Eric Van Cutsem · Thomas J. Vogl
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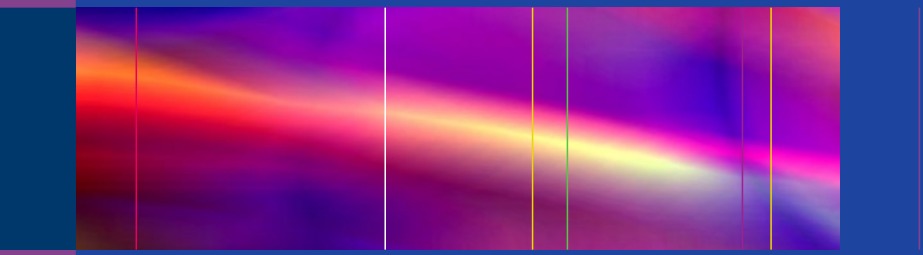

Locoregional Tumor Therapy

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Part IV Thermoablation

Introduction

1

René Adam

The efficacy of locoregional therapy is well established for most tumors and is related to the fact that malignant tumors are mainly vascularized by their arterial supply. Hepatic arterial infusion (HAI) has been an appealing investigational method over the last three decades for patients with tumors confined to one organ in whom it has reproducibly yielded a significant higher concentration of drugs, with consequently higher response rates than systemic therapy.

The progress made recently in chemotherapy agents, in microspheres able to embolize more efficiently the microvasculature of tumors as well as to load efficient drugs able to diffuse within the organ (drug-eluting beds – DEB) or to be loaded with radioactive agents to serve as a source of internal radiation (radioembolization), has reactivated the interest for regional therapy in the recent years. In addition, the spectrum of intraarterial antitumor substances became much broader which are mostly able to combine with the new degradable starch microspheres (DSM). Finally the tremendous technical progress made by interventional radiologists allows now this therapy to be performed mini invasively.

Along with this higher efficacy, the role of these therapies is changing in between the two standards of therapy consisting on surgical resection of the tumor in one side and systemic therapy on the other side. Surgery is still the only treatment able to completely remove the tumor with safe margins offering the best chances of long-term survival and even cure. By this way, locoregional therapy is still reserved to non-resectable patients or patients unfit for surgery.

On the other hand, especially when dealing with metastatic disease, the role of locoregional therapies is reserved to tumors located in one organ, after a complete workup to look for another metastatic site that would preclude their use. In this latter case, systemic chemotherapy is the preferred approach.

These therapies benefit now from lessons learned from the past. The history of intraarterial chemotherapy for liver metastases is interesting on this regard, showing that in the past, patients were for long very well controlled in their hepatic disease but developed extrahepatic metastases that finally determined their fatal outcome. The combination of intraarterial infusion with systemic administration of chemotherapy is able today to prevent in some extent this unfavorable outcome. Another example of the evolution of the ideas is the present recognition of radiofrequency as a potentially curative treatment of HCC owing to the

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effective ablation of liver tumors of up to 25 mm in diameter, achieving in this case almost equivalent results as surgery.

But, in addition to the competitive efficacy of the other therapies, locoregional treatments are also faced with their higher complexity, leading sometimes to deny their recognized efficacy for a more simple approach by systemic chemotherapy. The expertise of interventional radiologists and surgeons and the open mind of medical oncologists to accept these approaches is the prerequisite for these locoregional therapies to play all their important roles. Also critical is their cost-effectiveness to be compared with the conventional treatments.

In this book, an update of the role of locoregional therapies is extensively made by experts in liver, lung, and head and neck tumors. No doubt that this will allow to precise their increasing role in the larger and larger armamentarium of available treatments for malignant tumors.

Part I

Basics of Regional Tumor Therapies

Pharmacokinetic Aspects of Regional Tumor Therapy

2

Martin Czejka and Katharina Schüller

2.1 Introduction

The aim of a safe and efficient drug therapy is to direct the agent as near as possible to its target where it generates its maximum pharmacological effect while keeping side effects at a minimum.

Contrary to effects of a drug on the organism (pharmacology), the organism itself exerts an effect on the fate of a drug in man in a time-dependent manner. This pharmacokinetic fate comprises absorption, distribution, metabolism, and complete elimination from the body (ADME).

Although these processes are rather complex and determined by various endogenous and exogenous factors, pharmacokinetic parameters for each single drug are available. Table 2.1 gives an overview for the most relevant parameters for clinical evaluation.

The concentration of a drug in the target organ can be increased by using special applications such as regional drug administration. By changing the actual physiological conditions of the target organ (for instance, by occlusion of a blood vessel), regional administration increases the absorption rate of the chemotherapeutic agent from the blood into the tumor tissue. As a consequence, blood flow is decreased through the affected organ, and tissue-extraction rate is accelerated or increased.

So regional administration combined with a temporary occlusion of the supplying vessels is a valuable therapeutic option, especially for the chemotherapeutic treatment of liver tumors and liver metastases, respectively.

2.2 Hepatic Blood Flow (Q_{hep})

The perfusion of the liver is a main factor of the regional administration. Hepatic blood flow is the sum of portal vein (1,050 ml/min) and common hepatic artery (300 ml/min) blood flow. Therefore, Q_{hep} is about 1,500 ml/min (≈90 l/h).

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Table 2.1 Clinical relevant pharmacokinetic parameters [1]

PK parameter	Dimension	Relevance
$t_{1/2}$zp	Time	Transfer from blood to deep compartment
$t_{1/2}$el	Time	Elimination half-life from the body
c_{max}	Concentration/volume	Peak concentration in blood or tissue
t_{max}	time	Time to reach c_{max}
AUC	Concentration/volume × time	Area under concentration-time curve
Cl_{tot}	Volume/time	Total body clearance
Vd	Volume	Volume of distribution

2.3 Hepatic Extraction Rate (E_{hep})

E_{hep} is calculated as follows by the arterial and venous drug concentration during liver passage.

$$E_{hep} = \frac{conc_{arterial} - conc_{venous}}{conc_{arteria}} = Cl_{freedrug} \times conc_{freedrug}$$

E_{hep} ranges from 0.0 (=no extraction) to 1.0 (=complete extraction). An E_{hep} of 0.8 indicates the elimination and metabolism of 80 % of the drug entering the liver leaving 20 % of the administered drug to exit the liver through the liver veins.

2.4 Hepatic Clearance (Cl_{hep})

Cl_{hep} is defined as the volume of blood passing through the liver that is cleared from a compound per time. Hepatic clearance is based on the whole body clearance minus the renal clearance and the mostly quantitative not relevant non-hepatic, nonrenal clearance by other organs (e.g., skin or lung). Cl_{hep} depends on the blood flow through the liver, the liver cell mass, and the activity of drug-metabolizing enzymes. It is the product of E_{hep} and the blood flow through the organ (Q_{hep}).

$$Cl_{hep} = Q_{hep} \times E_{hep}$$

Considering the hepatic extraction of a drug, its tissue penetration does not only depend on physiological conditions (as already mentioned) but also on the physicochemical properties of the molecule as well. Besides the drug there are some other factors with impact on the hepatic clearance (see Table 2.2).

Despite their chemical heterogeneity, a number of different cytostatic agents can be used for regional intraarterial treatment (see Table 2.3). The most important assumption for the drug is a so-called first-pass metabolism or first-pass effect. Per definition first-pass effect is the sum of all processes (distribution and metabolism) occurring during the first liver passage of a drug before the drug reaches systemic blood circulation and becomes available in the whole body.

Table 2.2 Factors that have an influence on E_{hep} of a drug

Parameter	Mechanism
Blood flow	Distribution rate
Tissue uptake	Absorption mechanism (diffusion, active transport)
Protein binding	Intravascular depot
Liver diseases	Altered vascularization, dysproteinemia
Cytostatic	Physicochemical properties (lipophilicity, pka value, ionization) metabolism (phases I and II)
Occlusion method	Means and duration of occlusion, amount of particles

Table 2.3 Pharmacokinetic parameters (after IV administration) of cytostatic agents that are suitable for intraarterial administration due to their first-pass effect [2, 3]

Drug	Vd (l)	Cl_{tot} (l/min)	$t_{1/2}$ (h)	Metabolism
Doxorubicin	≈1.500	1.2	30	Liver
Epirubicin	≈2.000	1.2	35	Liver
5-Fluorouracil	16	2.0	0.3	Ana-, catabolism
Irinotecan	200–400	0.5	15	Liver
Mitomycin C	≈50	1.1	0.6	Blood metabolites
Pt-agents	30 (UF)	0.04	150	Blood metabonates
Gemcitabine	85	0.8–1.5	0.5–1.5	Liver, leucocytes
Carmustine	250	≈4.2	1.5	Metabonates

UF ultra filtrate

By comparing the intraarterial/intravenous AUC ratio, chemoembolization leads to a therapeutic advantage (TA), calculated as follows:

$$TA = \frac{\dfrac{AUC_{hep}}{AUC_{blood}}\ \text{i.a.}}{\dfrac{AUC_{hep}}{AUC_{blood}}\ \text{i.v.}}$$

In comparison to IV administration, decreasing hepatic perfusion results in a higher regional distribution rate.

$$RA = 1 + \frac{Cl_{tot}}{Q_{hep} \times (1 - E_{hep})}$$

Regional application combines decreasing side effects and higher levels of toxicity (increased apoptosis rate) [4]. The RA gets more intense the faster the cytostatic distributes into the tissue and the higher its extraction rate from the body.

2.5 Pharmacokinetic Data Using Degradable Starch Microspheres (DSM)

A successful embolization can be characterized by comparing the main pharmacokinetic parameters with data obtained after conventional administration. AUC_{last} and c_{max} are the most suitable values for calculating the shift of the drug's concentration from blood to tissue.

Depending on the chemotherapeutic agent, the administration of DSM leads to a decrease of systemic circulation from 20 to 60 %. It is the most important requirement that the chemotherapeutic does not bind to DSM or red blood cells [5].

So far most of the studies concerning pharmacokinetic data of cytostatic agents after the embolization of the common hepatic artery used DSM. The findings in Table 2.4 from several studies show between 19 and 98 % reductions in plasma drug concentrations. The reduced systemic drug exposure may be seen as an increased first-pass extraction during the prolonged time of the drug in the occluded target area. The higher first-pass extraction of the drug in the target compartment will lead to a lower dose of drug reaching the systemic circulation and subsequently to fewer side effects [6, 14]. Besides the chemotherapeutics given in Table 2.4, one of the most currently irinotecan is administered intraarterially after chemoembolization as well [19]. Irinotecan (CPT-11) is a prodrug and needs to be activated in the body. The drug shows poor affinity to the responsible enzyme (human carboxylesterase); therefore, only small amounts of the pharmacologic active metabolite SN-38 are formed (about 10 % of the parent compound). This activation can be improved by regional administration to the liver leading to higher amounts of SN-38 in the blood and tissue.

Table 2.4 Mean reduction of plasma AUC in patients with HCC using DSM

Drug	Tumor type	AUC decrease (%)	*N*	References
Mitomycin C	Primary and secondary liver cancer	33	87	[6] [7] [8] [9] [10] [11]
Doxorubicin	Primary and secondary liver cancer	19	5	[12] [13]
Carmustine (BCNU)	Primary and secondary liver cancer	62	5	[14]
Fotemustine	Primary and secondary liver cancer	53	4	[15]
5-FU	Primary and secondary liver cancer	38	8	[16]
Floxuridine	Colorectal liver metastasis	34	3	[10]
Cisplatin	Colorectal liver metastasis	38	4	[17]
Cisplatin and sodium thiosulfate	Head and neck cancer	98	6	[18]

Table 2.5 Average AUC ratio, measured as peripheral plasma AUC of MMC with and without DSM in patients with HCC

DSM (mg)	MMC (mg/m^2)	*N*	AUC ratio	95 % CI	References
360	15	36	0.74	0.62–0.87	[6]
360	10	6	0.70	0.55–0.88	[7]
					[9]
900	5–10	11	0.61	0.47–0.80	[7]
					[9]
540	3	7	0.73	0.62–0.86	[9]
900	9	10	0.55	n.s.	[8]
360	10	3	0.80	n.s.	[10]
450–900	18	14	0.55	n.s.	[11]
60	20	7	No effect	n.s.	[20]

n.s. not specified

Table 2.6 Ratio of cytostatic drugs in tumor and healthy liver tissue (with and without DSM) in vivo (rat, rabbit)

			Tumor/liver ratio[a]		
Species	Tumor type	Drug	Without DSM	With DSM	References
Rabbit	Liver	5-FU	0.63	3.59	[21]
Rat	Liver	5-FU	0.38	2.25	[22]
Rat	Liver	Doxorubicin	1.3	8.3	[23]
Rabbit	Liver	Doxorubicin	0.25	1.24	[24]
Rabbit	Liver	Doxorubicin	0.4	1.01	[25]
Rat	Liver	Tauromustine	0.47	2.16	[26]
Rabbit	Liver	Carboplatin	0.94	6.81	[27]
Rat	Lung	Carboplatin	1.19	2.11	[28]
Rat	Liver	Docetaxel	0.67	1.38	[29]

[a]Substance-dependent measurements, intervals from 15 to 480 min

Numerous investigations characterized the combination of mitomycin C (MMC) with different amount of DSM. The AUC ratio is relatively consistent from 0.55 to 0.80 as can be seen in Table 2.5. Administration of 60 mg DSM did not show any effect; obviously this amount was too low for any occlusion of blood vessels.

More data about the distribution of other cytostatic agents into tumor and healthy tissue using DSM in animals and patients are in Tables 2.6 and 2.7. Table 2.6 gives an overview of experimental findings in animals.

Table 2.7 presents data of human biopsy samples indicating that DSM leads to an increased uptake of drug into tumor tissue. Intraarterial application of DSM and a cytotoxic drug leads to an increased drug concentration in the tumor compartment as well as DSM-induced increase of tumor versus normal tissue drug concentration ratio.

Table 2.7 Mean ratio of drug concentration in tumor and healthy liver tissue (with and without DSM) in patients with secondary liver cancer or oral cancer

		Tumor AUC		Tumor/liver ratio			
Drug	Tumor type	Without DSM	With DSM	Without DSM	With DSM	*N*	References
99mTc-DTPA	Secondary liver cancer	0.87 ± 0.4 (10^{-7} × CPM s/pixel)	1.11 ± 0.5 (10^{-7} × CPM s/pixel)	0.33 (10^{-7} × CPM s/pixel)	0.35 (10^{-7} × CPM s/pixel)	5	[10]
2 mCi		After 3 min	After 3 min	After 3 min	After 3 min		
FUdR	Secondary liver cancer	5.9 ± 4.4 (nmol/g)	17.1 ± 9.4 (nmol/g)	0.16 ± 0.09 (nmol/g)	0.63 ± 0.13 (nmol/g)	14	[30]
0.15 mg/kg		After 5 min	After 5 min	After 5 min	After 5 min		
DDP	Secondary liver cancer	0.67 ± 0.5 µg/ml	3.03 ± 1.6 µg/ml	0.68 ± 0.6 µg/ml	0.93 ± 0.1 µg/ml	8	[17]
25 mg/m^2		After 15 min	After 15 min	after 15 min	After 15 min		
DDP	Oral cancer	19.8 ± 4.7 µmol/L × h	89.6 ± 31.3 µmol/L × h	n.s.	n.s.	6	[18]
150 mg/m^2 + STS 9 g/m^2							

n.s. not specified

2.6 Further Chemoembolization Tools

Besides DSM other materials for chemoembolization have been developed recently. In trans-arterial chemoembolization (TACE) DSM, polyvinyl alcohol polymers, Gelfoam, and gelatin-based microspheres (Embosphere) are used to keep systemic circulation of a chemotherapeutic at a minimum. Polyvinyl alcohol polymers and superabsorbent polymer microspheres (SAP, HepaSphere®, QuadraSphere®) can be loaded with a compound to become drug-eluting beads (DEB, DEBDOX, DEBIRI). In the following Tables 2.8, 2.9, 2.10, and 2.11, various agents used for chemoembolization and their effect on maximum plasma concentrations of antineoplastic drugs as well as corresponding tumor concentrations and tumor/liver ratios in animals and patients are listed.

Combination of DSM or other occlusion agents and chemotherapy intraarterially reduced systemic exposure to chemotherapy in animals and patients, manifested not only in pharmacokinetic parameters but also in reduced hematological toxicity [6]. Comparative pharmacokinetic studies between various occlusion agents still need to be investigated in further studies. In conclusion, chemoembolization with DSM and other agents is a valuable therapeutic option in palliative and neoadjuvant medicine as evident in the following chapters.

Table 2.8 Effects of different permanent embolization materials on maximum plasma concentrations in animals

Drug	Species	Material	Tumor type	Reduction of c_{max} in plasma	References
Carboplatin	Rabbit	Embosphere	Liver	84 % after 30 min	[31]
	Rabbit	DEBDOX	Liver	82 % after 20 min	[32]
Doxorubicin	Rabbit	Quadra-Sphere	Liver	54 % after 10 min	[33]
Irinotecan	Sheep	DEBIRI	Lung	80 % after 10 min	[34]
SN 38				No effect	
Irinotecan	Rabbit	DEBIRI	Liver	48 % from 10–60 min	[35]
SN 38				34 % after 2 h	

Table 2.9 Effects of different permanent embolization materials on concentration in tumor tissue and on tumor/liver ratios in animals

Drug and embolization material	Tumor type	Species	Mean tumor concentration		Tumor/liver ratio		References
			i.a. (µg/g)	i.a. with embolization (µg/g)	i.a.	i.a. with embolization	
Carboplatin 5 mg/kg (Embospere)	Liver	Rabbit	4.01	20.33	1	2.5	[31]
Doxorubicin 11.25 mg (DEBDOX)	Liver	Rabbit	58	239.5	n.s.	n.s.	[32]
Doxorubicin 5 mg (DEBDOX)	Liver	Rabbit	n.s.	26.1	n.s.	17.8–16.1	[36]
Doxorubicin 4 mg (QuadraSphere)	Liver	Rabbit	153.4	196.5	n.s.	n.s.	[33]
Irinotecan 12 mg (DEBIRI) SN-38	Liver	Rabbit	0.497 0.062	0.872 0.351	n.s.	n.s.	[35]

n.s. not specified

Table 2.10 Effects of different permanent embolization materials on maximum plasma concentrations in patients

Drug	Material	Tumor type	Mean AUC reduction	References
Doxorubicin 25–100 mg/m^2	DEBDOX	Untreated large/multifocal HCC patients	57 % after 0–7 d (compared to conventional TACE)	[37]
Doxorubicin 25–75 mg/m^2	Drug-eluting SAP microspheres	Unresectable HCC patients	58 % after 0–3 h (compared to conventional TACE)	[38]
Oxaliplatin 25–100 mg	HepaSphere	Colorectal liver metastasis and intrahepatic cholangiocarcinoma patients	45 % after 0–7 d (compared to FOLFOX)	[39]

d days

Table 2.11 Effects of different permanent embolization materials on concentration in tumor tissue and on tumor/liver ratios in patients

Drug/embolization material	Tumor type	Tumor AUC		Tumor/liver ratio		References
		Control	With emboli-sation	Control	With emboli-sation	
Oxaliplatin 25–100 mg OEM (Hepa-Sphere)	Colorectal liver metastasis and intrahepatic cholangiocarcinoma patients	n.s.	n.s.	1.08–1.38 (FOLFOX i.v.)	1.27–71.2	[39]
Doxorubicin 75–150 mg DEBDOX	Unresectable HCC patients	n.s.	5.0 µM mean level after 8 h 0.65 µM mean level after 32–36 d	n.s.	n.s.	[40]

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Embolization Materials, Catheters, and Intra-arterial Ports

3

Geert A. Maleux

3.1 Introduction

Catheter-directed embolization therapies for oncologic indications are increasingly gaining importance. Basically, these minimally invasive therapies include locoregional, tumoricidal therapies, pre-, or postoperative adjunctive treatments as well as palliative management options. Although different materials are used depending on the indications, the interventional approach is in most of the cases similar: a diagnostic catheter is placed in the feeding, large artery, and through this guiding catheter, a coaxial "microcatheter" is placed with its tip as close as possible to the target tumoral implants. Once the microcatheter is correctly positioned, chemotherapeutic agents can be carefully injected in order to obtain very high drug concentrations within the tumor and low(er) drug concentrations within the peripheral blood, resulting in high response rates and low(er) systemic toxicity rates. Additionally, occluding microparticles can be injected during or immediately after the chemotherapeutic infusion in order to add an ischemic effect or to create a slower washout phenomenon of the injected cytostatic agents. In case of emergency conditions of bleeding tumors, transcatheter injection of embolics without chemotherapeutic agents may be sufficient to stabilize the patient's condition.

In this chapter, an overview of different minimally invasive, transcatheter therapies for tumor treatment, including transarterial chemo-infusion with or without insertion of a permanent portsystem, transarterial (chemo)embolization, yttrium-90 infusion, and isolated liver perfusion, will be given. Also, a brief overview of interventional techniques to treat tumor-related hemorrhage will be presented, and finally, a short overview of percutaneous ablative devices will be given.

1. *Transarterial Chemo-infusion of Metastatic Liver Tumors*
   1.1. *Rationale*
      1.1.1. Liver metastases are perfused mainly by the hepatic artery, whereas normal liver tissue is primarily supplied by the portal vein.
      1.1.2. Certain drugs have high hepatic extraction.
      1.1.3. The liver is often the first site of metastases; eliminating liver metastases may prevent extrahepatic disease.
      1.1.4. Many drugs have a steep dose–response disease.
      1.1.5. Drugs with a high total body clearance are very effective.

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1.2. *Indications*
- 1.2.1. Palliative chemotherapeutic treatment of liver-only or liver-predominant metastases, mainly as rescue for liver metastases refractory to all conventional intravenous chemotherapeutic lines.
- 1.2.2. Downstage the number and volume of liver metastases prior to surgical resection or any other percutaneous ablative therapy. This approach can be used as first, second, or as last chemotherapeutic line.

1.3. *Technique*
- 1.3.1. Repeat catheterization
  - (a) Under local anesthesia, repeat catheterization of the feeding hepatic arteries with use of a diagnostic catheter (4–5 French) and coaxial microcatheter.
  - (b) Diagnostic catheter: 4–5 F cobra-shaped, Simmons I or Simmons II catheter.
  - (c) Microcatheter: large-bore 2.5–3.0 F microcatheter.
- 1.3.2. Port-catheter

  Insertion of a permanent arterial portsystem from the femoral or axillary artery. Before each chemotherapeutic session, patency and position of the port has to be verified. Procedure under local anesthesia.
- 1.3.3. Choice of technique depends of:
  - (a) Experience of the interventional radiologist
  - (b) Short interval between two sessions (<2 weeks) and many sessions foreseen (>5 sessions): portsystem > repeat catheterization
  - (c) Long interval (at least 2–4 weeks) between two sessions and potentially only a few sessions foreseen: repeat catheterization > port system

1.4. *Which Chemotherapeutic Agents for Which Metastases?*
- 1.4.1. Mitomycin C for breast cancer related liver metastases
- 1.4.2. Oxaliplatin for colorectal related liver metastases
- 1.4.3. Fotemustine for ocular melanoma related liver metastases
- 1.4.4. 5-FU + floxuridine for colorectal related liver metastases

Reference list: references [1–7]

2. *Chemoembolization of Primary and Secondary Liver Tumors*

2.1. *Rationale*
- 2.1.1. See chemo-infusion of metastatic liver metastases.
- 2.1.2. Addition of embolic agents:
  - (a) Reduce the washout effect of infused chemotherapeutic agents.
  - (b) Ischemia may induce cellular pump destruction which may lead to better uptake of cytotoxic agents by the tumoral cells.
  - (c) Persistent ischemia may induce tumor necrosis.

