of the newer techniques relative to infusion chemotherapy remains controversial in terms

Executive summary

- Locoregional chemotherapy delivers anticancer drugs directly to the site of the malignancy, avoiding first-pass metabolism and minimizing systemic side effects; thus, this drug-delivery strategy has become a popular approach for local disease control.
- Isolated limb perfusion chemotherapy is a localized approach to administer an anticancer drug to the artery of the limb of patients with localized melanoma. By applying a tourniquet at the root of the limb, it prevents cytotoxic agents from entering the circulatory system, therefore, minimizing systemic toxicities caused by the chemotherapeutic.
- Heated intraperitoneal chemotherapy has become a popular strategy for treating peritoneal cancers after initial surgical resection. Heated chemotherapy further improves the efficacy of the locally administered anticancer drug.
- Intrapleural perfusion hyperthermo-chemotherapy is primarily utilized for the treatment of pleural metastasis of cancers that originated from elsewhere in the body. It appears to be a safe alternative to intravenous infusion and provides improved local disease control.
- Isolated hepatic perfusion chemotherapy takes advantage of the localized delivery of an anticancer drug to the liver, sparing the other healthy organs from exposure to the toxic chemotherapy; thus, perfusion chemotherapy may be performed multiple times within a short period of time.
- Transarterial chemoembolization is a minimally invasive procedure, which does not require a surgery. An infusion catheter inlet is inserted into the femoral artery of the groin and guided to the liver. An anticancer drug and an embolic agent are co-administered into the liver. The rationale for including a biodegradable embolic agent is to partially block the blood supply of the tumor.
- Gliadel wafer is so far the only US FDA-approved, chemotherapy-coated brain implant for gliomas. The wafer releases carmustine in a sustained-release pattern from the tumor cavity to the surrounding brain tissues. The polymer-based biodegradable wafer dissolves slowly over the course of three weeks, thus, no surgical procedures are required to remove the device after the drug has been released.
- Lymphatic chemotherapy is a locoregional chemotherapy targeting the lymphatic system to where many cancers initially metastasize. Nanoparticle-based chemotherapies are often used to deliver anticancer drugs to tumor-draining lymph nodes and the surrounding lymph basin.

of their improvement in patient survival rate. Furthermore, many localized chemotherapies often require more sophisticated surgical devices, such as the double-balloon catheter in transarterial chemoembolization, making the widespread use of such procedures challenging. Moving forward, careful evaluation of the safety and procedure-associated morbidity of localized drug-delivery strategies may lay the foundation of replacing intravenous chemotherapy with more effective, less toxic regional chemotherapy.

Financial & competing interests disclosure

The authors acknowledge the American Cancer Society, the Susan G Komen for the Cure and the NIH K-INBRE network for financial support. S Cai acknowledges an Eli Lilly predoctoral fellowship and TR Bagby acknowledges a PhRMA predoctoral fellowship. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Bibliography

Papers of special note have been highlighted as:
- ▪ of interest
- ▪▪ of considerable interest

1 Wheatley-Price P, Shepherd FA. Targeting angiogenesis in the treatment of lung cancer. *J. Thorac. Oncol.* 3(10), 1173–1184 (2008).

2 Martin V, Liu D, Gomez-Manzano C. Encountering and advancing through antiangiogenesis therapy for gliomas. *Curr. Pharm. Des.* 15(4), 353–364 (2009).

3 Grothey A, Galanis E. Targeting angiogenesis: progress with anti-vegf treatment with large molecules. *Nat. Rev. Clin. Oncol.* 6(9), 507–518 (2009).

4 Vidal L, Gafter-Gvili A, Shpilberg O. Immunotherapy for patients with follicular lymphoma: the contribution of systematic reviews. *Acta Haematol.* 125(1–2), 23–31 (2011).

5 Brun JL, Dalstein V, Leveque J *et al.* Regression of high-grade cervical intraepithelial neoplasia with tg4001 targeted immunotherapy. *Am. J. Obstet. Gynecol.* 204(2), 169 e161–e168 (2011).

6 Song H, Sgouros G. Radioimmunotherapy of solid tumors: searching for the right target. *Curr. Drug Deliv.* 8(1), 26–44 (2011).

7 Bak XY, Dang HL, Yang J *et al.* Human embryonic stem cell-derived mesenchymal stem cells as cellular delivery vehicles for prodrug gene therapy of glioblastoma. *Hum. Gene. Ther.* (2011) (Epub ahead of print).

8 Kitamura A, Matsushita K, Takiguchi Y *et al.* Synergistic effect of non-transmissible sendai virus vector encoding the c-myc suppressor fuse-binding protein-interacting repressor plus cisplatin in treatment of malignant pleural mesothelioma. *Cancer Sci.* 102(7), 1366–1373 (2011).

9 Eager RM, Nemunaitis J. Clinical development directions in oncolytic viral therapy. *Cancer Gene. Ther.* 18(5), 305–317 (2011).

10 Khouri IF, Bassett R, Poindexter N *et al.* Nonmyeloablative allogeneic stem cell transplantation in relapsed/refractory chronic lymphocytic leukemia: long-term follow-up, prognostic factors, and effect of human leukocyte histocompatibility antigen subtype on outcome. *Cancer* DOI:10.1002/cncr.26091 (2011) (Epub ahead of print).

11 Bubalo JS, Cherala G, Mccune JS, Munar MY, Tse S, Maziarz R. Aprepitant pharmacokinetics and assessing the impact of aprepitant on cyclophosphamide metabolism in cancer patients undergoing hematopoietic stem cell transplantation. *J. Clin. Pharmacol.* (2011) (Epub ahead of print).

12 Goussetis E, Constantoulakis P, Kitra V *et al.* Successful bone marrow transplantation in a pediatric patient with chronic myeloid leukemia from a hla-identical sibling selected by preimplantation hla testing. *Pediatr. Blood Cancer* 57(2), 345–347 (2011).

13 Kroon BB, Noorda EM, Vrouenraets BC, Van Slooten GW, Nieweg OE. Isolated limb perfusion for melanoma. *Surg. Oncol. Clin. N. Am.* 17(4), 785–794, viii–ix (2008).

14 Kroon HM, Thompson JF. Isolated limb infusion: a review. *J. Surg. Oncol.* 100(2), 169–177 (2009).

15 Esquivel J. Technology of hyperthermic intraperitoneal chemotherapy in the united states, Europe, China, Japan, and Korea. *Cancer J.* 15(3), 249–254 (2009).

16 Mujoomdar AA, Sugarbaker DJ. Hyperthermic chemoperfusion for the treatment of malignant pleural mesothelioma. *Semin. Thorac. Cardiovasc. Surg.* 20(4), 298–304 (2008).

17 Jones A, Alexander HR Jr. Development of isolated hepatic perfusion for patients who have unresectable hepatic malignancies. *Surg. Oncol. Clin. N. Am.* 17(4), 857–876, x (2008).

18 Alexander HR Jr, Butler CC. Development of isolated hepatic perfusion via the operative and percutaneous techniques for patients with isolated and unresectable liver metastases. *Cancer J.* 16(2), 132–141 (2010).

19 Oliveri RS, Wetterslev J, Gluud C. Transarterial (chemo)embolisation for unresectable hepatocellular carcinoma. *Cochrane Database Syst. Rev.* (3), CD004787 (2011).

20 Nune SK, Gunda P, Majeti BK, Thallapally PK, Forrest ML. Advances in lymphatic imaging and drug delivery. *Adv. Drug Deliv. Rev.* 63(10–11), 876–885 (2011).

21 Cai S, Yang Q, Bagby TR, Forrest ML. Lymphatic drug delivery using engineered liposomes and solid lipid nanoparticles. *Adv. Drug Deliv. Rev.* 63(10–11), 901–908 (2011).

22 Koops HS, Vaglini M, Suciu S *et al.* Prophylactic isolated limb perfusion for localized, high-risk limb melanoma: results of a multicenter randomized Phase III trial. European organization for research and treatment of cancer malignant melanoma cooperative group protocol 18832, the world health organization melanoma program trial 15, and the north american perfusion group southwest oncology group-8593. *J. Clin. Oncol.* 16(9), 2906–2912 (1998).