2.2. *Indications for Primary Liver Tumors*
- 2.2.1. First-line therapy for unresectable, liver-only hepatocelllar carcinoma
- 2.2.2. Rescue therapy for cholangiocarcinoma refactory to medical management

2.3. *Indications for Secondary Liver Tumors*
- 2.3.1. Rescue therapy for liver-only or liver-predominant metastases refractory to most/all conventional chemotherapeutic lines
  - (a) Colorectal metastases
  - (b) Neuroendocrine metastases
  - (c) Pancreatic carcinoma metastases
  - (d) Malignant melanoma metastases
  - (e) Renal cell carcinoma metastases

2.3.2. First- or second-line therapy for liver-only or liver-predominant metastases (experimental for colorectal metastases)
2.3.3. Third-line therapy for liver-only colorectal metastases (drug-eluting beads with irinotecan)

2.4. *Technique of Chemoembolization*
2.4.1. Conventional chemoembolization
(a) Local anesthesia
(b) Selective catheterization of the hepatic artery and subsequently of the feeding arteries of the tumoral lesion(s)
(c) Slow injection under fluoroscopic guidance of the mixture of chemotherapeutic agents and Lipiodol (Laboratoires Guerbet, Aulnay-sous-Bois, France)
- Doxorubicin
- Cisplatin
- Mitomycin C
- Combination of abovementioned agents

(d) Injection of microparticles mixed with contrast medium
- Polyvinyl alcohol (PVA) microparticles
  - Contour (Boston Scientific Corp., Natick, MA, USA)
  - PVA (Cook Medical, Bjaeverskov, Denmark)
- Calibrated microspheres
  - Embospheres (Merit Medical Systems Inc., South Jordan, UT, USA)
  - Bead Block (Terumo, Leuven, Belgium)
  - Embozene (CeloNova BioSciences Inc., San Antonio, TX, USA)
- Resorbable particles
  - Starch microspheres (Embocept®S, PharmaCept Berlin, Germany)
  - Spongostan (Ferrosan Medical Devices, Soeborg, Denmark)
  - Curaspon (P3 Medical Ltd., Bristol, UK)

2.4.2. Chemoembolization with drug-eluting beads
(a) Local anesthesia, except when using Irinotecan-loaded microparticles (epidural or general anesthesia).
(b) Selective catheterization of the hepatic artery and subsequently of the feeding arteries of the tumoral lesion(s).
(c) Slow injection under fluoroscopic control of the mixture of drug-eluting beads and contrast medium.
- HepaSphere (Merit Medical, UT, USA)
  - Doxorubicin
  - Oxaliplatin
  - Cisplatin
- DC Beads (Biocompatibles, UK)
  - Doxorubicin
  - Irinotecan

(d) Stop embolization when flow is slowing down or when stasis of contrast medium is obtained in the feeding artery.

2.5. *Exclusion Criteria* (*Absolute and Relative Contraindications*)
2.5.1. Absolute contraindication for chemoembolization
(a) >50 % tumor involvement of the liver volume
(b) Active infection
(c) Liver function disturbances (bilirubin > 2.5 mg/dL)

(d) Macroscopic arterioportal fistula
(e) Main portal vein thrombosis
2.5.2. Relative contraindication for chemoembolization
(a) Reduced liver function (bilirubin >1.5>2.5 mg/dl)
(b) Child-Pugh B (drug-eluting beads are preferred)
(c) Partial or distal portal vein thrombosis
(d) Hepatic encephalopathy
(e) ECOG >1
(f) Renal insufficiency (contrast medium!)
2.6. *Complications*
2.6.1. Common complications
(a) Postembolization syndrome: >80 %
- Abdominal pain
- Fever < 38.5 °C
- Nausea
- Transient rise in liver function disturbances

2.6.2. Uncommon complications (<5 %)
(a) Liver abscess
- Hepaticojejunostomy (Whipple operation)
- Biliary stents

(b) Gallbladder necrosis
(c) Liver insufficiency
(d) Hepatorenal syndrome

Reference list: references [8–18]

3. *Radioembolization of Primary and Secondary Liver Tumors*
3.1. *Rationale*
Yttrium-90 is a pure beta-emitter with a half-life of 64.9 h. The radioactivity induces a tumoricidal effect when the radioactivity is >70 G (Gray). Yttrium-90 is incorporated in small resin-based (Sirtex, North Sydney, NSW, Australia) or glass-based (TheraSphere, Nordion, Ottawa, Canada) microspheres with a diameter of 30–35 μm. These microspheres are infused through a microcatheter into the hepatic artery.
3.2. *Indications*
Primary and secondary liver tumors in patients with liver-only or liver-predominant metastatic disease:
3.2.1. Hepatocellular carcinoma:
(a) Competitive technique to chemoembolization
(b) Presence of portal vein thrombosis
(c) Presence of TIPS
3.2.2. Metastases
(a) Salvage therapy for colorectal metastases in liver-only disease
(b) Salvage therapy for neuroendocrine liver metastases
(c) Metastases of ocular melanoma
3.3. *Palliative Therapy to Control the Tumor Burden*
Downstaging to surgical resection, percutaneous radiofrequency ablation, or liver transplantation (HCC)
Potentially curative in case of a small number of tumors: “radiation segmentectomy”
3.4. *Technique*
The yttrium-90 infusion procedure is preceded by an angiographic workup consisting in angiographic mapping of all hepatic arteries; in proximal coil occlusion of hepatoenteric arteries like the gastroduodenal artery, right gastric artery, and supraduodenal artery. Finally, a diagnostic concentration of Tc-99 is injected into

the microcatheter to assess the liver-long shunting, matching of the tumoral liver lesions, and the presence or absence of extrahepatic Tc-99 uptake.

3.5. *Absolute Contraindications*
- 3.5.1. Liver-lung shunt > 20 %
- 3.5.2. Mismatch between PET-CT and Tc-99 scintigraphy
- 3.5.3. Persistant extrahepatic TC-99 uptake
- 3.5.4. Reduced liver function (bilirubin > 1.5 mg/dL)
- 3.5.5. Tumor volume > 50 % of the total liver volume
- 3.5.6. Significant extrahepatic disease

3.6. *Relative Contraindications*
- 3.6.1. Liver-lung shunt > 10 % > 20 %
- 3.6.2. Reduced liver function >1.0 > 1.5 mg/dL
- 3.6.3. Discrete extrahepatic disease

3.7. *Complications*
- 3.7.1. Common complications
  - (a) Abdominal pain, fatigue (20–50 %)
  - (b) Gastroduodenal ulceration (5–10 %) as a result of nontarget embolization
- 3.7.2. Uncommon complications (<5 %)
  - (a) Pancreatitis
  - (b) Cholecystitis
  - (c) Liver failure
  - (d) Liver fibrosis and portal hypertension
  - (e) Radiopneumonitis

Reference list: references [19–25]

4. *Isolated Liver Perfusion ("Chemosaturation")*

4.1. *Rationale*

Perfusion of high concentration of chemotherapeutic agents through the liver and extraction once passed into the hepatic veins.

4.2. *Indications*

Liver metastases responding to melphalan: ocular melanoma and some types of sarcoma

4.3. *Technique*
- 4.3.1. General anesthesia.
- 4.3.2. Percutaneous placement of a catheter into the hepatic artery after coil occlusion of hepatoenteric arteries if required. Through this hepatic catheter: infusion of the chemotherapeutic drug, melphalan.
- 4.3.3. Placement of a double-balloon catheter into the inferior vena cava: one balloon is placed above the inflow of the hepatic veins, the other balloon is placed below the inflow of the hepatic veins. The occluded hepatic segment is connected through the inner lumen of the catheter with a filter device, extracting the residual amount of melphalan.

4.4. *Complications*
- 4.4.1. Device-related complications (vena cava wall dissection)
- 4.4.2. Complications related to general anesthesia
- 4.4.3. Complications related to temporary occlusion of the inferior vena cava (hypotension and related cardiac complications)
- 4.4.4. Complications related to melphalan:
  - (a) Neutropenia
  - (b) Thrombocytopenia
  - (c) Anemia
- 4.4.5. Hepatic failure

Reference list: references [26, 27]

5. *Embolotherapy for Oncologic Hemorrhagic Conditions*
   - 5.1. *Indications*
     - 5.1.1. Acute tumor-related bleeding
   - 5.2. *Pathophysiology*
     - 5.2.1. Intra- and peritumoral bleeding
     - 5.2.2. Erosion of surrounding (large) vessel by the tumor
   - 5.3. *Technique*
     - 5.3.1. Distal embolization of the tumoral mass ("bland embolization") with use of microparticles and microcoils
     - 5.3.2. Coil occlusion of the eroded artery
     - 5.3.3. Placement of a covered stent to exclude the erosion when coil embolization of the eroded vessel is not an option
       - (a) Aorta, iliac, or femoral arteries
       - (b) Subclavian, axillary, and carotid arteries
       - (c) Renal, superior mesenteric artery main branch
   - 5.4. *Which Tumoral Lesions?*
     - 5.4.1. Primary and secondary liver tumors
     - 5.4.2. Pancreascarcinoma
     - 5.4.3. Renal and bladder tumor
     - 5.4.4. Gynecological tumors
     - 5.4.5. Carcinomas in head and neck region

Summary of embolic agents for oncologic purposes

Embolic material	Brand name and manufacturer	Diameter of particles	Clinical indication
Nonresorbable microparticles			
Polyvinyl alcohol	Contour (Boston Scientific Corp.)	50–750 μm	Permanent occlusion adjunct for conventional chemoembolization
			Acute hemorrhagic conditions
	PVA (Cook Medical)		
Tris-acryl gelatin	Embosphere–EmboGold (Merit Medical)	100–900 μm	Permanent occlusion adjunct for conventional chemoembolization
			Acute hemorrhagic conditions
Polyvinyl alcohol hydrogel m..	Bead Block (Terumo)	50–900 μm	
Polyzene F-coated microspheres	Embozène (CeloNova)	50–1,200 μm	
Resorbable microspheres			
Starch microspheres	Embocept®S (Pharmacept)	35–50 μm	Mixture with chemotherapeutic drug/ adjunct to conventional chemoembolization

Embolic material	Brand name and manufacturer	Diameter of particles	Clinical indication
Gelfoam	Spongostan (Ferrosan Medical Devices)	Slurry made by physician	
Microcoils			
Fibered platinum coils	Target microcoils (Boston Scientific)	2–5.5 mm	Permanent vessel occlusion for acute bleeding
	Micro-tornado		
	Micronester (Cook Medical)	3–10 mm	Permanent vessel occlusion
Hydrogel-coated coils	AZUR microcoils (Terumo)	2–10 mm	Permanent vessel occlusion
Drug-eluting beads	HepaSphere (Merit Medical)	50–300 μm	Chemoembolization
	DC-beads (Biocompatibles)	50–300 μm	Chemoembolization
Yttrium-90 microspheres			
Resin based	SIR-spheres (Sirtex)	30–35 μm	Radioembolization of primary and secondary liver tumors
Glass based	TheraSpheres (Nordion)	30–35 μm	Radioembolization of primary and secondary liver lesions

6. *Percutaneous, Ablative Devices and Techniques*
   Most of percutaneous, ablative techniques are based on the development of heat (radiofrequency ablation, laser ablation, microwave ablation, focused ultrasound, irreversible electroporation) or cold (cryoablation) to kill tumor cells. In general, these ablative techniques are performed with a needlelike device which is positioned under image guidance, such as ultrasound, computed tomography, or even magnetic resonance imaging, into the tumor. The only exception is high-intensity focused ultrasound (HIFU) ablation. This is a totally noninvasive technique consisting in the formation of ultrasound rays that are focused into the tumor. Additionally, these techniques are very suitable for small (less than 3–5 cm) and few (less than 5) lesions.
   - 6.1. *Indications*
   - 6.2. *Radiofrequency Ablation*
     - 6.2.1. Primary and secondary liver tumors
     - 6.2.2. Lung tumors
     - 6.2.3. Kidney tumors
     - 6.2.4. Bone tumors
   - 6.3. *Laser Ablation*
     - 6.3.1. Liver tumors
   - 6.4. *Irreversible Electroporation*
     - 6.4.1. Pancreatic tumors
     - 6.4.2. Liver tumors
   - 6.5. *Microwave Ablation*
     - 6.5.1. Liver tumors

6.6. High-Intensity Ultrasound
6.6.1. Liver tumors
6.6.2. Pancreatic tumors
6.6.3. Uterine tumors
6.6.4. Bone tumors
Reference list: references [28–34]

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Part II

Intra-arterial Therapies: Liver

HCC

4

Franco Orsi

4.1 Introduction

Hepatocellular carcinoma (HCC) ranks among the most common cancers worldwide, representing the sixth most common one and the third cause of cancer-related death, and accounts for 7 % of all cancers [1]. HCC represents more than 90 % of primary liver cancers and is a major global health problem. Over the last three decades, the age-adjusted incidence of liver cancer has risen to 4.6 per 100,000 individuals. The incidence of HCC will likely continue to rise as the hepatitis C epidemic reaches maturity and nonalcoholic steatohepatitis becomes more prevalent. The incidence of HCC increases progressively with advancing age in all populations, reaching a peak at 70 years [2].

Approximately 90 % of HCCs are associated with a known underlying risk factor: the most frequent factors include chronic viral hepatitis (types B and C), alcohol intake, and aflatoxin exposure. In the developed Western world, only 20 % of cases can be attributed to HBV infection, while chronic hepatitis C appears to be the major risk factor [3].

Cirrhosis is the other most important risk factor for HCC and may be caused by chronic viral hepatitis, alcohol, and other inherited metabolic diseases. All etiologic forms of cirrhosis may be complicated by tumor formation, but the risk is higher in patients with hepatitis infection. Overall, one-third of cirrhotic patients will develop HCC during their lifetime [4].

Recent studies have shown that liver cancer incidence increases in parallel to portal pressure as directly measured [5] or in parallel to the degree of liver stiffness as measured by elastography [6, 7].

The presence of cirrhosis influences the chance for anticancer treatment, affecting their results. Then, many available treatments can have an adverse impact on cirrhosis and the exact cause of death, which could be either the underlying disease or HCC.

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4.2 Diagnosis

Early stage of HCC may be treated with potentially curative procedures such as resection, percutaneous ablation, and transplantation. Thus, there is an urgent need to identify better tools for detecting and characterizing these lesions in order to improve clinical outcome of HCC patients. Diagnosis of small HCC is feasible in 30–60 % of cases and this enables the application of curative treatments.

Until 2000, diagnosis was based on biopsy; then a panel of experts reported, for the first time, noninvasive criteria (see Table 4.1) for HCC, based on a combination of imaging and laboratory findings [8]. The dynamic radiological contrast enhancement in the arterial phase by CT, MRI, angiography, or US (CEUS) represents the most important finding for the radiological diagnosis of early HCC.

The clinical evaluation and management of HCC require a comprehensive, multidisciplinary approach that involves cancer surveillance and consideration of both surgical and medical therapies.

The implementation of such an approach has resulted in increased survival rates for HCC. The therapeutic approach for HCC can vary widely depending on the extent of disease: from potentially curative surgical resection and/or ablation for small localized tumors to liver transplantation or newer biologic therapies for more advanced disease. Advances in minimal invasive therapies, such as radiofrequency (RFA), microwave (MW) ablation, and transarterial chemoembolization (TACE), also continue to play a vital role in the management of more advanced stages and in pre- and perioperative transplant patients.

4.3 Staging Systems

Disease staging is particularly important in the management of HCC because it helps to predict prognosis and determine appropriate treatment options; the most effective staging systems incorporate information about both cancer stage and liver function, which is often affected by the underlining liver disease. The Child–Turcotte–Pugh (CTP = TAB IIa/IIb)

Table 4.1 Diagnostic algorithm for HCC in cirrhotic patients [8]

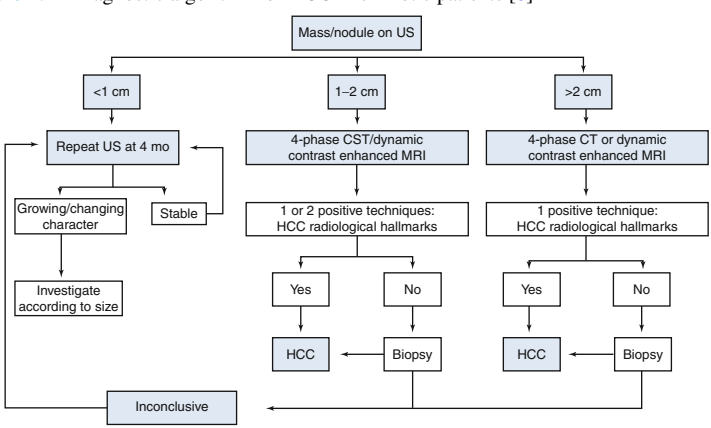
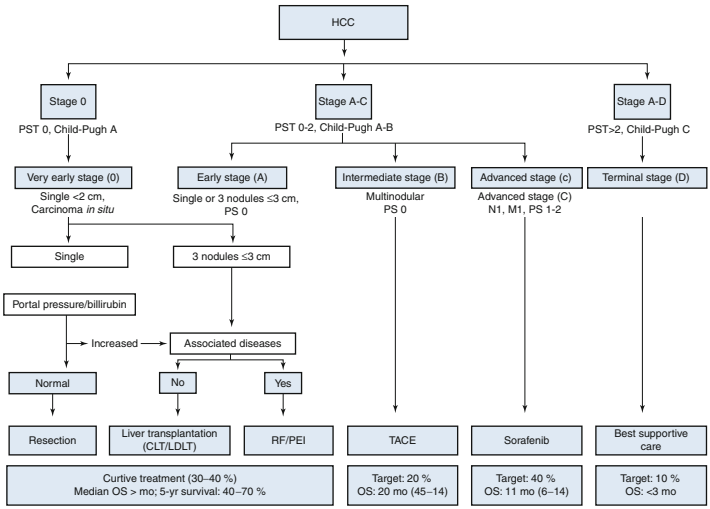


Table 4.2 Updated BCLC staging system and treatment strategy, 2011 (Reproduced from [20])



model is primarily an assessment of liver function and is intended to predict prognosis and stratify disease severity to facilitate transplant allocation [9]. While still used as a complementary tool to help with treatment decisions or evaluate progression and/or regression of disease, the CTP model has largely been replaced by the Model for End-Stage Liver Disease (MELD) score [10, 11]. MELD was originally developed at the Mayo Clinic and at that point was called the "Mayo End-Stage Liver Disease" score [12]. It was derived in a series of patients undergoing TIPS procedures. The score turned out to be predictive of prognosis in chronic liver disease in general, and – with some modifications – came to be applied as an objective tool in assigning need for a liver transplant. Higher MELD scores reflect more severe disease, poorer prognosis, and greater likelihood of liver transplantation, barring any absolute contraindications to transplantation [13–16]. While patients with HCC may be granted exception points that are added to their scores, the MELD system was not designed to assess HCC disease severity, and it does not provide good prognostic classification for these patients. The four major HCC staging systems include the American Joint Committee on Cancer's tumor-node-metastasis (TNM) model, the Okuda classification model, the Cancer of the Liver Italian Program (CLIP) score, and the Barcelona Clinic Liver Cancer (BCLC) staging system. The BCLC staging system has emerged as the most accurate and comprehensive cancer model to show consistent prognostic determination. The Barcelona Clínic Liver Cancer classification divides HCC patients in five stages (0, A, B, C, and D) according to preestablished prognostic variables and allocates therapies according to treatment-related status (Table 4.2) [17–19]. Thus, it provides information on both prognostic prediction and treatment allocation. Prognosis prediction is defined by variables related to tumor status (size, number, vascular invasion, N1, M1), liver function (Child–Pugh's), and health status (ECOG) (Tables 4.3a and 4.3b). Treatment allocation incorporates treatment-dependent variables, which have been shown to influence therapeutic outcome, such as bilirubin, portal hypertension, or presence of symptoms – ECOG. While

Table 4.3a Child–Pugh score system

Measure	1 point	2 points	3 points
Total bilirubin, µmol/l (mg/dl)	<34 (<2)	34–50 (2–3)	>50 (>3)
Serum albumin, g/l	>35	28–35	<28
PT INR	<1.7	1.71–2.30	>2.30
Ascites	None	Mild	Moderate to severe
Hepatic encephalopathy	None	Grade I–II (or suppressed with medication)	Grade III–IV (or refractory)

The score employs five clinical measures of liver disease. Each measure is scored 1–3, with 3 indicating most severe liver function impairment [21]

Table 4.3b Child–Pugh score classification

Points	Class	One-year survival (%)	Two-year survival
5–6	A	100	85
7–9	B	81	57
10–15	C	45	35

Chronic liver disease is classified into Child–Pugh class A to C, employing the added score from above

future studies incorporating genomic and proteomic profiles of patients and their cancers will provide even more accurate prognostic data and more individualized therapy, the BCLC model is currently the most comprehensive and widely accepted staging system for HCC.

4.4 Prognosis

The prognosis of advanced hepatocellular carcinoma (HCC) remains poor, particularly for patients with portal vein tumor thrombosis and extrahepatic metastases (median survival: 3–6 months)

The Tokyo index is a new and simple indicator for prognosis for survival

Tokyo score			
Parameter	0	1	3
Albumin (g/dl)	>3.5	2.8–3.5	<2.8
Bilirubin (mg/dl)	<1	1–2	>2
Tumor size (cm)	<2	2–5	>5
Tumor foci	<3	1–3	>3

Patients with a score up to 2 do have a relative good prognosis. Patients with a total score between 4 and 6 do have a 2-years survival expectation of 50 %.

4.5 Therapy

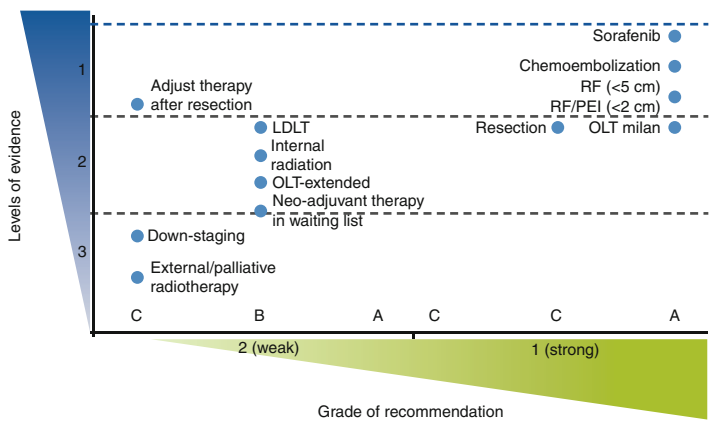
In oncology, the benefits of treatments should be assessed through randomized controlled trials and meta-analysis. Few medical interventions have been thoroughly tested in HCC, in contrast with other cancers with a high prevalence worldwide, such as lung, breast, colorectal, and stomach cancer. As a result, the strength of evidence for most interventions in HCC is far behind the most prevalent cancers worldwide. The level of evidence for efficacy according to trial design and endpoints for all available treatments in HCC and the strength of recommendations according to grade are summarized in Table 4.4.