23 Yang XJ, Huang CQ, Suo T *et al.* Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from gastric cancer: final results of a Phase III randomized clinical trial. *Ann. Surg. Oncol.* 18(6), 1575–1581 (2011).

24 Vogelzang NJ, Rusthoven JJ, Symanowski J *et al.* Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J. Clin. Oncol.* 21(14), 2636–2644 (2003).

25 Van Iersel LB, Koopman M, Van De Velde CJ *et al.* Management of isolated nonresectable liver metastases in colorectal cancer patients: a case-control study of isolated hepatic perfusion with melphalan versus systemic chemotherapy. *Ann. Oncol.* 21(8), 1662–1667 (2010).

26 Kudo M, Imanaka K, Chida N *et al.* Phase III study of sorafenib after transarterial chemoembolisation in japanese and korean patients with unresectable hepatocellular carcinoma. *Eur. J. Cancer* (2011).

27 Creech OJ, Krementz ET, Ryan RF, Winblad JN. Chemotherapy of cancer: regional perfusion utilizing an extracorporeal circuit. *Ann. Surg.* 148(4), 616–632 (1958).

- **Development of isolated limb perfusion.**

28 Stehlin JSJ. Hyperthermic perfusion with chemotherapy for cancers of the extremities. *Surg. Gynecol. Obstet.* 129(2), 305–308 (1969).

29 Thompson JF, Gianoutsos MP. Isolated limb perfusion for melanoma: effectiveness and toxicity of cisplatin compared with that of melphalan and other drugs. *World J. Surg.* 16(2), 227–233 (1992).

30 Daryanani D, De Vries EG, Guchelaar HJ, Van Weerden TW, Hoekstra HJ. Hyperthermic isolated regional perfusion of the limb with carboplatin. *Eur. J. Surg. Oncol.* 26(8), 792–797 (2000).

31 Eggermont AM, Van Geel AN, De Wilt JH, Ten Hagen TL. The role of isolated limb perfusion for melanoma confined to the extremities. *Surg. Clin. North Am.* 83(2), 371–384, ix (2003).

32 Lienard D, Eggermont AM, Koops HS *et al.* Isolated limb perfusion with tumour necrosis factor-α and melphalan with or without interferon-gamma for the treatment of in-transit melanoma metastases: a multicentre randomized Phase ii study. *Melanoma Res.* 9(5), 491–502 (1999).

33 De Wilt JH, Ten Hagen TL, De Boeck G, Van Tiel ST, De Bruijn EA, Eggermont AM. Tumour necrosis factor alpha increases melphalan concentration in tumour tissue after isolated limb perfusion. *Br. J. Cancer* 82(5), 1000–1003 (2000).

34 Fraker DL, Alexander HR, Andrich M, Rosenberg SA. Treatment of patients with melanoma of the extremity using hyperthermic isolated limb perfusion with melphalan, tumor necrosis factor, and interferon gamma: results of a tumor necrosis factor dose-escalation study. *J. Clin. Oncol.* 14(2), 479–489 (1996).

35 Klaase JM, Kroon BB, Van Geel AN, Eggermont AM, Franklin HR. Systemic leakage during isolated limb perfusion for melanoma. *Br. J. Surg.* 80(9), 1124–1126 (1993).

36 Vrouenraets BC, Kroon BB, Ogilvie AC *et al.* Absence of severe systemic toxicity after leakage-controlled isolated limb perfusion with tumor necrosis factor-α and melphalan. *Ann. Surg. Oncol.* 6(4), 405–412 (1999).

37 Cornett WR, Mccall LM, Petersen RP *et al.* Randomized multicenter trial of hyperthermic isolated limb perfusion with melphalan alone compared with melphalan plus tumor necrosis factor: American college of surgeons oncology group trial z0020. *J. Clin. Oncol.* 24(25), 4196–4201 (2006).

38 Wray CJ, Benjamin RS, Hunt KK, Cormier JN, Ross MI, Feig BW. Isolated limb perfusion for unresectable extremity sarcoma: results of 2 single-institution Phase 2 trials. *Cancer* 117(14), 3235–3241 (2011).

39 Deroose JP, Burger JW, Van Geel AN *et al.* Radiotherapy for soft tissue sarcomas after isolated limb perfusion and surgical resection: essential for local control in all patients? *Ann. Surg. Oncol.* 18(2), 321–327 (2011).

40 Bonvalot S, Rimareix F, Causeret S *et al.* Hyperthermic isolated limb perfusion in locally advanced soft tissue sarcoma and progressive desmoid-type fibromatosis with tnf 1 mg and melphalan (t1-m hilp) is safe and efficient. *Ann. Surg. Oncol.* 16(12), 3350–3357 (2009).

41 Di Filippo F, Giacomini P, Rossi CR *et al.* Hyperthermic isolated perfusion with tumor necrosis factor-α and doxorubicin for the treatment of limb-threatening soft tissue sarcoma: the experience of the italian society of integrated locoregional treatment in oncology (SITILO). *In Vivo* 23(2), 363–367 (2009).

42 Thompson JF, Kam PC, Waugh RC, Harman CR. Isolated limb infusion with cytotoxic agents: a simple alternative to isolated limb perfusion. *Semin. Surg. Oncol.* 14(3), 238–247 (1998).

- **Development of isolated limb infusion.**

43 Thompson JF, Kam PC. Isolated limb infusion for melanoma: A simple but effective alternative to isolated limb perfusion. *J. Surg. Oncol.* 88(1), 1–3 (2004).

44 Lindnér P, Doubrovsky A, Kam PC, Thompson JF. Prognostic factors after isolated limb infusion with cytotoxic agents for melanoma. *Ann. Surg. Oncol.* 9(2), 127–136 (2002).

45 Kroon HM, Moncrieff M, Kam PC, Thompson JF. Outcomes following isolated limb infusion for melanoma. A 14-year experience. *Ann. Surg. Oncol.* 15(11), 3003–3013 (2008).

46 Brady MS, Brown K, Patel A, Fisher C, Marx W. A Phase II trial of isolated limb infusion with melphalan and dactinomycin for regional melanoma and soft tissue sarcoma of the extremity. *Ann. Surg. Oncol.* 13(8), 1123–1129 (2006).

47 Lindnér P, Doubrovsky A, Kam PC, Thompson JF. Prognostic factors after isolated limb infusion with cytotoxic agents for melanoma. *Ann. Surg. Oncol.* 9(2), 127–136 (2002).

48 Beasley GM, Petersen RP, Yoo J *et al.* Isolated limb infusion for in-transit malignant melanoma of the extremity: a well-tolerated but less effective alternative to hyperthermic isolated limb perfusion. *Ann. Surg. Oncol.* 15(8), 2195–2205 (2008).

49 Beasley GM, Caudle A, Petersen RP *et al.* A multi-institutional experience of isolated limb infusion: defining response and toxicity in the US. *J. Am. Coll. Surg.* 208(5), 706–715, discussion 715–707 (2009).

50 Barbour AP, Thomas J, Suffolk J, Beller E, Smithers BM. Isolated limb infusion for malignant melanoma: predictors of response and outcome. *Ann. Surg. Oncol.* 16(12), 3463–3472 (2009).

51 Beasley GM, Petersen RP, Yoo J *et al.* Isolated limb infusion for in-transit malignant melanoma of the extremity: a well-tolerated but less effective alternative to hyperthermic isolated limb perfusion. *Ann. Surg. Oncol.* 15(8), 2195–2205 (2008).

52 Robert C, Thomas L, Bondarenko I *et al.* Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N. Engl. J. Med.* 364(26), 2517–2526 (2011).

53 Chapman PB, Hauschild A, Robert C *et al.* Improved survival with vemurafenib in melanoma with braf v600e mutation. *N. Engl. J. Med.* 364(26), 2507–2516 (2011).

54 Cavaliere F, De Simone M, Virzi S *et al.* Prognostic factors and oncologic outcome in 146 patients with colorectal peritoneal carcinomatosis treated with cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy: Italian multicenter study S.I.T.I.L.O. *Eur. J. Surg. Oncol.* 37(2), 148–154 (2011).

55 Elias D, Bonnay M, Puizillou JM *et al.* Heated intra-operative intraperitoneal oxaliplatin after complete resection of peritoneal carcinomatosis: pharmacokinetics and tissue distribution. *Ann. Oncol.* 13(2), 267–272 (2002).