Recommendations in terms of selection for different treatment strategies should be based on evidence-based data in circumstances where all potential efficacious interventions are available. However, multidisciplinary HCC tumor boards, including hepatologists, surgeons, oncologists, radiologists, interventional radiologists, pathologists, and translational researchers, should discuss any single HCC patient according to the international guidelines, and treatment strategies should be adapted to local regulations and/or team capacities and cost–benefit strategies.

4.5.1 Surgical Approach

The best treatment options with curative intent for patients with HCC are liver resection or transplantation, although the role of hepatic ablative therapies has also been recognized. Surgical resection has emerged as the primary treatment in carefully selected patients of HCC. With the advances in surgical and radiological techniques, the perioperative mortality has been reduced to less than 5 % depending on the extent of resection and hepatic reserve. Modern standards of HCC resection in cirrhotic patients are defined as follows: expected 5-year survival rates of 60 %, with a perioperative mortality of 2–3 % and blood transfusion requirements of less than 10 % [23–27]. Anatomic resections aiming at 2 cm margins provide better survival outcome than narrow resection margins <1 cm [28] and are

Table 4.4 Representation of EASL–EORTC recommendations for treatment according to levels of evidence (NCI classification) and strength of recommendation (grade system) [22]



recommended only in case that the maintenance of appropriate function to the remnant liver volume is ensured. In patients properly selected according to liver functional status, the main predictors of survival are tumor size, tumor number, presence of microsatellites, and vascular invasion [29]. The Japanese Nationwide Survey has shown that a cutoff below 2 cm is an independent predictor of survival in a series of thousands of patients [30]. Five-year survival rate for patients with HCC ≤ 2 cm was of 66 %, compared with 52 % for tumors 2–5 cm and 37 % for tumors >5 cm. Multinodularity also predicts survival, with 5-year survival rates after resection of single tumors of 57 and 26 % for three or more nodules, respectively.

Liver transplantation is the first treatment choice for patients with small multinodular tumors (≤3 nodules ≤ 3 cm) or those with single tumors ≤5 cm and advanced liver dysfunction. Theoretically, transplantation may simultaneously cure the tumor and the underlying cirrhosis. The role of liver transplantation as the mainstay of treatment for the majority of patients with HCC has evolved in the last few decades. Historically, the Milan criteria have been considered the gold standard for selecting patients: single HCC ≤5 cm or up to three nodules ≤3 cm [31]. Following these criteria and according to modern standards, *perioperative mortality*, *1- and 5-year mortality* are expected to be 3 %, ≤10 %, and ≤30 %, respectively. Living-donor liver transplantation has emerged as a way to expand the donor pool and has influenced the role of transplantation for HCC, especially in communities with little access to cadaveric transplantation. Salvage transplantation is an alternative option as it allows a window for the biologically less favorable lesions to declare tumor behavior. Salvage transplantation also decreases the burden on transplant resources. Three years survival expectation was 60–80 %.

4.5.2 Systemic Therapy

Systemic chemotherapy does not play a central role in the treatment of HCC due to the issue of low sensitivity for chemotherapeutic agents and the difficulties in administering a sufficient dose due to chronic liver dysfunction. Systemic treatment by mean of biologicals is the new frontier for advanced stage HCC. Sorafenib, an oral protein kinase inhibitor, is a systemic drug that has been licensed for the treatment of hepatocellular carcinoma (HCC). An international, phase III, placebo-controlled trial could show a minimal but demonstrated advantage in the median OS for the sorafenib group.

4.5.3 Minimally Invasive Locoregional Therapies

Locoregional hepatic tumor therapies include intra-arterial, percutaneous, and external therapies:

Intra-arterial Therapies

1. Hepatic arterial infusion (HAI)
2. Transarterial chemoembolization (TACE)
3. Transarterial embolization (TAE)
4. Y90 Radio embolization (Y90RE)
5. Percutaneous hepatic chemoperfusion (PHP)

Percutaneous Therapies

1. Percutaneous ethanol injection (PEI)
2. Local ablative techniques (radiofrequency ablation, RFA/microwave ablation, MWA/laser-induced thermotherapy, LITT)
3. Combined therapies (usually intra-arterial and local ablative

External Therapies
1. External radiation therapy (EBRT)
2. High-intensity focused ultrasound

4.5.3.1 Intra-arterial Therapies

Clinical conditions:

- Patients with big uninodular or multinodular HCC
- Sufficient liver function
- No infiltration of other big vessels
- No distal metastases influencing the prognosis

Hepatic Arterial Infusion (HAI)

Chemotherapeutic Agents: 5-Fluorouracile, Cisplatin, Mitomycin C

The concept of regional chemotherapy for hepatic metastases via HAI is based on several principles. First, hepatic tumors (both primary and metastatic ones) derive their blood supply from the hepatic artery, while normal hepatocytes are perfused mostly from the portal circulation [32]. Thus, infusion of chemotherapy via the hepatic artery could achieve toxic levels in tumor cells with relative sparing of normal hepatic parenchyma. Second, extraction of drug from the hepatic arterial circulation via the first-pass effect can result in high local concentrations and minimal systemic toxicity. The ideal agent should have a high dose–response curve, high extraction rate, and rapid total body clearance once infusion is discontinued. Intra-arterial chemotherapy is one of the possible treatment options for patients with advanced HCC not candidate for hepatic resection, percutaneous ablation, and transcatheter arterial chemoembolization. Patients with advanced HCC are increasingly treated in Japan with hepatic arterial infusion chemotherapy (HAIC). HAIC may provide moderate therapeutic efficacy and survival benefit with substantially tolerable toxicity profiles in patients with advanced HCC.

A dedicated arterial infusion catheter is placed through the left subclavian artery with the tip located into the coiled GDA. A side hole is made at the level of proper hepatic artery in order to deliver the drug into the arterial bloodstream. Proximal end of infusion catheter is connected with a reservoir (port) which is surgically placed in a subcutaneous pocket, below the clavicle. In BCLC treatment strategy flowchart, selective intra-arterial chemotherapy is not recommended for the management of HCC (*evidence 2A*; *recommendation 2B*).

Transarterial Chemoembolization (TACE)

Chemotherapeutic Agents: Doxorubicin, Cisplatin, Mitomycin C

Chemoembolization is the most widely used primary treatment for unresectable HCC [30, 33, 34] and the recommended first-line therapy for patients at intermediate stage of the disease [20, 35, 36]. HCC has an intense neo-angiogenic activity during its progression. The rationale for TACE is that the intra-arterial infusion of a cytotoxic agent followed by embolization of the tumor-feeding blood vessels will result in a strong cytotoxic and ischemic effect.

TACE should be distinguished from the Lipiodol TACE (cTACE), drug-eluting beads TACE (debTACE), and bland embolization (TAE, and micro-bland TAE).

- *cTACE* combines transcatheter delivery of chemotherapy emulsioned with Lipiodol followed by embolization of the feeding arteries. Chemoembolization achieves partial responses in 15–55 % of patients and significantly delays tumor progression and macrovascular invasion. Survival benefits were obtained in two studies [37, 38]

Meta-analysis of some RCT showed a beneficial survival effect of TAE/cTACE in comparison to the control group [36]. Sensitivity analysis showed a significant benefit of cTACE with cisplatin or doxorubicin in four studies, but none with embolization (using old embolic materials) alone in three studies. Overall, the median survival for intermediate HCC cases is expected to be around 16 months, whereas after chemoembolization the median survival is about 20 months. As a result of these investigations, TACE has been established as the standard of care for patients who meet the criteria for the intermediate stage of the BCLC staging system.

Treatment-related deaths are expected in less than 2 % of cases, and the best candidates are patients with preserved liver function and asymptomatic multinodular tumors without vascular invasion or extrahepatic spread. Patients should present relatively well-preserved liver function (mostly Child–Pugh A or B7 without ascites). Patients with liver decompensation or more advanced liver failure should be excluded since the ischemic insult can lead to severe adverse events [39]. There is no good evidence for which is the best chemotherapeutic agent and the optimal re-treatment strategy. Superselective chemoembolization is recommended to minimize the ischemic insult to non-tumoral tissue.

cTACE, debTACE, and TAE are usually performed through the femoral artery percutaneous approach. A selective angiography of proper hepatic artery has to be performed in order to define the liver vasculature and detect the tumor-feeding vessels. With the help of selective catheters and microcatheters, a superselective embolization of tumor-feeding arteries may be achieved, sparing the unaffected areas of the liver parenchyma. Endpoint for a better result should be the vascular shutdown to the tumor. Despite selecting the patients and performing a superselective embolization, TACE is not without risks. Complication may range from postembolization syndrome (of variable intensity) to liver abscesses, hepatic insufficiency, and ischemic cholecystitis, or cases of death have even been also described.

- *DEBTACE*. The ideal TACE scheme should allow maximum and sustained intratumoral concentration of the chemotherapeutic agent with minimal systemic exposure, along with calibrated tumor vessel obstruction. DEBTACE is performed by injecting microspheres loaded with antiblastic drug, such as doxorubicin. Unlikely to the cTACE, where the injected drug is quickly release into the systemic circulation, drug-eluting beads provide a gradual release of the chemotherapy agent into the tumor, reducing the systemic side effect and maximizing the local efficacy against tumor cells. Embolic microspheres have the ability to sequester chemotherapeutic agents and release them in a controlled mode over a 1-week period. This strategy has been shown to increase the local concentration of the drug with negligible systemic toxicity [40]. However, a randomized phase II study comparing TACE and TACE-DEB reported a nonsignificant trend of better antitumoral effect [41] in the latter arm.

Transarterial Embolization (TAE)

In the majority of published studies on HCC treatment with TAE, the reported embolic agent is gelatine sponge, which may induce only temporarily ischemia and without distal tumor vessel embolization. Only recently, few new studies on new embolic agents, such as resin or gelatine microspheres, are available. Even if there is no evidence for a better

survival benefit from DEB TACE than TACE and also TAE, if performed with small particles (40/100 μm), there is an increasing general consensus about the need to use the smallest available particles in treating HCC, in order to achieve a better, durable, and deeper embolic effect, independently by the use of drug or not [42–45]. Few papers on HCC treatment with TAE, using very small particles, reported an interesting safety profile with local results comparable with DEBTACE/TACE series [46]. However, based on data coming from old papers on TAE with gelatin sponge, *BCLC doesn't recommend the use of TAE for HCC.*

Y90 Radio Embolization (Y90RE)

Radioembolization is defined as the infusion of very small (<40 μm) microspheres containing yttrium-90 (90Y) [47–49] into the hepatic artery. Due to the hypervascularity of HCC, intra-arterial injection of microspheres will be preferentially delivered to the tumor-bearing area and selectively emit high-energy, with a low-penetrating radiation to the tumor. This treatment should be reserved only to centers with sophisticated equipments and trained interventional radiologists in cooperation with nuclear medicine specialists, in order to reduce the potential risk of possible serious side effects: severe lung shunting and intestinal radiation should be prevented prior to the procedure. This treatment can be safely used in patients with portal vein thrombosis, where it seems to obtain the best clinical results [48]. Recently, some studies reported a median survival time of 17.2 months for patients at intermediate stages and 12 months for patients at advanced stages and portal vein invasion [48–50]. Objective response rates ranged from 35 to 50 % [47–49]. Around 20 % of patients present liver-related toxicity and 3 % treatment-related death [47]. Despite the amount of data reported, there are no RCT testing the efficacy of 90Y radioembolization compared with chemoembolization or sorafenib in patients at intermediate or advanced stage, respectively. Further research trials are needed to establish a competitive efficacy role in this population (*BCLC = evidence 2A; recommendation 2B)*

Percutaneous Hepatic Chemoperfusion (PHP)

Percutaneous hepatic perfusion (PHP) is a regionalized, minimally invasive approach to cancer treatment currently undergoing phase II and phase III clinical testing in melanoma, CRC, and NET metastatic patients. PHP may treat a variety of hepatic tumors, including HCC, by isolating the liver and exposing the organ to high-dose chemotherapy [51]. As demonstrated in clinical trials, patients treated by PHP can tolerate much higher doses of chemotherapeutic agents than those receiving traditional systemic chemotherapy without increased toxicities.

Using a system of catheters and filters, PHP isolates the liver from the circulatory system and infuses a chemotherapeutic agent directly to the liver via the hepatic artery. The venous effluent from the liver is then filtered outside of the body and the filtered blood is returned into the jugular vein. PHP is a repeatable procedure and can be performed in an operating room or a radiology suite under general anesthesia. There are very few experiences in the treatment of HCC patients; however, the complexity of this revolutionary technique represents the main limitation. Further studies and a longer experience are needed before to treat HCC patient with PHP outside protocol studies.

4.5.4 Study Results: Neoadjuvant Therapies (HAI/Chemoembolization)

Author	*N*	Concept	Intra-arterial therapy	RR (%)	Median survival (mo)	Years survival (%)
Gerunda et al. (2000) [52]	89	TACE + LR vs. LR vs. TACE	1×: 50 mg epirubicin + Gelfoam	ND	Overall survival: TACE + LR vs. TACE/ LR: $p < 0.05$	1 y: 85 vs. 71 vs. 68 5 y: 43 vs. 38 vs. 0
Graziadei et al. (2003) [53]	48	TACE + LT	70 mg epirubicin + Lipiodol (±PVA particles) every 6–8 weeks	CR: 30 PR: 67	ND	1 y: 98 2 y: 98 5 y: 94
Yao et al. (2005) [54]	30	TACE ± RFA ± PEI + LT	ND	Down staging: 70	ND	1 y: 89 2 y: 82
Bharat et al. (2006) [55]	100	TACE (78 %), RFA (11 %), PEI (2 %), TACE + RFA (9 %) + LT vs. LT	50 mg cisDDP + 20 mg doxorubicin + 10 mg MMC + particles every 4–6 weeks	path RR: signif. advantage for neoadj. therapy	5 y OS(%): 82 vs. 52 (no difference in pT0 and pT1)	ND
Obed et al. (2007) [56]	74	TACE + LT vs. TACE vs. no therapy	50 mg epirubicin + Lipiodol every 6 weeks	After TACE: 29 PD: 70	92 vs. 8 vs. 4	ND
Zangos et al. (2007) [57]	48	TACE + LITT	10 mg/m^2 MMC + Lipiodol + DSM 3× every 4 weeks	RR: 67 SD: 25 PD: 8	36	ND
Hoffmann et al. (2008) [58]	208	TACE ± sorafenib + LT	4× carbo-DDP + Lipiodol			
Zhou et al. (2009) [59]	108	TACE vs. control	3× 1,000 mg 5-FU + 20 mg MMC + 5 mg cisDDP + Lipiodol every 4–9 weeks	Path. RR: ≤50 %: 40.4 vs. 94.6 50–100 %: 59.6 vs. 5.4 ($p < 0.01$)	ND	DfS(1 y, 3 y, 5 y): 49, 26, 13 vs. 39, 21, 9 OS (1 y, 3 y, 5 y): 73, 40, 31 vs. 70, 32, 21 $p > 0.05$

Author	*N*	Concept	Intra-arterial therapy	RR (%)	Median survival (mo)	Years survival (%)
Choi et al. (2009) [60]	16	TACE + radiation + LR	50 mg doxorubicin + Lipiodol + Gelfoam median: 3×/ patient	12 CR: 0 PR: 2 PD: 3	13	ND
Schaudt et al. (2009) [61]	27	TACE/TACE + PEI/LITT + LT	10 mg MMC + Lipiodol + DSM every 3–6 weeks	TACE (*N* = 15): PR/SD: *N* = 14	OS (TACE vs. non-TACE): 82 vs. 61 %	ND

LR liver resection, *LT* liver transplantation, *RFA* radiofrequency ablation, *LITT* laser-induced thermotherapy, *y* years

Recommendation (for borderline operable tumors):

Concept	Intra-arterial chemoembolization
Access	Catheter via A. femoralis in A. hepatica propria
Therapy	50 mg/m^2 doxorubicin + 300 mg amilomer (over 20–30 min)
	± 60 mg/m^2 cisplatin (over 20–30 min)
	2× every 3–4 weeks
	LR/LT after further 4 weeks

Further clinical studies are required.

4.5.5 Study Results: Adjuvant Therapy (HAI/Chemoembolization)

Author	*N*	Concept	Intra-arterial therapy	Median survival (mo)	Years survival/ DfS (%)
Lai et al. (1998) [62]	66	LR + TACE + IV chemo-therapy vs. LR (control)	3× 10 mg cisDDP + Lipiodol + 40 mg/m^2 doxorubicin IV every 2 months	ND	DfS (1, 2, 3 y): 50, 36, 18 vs. 69, 53, 48 ($p = 0.04$)
Ono et al. (2001) [63]	108	HAI/IV vs. control (meta-analysis of 3 protocols)	1. 1× 40 mg/m^2 epirubicin + oral 300 mg/d tegafur vs. control 2. 1× 40 mg/m^2 epirubicin + IV 40 mg/m^2 epirubicin every 3 months + 300 mg/d carmofur (2 years) vs. control 3. IV 40 mg/m^2 epirubicin every 2 months (1 year) vs. control	OS: significant advantage in patients without adjuvant treatment $p = 0.02$	DfS (3, 5 y): 37, 28 vs. 42, 26 $p = 0.324$
Wen et al. (2006) [64]	28	LR + HAI	d1: 250 mg FUDR d4: 10 mg doxorubicin d7: 4 mg MMC 8 cycles (1st and 2nd year after resection)	ND	1 y: 11 3 y: 7 5 y: 5
Li et al. (2006) [65]	131	A: LR vs. B: LR + TACE vs. C: LR + TACE + PVC	3× 30 mg doxorubicin + 20 mg mitomycin + 80–100 mg cis- or carbo-DDP + Lipiodol	ND	DfS (1, 3, 5 y): 87, 66, 48 vs. 87, 77, 61 vs. 96, 85, 73 A vs. C: $p = 0.005$ A vs. B and B vs. C: $p > 0.05$
Peng et al. (2009) [66]	116	TACE vs. control	500 mg/m^2 5-FU + 30 mg/m^2 doxorubicin + Lipiodol + Gelfoam (2–5 cycles monthly)	13 vs. 9	Estimated survival rates (1, 3, 5 y): 51, 34, 22 vs. 33, 17, 9
Zhou et al. (2009) [59]	115	LR + TACE vs. LR	200 mg/m^2 carbo-DDP + 6 mg/m^2 MMC + Lipiodol + 40 mg/m^2 epirubicin	14 vs. 23	OS(1, 3, 5 y): 56, 19, 18 vs. 81, 33, 23
Zhong et al. (2010) [67]	659	LR + TACE vs. LR (meta-analysis)	Doxorubicin, epirubicin, MMC, 5-FU, carbo-DDP + Lipiodol ± Gelfoam	49 vs. 41 (15 vs. 9 for patients with palliative LR)	ND

PVC portal vein chemotherapy, *d* days, *mo* months

4.5.6 Study Results: Palliative Therapy

Llovet et al. (2002) [38]

Concept	TAE vs. TACE vs. BSC
N	112 (37 vs. 40 vs. 35)
Therapy	TA(C)E: Gelfoam ± 75, 50, or 25 mg/m^2 doxorubicin + Lipiodol
Frequency	Every 2 and 6 mo, then every 6 mo
Median survival (mo)	25 vs. 29 vs. 18 1, 2, 3 y (%): 75, 50, 29 vs. 82, 63, 29 vs. 17, 0, 0 ($p = 0.009$)
Toxicity ($N \geq$ grade III)	TAE: 7 vs. TACE: 11 (cholecystitis, ischemic hepatitis, liver abscess, liver failure, gastrointestinal bleeding)
Conclusion	Therapeutic advantage for TACE, comparable results for TAE and BSC. Chemoembolization is the therapeutic standard for patients with unresectable HCC with adequate liver functions

Furuse et al. (2003) [68]

Concept	TACE
N	17
Access	via A. femoralis (A. hepatica distal of A. gastroduodenalis, left or right)
Therapy	40 mg/m^2 epirubicin + amilomer (DSM)
Frequency	Every 4–6 weeks
Response (%)	RR: 53
Median survival	22 mo 2 y (%): 45
Toxicity (%)	Pain (44), nausea (44), vomiting (22), fever (44), leukopenia (44)
Conclusion	In opposite to a lot of other TACE studies with nondegradable embolic materials, severe toxicities were not seen in this one. The promising response rates have to be reevaluated in bigger randomized studies

Huo et al. (2003) [69]

Concept	TACE + PAI vs. PAI
N	108
Therapy	TACE: 20–30 mg doxorubicin + Lipiodol + Gelfoam PAI: 50 % acetic acid
Frequency	TACE + PAI: max. 3× PAI: 2×/week
Median survival	1, 3 y: TACE + PAI vs. PAI: 100, 69 vs. 96, 32 ($p = 0.008$)
Toxicity (%)	TACE: fever, pain, elevation of liver enzymes (most of patients) PAI: mild
Conclusion	Sequential therapy with TACE and PAI is superior to repeated PAI therapies alone

Dettmer et al. (2006) [70]

Concept	(1) TACE + PEI vs. (2) PEI vs. (3) PEI after TACE vs. (4) PEI after BSC
N	101
Therapy	PEI: 96 % sterile Äthanol TACE: 50 mg/m^2 cisDDP + 50 mg/m^2 doxorubicin + 450–900 mg amilomer (DSM) + 5–30 ml Lipiodol
Frequency	ND
Median survival	1, 3 y: 73 %, 47 % 1, 3, 5 y (%):(1) 90, 52, 43 ($N = 37$)/(2) 65, 50, 37 ($N = 34$)/(3) 91, 40, 30 ($N = 10$)/(4) 50, 23, 12 ($N = 20$) (1) vs. (4) $p < 0.001$
Toxicity (%)	TACE ($N = 67$): 10.4 % (2× leucopenia, 1× pancytopenia, 2× dissection of A. hepatica, 1× liver failure (reversible), 1× inguinal hamatoma) PEI ($N = 268$): 25.7 %
Conclusion	Patients stratified to a combination of TACE and PEI can expect longer survival than those stratified to repeated PEI alone. Furthermore, patients with large or multiple tumors in good clinical status may also profit from a combination of TACE and reconsideration for secondary PEI

Takayasu et al. (2006) [34]

Concept	Prospective cohort study of TACE
N	8,510
Therapy	Doxorubicin + cisDDP + Lipiodol + Gelfoam
Frequency	ND
Median survival	1-, 3-, 5- und 7-Jahresüberleben (*N* = 8,510): 82 %, 47 %, 26 %, 16 % Stadium T2 1-, 3- und 5-Jahresüberleben (*N* = 2,934): 90 %, 57 %, 32 % Stadium T3 1-, 3- und 5-Jahresüberleben (*N* = 2,949): 80 %, 39 %, 20 % Medianes Überleben 34 Monate
Toxicity	Mortality of TACE: 0.5 %
Conclusion	TACE showed safe therapeutic modality with a relatively high 5-year survival rate for unresectable HCC patients

Kirchhoff et al. (2007) [71]

Concept	Retrospective cohort study of TACE
N	47
Therapy	50 mg/m^2 cisDDP + 50 mg/m^2 doxorubicin + 450–900 mg amilomer (DSM) + Lipiodol
Frequency	Every 6 weeks
Response	CR: 0, PR: 36 %, NC: 55 %, PD: 9 %
Median survival	1 y, 2 y, 3 y: 75 %, 59 %, 41 % OS 26 mo
Toxicity (%)	Grad III: 7.1 % (*N* = 8); grad IV: 3.6 % (*N* = 4)
Conclusion	DSM and Lipiodol were combined successfully in the palliative TACE treatment of advanced HCC resulting in high rates of tumor response and survival at limited toxicity