56 Evers DJ, Verwaal VJ. Indication for oophorectomy during cytoreduction for intraperitoneal metastatic spread of colorectal or appendiceal origin. *Br. J. Surg.* 98(2), 287–292 (2011).

57 Deraco M, Baratti D, Cabras AD *et al.* Experience with peritoneal mesothelioma at the milan national cancer institute. *World J. Gastrointest. Oncol.* 2(2), 76–84 (2010).

58 Baratti D, Vaira M, Kusamura S *et al.* Multicystic peritoneal mesothelioma: outcomes and patho-biological features in a multi-institutional series treated by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (hipec). *Eur. J. Surg. Oncol.* 36(11), 1047–1053 (2010).

59 Chua TC, Yao P, Akther J, Morris DL. Impact of tumor angiogenesis in peritoneal mesothelioma after radical cytoreduction and hyperthermic intraperitoneal chemotherapy. *Pathol. Oncol. Res.* 16(2), 217–222 (2010).

60 Glehen O, Gilly FN, Arvieux C *et al.* Peritoneal carcinomatosis from gastric cancer: a multi-institutional study of 159 patients treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. *Ann. Surg. Oncol.* 17(9), 2370–2377 (2010).

61 Glehen O, Gilly FN, Boutitie F *et al.* Toward curative treatment of peritoneal carcinomatosis from nonovarian origin by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy: a multi-institutional study of 1,290 patients. *Cancer* 116(24), 5608–5618 (2010).

62 Piso P, Slowik P, Popp F, Dahlke MH, Glockzin G, Schlitt HJ. Safety of gastric resections during cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis. *Ann. Surg. Oncol.* 16(8), 2188–2194 (2009).

63 Sugarbaker PH, Graves T, Debruijn EA *et al.* Early postoperative intraperitoneal chemotherapy as an adjuvant therapy to surgery for peritoneal carcinomatosis from gastrointestinal cancer: pharmacological studies. *Cancer Res.* 50(18), 5790–5794 (1990).

▪▪ **Describes development of intraperitoneal chemotherapy for peritoneal carcinomatosis.**

64 Fujimoto S, Takahashi M, Mutou T, Kobayashi K, Toyosawa T. Successful intraperitoneal hyperthermic chemoperfusion for the prevention of postoperative peritoneal recurrence in patients with advanced gastric carcinoma. *Cancer* 85(3), 529–534 (1999).

▪▪ **A clinical trial of intraperitoneal hyperthermic chemoperfusion in patients with advanced gastric carcinoma.**

65 Elias D, Sideris L, Pocard M *et al.* Efficacy of intraperitoneal chemohyperthermia with oxaliplatin in colorectal peritoneal carcinomatosis. Preliminary results in 24 patients. *Ann. Oncol.* 15(5), 781–785 (2004).

66 Verwaal VJ, Van Ruth S, De Bree E *et al.* Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J. Clin. Oncol.* 21(20), 3737–3743 (2003).

67 Esquivel J, Sticca R, Sugarbaker P *et al.* Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of peritoneal surface malignancies of colonic origin: a consensus statement. Society of surgical oncology. *Ann. Surg. Oncol.* 14(1), 128–133 (2007).

68 Jacquet P, Stephens AD, Averbach AM *et al.* Analysis of morbidity and mortality in 60 patients with peritoneal carcinomatosis treated by cytoreductive surgery and heated intraoperative intraperitoneal chemotherapy. *Cancer* 77(12), 2622–2629 (1996).

69 Stephens AD, Alderman R, Chang D *et al.* Morbidity and mortality analysis of 200 treatments with cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy using the coliseum technique. *Ann. Surg. Oncol.* 6(8), 790–796 (1999).

70 Averbach AM, Chang D, Koslowe P, Sugarbaker PH. Anastomotic leak after double-stapled low colorectal resection. *Dis. Colon Rectum.* 39(7), 780–787 (1996).

71 Matsuzaki Y, Shibata K, Yoshioka M *et al.* Intrapleural perfusion hyperthermo-chemotherapy for malignant pleural dissemination and effusion. *Ann. Thorac. Surg.* 59(1), 127–131 (1995).

72 Matsuzaki Y, Edagawa M, Shimizu T *et al.* Intrapleural hyperthermic perfusion with chemotherapy increases apoptosis in malignant pleuritis. *Ann. Thorac. Surg.* 78(5), 1769–1772 (2004).

73 Shigemura N, Akashi A, Ohta M, Matsuda H. Combined surgery of intrapleural perfusion hyperthermic chemotherapy and panpleuropneumonectomy for lung cancer with advanced pleural spread: a pilot study. *Interact. Cardiovasc. Thorac. Surg.* 2(4), 671–675 (2003).

74 Monneuse O, Beaujard AC, Guibert B *et al.* Long-term results of intrathoracic chemohyperthermia (itch) for the treatment of pleural malignancies. *Br. J. Cancer* 88(12), 1839–1843 (2003).

75 Ausman RK. Development of a technic for isolated perfusion of the liver. *N.Y. State J. Med.* 61, 3993–3997 (1961).

▪ **Development of isolated hepatic perfusion chemotherapy.**

76 Grover A, Alexander HRJ. The past decade of experience with isolated hepatic perfusion. *Oncologist* 9(6), 653–664 (2004).

77 Alexander HRJ, Bartlett DL, Libutti SK, Fraker DL, Moser T, Rosenberg SA. Isolated hepatic perfusion with tumor necrosis factor and melphalan for unresectable cancers confined to the liver. *J. Clin. Oncol.* 16(4), 1479–1489 (1998).

78 Pingpank JF, Libutti SK, Chang R *et al.* Phase i study of hepatic arterial melphalan infusion and hepatic venous hemofiltration using percutaneously placed catheters in patients with unresectable hepatic malignancies. *J. Clin. Oncol.* 23(15), 3465–3474 (2005).

▪▪ **A clinical trial of percutaneous hepatic perfusion in patients with unresectable hepatic cancers.**

79 Ravikumar TS, Pizzorno G, Bodden W *et al.* Percutaneous hepatic vein isolation and high-dose hepatic arterial infusion chemotherapy for unresectable liver tumors. *J. Clin. Oncol.* 12(12), 2723–2736 (1994).

80 Pingpank JF, Libutti SK, Chang R *et al.* Phase I study of hepatic arterial melphalan infusion and hepatic venous hemofiltration using percutaneously placed catheters in patients with unresectable hepatic malignancies. *J. Clin. Oncol.* 23(15), 3465–3474 (2005).

81 Pingpank JF, Hughes MF, Faries MB *et al.* A Phase III random assignment trial comparing percutaneous hepatic perfusion with melphalan (PHP-mel) to standard of care for patients with hepatic metastases from metastatic ocular or cutaneous melanoma. Presented at: *American Society of Clinical Oncology Annual Meeting.* Chicago, IL, USA, 4–10 June 2010.

82 Doyon D, Mouzon A, Jourde AM, Regensberg C, Frileux C. Hepatic, arterial embolization in patients with malignant liver tumours (author's transl). *Ann. Radiol. (Paris)* 17(6), 593–603 (1974).

83 Shin SW. The current practice of transarterial chemoembolization for the treatment of hepatocellular carcinoma. *Korean J. Radiol.* 10(5), 425–434 (2009).

84 Takayasu K, Arii S, Ikai I *et al.* Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. *Gastroenterology* 131(2), 461–469 (2006).

▪▪ **A clinical trial of transarterial chemoembolization in patients with unresectable hepatocellular carcinoma.**

85 Oliveri RS, Wetterslev J, Gluud C. Transarterial (chemo)embolisation for unresectable hepatocellular carcinoma. *Cochrane Database Syst. Rev.* 3, CD004787 (2011).

86 Zhong JH, Li LQ. Postoperative adjuvant transarterial chemoembolization for participants with hepatocellular carcinoma: a meta-analysis. *Hepatol. Res.* 40(10), 943–953 (2010).

87 Giannini EG, Bodini G, Corbo M *et al.* Impact of evidence-based medicine on the treatment of patients with unresectable hepatocellular carcinoma. *Aliment Pharmacol. Ther.* 31(4), 493–501 (2010).