Ishida et al. (2008) [72]

Concept	TACE after TAE
N	13
Therapy	d1: 4–8 mg MMC + DSM followed by 1,250 mg 5-FU + 25–50 mg cisDDP 125 mg FA d7: 1,250 mg 5-FU + 25–50 mg cisDDP 125 mg FA
Frequency	Every 2 weeks
RR	CR: 1, PR: 12 RR: 86.7 %
Survival	1-, 2, 3 y (%): 100, 29, 10 Median survival (mo): 20.4
Toxicity (*N*)	Thrombocytopenia (>grade III): 8, abdominal pain (grade I–III): most of the patients, duodenal ulcer (II + III): 3
Conclusion	This novel TACE concept achieves favorable results and is useful in treating patients with multifocal HCC

Salem et al. (2010) [47]

Concept	HAI of ^{90}Y (single-center prospective)
N	291
Therapy	1–5 dosages (100–120 Gy/therapy), glass-based device
Results	TtP: 8 mo OS (BCLC B vs. Child–Pugh A): 17 vs. 14 mo RR (CR, PR): 42 %
Toxicity	Bilirubin (grade III + IV): 19 %, fatigue: >50 %, diarrhea (some)
Conclusions	Patients with Child–Pugh A disease, with or without PVT, benefited most from the therapy. Patients with Child–Pugh B disease who had PVT had poor outcomes. These data can be used to design future Y90 trials and to describe Y90 as a potential treatment option for patients with HCC

Carr et al. (2010) [73]

Concept	Comparison of TACE and HAI ^{90}Y (single-center 2 cohort experience analyze, retrospectively)
N	932
Inclusion criteria	No candidates for surgical resection, RFA or hepatic transplantation
Therapy	TACE (catheter): 125 mg/m^2 cisDDP (30 min) + dexamethasone Embolization: Gelfoam or Embospheres (100–300/μm) Every 8–12 weeks HAI ^{90}Y: single dose (after early progress second treatment possible)
Results	TACE ($N=691$), HAI ^{90}Y ($N=99$), no treatment ($N=142$) OS: 8.5 (TACE), 11.5 (HAI ^{90}Y), 2.0 (untreated) RR (CR, PR, SD): 89 % (TACE), 76 (HAI ^{90}Y) RR (%): 65; PfS: 10.5 mo, CR: $N=3$, PR: $N=8$; OS: 27.5 mo
Toxicity (HAI)	Hematological (grade III + IV): $N=9$, non-hematological (grade II + IV): $N=4$
Conclusions	^{90}Y and TACE seem to be equivalent regional therapies for patients with unresectable HCC

Lammer et al. (2010) [41]

Concept	Comparison of doxorubicin-eluting-bead embolization with TACE
N	212
Therapy	4 ml DC beads (2 vials) with 150 mg doxorubicin vs. 50–75 mg/m^2 doxorubicin + Lipiodol + particles (e.g., PVA, Gelfoam)
Frequency	Every 2 months
RR (at 6 months)	DC beads: CR: 27, PR: 25 TACE: CR: 22, PR: 21 RR (%): 52 vs. 44 ($p=0.11$)
Survival	ND
Toxicity (*N*)	No statistical difference for primary safety endpoints
Conclusion	DC bead embolization leads to lower systemic doxorubicin levels with less systemic side effects. The activity is comparable to classical TACE

Nagano (2010) [74]

Concept	HAI + IFN-α (s.c.)
N	55
Therapy	d1–5, 8–12: 300 mg/mm^3/d 5-FU + 3×/week 5 Mio IU IFN-α (s.c.) week 3 and 4: only IFN
Frequency	1×
RR	CR: 8, PR: 4 RR: 44 %
Survival	1 y, 3 y (responders): 83, 31 median survival (mo): 12
Toxicity (*N*)	Fever, chills, flue-like syndrome (grade I + II) Fatigue, nausea (grade I)
Conclusion	This therapy might be a promising strategy for patients with advanced HCC

Kucuk et al. (2010) [75]

Concept	Comparison of TACE and HAI ^{90}Y (single-center 2 cohort experience analyze, retrospectively)
N	932
Inclusion criteria	No candidates for surgical resection, RFA, or hepatic transplantation
Therapy	TACE (catheter): 125 mg/m^2 cisplatin (30 min) + dexamethasone Embolization: Gelfoam or Embospheres (100–300/μm) Every 8–12 weeks HAI ^{90}Y: single dose (after early progress second treatment possible)
Results	TACE (*N* = 691), HAI ^{90}Y (*N* = 99), no treatment (*N* = 142) OS: 8.5 (TACE), 11.5 (HAI ^{90}Y), 2.0 (untreated) RR (CR, PR, SD): 89 % (TACE), 76 (HAI ^{90}Y) RR (%): 65; PfS: 10.5 mo; CR: *N* = 3; PR: *N* = 8; OS: 27.5 mo
Toxicity (HAI)	Hematological (grade III + IV): *N* = 9, non-hematological (grade II + IV): *N* = 4
Conclusions	^{90}Y and TACE seem to be equivalent regional therapies for patients with unresectable HCC

Kondo et al. (2011) [76]

Concept	HAI
N	24 with portal vein tumor thrombosis
Therapy	65 mg/m^2 cisDDP (in 70 ml)
Frequency	Every 4–6 weeks
RR	CR: 1, PR: 4 RR: 21 %
Survival	1 y, 2 y (%): 38, 16 OS: 7 mo
Toxicity (*N*)	Anorexia, nausea, fatigue, liver enzymes (grade III + IV)
Conclusion	Safe and well-tolerated therapy for this special group of patients

Bonomo et al. (2010) [46]

Concept	mbTAE = micro-bland embolization
N	66 patients with HCC (single or multiple nodules)
Therapy	Microparticles (40 and/or 100 µm) injection until blood shut down
Frequency	On demand, according to the imaging follow-up
Results (RECIST)	OR (CR + PR) = 58 % DS (OR + SD) = 76 %
Survival	1 y, 2 y (%): 96, 92
Toxicity (*N*)	No/very low post-embolization syndrome
Conclusion	Safe and well-tolerated therapy with very high local results and survival benefits

Ibrahim et al. (2011) [77]

Concept	Downstaging of HCC with ^{90}Y (single-center, prospectively)
N	8
Inclusion criteria	HCC with involved caudate lobe
Therapy	single dose mostly (range 1–3)
Results	CR: *N* = 1 (WHO), *N* = 3 (EASL guidelines) OS: 25 mo (censored) PfS: 10 mo
Toxicity (HAI)	Fatigue: 50 %, bilirubin (grade III): *N* = 1
Conclusions	^{90}Y appears to be a feasible, safe, and effective treatment with unresectable caudate lobe HCC

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CRC Liver Metastases

5

M. Peeters

5.1 Introduction

The liver is the most common metastatic site in patients with colorectal carcinoma (CRC) [1]. Twenty-five per cent (25 %) of CRC patients have clinically detectable liver metastases at the initial diagnosis and approximately 50 % develop liver metastases during their disease course, with median survival rates of less than 8 months, without any treatment [2, 3]. Currently, complete surgical resection plus perioperative chemotherapy, sometimes in combination with other local treatment modalities, such as radiofrequency ablation (RFA), remains the only potentially curative option for CRC patients with LM and, despite lack of evidence from randomized controlled trials (RCT), has become the standard of care [4, 5]. In fact a 5-year survival for resectable patients is reported to range from 40 to 60 % [6] while is less than 25 % for patients who do not undergo surgery [7]. Unfortunately, only a minority of patients (10–20 %) with CLM are considered eligible for resection, while about 80 % of them have liver disease considered unresectable at presentation [8, 9]. Furthermore, the vast majority of patients undergoing resection will develop recurrent LM within 2 years of surgery. Recent years have seen several advances in the management of CLM, thanks to the development of new systemic chemotherapies, targeted biologic agents, as well as locoregional hepatic therapies (RHT), including ablative technologies and transarterial treatments, which can facilitate downsizing of CLM, converting initial unresectable metastases to resectable, reducing recurrences, and prolonging survival and quality of life of patients who remain unsuitable for resection. A multidisciplinary team approach, including surgeons, oncologists, molecular pathologists, and diagnostic and interventional radiologists with expertise in hepatobiliary disease, represents the best way to offer optimal individualized treatment to the patients.

5.1.1 Locoregional Hepatic Treatments

Locoregional Hepatic treatments (RHT), have recently emerged as part of the management strategies of CLM, both in patients with resectable and in those with unresectable liver disease. RHT can be subdivided into two groups, including ablative therapies and arterial therapies, used as stand-alone therapy, or in combination with other treatments.

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5.1.2 Ablative Treatments

Ablative options for CLM are subdivided into thermal and nonthermal modalities. Thermal modalities include cold ablation therapies, such as cryoablation therapy, and hot ablation therapy, such as radiofrequency ablation, which is the most commonly used focused destruction technology in the treatment of CLM. RFA induces tumor necrosis by achieving local hyperthermia with temperatures exceeding 58 °C [10]. The principal goal is to achieve tumor destruction and hepatic disease control, while maximally sparing the nontumorous liver parenchyma. Hence, it is characterized by low morbidity, low mortality, and technical feasibility [11]. However, the local recurrence rates for current RFA have been reported as 9–21 % (20, 21 locoregional), and it has been associated with tumor size and location of the lesion. Indeed it is usually ineffective in tumors >3 cm in size and in tumors located in proximity of large blood vessels [12, 13]. Even if analysis of results is difficult, because of the several selection bias due to nonrandomization, mostly of published studies [14–24] and a recent meta-analysis [24] have shown that RFA is less effective than surgical resection in the treatment of resectable CLM, with an overall 5-year survival rate of 27–50 % and a local recurrence rate of 11–37 %. So it is actually recommended as a good alternative for those patients who refuse or are not eligible for surgery (e.g., comorbidities) and in the context of hepatic parenchymal-sparing approaches. Evidence-based evaluation of RFA in the treatment of unresectable CLM is also difficult, because of the lack of power of the available studies and the heterogeneity of the included patients. However, RFA seems to be effectively in combination with chemotherapy [25] and surgery [26] in selected patients with unresectable CLM, leading an improvement in progression-free survival, while benefit on overall survival is not clear. The need for a randomized controlled trial seems essential in order to show the effectiveness of combined treatments in this subset of patients. MWA is a newer technology which induces tumor coagulative necrosis by utilizing high-frequency electromagnetic radiation [27]. Mostly of data are available on the effectiveness of MWA in the treatment of CLM became from retrospective series, reflecting outcomes for a large variety of liver tumors. These data have shown that MWA is comparable to RFA both in terms of survival rates and local recurrence rates [12, 28]. A randomized trial is needed to compare these two ablative technologies in the treatment of CLM.

5.1.3 Hepatic Arterial Treatments

Hepatic arterial treatments may be divided into embolic and non-embolic. The most commonly embolic procedure performed to treat CLM is the transarterial chemoembolization (TACE), while other treatments, such as transarterial chemotherapy infusion (TACI), transarterial embolotherapy (TAE), and radioembolization using yttrium-90, are less commonly used. TACE allows to infuse chemotherapeutic agents followed by embolic particles into the hepatic arteries supplying the liver tumors, sparing the surrounding normal hepatic parenchyma, which is supplied by the portal vein. Several trials have investigated the potential role of TACE in the management of CLM, reporting interesting, but insufficient, results [29–34]. Therefore, TACE has still limited clinical indications and is considered as salvage therapy for patients with liver metastases from chemo-refractory colorectal cancer. The development of new embolizing agents, such as polymer-based microparticles (DC) loaded with the cytotoxic agent irinotecan, led to a new type of TACE, called DEBIRI,

characterized by higher tumor selectivity and less drug systemic exposure, compared with classical TACE. Several trials have explored the activity of DEBIRI in patients with unresectable liver metastases from CRC, showing very promising results, both as single agent and in combination with chemotherapy, indicating that DEBIRI could be proposed as palliative therapy for this subset of CRC patients [35–40]. Furthermore, the combination of intra-arterial infusion of DEBIRI, with the FOLFOX plus bevacizumab regimen, led to a 78 % RR and 35 % of downsizing to resection, in patients with unresectable, liver-limited CRC [41], and the randomized phase II trial (NCT00932438) is currently ongoing. Radioembolization is another embolic procedure, less commonly used for the treatment of chemo-refractory CRC patients, both as stand-alone and in combination with chemotherapy. It's a form of brachytherapy, which consists of the intrahepatic arterial selective injection of a high-energy beta-emitting radiation source, yttrium-90 (Y90), incorporated into glass or resin, embolic microspheres [42]. Resin-based microspheres (SIR-Spheres) in combination with adjuvant intra-arterial (HAI) floxuridine significantly increased tumor response and prolonged time to progression compared with HAI alone in a phase III trial on CRC patients with CLM [43], leading to its approval from FDA. Another phase III "SIRFLOX" study (NCT00724503) is evaluating whether a first-line treatment strategy of standard-of-care chemotherapy plus SIR-Spheres microspheres is more effective in delaying cancer progression than chemotherapy alone in patients with unresectable CLM. Primary results from the study are expected to be available in late 2014. As regards the other glass-based microspheres (TheraSpheres), limited data are available in clinical setting. An ongoing randomized phase III "EPOC" trial (NCT01483027) is investigating the efficacy of this technology in patients with CLM who failed first-line chemotherapy. Hepatic arterial infusion chemotherapy (HAC) is the most common within the non-embolic arteries treatments, often used in combination with chemotherapy order to improve tumor responses and survival rates, in patients with unresectable CLM. The tumor response reported from several studies ranged from 35 to 90 % (57–58–62 locoregional), with resectability rates of 50 % when used as first-line therapy and 20 % after failure with systemic chemotherapy [40, 44]. A meta-analysis of 10 selected randomized trials confirmed a greater tumor response to HAI than standard chemotherapy, but not survival differences were found [45]. Furthermore, the high occurrence of complications, such as hepatobiliary toxicity, arterial thrombosis, extrahepatic perfusion, and hemorrhage, discouraged its use, which is currently limited to only a few centers with enough experience.

5.1.4 Conclusion

The management of CLM is constantly evolving. Surgery remains the only curative option patients with CLM, but only a minority of them have resectable liver disease at presentation. The definition of "resectable" CLM has significantly evolved in the last years, and the development of new systemic chemotherapy regimens, novel biologic agents, and multiple HRT, which can facilitate downsizing of CLM, led to the a gradual increasing of the percentage of patients potentially eligible for curative liver resection. However, the most part of patients remain unsuitable for resection, and RHT offer an important option to control tumor burden, reducing recurrences and prolonging survival and quality of life in this subset of patients. In the near future, randomized clinical trials are needed to better understand the role of the various RHT options, the effective combinations with other systemic treatments, and the choice and sequence for their use in the treatment of the CLM patients.

5.2 Study Results

5.2.1 Adjuvant Regional Therapy

Kemeny et al. (1999) [46]

Concept	Adjuvant HAI after resection of colorectal liver metastases (randomized comparison of HAI + IV vs. IV)		
N	156		
Inclusion criteria	R0 resection		
Therapy	1. (HAI + IV): IV: 325 mg/m^2 5FU d1–5 (bolus) + 200 mg/m^2 FA (30 min) after 2 weeks HAI: 0.25 mg/kg FUDR 14 days (pump), repeat after 1 week 2. (IV): 6 × 200 mg/m^2 FA (30 min) + 370 mg/m^2 5FU d1–5, every 4 weeks		
Results	Median survival: 72.2 mo (HAI + IV) vs. 59.3 mo (IV) 2-year survival: 86 % (HAI + IV) vs. 72 % (IV), $p = 0.03$ 5-year survival: 61 % (HAI + IV) vs. 49 % (IV) 68 % (HAI + IV) vs. 52 % (IV); under exclusion of patients with extrahepatic metastases before recruitment and patients without treatment Local recurrence within the liver after 2 years: 7/74 patients (HAI + IV) vs. 30/82 (IV) Recurrence free liver after 2 years: 90 % (HAI + IV) vs. 60 % (IV), $p = 0.001$ 2-year rate progression-free survival: 57 % (HAI) vs. 42 % (IV), $p = 0.07$ Median PfS: 37.4 mo (HAI + IV) vs. 17.2 mo (IV)		
Toxicity	**Parameter**	**HAI + IV**	**IV**
	Neutropenia	18	21
	Diarrhea	29	14
	Nausea/vomiting	23	9
	Stomatitis	11	9
Conclusions	For patients who undergo resection of liver metastases from colorectal cancer, postoperative treatment with a combination of hepatic arterial infusion of floxuridine and intravenous fluorouracil improves the outcome		

mo month, *d* days

Kemeny et al. (2011) [47]

Concept	Randomized phase II of adjuvant HAI plus systemic chemotherapy with or without bevacizumab (singlecenter study)
N	73
Inclusion criteria	Liver resection
Therapy	HAI (4–5 weeks postsurgery via pump): 0.12 mg × kg × pump volume (30 ml) FUdR + 1 mg/d × 30 ml flow rate dexamethasone IV: 85 mg/m^2 oxaliplatin (oxaliplatin-naive patients) (2 h) or 150 mg/m^2 irinotecan (oxaliplatin-pretreated patients) + 400 mg/m^2 FA (2 h concurrently) + 2,000 mg/m^2 5-FU (48 h) d15 + 29 +/− 5 mg/kg bevacizumab d15 + 29
Results	RFS(%) 1 year: 73 vs. 83; 4 years: 37 vs. 46 (beva vs. no beva) 4-year survival (%): 81 vs. 85
Toxicity	Beva vs. no beva (*N*): abdominal pain: 1 vs. 3, thrombosis: 3 vs. 0, diarrhea: 6 vs. 1, AP and bilirubin (>3): 16 vs. 6
Conclusions	Addition of bevacizumab to HAI plus systemic therapy after liver resection does not increase the RFS or survival but appear to increase toxicity

5.2.2 Palliative Regional Therapies

Lorenz et al. (2000) [48]

Concept	Randomized comparison of HAI (5-FU/FS) with HAI (FUDR) and systemic chemotherapy (5-FU/FS)			
N	168			
Inclusion criteria	1st-line therapy, tumor load: <75 % of liver volume			
Therapy	1. (IA): 1,000 mg/m^2 5-FU (24 h) + 200 mg/m^2 FA (15 min) (d1–5) 2. (IA): 0.2–0.15 mg/kg/d FUDR (d1–14) 3. (IV): 1,000 mg/m^2 5-FU (24 h) + 200 mg/m^2 FA (15 min) (d1–5) every 3 weeks			
Results	All patients		Tumor load <25 %	
	TtP (mo): 9.2: 5.9: 6.6		TtP (mo): 11.6: 6.1: 5.5	
	OS (mo): 18.7: 12.7: 17.6		OS (mo): 23.3: 13.4: 21.7	
Toxicity (grade III + IV)	**Parameter**	**1**	**2**	**3**
	Nausea/vomiting	61	23	41
	Stomatitis	76	8	77
	Skin	33	4	49
	Diarrhea	33	11	32
	Abdominal pain	32	26	25
	Increase of liver enzymes value	4	25	15
Conclusions	HAI 5-FU/FS cannot be recommended as a routine therapy. There seems to be an advantage in patients with intrahepatic tumor burden of less than 25 %. An optimization of IA therapies needs further investigations			

Gray et al. (2001) [43]

Concept	Combination of SIR-Spheres (SIRT) and HAI vs. HAI alone (randomized phase III study)		
N	74		
Inclusion criteria	Unresectable liver metastases, chemotherapeutic naive and pretreated patients		
Therapy	HAI (port): 0.3 mg/kg/d FUDR (12 days) – 4 weekly intervals		
	SIRT: tumor volume <25, 25–50, >50 % of total volume SIRT-equivalent: 2, 2.5, or 3 GBq of ^{90}Y		
Results	Survival rates per year (%):		
		HAI	**SIRT + HAI**
	1 y	68	72
	2 y	29	39
	3 y	6	17
	5 y	0	3.5
Toxicity	No differences in grade III and IV events		
Conclusions	Combination of single SIRT with HAI is more effective than HAI alone		

y years

Voigt et al. (2002) [49]

Concept	Chemoembolization of liver metastases
N	11
Inclusion criteria	Inoperability, tumor progress after systemic therapies with 5-FU/FA, 5-FU/FA + CPT-11, 5-FU/FA + oxaliplatin
Therapy	d1, 2 (IA): 5 mg/m^2 MMC + 4.5 Mio IU IFN α2b + 20 mg dexamethasone + DSM (bolus) d1 (IA): 50 mg/m^2 oxaliplatin (120 min) d1+ 1,500 mg/m^2 5-FU (24 h) d1 (IV): 500 mg/m^2 FA (120 min) Repetition d 15–22
Results ($N = 10$)	PR: $N = 3$, MR: $N = 2$, SD: $N = 4$, PD: $N = 1$
Toxicity	Asthenia (grad I–II): $N = 10$, neurotoxicity (grade I–II): $N = 5$, nausea/vomiting (grade II): $N = 2$
Conclusions	Chemoembolization is an effective therapy in patients with liver metastases after failure of systemic chemotherapies

Pohlen et al. (2004) [50]

Concept	Chemoembolization of nonresectable liver metastases		
N	100		
Inclusion criteria	Inoperability, tumor load <70 % of liver volume		
Therapy	d1–5 (IA): 450 mg DSM + 5 Mio IU IFN α2b (app. 20 min) + 500 mg/m^2 FS (20 min) + 600 mg/m^2 5-FU (120 min) every 3 weeks		
Results	RR (%): CR 11, PR 59, SD 14, PD 17 TtP: 17 mo Median survival (total, *N* = 95): *24 mo* *<25 % tumor load (liver):* Median survival (*N* = 30): *39 mo*		
Toxicity	**Parameter**	**Grad 1–2 (%)**	**Grad 3–4 (%)**
	Nausea/vomiting	55	0
	Diarrhea	58	9
	Mucositis	44	3
	Leukopenia	28	0
	Total	55	12
Conclusions	Chemoembolization is an effective, life-prolonging, and well-tolerated therapy for patients with liver metastases of CRC		

Pohlen et al. (2006) [51]

Concept	Comparison of two intra-arterial therapy concepts (chemoembolization vs. HAI)		
N	60		
Inclusion criteria	Inoperability, tumor load: <70 % of liver volume		
Therapy (ART-I vs. ART-II)	ART-I (*N* = 24): d1–5 (IA-port): 300 mg/m^2 FA (20 min) + 600 mg/m^2 5-FU (120 min) every 3 weeks ART-II (*N* = 36): d1–5 (IA-port): 450 mg DSM + 5 Mio IU IFN α2b (app. 20 min) + 500 mg/m^2 FA (20 min) + 600 mg/m^2 5-FU (120 min) every 3 weeks		
Results	**Parameter**	**ART-I**	**ART-II**
	RR	50	69
	Median survival	14	26
Toxicity	**Parameter (% all grades)**	**ART-I**	**ART-II**
	Nausea/vomiting	70	55
	Diarrhea	62	64
	Mucositis	45	44
	Leukopenia	25	28
	Port-system infections	12	8
Conclusions	DSM-TACE is superior to HAI with higher response rates and fewer side effects. This combination should be evaluated in larger studies as first- or second-line therapy. The positive effect of the additional embolization is explained as a result of higher drug concentration within tumor tissue after blood-flow reduction by the starch microspheres		

Morise et al. (2006) [52]