88 Allgaier HP, Deibert P, Olschewski M *et al.* Survival benefit of patients with inoperable hepatocellular carcinoma treated by a

combination of transarterial chemoembolization and percutaneous ethanol injection – a single-center analysis including 132 patients. *Int. J. Cancer* 79(6), 601–605 (1998).

89 Poon RT, Ngan H, Lo CM, Liu CL, Fan ST, Wong J. Transarterial chemoembolization for inoperable hepatocellular carcinoma and postresection intrahepatic recurrence. *J. Surg. Oncol.* 73(2), 109–114 (2000).

90 Cammà C, Schepis F, Orlando A *et al.* Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. *Radiology* 224(1), 47–54 (2002).

91 Westphal M, Ram Z, Riddle V, Hilt D, Bortey E. Group. Ecotgs: Gliadel wafer in initial surgery for malignant glioma: long-term follow-up of a multicenter controlled trial. *Acta Neurochir. (Wien.)* 148(3), 269–275 (2006).

▪▪ **A clinical trial of chemo-wafer for brain cancers.**

92 Ewend M, Brem S, Gilbert M *et al.* Treatment of single brain metastasis with resection, intracavity carmustine polymer wafers, and radiation therapy is safe and provides excellent local control. *Clin. Cancer Res.* 13(12), 3637–3641 (2007).

93 Attenello F, Mukherjee D, Datoo G *et al.* Use of gliadel (bcnu) wafer in the surgical treatment of malignant glioma: a 10-year institutional experience. *Ann. Surg. Oncol.* 15(10), 2887–2893 (2008).

94 Stacker SA, Achen MG, Jussila L, Baldwin ME, Alitalo K. Lymphangiogenesis and cancer metastasis. *Nat. Rev. Cancer* 2(8), 573–583 (2002).

95 Nathanson SD. Insights into the mechanisms of lymph node metastasis. *Cancer* 98(2), 413–423 (2003).

96 Rao DA, Forrest ML, Alani AW, Kwon GS, Robinson JR. Biodegradable plga based nanoparticles for sustained regional lymphatic drug delivery. *J. Pharm. Sci.* 99(4), 2018–2031 (2010).

97 Liu J, Meisner D, Kwong E, Wu XY, Johnston MR. Translymphatic chemotherapy by intrapleural placement of gelatin sponge containing biodegradable paclitaxel colloids controls lymphatic metastasis in lung cancer. *Cancer Res.* 69(3), 1174–1181 (2009).

98 Chipman SD, Oldham FB, Pezzoni G, Singer JW. Biological and clinical characterization of paclitaxel poliglumex (ppx, ct-2103), a macromolecular polymer-drug conjugate. *Int. J. Nanomed.* 1(4), 375–383 (2006).

99 Cai S, Xie Y, Davies NM, Cohen MS, Forrest ML. Carrier-based intralymphatic cisplatin chemotherapy for the treatment of metastatic squamous cell carcinoma of the head & neck. *Therapeutic Delivery* 1(2), 237–245 (2010).

▪ **A preclinical study of lymphatic chemotherapy.**

100 Feng L, Zhang L, Liu M *et al.* Roles of dextrans on improving lymphatic drainage for liposomal drug delivery system. *J. Drug Target* 18(3), 168–178 (2010).

101 Lawson KA, Anderson K, Snyder RM *et al.* Novel vitamin e analogue and 9-nitro-camptothecin administered as liposome aerosols decrease syngeneic mouse mammary tumor burden and inhibit metastasis. *Cancer Chemother. Pharmacol.* 54(5), 421–431 (2004).

102 Trubetskoy VS, Whiteman KR, Torchilin VP, Wolf GL. Massage-induced release of subcutaneously injected liposome-encapsulated drugs to the blood. *J. Cont. Rel.* 50(1–3), 13–19 (1998).

103 Trubetskoy VS, Frank-Kamenetsky MD, Whiteman KR, Wolf GL, Torchilin VP. Stable polymeric micelles: lymphangiographic contrast media for gamma scintigraphy and magnetic resonance imaging. *Acad Radiol.* 3(3), 232–238 (1996).

104 Yoshikawa H, Satoh Y, Naruse N, Takada K, Muranishi S. Comparison of disappearance from blood and lymphatic delivery of human fibroblast interferon in rat by different administration routes. *J. Pharmacobiodyn.* 8(3), 206–210 (1985).