Concept	Chemoembolization of liver metastases of CRC (4) and stomach carcinoma (1)
N	5
Inclusion criteria	Inoperability
Therapy	d1 (IA): 80 mg CPT-11 + 8 mg MMC + DSM DSM – amount: 200–1,200 mg d7–14/15 (IA): 1,000 mg 5-FU (24 h) + 100 mg FS (3 h) + (IV) CPT-11, tegafur/uracil, cisplatin (in patients with extrahepatic lesions)
Results	RR (%): 13.1; 55.7; 65.6; 50.0; 0
Toxicity	Abdominal pain, nausea/vomiting, leukopenia
Conclusions	Chemoembolization with DSM and CPT-11 is an effective therapy for patients with advanced tumor disease, especially with liver metastasis. It is recommended as neoadjuvant therapy or after failure of systemic tumor therapies in second line

Fiorentini et al. (2007) [39]

Concept	Chemoembolization with irinotecan-eluting beads (multicenter prospectively)
N	20
Inclusion criteria	Unresectable liver metastases, after systemic chemotherapy failure, tumor burden <75 %
Therapy	DEBIRI: irinotecan 100 mg, 50 % reduction after first cycle (if tox. occurred grade IV) every 3 weeks
Results	RR: 16/20, OS: 15/20 alive by median follow-up of 200 days
Toxicity	Fever (grade 2, 2 days): $N=20$, abdominal pain (grade II + III, 12 h): $N=10+5$, nausea + vomiting (grade II, 11 h): $N=20$
Conclusions	TACE with irinotecan-eluting beads is feasible in patients with liver metastases from CRC

Boige et al. (2008) [53]

Concept	Hepatic arterial infusion of oxaliplatin plus intravenous 5-FU/FA (singlecenter prospectively)
N	44
Inclusion criteria	Unresectable liver metastases, after systemic chemotherapy failure
Therapy	HAI (catheter): 100 mg/m^2 oxaliplatin (2 h) d1 IV: 200 mg/m^2 FA + 400 mg/m^2 5-FU (bolus) d1 followed by 2,400 mg/m^2 5-FU (over 48 h); every 2 weeks
Results	RR (%): 55, PR: 62 ($N=24$), PFS: 7.0 mo, OS: 16 mo
Toxicity	Neutropenia (all grades): $N=21$, neuropathy (all grades): $N=40$, abdominal pain (all grades): 21, thrombocytopenia (all grades): $N=15$, others
Conclusions	HAI oxaliplatin and systemic chemotherapy with 5-FU/FA is feasible, safe with promising results

Idelevich et al. (2009) [54]

Concept	Hepatic arterial infusion of irinotecan, 5-FU/FA plus UFT (singlecenter prospectively)
N	31
Inclusion criteria	Unresectable liver metastases, no prior chemotherapy
Therapy	HAI (port): 120 mg/m^2 irinotecan (30 min) followed by 20 mg/m^2 FA (30 min) and 500 mg/m^2 5-FU (2 h) d1, 14 200 mg/m^2/d UFT + 30 mg/d FA d1–22 (two divided daily doses) every 4 weeks
Results	RR (%): 65, PR: $N=20$, PD: $N=1$; TtP: 12 mo; OS: 36 mo
Toxicity	Hematologic (grade III): $N=5$, non-hematologic (grade III + IV): $N=6$, catheter dislocation: $N=1$
Conclusions	HAI irinotecan with UFT/FA is a feasible and effective treatment for nonresectable CRC liver metastases

Seki et al. (2009) [55]

Concept	Hepatic arterial infusion followed by systemic chemotherapy (singlecenter retrospectively)
N	20
Inclusion criteria	Unresectable liver tumor (involvement of all segments or inadequate liver remnant or involvement of all three main veins or unresectability of retrohepatic vena cava or bifurcation of portal vein), no prior chemotherapy with irinotecan or oxaliplatin
Therapy	HAI (port): 1,000 mg/m^2 5-FU (5 h) weekly till progression then
	Systemic chemotherapy: FOLFOX4 (*N* = 13) or FOLFOX6 (*N* = 7)
Results	HAI: RR (%): 85; TtP: 11.6 mo, PR: *N* = 17
	FOLFOX: RR (%): 35; TtP: 5.1 mo, PR: *N* = 7
	OS: 30.1 mo
Toxicity (HAI)	Leukopenia (grade I + II): *N* = 8, anemia (grade I + II): *N* = 7, thrombocytopenia (grade I-III): *N* = 9, nausea (grade I + II): *N* = 6, fatigue (grade I + II): *N* = 9
Conclusions	Sequence of HAI and systemic chemotherapy is a promising treatment strategy

Fujimoto et al. (2009) [56]

Concept	Hepatic arterial infusion of 5-FU (singlecenter prospectively)				
N	72				
Inclusion criteria	Unresectable synchronous or metachronous liver metastases (involvement of three or four segments, inadequate liver remnant or involvement of essential intrahepatic vascular structures)				
Therapy	HAI (port or pump): Protocol 1: 360 mg/m^2/d 5-FU (7 days) followed by 180 mg/m^2/d 5-FU (21 days) followed by 7 days free of chemotherapy then 180 mg/m^2/d 5-FU (7 days) Protocol 2: 360 mg/m^2/d 5-FU (14 days) followed by 7 days free of chemotherapy followed by 180 mg/m^2/d 5-FU (7 days), continued by the 7 days chemo-non chemo-rhythm Protocol 3: 1,000 mg/m^2 (5 h) 5-FU once a week Protocol 4: 120 mg/m^2/d 5-FU (21 days), alternating with normal saline (7 days) + 4 mg/m^2/d MMC once a month				
Results	**Protocol**	***N***	**RR**	**CR**	**Resection rate (%)**
	1	12	50	8	0
	2	9	67	22	33
	3	40	20	5	5
	4	11	64	27	18
	Total	72	38	11	10
	RR: 38 %, median survival: 18 mo; 1-, 2-, 3-, 4-, 5-year survival rates (mo): 72, 32, 18, 10, 7				
Toxicity	Complication rate (%): 1: 75, 2: 77, 3: 65, 4: 90, total: 72				
Conclusions	HAI makes liver metastases resectable				

Vogl et al. (2009) [34]

Concept	Repeated chemoembolization (singlecenter prospectively)			
N	463			
Inclusion criteria	Unresectable liver metastases showing no response, disease progression or inacceptable toxicity to systemic chemotherapy (FOLFOX- and FOLFIRI-protocols)			
Therapy	TACE (catheter): 8 mg/m^2 MMC (*N*=243), MMC+1,000 mg/m^2 gemcitabine (*N*=153) or MMC+150 mg/m^2 irinotecan (*N*=67) Embolization: max. 15 ml/m^2 lipiodol followed by 200–450 mg DSM			
Results	RR: PR: 14.7 %, SD: 48.2 %, PD: 37.1 OS: 17.6 mo (with neoadj.), 14 mo (with palliate.), 8 mo (with sympt. therapy) OS (from primary diagnosis): 38 mo, OS (from start of TACE): 14 mo			
	Parameter	**MMC**	**MMC+gemcitabine**	**MMC+irinotecan**
	RR (%)	13.6	11.1	19.4
	OS (mo)	14.0	13.9	14.0
Toxicity (HAI)	Leukopenia (grade I+II): *N*=8, anemia (grade I+II): *N*=7, thrombocytopenia (grade I-III): *N*=9, nausea (grade I+II): *N*=6, fatigue (grade I+II): *N*=9			
Conclusions	TACE as a minimally invasive therapy option for palliative treatment of liver metastases of CRC			

Khouri et al. (2010) [57]

Concept	Hepatic arterial infusion of raltitrexed and oxaliplatin (singlecenter retrospectively)
N	17
Inclusion criteria	Unresectable liver tumor, failure of at least two lines of chemotherapy (including oxaliplatin and irinotecan)
Therapy	HAI (port): 3 mg/m^2 raltitrexed (1 h) followed by 130 mg/m^2 oxaliplatin (2 h) every 3 weeks
Results	RR (%): 65; PfS: 10.5 mo, CR: *N*=3, PR: *N*=8; OS: 27.5 mo
Toxicity (HAI)	Hematological (grade III+IV): *N*=9, non-hematological (grade II+IV): *N*=4
Conclusions	Intra-arterial application of raltitrexed and oxaliplatin is feasible and promising

Cosimelli et al. (2010) [58]

Concept	HAI ^{90}Y in patients with liver metastases from CRC (prospective multicenter phase II study)
N	50
Inclusion criteria	Unresectable liver tumor, failure of standard chemotherapy (including FOLFOX and FOLFIRI)
Therapy	Single dose of ^{90}Y resin microspheres (three patients with two applications)
Results	RR (CR, PR): 24 %; CR: $N=1$, PR: $N=11$ TtP: 3.7 mo OS: 12.6 mo; 1-, 2-year survival rates (%): 50.4, 19.6
Toxicity (HAI)	1 death after renal failure, 1 death after liver failure Early (0–48 h): fever ($N=4$), pain ($N=3$), hematoxicity ($N=1$) Intermediate (3–30 days): fever ($N=3$), pain ($N=5$), jaundice, nausea, fatigue ($N=1$) Late: GI ulcers ($N=2$)
Conclusions	Radioembolization is able to produce meaningful responses and disease stabilization

Hendlisz et al. (2010) [59]

Concept	HAI ^{90}Y in combination with 5-FU infusion (B) vs. the infusion alone (A) (randomized prospective multicenter phase III study)
N	46
Inclusion criteria	Unresectable liver tumor, failure of standard chemotherapy (including FOLFOX and FOLFIRI)
Therapy	A: IV: 300 mg/m^2/d 5-FU d1–14 (every 3 weeks) B: IA: ^{90}Y + IV: 225 mg/m^2/d 5-FU d1–14; after 1 week: 300 mg/m^2/d 5-FU d1–14 (every 3 weeks)
Results	RR (PR): A: 0; B: 10 % ($p=0.22$) TtLP: A:B = 2.1:5.5 mo ($p=0.003$) TtP: A:B = 2.1:4.5 ($p=0.03$) OS: A:B = 7.3:10.0 ($p=0.8$)
Toxicity	A: grade III + IV: $N=6$ B: grade III + IV: $N=1$ ($p=0.1$)
Conclusions	Radioembolization with ^{90}Y-resin plus 5-FU is well tolerated and improves response rates compared to 5-FU alone

Lee et al. (2011) [60]

Concept	HAI of 5-FU/FA as salvage treatment for refractory liver metastases from CRC (singlecenter, retrospective)
N	14
Inclusion criteria	All patients after failure of any systemic 5-FU-based therapy
Therapy	HAI (port): 800 mg/m^2 5-FU (24 h) d1–5 + 200 mg/m^2 FA d1–5 every 4 weeks
Results	RR (%): 7; OS: 10.7 mo, TtP: 4.3 mo
Toxicity	Oral mucositis: *N* = 13, vomiting: *N* = 6, abdominal pain: *N* = 6, liver dysfunction: *N* = 17
Conclusions	HAI 5-FU/FA is well tolerated and shows modest efficacy

Martin et al. (2011) [37]

Concept	Chemoembolization of liver metastases of CRC after failing systemic chemotherapy (multicenter single-arm study)
N	55
Inclusion criteria	Liver tumor burden >50 %, after systemic chemotherapy failure
Therapy	DEBIRI: irinotecan 100 mg (50–200 mg) median 2 courses
Results	Overall 12-month RR (%): 40; CR: 15 (*N* = 8), PR: 25 (*N* = 14)
Toxicity	Overall adverse event rate: 28 %; nausea, vomiting, liver dysfunction (3 % grade III)
Conclusions	DEBIRI is an acceptable therapy for this treatment

Samaras et al. (2011) [61]

Concept	HAI plus systemic chemotherapy (retrospective singlecenter study)
N	23 (12 combination of HAI + systemic; 11 HAI alone)
Inclusion criteria	Bilobar disease, one or two previously lines of chemotherapy
Therapy	HAI (pump): 0.12 mg × kg × pump volume (30 ml) FUdR (14 days) + 20 mg dexamethasone IV: 100 mg/m^2 oxaliplatin (d1) over 46 h (*N* = 1: oxaliplatin +150 mg/m^2 irinotecan) every 2 weeks
Results	OS: 15.6 mo; PFS: 3.9 mo; hepatic PFS: 5.5 mo No difference in OS or hepatic PFS within both groups (trend toward improved PFS for combination)
Toxicity	Diarrhea (*N* = 4), infections (*N* = 3), enterocolitis (*N* = 3) biliary toxicity grade III (*N* = 1)
Conclusions	FUDR-HAI improves PFS and results in a trend toward improved OS

Chua et al. (2011) [62]

Concept	HAI ^{90}Y in combination with 5-FU infusion (prospective singlecenter study)
N	140 (133 with single treatment)
Inclusion criteria	Unresectable liver tumor, progression under chemotherapy
Therapy	IV: 225 mg/m^2/d 5-FU d1–7 IA: ^{90}Y (first) + IV: 225 mg/m^2/d 5-FU d1–7
Results	RR: CR: *N* = 2, PR: *N* = 43, PD: *N* = 51 OS: 9 mo; 1-,2-, and 3-year survival (%): 42, 22, 20
Toxicity	Early complications: 26 % (nausea, vomiting, gastritis, intestinal ulceration, abdominal pain) Delayed complications: 5 % (radiation-induced liver dysfunction, intestinal ulceration, gall-bladder/biliary-related complication
Conclusions	Combined modality therapy appears to improve tumor response rates

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Liver Metastases of Neuroendocrine Tumors and CCC

6

Thomas Ettrich and Thomas Seufferlein

6.1 Liver Metastases of Neuroendocrine Tumors

6.1.1 Introduction

With an increasing annual incidence of about 5/100,000, neuroendocrine tumors (NET) are relatively rare tumors [1]. They originate from different types of hormone-producing neuroendocrine cells located not only in endocrine glands like the thyroid but in almost every tissue. Even when NET can arise in almost every part of the body, the lung (about 30 % of all NETs) and the gastroenteropancreatic system – so-called GEP (small intestine 17 %, colorectal 12 %, pancreatic 7 %) – are the most common locations [1]. Especially, the GEP-NETs are often diagnosed at an already advanced tumor stage (UICC IV) exhibiting liver metastases. There are two different groups of GEP-NETs – hormonally inactive (70 %) and hormonally active (30 %) tumors that produce different types of hormones including insulin (insulinoma), gastrin (gastrinoma), or serotonin. The patient's clinical symptoms depend on the type of hormone produced: e.g., insulin, hypoglycemia; gastrin, peptic ulcers; and serotonin, flush.

For the classification of NETs, there are different classification systems. The most commonly used ones are the TNM classification and the WHO 2010 classification system. While the TNM classification depends on the primary localization of the tumor (e.g., pancreas), the WHO classification depends only on the grading and the mitotic activity of the tumor (determined, e.g., using the ki67 proliferation index). The WHO classification discriminates three groups of NETs: two well-differentiated types, neuroendocrine tumor (NET G1) with low mitotic activity (ki67 < 2 %) and NET G2 with moderate mitotic activity (ki67 3–20 %), and a poorly differentiated tumor type called neuroendocrine carcinoma (NEC) G3 with a high mitotic activity (ki67 > 20 %).

6.1.1.1 Treatment Options

Because of various treatment options, NETs should always be treated in a multidisciplinary setting. Although novel therapeutic strategies, e.g., the peptide radio receptor therapy (PRRT), have been introduced during the last years, complete oncological tumor resection

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is the only curative treatment for NETs independent of the tumor localization or WHO classification.

Metastasized, poorly differentiated NEC G3 tumors, independent of their primary localization, should be treated with systemic chemotherapy. A common combination in this situation is cisplatin or carboplatin plus etoposide. The latter carboplatin/etoposide achieves a response rate (RR) of 41–67 % and a median overall survival (mOS) of 15–19 months [2, 3]. This combination is also recommended by the guidelines of the European Neuroendocrine Tumor Society (ENETS) [4]. Other combinations like capecitabine/oxaliplatin (RR 23 %) are also an option [5].

In the palliative situation, there are several systemic and locoregional treatment options particularly for well-differentiated G1 and G2 NETs of the GEP system. Somatostatin analogues (SSA) like octreotide are widely used and recommended as first therapeutic agents especially in GEP-NETs. The main indication for the use of somatostatin analogues is treatment of hormonally active NETs that cause hormone-related clinical syndromes like flush. SSAs block the release of various active agents that cause clinical syndromes reducing symptom burden and improving quality of life. In addition, SSAs exhibit also an antiproliferative effect especially in midgut NETs, even if they are nonfunctioning. It could be demonstrated that SSAs prolong the time to progression (TTP) of these tumors compared to placebo (14.3 months vs. 6 months) [6].

There are differences with respect to treatment due to the site of the primary tumor. It is known that, e.g., NETs of the small intestine and colon are not very sensitive to any systemic chemotherapy whereas pancreatic NETs do respond to systemic treatment. In pancreatic NETs, systemic chemotherapy with, e.g., streptozocin + 5-FU or doxorubicin reduces hormonal symptoms and results in an objective tumor response in 20–35 % of the patients [4]. An exceptionally high and durable response rate of metastatic NETs of the pancreas has been reported for the combination of capecitabine and temozolomide, but the level of evidence for this treatment is currently rather low [7]. Taken together, systemic chemotherapy is a validated and well-tolerated therapeutic option in pancreatic NETs. In the recent years, novel targeted drugs like everolimus, an mTOR inhibitor, and sunitinib, a multi-tyrosine kinase inhibitor, both often combined with SSAs improved TTP (sunitinib vs. placebo, 11.4 vs. 5.5 months; everolimus vs. placebo, 11.4 vs. 5.4 months, respectively) in well-differentiated pancreatic NETs in two randomized controlled phase 3 trials [8, 9].

Finally, there is the peptide radio receptor therapy (PRRT) with radiolabeled somatostatin analogues as a systemic therapeutic option in somatostatin-receptor-positive NETs (measured by SSA scintigraphy or Ga68-DOTATOC-PET-CT scan). Indeed, treatment with radiolabeled somatostatin analogues is a promising new tool for the management of patients with inoperable or metastasized neuroendocrine tumors. The results are encouraging (e.g., RR 28 %, TTP 33 months) although a direct, prospective, randomized comparison between the PRRT and other treatment options is missing [10].

6.1.1.2 Capabilities for Regional Tumor Therapy

There are various indications in the treatment of NETs for the use of regional tumor therapies like TAE/TACE, RFTA/LITT, and SIRT, especially in the case of liver metastases of functional NETs. Here, reducing tumor burden is paramount to diminish clinical side effects of the hormone-producing tumor like flush or diarrhea. In particular in midgut or rectum NETs with low sensitivity to systemic chemotherapy, locoregional treatment strategies in combination with SSAs are a valuable therapeutic option especially for patients with liver metastases and hormonally active tumors. As demonstrated by the list of trials outlined below, TTP and RR under these treatments vary. This is due to the rarity of these

tumors and consequently low number of patients. There is no gold standard for locoregional tumor therapies, neither for the modality (TAE/TACE or SIRT) nor for the chemotherapeutic agents used for chemoembolization [11–18]. Even combinations of SIRT and PRRT have been investigated [19, 20]. In general, for oligonodular metastatic deposits in the liver, local resection or RFA and/or LITT is recommended. In multinodular disease with higher tumor load, TACE or TAE is the treatment of choice. In conclusion regional tumor therapy should always be an important part of the multidisciplinary treatment of NET patients, especially in the case of well-differentiated NETs of the gastroenteropancreatic system.

6.2 Study Results: Liver Metastases of Neuroendocrine Tumors

Kress et al. (2003) [15]

Concept	TACE of advanced liver metastases of neuroendocrine tumors (retrospective analysis)
N	26 (10× carcinoid syndrome, 2× midgut tumors, 7× pancreatic tumors, 2× malignant insulinomas, 1× stomach carcinoid, 4× CUP)
Tumor burden	*N* = 3, <25 %; *N* = 11, 25–50 %; *N* = 6, 50–75 %; *N* = 6: >75 %
Therapy	20–40 mg doxorubicin in 5 ml lipiodol + 250 mg Gelfoam or PVA microspheres 1–4 procedures
Response rates (%)	PR, 8; SD, 54; PD, 19
Survival	Median survival: 14 mo (after TACE), 54 mo (after diagnosis) 5 y survival (%), 48 (after diagnosis)
Toxicity	4× minor complications (hematoma of the groin, lipiodol in the pancreas, nausea/vomiting) 5× major complications (renal failure, hypotension, liver failure)
Conclusions	In this retrospective study, patients with low (50 %) tumor burden and high (150 %) lipiodol uptake responded better to TACE than end-stage patients

mo month

Fiorentini et al. (2004) [12]

Concept	TACE in liver metastases of neuroendocrine tumors (phase II study)
N	10
Inclusion criteria	Unresectable and chemotherapy refractory
Therapy	IA: 10 mg/m^2 MMC + 50 mg/m^2 cisDDP + 30 mg/m^2 epirubicin followed by 15 mg/ml Gelfoam in 5–10 ml lipiodol
Response rates	CR, 2×; PR, 5×
Survival	Median survival: 22 mo
Toxicity	Abdominal pain, elevation of liver enzymes, liver abscess ($N = 1$)
Conclusions	Chemoembolization improves the clinical condition of patients with liver metastases. Future therapies will be based on specific tumor biology and will be customized for each individual patient combining different procedures including TACE

Touzios et al. (2005) [17]

Concept	Aggressive management of liver metastases of carcinoids and neuroendocrine tumors of the pancreas (retrospective analysis)			
N	153 (84 + 69)			
N (liver metastases)	60 (36 + 24)			
Inclusion criteria	All relevant pat. (01/1990 bis 07/2004)			
Treatment ($N = 60$)	1. Not aggressive (resection of primary tumors) $n = 23$ 2. Aggressive (a) Resection/ablation (R/A) $n = 19$ (b) TACE +/− R/A $n = 18$ TACE: cisDDP + doxorubicin + MMC			
Survival	**Parameter**	**Not aggressive**	**Aggressive treatment**	
	R/A	TACE +/− R/A	42	28
	Morbidity (%)	25	42	28
	Symptomatic improvement (%)	42	95*	88*
	Median OS (Mo)	20	>96*	50*
	5-OS(%) 25 72* 50*	25	72*	50*
Conclusion	Aggressive management improves survival of the patients, and chemoembolization improves the success rate of this strategy			

*$p < 0.05$

McStay et al. (2005) [20]

Concept	HAI of yttrium 90 (^{90}Y)-tetraazacyclododecane tetraacetic acid (DOTA) lanreotide
N	23
Inclusion criteria	Progressive large-volume somatostatin receptor-positive liver metastases
Therapy	1 GBq ^{90}Y-DOTA +/− PVA particles
Response rates	PR, 3/19 (16 %); SD, *N* = 12 (63 %); PD, *N* = 4 (21 %)
	Clinical improvement, 61 %
Survival	1 y, 63 %
Toxicity	2× acute renal impairment, abdominal pain, nausea, pyrexia, elevation of liver enzymes (*N* = 11)
Conclusions	Hepatic intra-arterial injection of 90Y-DOTA-lanreotide is a safe and effective palliative treatment for these patients

Gupta et al. (2005) [13]

Concept	TAE or TACE for liver metastases (retrospective analysis)
N	69 (carcinoid) + 54 (pancreatic islet cell carcinoma)
Therapy	TAE: PVA or Gelfoam
	TACE: chemotherapy followed by embolic material
	In patients with hormonal symptoms: octreotide s.c.
Response rates	Carcinoid: PR, 67 %; MR, 9 %
	TAE: 6× likely to respond ($p = 0.002$)
	Islet cell Ca: PR, 35 %; MR, 2 %
	TACE vs. TAE: 50 % vs. 25 % ($p = 0.06$)
Survival	Median survival for patients with carcinoid: 34 mo
	PFS: 23 mo
	1 y, 2 y, 5 y: 95, 69, 29 %
	Median survival for patients with islet cell carcinoma: 23 mo
	PfS: 16 mo
	1 y, 2 y, 5 y: 67, 49, 14 %
Toxicity	Postembolization syndrome (SAE: 9 %); hepatorenal syndrome, *N* = 7; sepsis, *N* = 6
Conclusions	Patients with carcinoid tumors had a better outcome than patients with islet cell carcinomas. The addition of intra-arterial chemotherapy to HAE did not improve the outcome of patients with carcinoid tumors, but patients with islet cell carcinomas seemed to benefit

y years

Osborne et al. (2006) [16]

Concept	Selective TAE for liver metastases (retrospective analysis)
N	84 (carcinoid, pancreatic neuroendocrine tumors)
Therapy	PVA (250–355 or 500–700 µm) 161 embolization procedures (1–4/patient)
Response rates	PR, 11/23 (48 %); SD, 12/23 (52 %)
Survival	Median survival: 36 mo (after TAE), 44 mo (carcinoid), 31 mo (pancreatic endocrine tm), 15 mo (poorly differentiated tm)
Toxicity	Postembolization syndrome (100 %), nausea, fever, elevation of liver enzymes, severe hypertension (11 %)
Conclusions	Hepatic artery embolization frequently results in clinical and radiographic responses in patients with unresectable liver metastases from carcinoid or pancreatic endocrine tumors

Ho et al. (2007) [14]

Concept	TAE or TACE for liver metastases (retrospective analysis)
N	31 (carcinoid) + 15 (pancreatic islet cell carcinoma)
Therapy	TAE: PVA or Gelfoam (7 procedures) TACE: 50 mg cisDDP + 20 mg doxorubicin + 10 mg MMC + lipiodol + PVA or Gelfoam (86 procedures) 1 cycle (4–6 weeks between application in both lobes)
Response rates	Carcinoid: PR, 5/22 (23 %); MR, 5/22; SD, 7/22 (32 %) Islet cell carcinoma: PR, 2/11 (18 %); MR, 3/11 (27 %); SD, 5/11 (45 %)
Survival	Median survival: 978 d (similar for both diagnostic groups) PFS: 23 mo 1 y, 2 y, 3 y, 4 y, 5 y: 80, 66, 41, 38, 29 % (Carcinoid, 86, 79, 43, 38, 32 %; islet cell carcinoma, 73, 52, 52, 52, 35 %)
Toxicity	Postembolization syndrome (all), 4× death, 2× infection, 1× ulcer
Conclusions	The overall survival time after hepatic artery chemoembolization or HAE among patients with neuroendocrine tumors is approximately 3.5 years. The presence of extrahepatic metastasis or an unresected primary tumor should not limit the use of hepatic artery chemoembolization or HAE

d days

Christante et al. (2008) [11]

Concept	HAI + TACE for liver metastases + octreotide (retrospective analysis)
N	77 (61 carcinoid, 16 islet cell carcinoma)
Therapy	HAI (3 × 4 monthly): 5-FU, followed by TACE: 100 mg cisDDP + 30 mg doxorubicin + 15 mg MMC + lipiodol (4 monthly between application in both lobes)
Response rates	RR, 43 (58 %); SD, 16 (22 %); OR, 80 % Carcinoid: PR, 60 %; SD,19 %; OR, 79 % Islet cell carcinoma: PR, 50 %; SD, 31 %; OR, 81 %
Survival	Median survival (total): 39 mo Carcinoid: 51 mo Islet cell carcinoma: 29 TAE or TACE vs. TAE + TACE (total): 36–44 vs. 39 Carcinoid: 31–80 vs. 51 Islet cell carcinoma: 20–23 vs. 29 PFS (total): 19 mo 1 y, 5 y (total): 78, 27 %
Toxicity	ND
Conclusions	The addition of hepatic artery chemoinfusion to chemoembolization offers a high probability of clinical benefit to patients who, otherwise, have only limited therapeutic options and a dismal survival

Kennedy et al. (2008) [21]

Concept	Radioembolization (retrospective analysis)
N	148
Therapy	185 procedures (resin ^{90}Y-microspheres with medium activity of 1.14 GBq)
Response rates	Imaging response (CT/MRI/OctreoScan): 91 % SD: 42/185 (22.7 %) PR: 112/185 (60.5) CR: 5/185 (2.7 %) PD: 9/185 (4.9 %)
Survival	Median survival: 70 mo PFS (total): 19 mo 1, 5 y (total): 78, 27 %
Toxicity	None, 67 %; fatigue, 6.5 %; nausea, 3.2; pain, 2.7 %; ascites, 0.5 %
Conclusions	Radioembolization with 90Y-microspheres to the whole liver or lobe with single or multiple fractions is safe and produces high response rates, even with extensive tumor replacement of normal liver and/or heavy pretreatment

Vogl et al. (2009) [18]

Concept	Comparison of two different TACE protocols (retrospective analysis)
N	48
Therapy	TACE 1: 8 mg/m^2 MMC + lipiodol + DSM TACE 2: 8 mg/m^2 MMC + 1,200 mg/m^2 gemcitabine + lipiodol + DSM (4 monthly between application in both lobes) every 4 weeks
Response rates	RR, 43 (58 %); SD, 16 (22 %); OR, 80 % Carcinoid: PR, 60 %; SD, 19 %; OR, 79 % Islet cell carcinoma: PR, 50 %; SD, 31 %; OR, 81 %
Survival	Median survival (total): 39 mo Carcinoid: 51 mo Islet cell carcinoma: 29 mo TAE or TACE vs. TAE + TACE (total): 36–44 mo vs. 39 mo Carcinoid: 31–80 mo vs. 51 mo Islet cell carcinoma: 20–23 mo vs. 29 mo PFS (total): 19 mo 1, 5 y (total): 78, 27 %
Toxicity	TACE 1: mild (nausea, vomiting (28 %), abdominal pain (11 %)) TACE 2: mild (nausea, vomiting (17 %), pain (10 %))
Conclusions	Transarterial hepatic chemotherapy using mitomycin C and gemcitabine can be an effective therapeutic protocol for controlling local metastases and improving survival time in patients with hepatic metastases from neuroendocrine tumors

Kratochwil et al. (2010) [19]

Concept	HAI or IV application of ^{68}Ga-DOTA-TOC
N	15
Therapy	24 µg of peptide IV + 24 µg of peptide IA (4 weeks later)
Uptake of the emitter	Liver metastases: IV (average SUV_{max}), 17.7; (average SUV_{mean}), 14.1 IA (average SUV_{max}), 60.8; (average SUV_{mean}), 51.8 Primary tumor: IV (average SUV_{max}), 22.5; (average SUV_{mean}), 72.1 IA (average SUV_{max}), 119.9; (average SUV_{mean}), 436.4
Conclusions	This study showed that uptake of DOTATOC is commonly several fold higher after selective IA administration in comparison with IV injection in both the primary tumor and in liver metastases of neuroendocrine cancer. Therefore, intra-arterial DOTATOC is a promising drug for regionally intensified radiopeptide therapy

6.3 Cholangiocarcinoma (CCC)

6.3.1 Introduction

CCC is an adenocarcinoma that originates in the bile duct system. Cholangiocarcinoma is a rare type of cancer with an annual incidence of 1–2/100,000 [22].

CCC is considered to be an incurable malignancy unless the tumor is surgically resected. However, most patients, in particular those with intrahepatic CCC, have an advanced stage disease at the time of diagnosis and are not resectable in curative intention. Standard of care in the palliative setting is systemic chemotherapy with cisplatin and gemcitabine that improves overall survival compared to gemcitabine as demonstrated by a randomized controlled phase 3 trial (OS 11.7 vs. 8.1 months) [23]. To prevent serious tumor complications like malignant bile duct obstruction with resulting cholestasis and cholangitis, regional tumor therapies like the endoscopic photodynamic therapy (PDT) in the bile ducts is an option. PDT has been shown to prolong overall survival vs. best supportive care (OS 21 vs. 7 months) [24, 25].

Other regional tumor therapies like TAE, TACE, or RFTA are currently not standard of care for the treatment of CCC. However, as shown in the listing of trials below, especially TACE with drugs like gemcitabine and/or cisplatin exhibits promising results (OS: gemcitabine + cisplatin vs. gemcitabine alone, 14 vs. 6 months) compared to systemic chemotherapy alone [26]. Nevertheless at the moment, there is too few data for this regional therapy to become a standard of care. In individual cases like intolerable toxicity of systemic treatment or contraindications for systemic chemotherapy, regional therapeutic strategies such as TACE are a treatment option in patients with inoperable CCC.

6.3.2 Study Results: CCC

Ortner et al. (2003) [24]

Concept	Stenting plus subsequent photodynamic therapy vs. stenting alone
N	39
Therapy	PDT (Photofrin) + stent (group A) 20 vs. stent (group B) 19
Survival	Group A: 493 days Group B: 98 days ($p < 0.0001$)
Toxicity	Nonfatal: group A, 35 % (cholangitis, stenosis, photosensitivity) group B, 37 % (cholangitis) Fatal: group A, 90 % (cholangitis/sepsis, pulmonary embolism, cachexia, cardiac failure, metastases, chronic renal failure) group B, 100 % (cholangitis/sepsis, pulmonary embolism, cachexia, cardiac failure, metastases)
Conclusions	PDT given in addition to BSC improves survival in patients with nonresectable CCC

Kirchhoff et al. (2005) [27]

Concept	Combination of systemic and regional chemotherapy
N	8
Therapy	IV: 1,000 mg/m^2 gemcitabine (3× weekly) TACE: 50 mg/m^2 doxorubicin + 50 mg/m^2 cisDDP + DSM every 4 weeks
Response rates	PR, *N* = 3; SD, *N* = 5 TTP: 7 mo
Survival	12 mo
Toxicity	No severe toxicity, nausea, and fever
Conclusions	The present results indicate that a combination of systemic gemcitabine and repeated regional chemoembolization is well tolerated and may enhance the effect of palliation in a selected group of patients with intrahepatic nonresectable CCC

Cantore et al. (2005) [28]

Concept	Combination of systemic and regional chemotherapy
N	30 (25 intrahepatic cholangiocarcinomas, 5 gallbladder carcinomas)
Therapy	IV: 200 mg/m^2/d 5-FU (d1–14) HAI: 50 mg/m^2 doxorubicin + 60 mg/m^2 cisDDP every 3 weeks
Response rates	CR, 1 (3 %); PR, *N* = 11 (37 %); SD, *N* = 12 (40 %) Median PfS: 7 mo
Survival	Median survival: 13 mo 1 y, 2 y: 54, 20 %
Toxicity	Cumulative Grade III: 37 % (leukopenia, nausea/emesis, mucositis, alopecia)
Conclusions	This novel combined locoregional and systemic chemotherapeutic regimen was found to be active and safe for patients with advanced biliary tract carcinoma

Burger et al. (2005) [29]

Concept	TACE with doxorubicin-eluting beads
N	17
Therapy	100 mg cisDDP + 50 mg doxorubicin + 10 mg MMC + lipiodol + PVA or Embosphere (mostly 1 therapy)
Response rates	ND
Survival	Median survival: 23 mo
Toxicity	9/17 without side effects, *N* = 5: nausea/vomiting, diarrhea, hypertension, abdominal pain, tachycardia
Conclusions	The results suggest that TACE was effective at prolonging survival of patients with unresectable cholangiocarcinoma. Therefore, for these patients, TACE may provide an appropriate palliation

Zoepf et al. (2005) [25]

Concept	Stenting plus subsequent photodynamic therapy vs. stenting alone (randomized study)
N	32
Therapy	PDT (2 mg/kg photosan-3 IV prior to laser irradiation) + stent (group A) 16 vs. stent (group B) 16
Survival	Group A: 21 months Group B: 7 months ($p < 0.01$)
Toxicity	Group A: serious infectious complications 4/16 Group B: serious infectious complications 1/16
Conclusions	PDT is minimally invasive but shows a considerable postinterventional cholangitis rate. PDT has the potential to result in a changeover of current palliative treatment of bile duct cancer

Vogl et al. (2006) [30]

Concept	Dose finding study for intra-arterial application of gemcitabine –/+DSM
N	24
Therapy	HAI, 1,000 mg/m^2 (d1 + 8); dose step, 200 mg/m^2 (3 patients/group) – till MTD TACE, starting at 1,400 mg/m^2 + DSM; dose step, 200 mg/m^2 – till MTD
Response rates	HAI: MTD, 1,400 mg/m^2 SD, *N* = 9/12 (75 %) TTP, 4 mo TACE: MTD, 1,800 mg/m^2 SD, *N* = 11/12 (92 %) TtP, 7 mo
Survival	HAI, 13 mo; TACE, 20 mo
Toxicity	MTD criteria: myelosuppression (for HAI and TACE)
Conclusions	This clinical study indicates that the intra-arterial application of gemcitabine with doses higher than the recommended 1,000 mg/m^2 is well tolerated if combined with microspheres and yields interesting results in patients who do not respond to systemic chemotherapy

Mambrini et al. (2007) [31]

Concept	Combination of oral and regional chemotherapy
N	20
Therapy	Oral: 1,000 mg/m^2/bid capecitabine (d2–15) HAI: 50 mg/m^2 doxorubicin + 60 mg/m^2 cisDDP every 3 weeks
Response rates	PR, *N* = 6 (32 %); SD, *N* = 9 (48 %) Median PfS: 12 mo
Survival	Median survival: 18 mo 1 y: 74 %
Toxicity	Cumulative Grade III: 35 % (neutropenia, nausea/emesis, mucositis, alopecia)
Conclusions	This combined locoregional and oral chemotherapeutic approach seems to be active and safe with a good survival response

Herber et al. (2007) [32]

Concept	TACE (retrospective study)
N	15
Therapy	10 mg MMC + lipiodol every 8 weeks (total of 58 procedures)
Response rates	PR, *N* = 1; SD, *N* = 9
Survival	Median survival: 21 mo 1, 2, 3 y: 55, 28, 28 %
Toxicity	6/15 patients: PES; 1 gastric ulceration
Conclusions	TACE is a safe procedure with a moderate number of complications for patients suffering from inoperable CCA. According to recently published data on IV chemotherapy, we suggest that TACE might be able to prolong survival in selected patients who are not (any more) amenable to systemic treatment modalities

Kim et al. (2008) [33]

Concept	HAI or TACE (retrospective review)
N	49
Therapy	HAI (*N* = 13): 2 mg/kg cisDDP TACE (*N* = 21): 2 mg/kg cisDDP + lipiodol + Gelfoam HAI + TACE (*N* = 15)
Response rates	PR, *N* = 10; SD, *N* = 15
Survival	Median survival: 12 mo 1, 2, 3 y: 46, 38, 30 %
Toxicity	Nausea/vomiting, fever
Conclusions	Hepatic intra-arterial chemotherapy is well tolerated and may be effective to prolong survival of patients with unresectable ICC

Aliberti et al. (2008) [34]

Concept	TACE with doxorubicin-eluting beads
N	11
Therapy	75–150 mg doxorubicin preloaded beads (100–300/300–500 μm) (total of 29 procedures)
Response rates	RR: 100 %
Survival	Median survival: 13 mo
Toxicity	Hepatic abscess ($N=1$), nausea/vomiting, abdominal pain, fever
Conclusions	Doxorubicin-eluting beads-TACE of 100–150 mg may be an appropriate palliative therapy for CCC

Gusani et al. (2008) [26]

Concept	Gemcitabine-based TACE
N	42
Therapy	1,250 mg/m^2 up to 2,250 mg/m^2 gemcitabine –/+100–125 mg/m^2 cisDDP or 85–100 mg/m^2 oxaliplatin + Embosphere (Total of 199 procedures)
Response rates	SD: 20; PD: 15 (7 without evaluation)
Survival	Median survival: 9 mo Gemcitabine + cisDDP vs. gemcitabine alone: 14 vs. 6 mo
Toxicity	Grade IV, $N=2$; Grade III, $N=5$ (abdominal pain, hyperbilirubinemia, thrombocytopenia)
Conclusions	This report represents the largest series to date regarding hepatic-artery-directed therapy for unresectable cholangiocarcinoma and provides evidence in favor of TACE as an interesting treatment modality in unresectable cholangiocarcinoma

Poggi et al. (2009) [35]

Concept	TACE with oxaliplatin-eluting beads + systemic chemotherapy vs. systemic chemotherapy alone (historical comparison)
N	9 (combination), 11 (historical group)
Therapy	TACE: 50 mg oxaliplatin preloaded beads (HepaSpheres) (total 30 procedures) + IV: 85 mg/m^2 oxaliplatin + 1,000 mg/m^2 gemcitabine (2–4 weeks after TACE) vs. IV: 85 mg/m^2 oxaliplatin + 1,000 mg/m^2 gemcitabine
Response rates	TACE +: PR, 4/9 (44 %); SD, 5/9 (56 %); PfS: IV: PD, 8/11 (73 %)
Survival	PfS: TACE +, 8 mo IV, 3 mo Median survival: TACE+, 13 mo IV, 30 mo
Toxicity	Abdominal pain (24 %), cholangitis, hypertensive crisis, nausea/vomiting, neutropenia
Conclusions	These data suggest that OEM-TACE associated with systemic chemotherapy in the treatment of advanced unresectable ICC is a safe and feasible treatment

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Liver Metastases of Other Indications

7

Michel Ducreux

7.1 Introduction

Locoregional treatment of liver metastases has been developed especially for tumors that give liver-limited metastases. For all the tumors types and especially for the less usual that are presented in this chapter, the aim is to increase the amount of the drug delivered to the tumor and to decrease systemic toxicity. On the other hand, locoregional treatment in these specific settings may help to increase the activity of the drug especially for rather orphan tumors such as melanoma and pancreatic cancer for instance. Another aim is to fight against the appearance of resistance to systemic treatment (pancreatic carcinoma, breast cancer). In aggressive diseases such as pancreatic carcinoma and melanoma, it is obvious that the indications of locoregional treatment directed to the liver should not be proposed if there is any suspicion of extrahepatic disease. This requirement is not mandatory in tumors such as breast carcinoma in which the prognosis may be linked to liver involvement. In these tumors, liver locoregional treatment could be at least considered even if there is extrahepatic disease when the liver metastases are able to rapidly shorten the survival of the patients.

Some of the inclusion criteria for arterial liver treatment are common to all these rare indications:

- Tumor mass <50 % liver volume
- Normal vessel system, which allows the placement of the catheter into the A. gastroduodenalis or A. hepatica propria
- Open portal vein
- No ascites

Some of the inclusion criteria are true for melanoma and breast carcinoma but not for pancreatic adenocarcinoma because liver surgery is approximately never considered in this disease:

- Nonresectable tumors
- Relapsed metastases after liver resection
- Metastases in both lobs
- General contraindications for operation
- Refusal of operation by patient

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These unusual indications clearly need a multidisciplinary discussion including oncologists, interventional radiologists, diagnostic radiologists, surgeons, and pathologists.

Treatment of metastases is always difficult especially when they are related to a very aggressive disease such as pancreatic carcinoma or uveal melanoma. On the other hand, 80–90 % of metastases due to these two cancers appear in the liver. These two arguments gave a strong rationale for the use of HAI or chemoembolization in adjuvant setting.

7.2 Liver Metastases of Pancreatic Adenocarcinoma

7.2.1 Adjuvant Treatment

Beger et al. (1999) [1]

Concept	Resection + intra-arterial chemotherapy vs. resection alone
N	51
Access	Catheter via A. femoralis in truncus coeliacus
Therapy	d1: 10 mg/m^2 mitoxantrone (over 1 h) d2–4: 170 mg/m^2 FA (over 10 min) + 600 mg/m^2 5-FU (over 2 h) d5: 60 mg/m^2 cisDDP (over 1 h)
Frequency	Every 4 weeks
Survival	23 mo vs. 11 mo R0-resection (at 4 years): 54 vs. 10 %
Hepatic metastasis	Reduction to 17 %
Toxicity	No severe local side effects
Conclusion	The results demonstrate that CAI is well tolerated, reduces the risk of liver metastasis, and increases the survival time of pancreatic cancer patients

d days, *mo* months

Cantore et al. (2006) [2]

Concept	Resection + intra-arterial chemotherapy ±IV gemcitabine
N	47
Access	Catheter via A. femoralis in truncus coeliacus
Therapy	5FU 750 mg/m^2, leucovorin 75 mg/m^2, epirubicin 45 mg/m^2, carboplatin 225 mg/m^2 (FLEC regimen)
Frequency	Every 3 weeks
Survival	Median disease-free-survival: 16.9 months, median overall survival: 29.7 months
Hepatic metastasis	62 % of recurrence
Toxicity	Main grade 3 toxicity related to HAI was only nausea/vomiting in 4 % of the patients
Conclusion	FLEC regimen with or without gemcitabine is active with a very mild toxicity and results are very encouraging in an adjuvant setting

Hayashibe et al. (2007) [3]

Concept	Resection + intra-arterial chemotherapy vs. resection alone (non randomized)
N	22
Access	Catheter via A. femoralis in proper hepatic artery
Therapy	5FU 500 mg/m^2 180 min infusion + cisplatin 10 mg/m^2
Frequency	weekly “as much as possible”
Survival	15.8 mo vs. 13.4 mo NS
Hepatic metastasis	33 % in the treated group vs. 54 % in the control group
Toxicity	No severe local side effects
Conclusion	In patients with pancreatic cancer who underwent the curative operation, the intra-arterial adjuvant chemotherapy had the tendency to suppress the rate of liver metastasis and improve cumulative survival

7.2.2 Metastatic Disease

Homma and Niitsu (2002) [4]

Concept	Hepatic arterial infusion
N	31
Access	Catheter into A. femoralis to celiac artery
Therapy	20 mg/m^2 cisDDP (d1, 3, 5) + 500 mg/m^2 5-FU (d1–7)
Frequency	Every 4 weeks
Survival	1, 2, 3 y: 67, 31, 14 % Median survival: 16 mo
Toxicity	Cytopenia (grade II): *N* = 11, transient nausea, mild anorexia
Conclusion	In patients with stage IV advanced pancreatic carcinoma, arterial infusion chemotherapy after hemodynamic change was found to be effective against both primary tumors and metastatic liver lesions

y years

Vogl et al. (2006) [5]

Concept	Intra-arterial dose finding of gemcitabine +/6 starch microspheres
N	24
Access	Catheter into A. femoralis placed in the truncus coeliacus
Therapy	HAI: initial dose, 1,000 mg/m^2 (d1 + d8) every 2 weeks (max. 6 cycles); dose steps, 200 mg/m^2 (till MTD) TACE: initial dose, HAI-MTD – 1 dose-step, + microspheres
MTD	HAI: 1,600 mg/m^2 TACE: 1,800 mg/m^2
Response rates	TtP HAI: 4 mo TACE: 7 mo
Survival	Median survival HAI: 14 mo TACE: 20 mo
Toxicity	Myelosuppression (grade III)
Conclusion	This clinical study indicates that the intra-arterial application of gemcitabine with doses higher than the recommended 1,000 mg/m^2 is well tolerated if combined with microspheres and yields respectable results in patients who do not respond to systemic chemotherapy

Cantore et al. (2003) [6]

Concept	Intra-arterial chemotherapy vs. IV gemcitabine
N	71 vs. 67
Access	Catheter via A. femoralis in truncus coeliacus
Therapy	5FU 1,000 mg/m^2, leucovorin 100 mg/m^2, epirubicin 60 mg/m^2, carboplatin 300 mg/m^2 (FLEC regimen)
Frequency	Every 3 weeks
Response rate	14 % for FLEC vs. 5.9 % for gemcitabine (NS)
Survival	Median overall survival: 7.9 months in the FLEC group vs. 5.8 months in the gemcitabine group ($p=0.13$)
Toxicity	Main grade 3 toxicity related to IAC was only nausea/vomiting in 4 %; regarding gemcitabine, grade 3 toxicities were anemia 8 %, leukopenia 8 %, thrombocytopenia 17 %, and nausea/vomiting 4 %
Conclusion	FLEC regimen with or without gemcitabine is active with a very mild toxicity and results are very encouraging in an adjuvant setting

Ikeda et al. (2007) [7]

Concept	HAI + IV therapy
N	33
Access	Port system (catheter into A. subclavia or right A. femoralis)
Therapy	IV: 1,000 mg/m^2 gemcitabine (over 30 min) d1, 8, 15 HAI: 250 mg/m^2 5-FU d1–5
Frequency	Every 4 weeks
Response rates	PR: $N=8$ (24 %), PD: 9 (27 %)
Survival???	
Toxicity	Leukopenia (grade III), $N=8$; thrombocytopenia, $N=6$; non-hematologic (grade III), $N=5$
Conclusion	For patients with advanced pancreatic cancer, HAI with systemic chemotherapy appeared to be effective and may prolong survival

Azizi et al. (2011) [8]

Concept	TACE for liver metastases
N	32
Access	Femoral arterial access, advanced into the relevant segmental artery
Therapy	8 mg/m^2 MMC + 40 mg/m^2 cisDDP + 1,000 mg/m^2 gemcitabine + lipiodol + 200–450 mg DSM
Frequency	Every 4–8 weeks
Response rates	PR: $N=3$ (9 %), SD: $N=23$ (72 %), PD: $N=6$ (19 %)
Survival	Median survival: 16 mo (SD: 20 mo, PD: 5 mo)
Toxicity	No major complications
Conclusion	Repetitive TACE resulted in a relevant response for the control of liver metastases of pancreatic cancer with respectable median survival time

Recommendations
Locoregional treatment of liver metastases of pancreatic adenocarcinoma remains a matter of research. It is conceptually interesting for the treatment of pancreatic carcinoma even if recent polychemotherapy has given interesting results (FOLFIRINOX, gemcitabine + nab-paclitaxel). In adjuvant setting the data are scarce, but considering the high level of liver recurrence after surgical excision of pancreatic cancer and even if systemic treatment has given some hope, it could be considered in future trials.