105 Luo G, Yu X, Jin C *et al.* Lyp-1-conjugated nanoparticles for targeting drug delivery to lymphatic metastatic tumors. *Int. J. Pharm.* 385(1–2), 150–156 (2010).

106 Xie Y, Bagby TR, Cohen MS, Forrest ML. Drug delivery to the lymphatic system: Importance in future cancer diagnosis and therapies. *Exp. Opin. Drug Deliv.* 6(8), 785–792 (2009).

▪ **Reviewed a variety of strategies for lymphatic drug delivery.**

107 Balch CM, Gershenwald JE, Soong SJ, Thompson JF. Update on the melanoma staging system: the importance of sentinel node staging and primary tumor mitotic rate. *J. Surg. Oncol.* 104(4), 379–385 (2011).

108 Kim HK, Kim S, Park JJ, Jeong JM, Mok YJ, Choi YH. Sentinel node identification using technetium-99m neomannosyl human serum albumin in esophageal cancer. *Ann. Thorac. Surg.* 91(5), 1517–1522 (2011).

109 Sadeghi R, Zakavi SR, Forghani MN *et al.* The efficacy of tc-99m sestamibi for sentinel node mapping in breast carcinomas: comparison with tc-99m antimony sulphide colloid. *Nucl. Med. Rev. Cent. East Eur.* 13(1), 1–4 (2010).

110 Khoury-Collado F, Murray MP, Hensley ML *et al.* Sentinel lymph node mapping for endometrial cancer improves the detection of metastatic disease to regional lymph nodes. *Gynecol. Oncol.* 122(2), 251–254 (2011).

111 Markl B, Moldovan AI, Jahnig H *et al.* Combination of *ex vivo* sentinel lymph node mapping and methylene blue-assisted lymph node dissection in gastric cancer: a prospective and randomized study. *Ann. Surg. Oncol.* 18(7), 1860–1868 (2011).

112 Milandri C, Calzolari F, Passardi A *et al.* Intra-arterial chemotherapy of advanced pancreatic cancer: a single center experience. *Hepatogastroenterology* 54(80), 2373–2377 (2007).

113 Tsushima Y, Miyazaki M, Taketomi-Takahashi A, Endo K. Feasibility of measuring human pancreatic perfusion *in vivo* using imaging techniques. *Pancreas* 40(5), 747–752 (2011).

114 Maurer CA, Borner MM, Lauffer J *et al.* Celiac axis infusion chemotherapy in advanced nonresectable pancreatic cancer. *Int. J. Pancreatol.* 23(3), 181–186 (1998).

115 Aigner KR, Gailhofer S. Celiac axis infusion and microembolization for advanced stage III/IV pancreatic cancer – a Phase II study on 265 cases. *Anticancer Res.* 25(6C), 4407–4412 (2005).

116 Lygidakis NJ, Sgourakis G, Aphinives P. Upper abdominal stop-flow perfusion as a neo and adjuvant hypoxic regional chemotherapy for resectable gastric carcinoma. A prospective randomized clinical trial. *Hepatogastroenterology* 46(27), 2035–2038 (1999).

117 Kuemmerle A, Decosterd LA, Buclin T *et al.* A Phase I pharmacokinetic study of hypoxic abdominal stop-flow perfusion with gemcitabine in patients with advanced pancreatic cancer and refractory malignant ascites. *Cancer Chemother. Pharmacol.* 63(2), 331–341 (2009).

118 Begossi G, Belliveau JF, Wanebo HJ. Pelvic perfusion for advanced colorectal cancers. *Surg. Oncol. Clin. N. Am.* 17(4), 825–842, ix–x (2008).

119 Guadagni S, Fiorentini G, Palumbo G *et al.* Hypoxic pelvic perfusion with mitomycin c using a simplified balloon-occlusion technique in the treatment of patients with unresectable locally recurrent rectal cancer. *Arch. Surg.* 136(1), 105–112 (2001).

■ Websites

201 Open clinical trials of regional chemotherapy. http://clinicaltrials.gov

202 Isolated limb perfusion. http://medicineworld.org/cancer/mesothelioma/staging-of-pleural-mesothelioma.html