7.3 Liver Metastases of Melanoma

7.3.1 Hepatic Arterial Infusion

Becker et al. (2002) [9]

Concept	HAI or IV of fotemustine + SC IL-2 + IFN
N	48
Inclusion criteria	Liver and extrahepatic metastases
Therapy	d1: IA 100 mg/m^2 fotemustine (over 60 min) or IV 100 mg/m^2 fotemustine (over 15 min) d31–33: SC 10×10^6 IU/m^2 IL-2 (2×/d) d36, 38, 40: SC 10×10^6 IU/m^2 IFN + SC 5×10^6 IU/m^2 IL-2
Response rates	RR: 15 % ($N = 7$); (5 from the HAI group) HAI vs. IV: 22 vs. 8 % CR: $N = 1$; PR: $N = 6$
Survival	8.5 mo (HAI vs. IV: 369 vs. 349 d)
Toxicity	Thrombocytopenia, leukopenia (more prominent systemic side effects in the IV group)
Conclusions	Although objective responses were more frequent within the cohort receiving intra-arterial fotemustine, this difference did not translate into a significant benefit in overall survival. Of note, this overall survival is much longer than that repeatedly reported for stage IV uveal melanoma not treated with fotemustine, suggesting a therapeutic activity of this cytostatic drug even after systemic administration

Peters et al. (2006) [10]

Concept	HAI (retrospective study)
N	101
Inclusion criteria	Chemotherapeutic naive patients
Therapy	100 mg/m^2 fotemustine (over 4 h) Every 4 weeks
Response rates	RR: 36 % CR: *N* = 15; PR: *N* = 21; SD: *N* = 48 TtP: 9 mo
Survival	Median survival: 15 mo 1 y, 2 y, 3 y: 67, 29, 12 %
Toxicity	Grade III and IV: 11 % (mainly hematoxicity), grade II: (mainly hematoxicity) Complications with catheters: *N* = 21 (thrombosis, dislocation, obstruction, leakage)
Conclusions	Locoregional treatment with fotemustine is well tolerated and seems to improve outcome of this poor prognosis patient population

Siegel et al. (2007) [11]

Concept	HAI (retrospective study)
N	30 (18 uveal)
Inclusion criteria	Liver-limited disease
Therapy	100 mg/m^2 fotemustine (over 4 h) Every 4 weeks
Response rates	RR: 30 % PR: *N* = 9; SD: *N* = 10 TtP: 9 mo
Survival	Median survival: 14 mo 1 y, 2 y, 3 y: 67, 29, 12 %
Toxicity	≥ Grade III thrombocytopenia/30 %; ≥ grade 3 neutropenia: 7 %
Conclusions	Hepatic arterial fotemustine chemotherapy was well tolerated. Meaningful response and survival rates were achieved in ocular as well as cutaneous melanoma

Voelter et al. (2008) [12]

Concept	HAI (prospective study, historical control)
N	22
Inclusion criteria	High risk of liver metastases patients
Therapy	100 mg/m^2 fotemustine (over 4 h) Every 3 weeks
Response	NA – adjuvant treatment
Survival	Median survival: 9 years vs. 7.4 years for control group 5-year survival: 75 % vs. 56 %
Toxicity	50 % grade 3–4 hepatotoxicity including one patient with cholangitis 8 years later
Conclusions	Although these data suggest a survival benefit, it was not statistically significant. Confirming such a benefit would require a large, internationally coordinated, prospective randomized trial

Farolfi et al. (2011) [13]

Concept	HAI
N	23
Inclusion criteria	Patients after treatment failure of systemic therapy for hepatic metastases from melanoma (18 uveal)
Therapy	100 mg/m^2 fotemustine or 50 mg cisDDP Every 2–4 weeks
Response rates	Uveal melanoma ($n=18$) RR: 17 % Disease control rate: 39 % Disease control rate (PR + SD): 72 %
Survival	Median PFS: 6.2 months Median survival: 21 mo
Toxicity	No grade IV toxicity Grade III: fever in the absence of a detectable focus for 3 days ($N=3$), splenic infarction ($N=1$) treated conservatively, thrombocytopenia ($N=1$), and gastric ulcer ($N=1$)
Conclusions	IAC with fotemustine is well tolerated and is a valid choice for patients with a poor prognosis since median survival rates are among the longest reported

Heusner et al. (2011) [14]

Concept	HAI (retrospective analysis)
N	61
Inclusion criteria	Liver and extrahepatic metastases
Therapy	Melphalan Melphalan + fotemustine, dacarbazine, MMC, doxorubicin, or gemcitabine Every 4 weeks
Response rates	At 4 sessions: PR: 30 %; SD: 15 %; PD: 55 % At 6 sessions: PR: 19 %; SD: 57 %; PD: 24 %
Survival	Median survival: 10 mo Extrahepatic vs. hepatic metastases only: 6 vs. 14 mo ≤vs. >9 metastases: 17 vs. 9 mo
Toxicity	Liver failure in 1 patient (0.4 %), thrombopenia (20 %), leukopenia (16 %)
Conclusions	Intra-arterial sequential hepatic chemoperfusion offers a minimally invasive treatment in patients with hepatic uveal melanoma metastases with good survival times and an acceptable major complication rate

7.3.2 TACE

Mavligit et al. (1988) [15]

Concept	TACE
N	30
Inclusion criteria	Liver metastases
Therapy	Chemoembolization with cisplatin and polyvinyl sponge
Response rates	RR: 46 % CR: $N=1$; PR: $N=13$
Survival	11 mo
Toxicity	Primarily severe upper right quadrant abdominal pain, transient paralytic ileus, and nonicteric hepatitis
Conclusions	Hepatic arterial chemoembolization provided effective palliation, with good-quality survival among 46 % of patients with ocular melanoma metastatic to the liver

Patel et al. (2005) [16]

Concept	TACE
N	24
Inclusion criteria	Liver metastases
Therapy	Chemoembolization with BCNU dissolved in ethiodized oil, Gelfoam
Response rates	RR: 21 % CR: *N* = 1; PR: *N* = 4
Survival	5.2 mo
Toxicity	Grade 3 or 4 toxicity was experienced by eight patients (two hepatic vein thromboses and one portal vein thrombosis; one patient had a partial splenic infarct); one patient without prior treatment developed grade 3 thrombocytopenia that improved to grade 1 within 2 weeks, one renal insufficiency, two liver failures
Conclusions	Chemoembolization with BCNU is a useful palliative treatment for the control of hepatic metastases in uveal melanoma patients. However, progression in extrahepatic sites after stabilization of hepatic metastases requires further improvement in the therapeutic approach to this disease

Sato et al. (2008) [17]

Concept	TACE
N	31
Inclusion criteria	Liver metastases
Therapy	Chemoembolization with granulocyte-macrophage colony-stimulating factor, emulsified in ethiodized oil, Gelfoam
Response rates	RR: 32 % CR: *N* = 2; PR: *N* = 8
Survival	14.4 mo
Toxicity	Mild. MTD was not reached up to the dose level of 2,000 μg, and there were no treatment-related deaths
Conclusions	Immunoembolization with GM-CSF is safe and feasible in patients with hepatic metastasis from primary uveal melanoma. Encouraging preliminary efficacy and safety results warrant additional clinical study in metastatic uveal melanoma

Schuster et al. (2010) [18]

Concept	TACE
N	25
Inclusion criteria	Patients after treatment failure of systemic therapy for hepatic metastases from uveal melanoma
Therapy	100 mg/m^2 fotemustine + max 900 mg DSM or 50 mg cisDDP + max 900 mg DSM Every 2–4 weeks
Response rates	RR: 16 % PR: $N=4$; SD: $N=14$ Disease control rate (PR + SD): 72 %
Survival	Median PFS: 3 months (no significant difference between the fotemustine ($n=16$) and the cisplatin ($n=9$) group) Median survival: 5 mo
Toxicity	No grade IV toxicity Grade III: fever in the absence of a detectable focus for 3 days ($N=3$), splenic infarction ($N=1$) treated conservatively, thrombocytopenia ($N=1$), and gastric ulcer ($N=1$)
Conclusions	TACE is well tolerated and effective in pretreated patients with liver metastases from uveal melanoma. TACE should further be evaluated as first-line therapy in prospective randomized clinical trials

Firorentini et al. (2009) [19]

Concept	TACE with DC Beads loaded with irinotecan (DEBIRI)
N	10
Inclusion criteria	Liver metastases
Therapy	Irinotecan 100–200 mg preloaded in 2–4 ml beads of 100–300/300–500 µm 15 TACE procedures, 5 patients: 1, 5 patients 2 cycles
Response rates	3 patients reduction of 90 %, 3 patients reduction of 80 %, 4 patients reduction between 60 and 70 %
Survival	Median survival: NA Eight patients alive at the time of writing. Two patients with huge liver involvement died after 4 and 6 months due to rapid progression in the liver
Toxicity	No hematological toxicity or alopecia
Conclusions	Preliminary data but it seems that TACE adopting the new embolic material DC Beads with irinotecan is highly effective in liver metastases from uveal melanoma

7.3.3 High-Dose Hepatic Arterial Infusion and Hemofiltration

Pingpank et al. (2005) [20]

Concept	High-dose liver infusion of melphalan + hemofiltration, phase I study
N	28. 10 with uveal melanoma
Inclusion criteria	Liver metastases of various malignancies
Therapy	Double-balloon inferior vena cava (IVC) catheter system. Infusion of melphalan (30 min) and hemoperfusion of the liver effluent with drug filtration cartridges. First cohort of 12 patients 2 mg/kg, second cohort 3.5 mg/kg
Response rates	RR: 50 %
Survival	14.4 months
Toxicity	67 % grade 3–4 transient systemic toxicity
Conclusions	PHP with melphalan can be performed safely at an MTD of 3.0 mg/kg. Regional toxicity was minimal. Interesting activity has been observed even if it was not the main endpoint of this phase I trial

Recommendations

Uveal melanoma metastases occur most commonly in the liver. Even if recent treatment has been proven to be effective in metastatic melanoma (ipilimumab, vemurafenib), it remains very difficult to treat liver metastases of melanoma. This is particularly true for uveal melanoma which is able to specifically give limited liver metastases even very late after the treatment of the primary tumor. Surgery is the first choice in the treatment of these lesions but is frequently limited to one or two attempts of resection and then failed to control the disease due to its extension or the paucity of the remnant liver. In that setting, intra-arterial hepatic chemotherapy with fotemustine has given interesting results and should be considered in selected cases. Other options are TACE or PHP with high-dose melphalan but there are less data to support this kind of treatment.

7.4 Liver Metastases of Breast Cancer

7.4.1 HAI

Cocconi et al. (2005) [21]

Concept	HAI
N	10
Inclusion criteria	Liver metastases under systemic chemotherapy
Therapy	IA: 65 mg/m^2 (40–100 mg/m^2) docetaxel Every 3 weeks (max. 6 cycles)
Response rates	PR: 4/9; SD: 4/9
Survival	Median survival: 46 mo
Toxicity	Hematological (grad III): $N=6$, non-hematological (grad III): $N=2$ (pain, asthenia)
Conclusions	The administration of docetaxel via the hepatic artery is feasible with a highly interesting response

7.4.2 TACE

Giroux et al. (2004) [22]

Concept	Chemoembolization (retrospective analysis)
N	8
Inclusion criteria	Liver metastases under systemic chemotherapy
Therapy	100 mg cisDDP + 50 mg doxorubicin + 10 MMC + lipiodol + PVA Every 4 weeks (1–4 cycles)
Response rates	RR: 5/8; SD: 1/8
Survival	Mean survival: 49 mo (from primary diagnosis); 20 mo (from liver metastasis diagnosis); 6 mo (from TACE)
Toxicity	No complications related to TACE
Conclusions	Chemoembolization stabilizes or improves the liver tumor burden, which may palliate symptoms, but most patients go on to develop other metastatic sites, which eventually lead to death

Li et al. (2005) [23]

Concept	Chemoembolization vs. systemic chemotherapy (retrospective comparison)
N	48 (28, 20)
Inclusion criteria	Liver metastases under systemic chemotherapy
Therapy	TACE: 1,000 mg 5-FU or FUDR + 40–60 mg cisDDP (infusion) followed by 40–60 mg doxorubicin + lipiodol or Gelfoam IV: different anthracycline-based schedules or Taxotere + cisDDP Every 4 weeks
Response rates	RR (%): 35.7 vs. 7.1 ($p < 0.005$)
Survival	Median survival: 28.0 vs. 18.0 mo 1, 2, 3y (%): 63, 30, 13 vs. 34, 11, 0
Toxicity	TACE: leuko-/thrombocytopenia (grad I–II), elevation of liver enzymes (grad I–II) IV: leuko-/thrombocytopenia (grad I–IV), elevation of liver enzymes (grad I–II)
Conclusions	TACE treatment of liver metastases from breast cancer may prolong survival in certain patients. This approach offers new promise for the curative treatment of the patients with metastatic breast cancer

Vogl et al. (2011) [24]

Concept	Chemoembolization with two different schedules followed by LITT
N	161
Inclusion criteria	Liver metastases after mastectomy
Therapy	8 mg/m^2 MMC + lipiodol + 200–450 mg DSM ($N = 53$) or 8 mg/m^2 MMC + 1,000 mg/m^2 gemcitabine + lipiodol + 200–450 mg DSM ($N = 108$)
Response rates	After TACE: PR: 57 %; SD: 43 % Mean tumor reduction: MMC vs. MMC + gemcitabine: 27 % vs. 27 % After TACE + LITT: CR: 39 %; PR: 5 %; SD: 12 %
Survival	Median survival: 33 mo (5–101) 1, 2, 3, 5y (%): 89, 56, 37, 13 % MMC: 45 mo (5–101) MMC + gemcitabine: 26 mo (5–63) TtP: MMC vs. MMC + gemcitabine: 8 vs. 11 mo
Toxicity	No or only few symptoms under TACE (mild): fatigue, abdominal pain, fever, nausea/vomiting
Conclusions	TACE can be used for sufficient downstaging of liver metastatic lesions of breast cancer to allow laser-induced thermotherapy. A combination of mitomycin C and gemcitabine seems to improve the reduction achieved with TACE

7.4.3 Comparison of TACE vs. HAI

Duan et al. (2011) [25]

Concept	Comparison of TACE plus systemic chemotherapy vs. systemic chemotherapy alone
N	87 (44, 43)
Inclusion criteria	Liver metastases after mastectomy
Therapy	TACE: 5-FU or FUDR + cisDDP (infusion) followed by doxorubicin + lipiodol or Gelfoam IV: different anthracycline- or taxane-based schedules (82 %) or others Every 4 weeks (median: 6 cycles)
Response rates	RR (%): 59 vs. 35 ($p < 0.05$) CR: 14 vs. 9 %; PR: 12 vs. 6 %
Survival	Median survival: 29 mo (42 vs. 26 mo) $p = 0.027$ 1 y, 2 y, 3 y (%): 63, 48, 28 % (76, 67, 48 vs. 48, 30, 7 %)
Toxicity	Leukopenia: 39 vs. 46 %; hypochromia: 11 vs. 7 %; thrombocytopenia: 9 vs. 14 %; nausea/vomiting: 5 vs. 2 %; impairment of liver function: 11 vs. 9 %; Abdominal pain in most of the TACE + patients
Conclusions	The combined treatment of TACE and systemic chemotherapy may prolong survival for liver metastases in breast cancer after mastectomy

Recommendation
Breast carcinoma is rarely a disease with liver-limited metastases. However, liver metastases of breast carcinoma have a very poor prognosis. Considering this problem, it has been tried to use locoregional treatment in these cases. TACE seems to be active and could be proposed to every selected patients; experience of HAI is very scarce and no conclusion can be given.

7.5 Liver Metastases of Kidney Cancer

Nabil et al. (2008) [26]

Concept	TACE of liver metastases
N	22
Inclusion criteria	Liver metastases after resection of primary tumor
Therapy	TACE: 10 mg/m^2 mitomycin C alone (45 %) or in combination with 1,000–2,000 mg gemcitabine + lipiodol + 200–450 mg DSM Every 4 weeks (mean 6 cycles)
Response rates	RR (%): 14 PR: 14 % SD: 59 % PD: 27 %
Survival	Median survival: 7 mo (from start of TACE) no statistical difference between therapy concepts (MMC vs. MMC + gemcitabine)
Toxicity	Post-embolization syndrome (nausea, vomiting, or right upper quadrant pain) ($N=10$), puncture site hematoma ($N=1$), no major complications
Conclusions	TACE can result in a favorable local tumor response in patients with hepatic metastases from RCC, but survival results are still limited

Abdelmaksoud et al. (2012) [27]

Concept	Radioembolization with ^{90}Y
N	6
Inclusion criteria	Chemorefractory liver-dominant metastases from RCC
Therapy	Bilobar treatment with 120 Gy (infusion of ^{90}Y microspheres)
Response rates	Time to partial response: 133 days CR: $N=3$, PR: $N=1$, PD: $N=2$
Survival	Median survival: 300 days
Toxicity	Grad 1 + 2 toxicities in all patients (primarily fatigue)
Conclusions	^{90}Y hepatic treatment could be an option for patients with liver-dominant metastatic RCC, intolerant to targeted therapies

Recommendations

The number of patients with liver-limited disease of kidney cancer and treated with intra-arterial hepatic chemotherapy is very limited, and there is no possibility to propose any recommendation, even if some data are encouraging.

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Part III

Intra-arterial Therapies: Lung, Head and Neck

Chemoembolization of Lung Tumors

8

Thomas J. Vogl

8.1 Introduction

The incidence of lung cancer has increased enormously in the last century [1], and lung cancer is now one of the most common malignant diseases worldwide. In the United States, bronchogenic carcinoma is the second most common cancer for both men and women. In 2002, 169,400 new cases of bronchogenic carcinoma were diagnosed in the United States, and 154,900 people died of this disease, making bronchogenic carcinoma the leading cause of cancer-related death [2]. Pulmonary metastases from primary tumors at other sites are also a major problem: between 20 and 30 % of patients suffering from cancer develop pulmonary metastases [3]. The prognosis for patients with bronchogenic carcinomas or pulmonary metastases is poor. In patients with stage I and II bronchogenic carcinoma, resection offers the best chance for long-term survival [4–7], but only 25–30 % of such tumors are resectable [2, 4, 5]. The mean survival duration after diagnosis is 12 months for patients with bronchogenic carcinomas and less than 1 year for patients with unresectable pulmonary metastases. Five-year survival rates are 10 % for patients with bronchogenic carcinoma overall [4], 23–50 % for patients with bronchogenic carcinoma who undergo resection [6–9], and 1 % for patients with unresectable bronchogenic carcinomas. In patients who undergo resection of pulmonary metastases, the 5-year survival rate is 20–46 % [10–17].

Countless therapy regimens, including radiotherapy and chemotherapy [1], have been tested as alternatives to tumor excision or as neoadjuvant therapy in patients with bronchogenic carcinoma or pulmonary metastases. Although such regimens have shown promising results [18], the overall response rates remain poor.[1] For combined chemotherapy, the overall response rates are 20–50 % [19, 20]; for single-agent therapy with doxorubicin, the overall response rate is 20–30 %. The main limitation of these

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approaches has been the chemotherapy-associated toxicity when delivered via the intravenous route [21].

In the 1950s, isolated lung perfusion was developed as an experimental technique to improve the outcome in patients with pulmonary metastases from different tumors. The goal of isolated lung perfusion is to accomplish a closed circulation system by cannulation of pulmonary arteries and veins to allow injection into the lung of high-dose chemotherapy with minimal systemic toxicity [22, 23]. This idea was reintroduced in the 1980s and tested as a potential alternative to systemic chemotherapy [24, 25]. With isolated lung perfusion, it is possible to obtain drug concentrations near the tumor site twice as high as those achieved with systemic chemotherapy with only 25 % of the systemic dose [26]. Several recent animal studies have reconfirmed that tumor drug concentrations and therapeutic efficacy are significantly higher [27, 28] with isolated lung perfusion than with systemic chemotherapy. Despite these interesting results, isolated lung perfusion is not yet established clinically. The reasons for this may include the relative complexity and paucity of knowledge regarding the technical aspects of the procedure [29] combined with the limited number of robust human trials to date. The main limitation of isolated lung perfusion is that cannulation of pulmonary vessels is required, which necessitates either thoracotomy or other minimally invasive operative techniques [30] that cannot be repeated indefinitely. Furthermore, extracorporeal circulation is an integral part of these approaches [31–33].

An alternative to isolated lung perfusion is transpulmonary chemoembolization. Transpulmonary chemoembolization is performed percutaneously, obviating the need for more invasive procedures. In a CC 531 rat model, transpulmonary chemoembolization and isolated lung perfusion were both found to be equally superior to systemic chemotherapy in terms of response, and chemoembolization and isolated lung perfusion have shown similar results [34]. However, one of the most important benefits of transpulmonary chemoembolization over isolated lung perfusion is that transpulmonary chemoembolization can be repeated indefinitely, whereas isolated lung perfusion is most often a one-time therapy [35]. Transpulmonary chemoembolization is a form of transarterial chemoembolization, which is an established treatment option for primary and secondary liver tumors [36]. Transpulmonary chemoembolization is applicable to the treatment of several unresectable lung lesions because of their supply via the pulmonary artery [37]. The purpose of transarterial chemoembolization is to block the vessels supplying a tumor by injecting chemotherapy simultaneously with embolic material. With this approach, the deposit time of the injected cytostatic drugs in the lesion is extended [38] and an outflow into the periphery is avoided, thus reducing the incidence and the severity of the systemic side effects.

8.2 Study Results

8.2.1 Experimental Data

Schneider et al. (2002) [39]

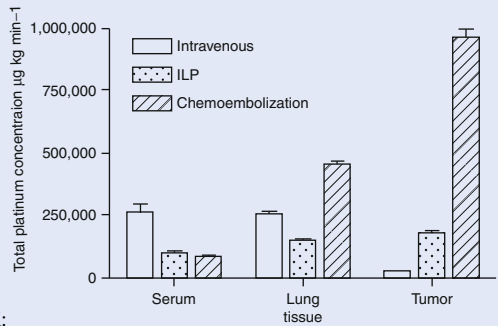
Model	Lung unilateral embolization with DSM ± carboDDP, rats: study of pulmonary microcirculation by measurement of FITC-labeled erythrocytes
N	12 (2 × 6)
Objective	Pulmonary microcirculation
Comparisons	1. unilateral embolization with DSM
	2. unilateral embolization with DSM + carboDDP
Embolization	30 mg/kg amilomer (DSM)
Results	Mean flow retardation: 14 min
	Original flow of erythrocytes: 21 min after embolization (Reperfusion and reversibility of microembolization)
	Confirmation of patency of the central pulmonary artery by pulmonary angiogram
	No cause of pulmonary edema through the additional application of carboplatin
Conclusions	For the first time unilateral microembolization of the lung could be established in an experimental model. By injection of DSM, reversible embolization on arteriolar and capillary level could be demonstrated without occlusion of the main branches of the pulmonary arteries. Alveolar-capillary membrane disorder as symptom of early toxicity could not be detected even with additional application of carboplatin

Schneider et al. (2002) [34]

Tumor model	Lung tumor model (adenocarcinoma), rats
N	25 (5×5)
Objective	Tumor control in lung metastases
Comparisons	1. ILP with buffered starch solution
	2. DSM mono
	3. CarboDDP I.V.
	4. ILP with carboDDP
	5. DSM + carboDDP
Embolization	Amilomer (DSM)
Results	Tumor volumes after 7 days after therapy (size differences):
	1. 422 mm^3
	2. 697 mm^3
	3. 70 mm^3
	4. −8 mm^3
	5. −17 mm^3
	3 vs. 4 + 5 $p < 0.005$
Conclusions	This is the first study to perform chemoembolization of the lung. Compared with i.v. therapy, chemoembolization was more effective without serious toxicity. Its efficacy was comparable with that of isolated lung perfusion but less stressful for a possible clinical application

ILP isolated lung perfusion

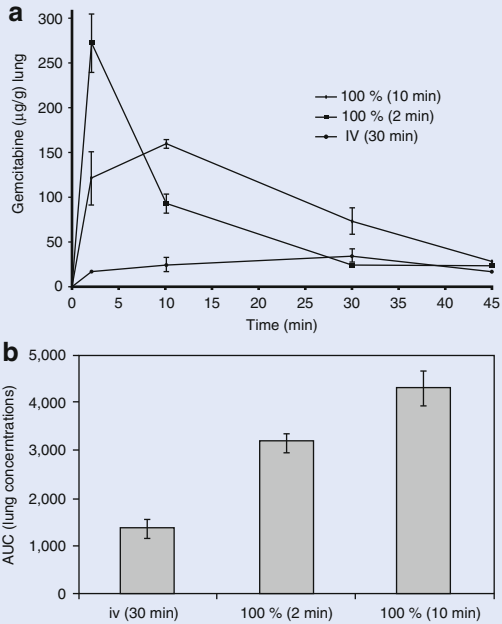
Pohlen et al. (2007) [40]

Model	TACE of lung tumor model (adenocarcinoma), rats
N	60 (3 groups of 5 animals each and 4 times of measurement (15, 30, 60, and 120 min)
Objective	Pharmacokinetics, histology of tumor tissue
Method	1. 45 mg/kg carboDDP I.V.
	2. ILP (15 mg/kg carboDDP)
	3. TACE (2 mg/kg DSM + 15 mg/kg carbDDP)
TACE	2 mg/kg DSM + 15 mg/kg carboDDP
Results	 PK:
	Histology:
	No fibrotic changes detected in any group. ILP and TACE group showed evidence of mild alveolar cell hyperplasia and pulmonary edema
Conclusions	This is the first study to measure the concentration of carboplatin during chemoembolization of the lung. Compared to intravenous therapy, chemoembolization produced higher tumor tissue concentrations. Comparing chemoembolization to ILP, there was also an increase of carboplatin in the tumor tissue, without histological damage of the surrounding lung parenchyma

Pohlen et al. (2007) [41]

Model	TACE of lung, pig
N	6
Objective	Safety and effectiveness of this method in a large animal model
Method	Puncture of femoral vein, selective exploration of the tumor-supplying pulmonary arteries, chemoembolization with DSM and carboplatin, documentation of survival, hemodynamic parameters, ventilation gas exchange, digital subtraction angiography (DSA), and pulmonary X-rays during and after chemoembolization
TACE	1–2 mg/kg DSM + 15 mg/kg carboDDP
Results	All the animals survived the operative procedure and chemoembolization. None of the animals showed clinical disturbances in the period between chemoembolization and sacrifice 6 months later. Body weight showed an increase
Conclusions	This is the first study of chemoembolization of the lung in a large animal model. The feasibility, mild hemodynamic acute effects and the absence of long-term toxicity were documented. These observations justify patient studies in unresectable lung tumors

van Putte et al. (2008) [42]

Concept	Isolated lung perfusion with gemcitabine in pigs (catheterization model of selective pulmonary artery perfusion (SPAP) combining the properties of isolated lung perfusion)
N	20
Procedure	Five groups ($N=4$, each) gemcitabine in a dose of 1 g/m^2 :
	SPAP with a normal pulmonary artery blood flow for 10 min
	SPAP with a normal pulmonary artery blood flow for 2 min
	Control (IV)
	SPAP for 2 min with 50 %
	SPAP for 2 min with 90 % flow reduction within the pulmonary artery
Results	The peak concentration of gemcitabine within the serum was significantly higher after SPAP for 2 min compared with i.v. infusion ($p=0.004$)
	
	Flow reduction during SPAP for 50 and 90 % did not result in a significantly different lung and serum AUC compared with SPAP without flow reduction
Toxicity	Histological examination: evidence of slight alveolar hyperplasia (more pronounced in the flow reduction groups with evident moderate congestion). No alveolar hyperplasia in the i.v. group. No abnormalities in the slight sections of the pulmonary artery in either the SPAP or the i.v. group
Conclusions	We advocate SPAP as a new method to be tested clinically to achieve downstaging of the tumor and lymph node status in lung cancer

8.2.2 Clinical Data

8.2.2.1 Practicability

Please note:

Inclusion criteria: relapsed liver metastases after partial liver resection, metastases in both liver sides, unresectable foci, general contraindications for operation, patients' decision, ≤5 lesions with ≤5 cm size per metastasis

Safety parameter for patients for sequential LITT

Treatment phase	Action
Before treatment	Hepatitis, fever, blood count, clotting (e.g., Hk, PTT, part. TPT)
Intraprocedural	Clinical investigations:
	Pulse, blood pressure, blood oxygen
	Medication:
	Local anesthesia (1 % mepivacaine)
	Sedation (diazepam)
	Antibiotics (2 g cefotiam)
	Analgesia (opiates, e.g., piritramide and pethidine i.v.)
Postprocerdural (immediately)	Clinical investigations:
	Pulse, blood pressure (every 30 min over 6 h)
	Medication:
	Analgesia (opiates, e.g., piritramide and pethidine i.v.)
	Antinausea (e.g., metoclopramide)
	Hydration
After 10 days	Hepatitis, fever, breathing frequency

8.2.2.2 Study Results

Isolated Lung Perfusion (ILP)

Schröder et al. (2002) [43]

Concept	Isolated lung perfusion with high-dose chemotherapy for the treatment of surgically relapsing or unresectable lung sarcoma metastasis
N	4
Inclusion criteria	Unilateral or bilateral sarcoma metastasis confined to a lobe or entire lung, drug-resistant metastasis and at least four previous surgical metastasectomies
Therapy	For 20–40 min at a rate of 0.3–0.5 l/min, a mean perfusion pressure lower than the own mean pulmonary artery pressure (inflow temperature: 41 °C or higher)
Results	Median follow-up: 12 months *N* = 3: alive and disease-free (*N* = 1 death from cerebral metastasis without autopsy evidence of local recurrence 13 months following ILP)
Toxicity	No systemic drug-related toxicity, all patients experienced transient pulmonary toxicity as noncardiogenic edema of the treated lung segments
Conclusions	Hyperthermic perfusion chemotherapy can be done safely and effectively. It represents a new treatment modality and deserves further investigations for patients with advanced, drug resistant, or surgically refractory, lung sarcoma metastasis

Hendriks et al. (2006) [9]

Concept	Isolated lung perfusion with melphalan for resectable lung metastases – phase I
N	16
Inclusion criteria	Resectable pulmonary metastases only
Therapy	15, 30, 45, 60 mg melphalan at 37 or 42 °C before resection
Results	Melphalan levels:
	First four levels: all but 1 patient undetectable systemic levels at 30 min after perfusion
	Final three levels: all patients had systemic leakage (far below the levels known from IV)
	Tumor situation: all patients alive after a mean follow-up of 14 months (range, 8–33 months)
	$N=7$: recurrent metastatic disease; $N=3$: pulmonary metastases after a mean disease-free interval of 9 months (range, 7–11 months)
Toxicity	$N=1$ (level 6): postoperative bleeding (reintervention)
	$N=2$ (level 7): lung edema (grade 3 CTC) and radiographic changes resembling a chemical pneumonitis of the whole perfused lung
	Highest cardiac toxicity: CTC grade 2 (level 6). Postoperative cardiac decompensation resulting in ankle edema
Conclusions	Isolated lung perfusion with MN combined with pulmonary metastasectomy is feasible. Dose-limiting toxicity occurred at a dose of 60 mg of MN at 37 °C, and the maximum tolerated dose was set at 45 mg of MN at 42 °C

TACE

Vogl et al. (2005) [44]

Concept	Transpulmonary chemoembolization for the treatment of unresectable lung tumors
N	23
TACE	Into the right or left pulmonary artery: lipiodol + 5 mg/m^2 mitomycin C + 200 – 450 mg DSM
Inclusion criteria	Unresectable lung metastases: colorectal carcinoma ($N=6$), renal cell carcinoma ($N=2$), leiomyosarcoma ($N=2$), and other origins ($N=13$)
Therapy intervals	2–4 weeks
Results	Enhancement of iodized oil:
	Moderate to high: 30 % of the embolized metastases
	Low to moderate: 70 %
	After the final course of TPCE: decrease in the size of the treated metastases, $N=8$
	RR: mean decrease in tumor volume of 56.8 % (6.36 mL) (range: 38.90 %–78.94 %)
Toxicity	The patients tolerated the TPCE procedure well (no fatal or major complications related to this step of treatment were observed)
Conclusion	Transpulmonary chemoembolization (TPCE) could be a well-tolerated palliative treatment option in patients with pulmonary metastases

Lindemayr et al. (2007) [45]

Concept	Transpulmonary chemoembolization for the treatment of unresectable lung tumors
N	26 lung metastases
TACE	Into the right or left pulmonary artery: lipiodol + 5 mg/m^2 mitomycin C + 200–450 mg DSM
Inclusion criteria	Unresectable and refractory to prior systemic therapy, good performance status with a Karnofsky index 70 %, and uncompromised lung function. No limitations regarding tumor size, vascularity, or chest wall invasion
Therapy intervals	2–4 weeks
Response rates	PR: 35 %
	SD: 26 %
	PD: 39 %
Toxicity	Postembolization syndrome: pain, nausea, and fever (easily managed)
Conclusion	Transpulmonary chemoembolization with DSM is a well-tolerated option in the treatment of lung cancer. Multidisciplinary efforts are needed to determine the additive benefit; thus, treatment of pulmonary metastases remains a major clinical challenge

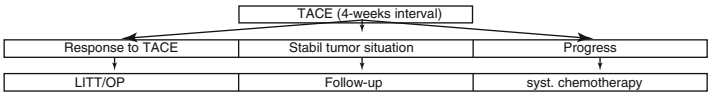
Vogl et al. (2008) [46]

Concept	Transpulmonary chemoembolization (TPCE) as a treatment for unresectable lung metastases
N	52 (106 lung metastases)
TACE	Into the right or left pulmonary artery: lipiodol + 5 mg/m^2 mitomycin C + 200–450 mg DSM
Inclusion criteria	Unresectable lung metastases: 46 patients had a mean of six metastases (range, 1 to 21), 6 patients had multiple metastases (>21) of different origins – colorectal carcinoma (*N* = 20), breast cancer (*N* = 6), renal cellular carcinoma (*N* = 5), thyroid cancer (*N* = 4), cholangiocellular carcinoma (*N* = 2), leiomyosarcoma
Therapy intervals	4 weeks (2–10 TPCEs), mean of 3.3 per patient
Results	PR: *N* = 16 (30.7 %), mean decrease in tumor volume: 56.38 % (range, 38.18 %–95.74 %)
	SD: *N* = 7 (13.5 %)
	PD: *N* = 29 (55.8 %), mean increase in tumor volume of 139.52 % (12.55 %–766.67 %)
	Mean TtP: 5.5 months (range, 1–67 months)
	Survival: mean of 17 months for all patients (95 % CI 13.7–20.2 months)
	Median survival time of all lesions: 21.1 months (95 % CI 4.2–38 months)
Toxicity	Overall, treatment was well tolerated without any major complications or even TPCE-associated mortality
Conclusion	Transpulmonary chemoembolization (TPCE) could be a well-tolerated palliative treatment option in patients with pulmonary metastases

Recommendation

Inclusion criteria:

- Size of tumor: ≤ 8 cm
- Amount of lesions: ≤ 5
- Unresectable/after systemic chemotherapy



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Head and Neck

9

Adorján F. Kovács

9.1 Introduction

The overwhelming majority of head and neck malignancies are squamous cell carcinomas of the oral cavity, pharynx, and larynx. Three modalities of therapy have established roles in the treatment of carcinoma of the head and neck: chemotherapy, radiation therapy, and surgery. The choice of modality depends upon factors such as the site and extent of the primary lesion, the likelihood of complete surgical resection, the presence of lymph node metastases, and others. Traditionally, smaller lesions (T1–T2) are quite effectively treated by either surgical excision or irradiation, whereas more advanced cancers (stage III–IV) are treated with combined modalities. In recent years, chemoradiation has become an accepted alternative to surgery and postoperative radiation therapy.

Among the many chemotherapy agents developed, cisplatin has proven efficacy on head and neck carcinomas. However, in chemotherapy trials for head and neck tumors, the highest rates for locoregional control and survival have been achieved when chemotherapy has been administered concomitantly with radiation therapy. To date, single-agent intravenous (IV) cisplatin chemoradiation still was not proven inferior to IV polychemotherapy and irradiation which offers the possibility to use cisplatin more effectively.

By increasing drug dosage, drug resistance can be overcome. However, a practical limitation to this strategy is toxicity to normal cells (mainly renal and gastrointestinal). Clinically, it is possible to deliver higher concentrations of cisplatin through pharmacologic and technical manipulations. One strategy is through intra-arterial (IA) delivery.

In the case of cisplatin, increase of plasma clearance can be accomplished by using the neutralizing agent thiosulfate. Thiosulfate reacts covalently with cisplatin to produce a complex that is still soluble but totally devoid of either toxicity or antitumor activity. The extent of reaction is a function of the concentration of both agents, and molar thiosulfate/cisplatin ratios in excess of ten are required. Thiosulfate is extensively concentrated in the urine leading to excellent protection against cisplatin-induced nephrotoxicity.

The head and neck region is particularly well suited for regional chemotherapy. Most patients who present with advanced carcinomas of the upper aerodigestive tract do not have demonstrable distant metastases. Furthermore, approximately one half of the patients have large, bulky lesions confined to one anatomic site, such as the tongue, pharyngeal wall, nasal cavity, and paranasal sinuses or larynx. Although many of these patients may have

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metastases to the regional cervical lymph nodes, it is usually uncontrolled tumor within the primary site that presents an immediate threat to life. The blood supply to these tumors is primarily derived from branches of the external carotid artery. Significant technical advances in angiography now permit repeated safe superselective micro-catheterization of the dominant nutrient artery using a coaxial approach, which serves to decrease blood flow and further increase therapeutic advantage.

The feasibility of selective IA cisplatin infusion for head and neck tumors has been established, and a number of studies have been reported. With respect to survival, randomized studies have to be considered because according to contemporary conviction only they can produce level 1 evidence. There is one such trial proving a survival benefit of *regional induction chemotherapy*. The EORTC conducted it to evaluate the role of preoperative IA chemotherapy on survival of patients with tumors of the oral cavity and oropharynx. Two hundred twenty-two eligible subjects were randomized either between surgery and preoperative IA chemotherapy. This latter group received vincristine and bleomycin from the catheter placed retrograde into the external carotid artery from the superficial temporal artery. The overall survival showed a statistically significant difference ($P = .048$) for floor of the mouth but not for posterior oral cavity and oropharynx groups. In the floor of the mouth group, median survival in the chemotherapy arm was estimated at 7 years compared with 3 years in the surgery arm. In the posterior oral cavity and oropharynx group, median survival was estimated at 3 years in both treatment arms [1].

The largest trial sequence using regional chemotherapy as *induction* for patients with oral and oropharyngeal cancers of all stages was conducted by Kovács and coworkers. They successfully integrated regional chemotherapy in a multimodality treatment and could demonstrate a survival benefit for patients with resectable tumors compared to a prognostic index [2]. They also proved that chemoembolization can safely be carried out in certain areas of the head and neck (floor of mouth, anterior oral tongue, mandibular alveolar ridge) either using degradable starch microspheres (Spherex®) or a suspension of cisplatin [3, 4]. Other agents also could be used for IA chemotherapy [5, 6].

The most comprehensive trial sequence of *intra-arterial chemoradiation* was conducted by Robbins and coworkers [7, 8]. They succeeded in accruing enough patients for valid statistical evaluation and maintained a consistent reproducible method (RADPLAT = radiotherapy and concomitant intra-arterial cisplatin). Results were impressive with regard to all possible end points, even in multicenter studies. Having started as treatment for unresectable patients, IA chemoradiation was developed as a regimen for organ preservation. Other study groups confirmed these favorable results, e.g. [9, 10]. Based on these promising results, a randomized trial was conducted in the Netherlands comparing RADPLAT with IV chemoradiation therapy [11]. Two hundred and thirty-nine subjects from five hospitals, with (functional) inoperable head and neck cancer, were randomly assigned to receive radiotherapy (70 Gy/35f for 7 weeks) combined with either four courses of IA cisplatin infusion on days 2, 9, 16, and 23 or IV cisplatin on days 1, 22, and 43. This trial could not prove a significant advantage of intra-arterial chemoradiation with respect to survival. Because a high proportion of subjects in the trial received the less effective technique of bilateral infusion, many questions remain about the value of this result. Moreover, significantly fewer problems with nausea and vomiting occurred in patients treated with IA chemoradiation, which should justify the higher interventional time and effort of IA chemotherapy as compared to the simple IV procedure.

Japan belongs to the countries with the highest experience with intra-arterial chemotherapy. It was Yokoyama who first reported superselective high-dose cisplatin infusion with simultaneous IV infusion of thiosulfate to neutralize cisplatin toxicity in 1998 in Japan. He reported that large tumors were gone with this therapy, and high-dose weekly cisplatin infusion did not cause serious side effects, which surprised Japanese head and

neck surgeons and radiation oncologists. Since then, IA chemotherapy has gained recognition and popularity again in Japan because the long history with the therapy has made it easy to accept. There are also variations of the prototypic Robbins method with reduced doses of cisplatin and new combinations and agents, e.g. [12].

Too often, the fundamental pharmacologic principles of IA therapy have been ignored, and response rates and survival have not been convincingly superior to those obtained with IV cisplatin. Enthusiasm for IA chemotherapy in head and neck cancer has also been thrown back by technical problems related to the placement of infusion catheters. Most studies involved percutaneous catheterization of the external carotid with or without implantable infusion pumps and indwelling catheters, and this was problematic because of infection and thrombosis. Significant technical advances in vascular radiology techniques now permit safe repetitive superselective catheterization of the smaller nutrient arteries of the tumor.

9.2 Study Results

Robbins et al. (2000) [7]

Concept	IA chemotherapy and radiation in stage III–IV head and neck cancer patients (Phase II; single center)			
N	213			
Inclusion criteria	Stage III–IV squamous cell carcinoma patients			
Therapy	IA, 150 mg/m^2 cisplatin; parallel IV, 9 g/m^2/30 min sodium thiosulfate followed by 12 g/m^2/12 h sodium thiosulfate (weekly for 4 weeks); concomitantly radiotherapy, 1.8–2 Gy per fraction; total dose, 68–72 Gy			
Results	Response 2 months after radiation: CR primary site, 171 of 213 (80 %)			
	Patients with clinical node-positive disease: 171 of 189 (90.5 %)			
	Median follow-up: 30 months			
	5-year overall survival: 38.8 %			
	5-year cancer-related survival: 53.6 %			
	5-year disease above the clavicles survival: 74.3 %			
Toxicity	**Parameter**	**Grade 3**	**Grade 4**	**Grade 5**
	Mucosa	54	2	
	Hematologic	14	3	
	Gastrointestinal	2		
	Neurologic	6	1	2
	Cardiovascular	7		1
	Others			3 (pneumonia)
Conclusions	IA chemoradiation is a new strategy that could offer patients an improved survival outcome while avoiding major loss of organ function			

Samant et al. (2001) [9]

Concept	Intra-arterial cisplatin and radiation by advanced head and neck patients with and without bone and cartilage invasion		
N	135: $n=45$ (group 1) with bone and cartilage invasion; $n=90$ (group 2) without bone and cartilage invasion		
Inclusion criteria	Patients with a T4 primary cancer of the head and neck with and without bone and cartilage invasion		
Therapy	IA, 4×150 mg/m^2 cisplatin; parallel IV, 9 g/m^2/15–20 min sodium thiosulfate followed by 12 g/m^2/6 h sodium thiosulfate (on days 1, 8, 15, 22); concomitant radiotherapy, 2 Gy per fraction once a day, 5 days a week; total dose, 66–74 Gy in 35 fractions during 7 weeks		
Results	**Response after chemoradiation**	**Group 1**	**Group 2**
	CR	30	64
	PR	5	10
	NR	1	2
	Not evaluable	9	14
	CR-rate	66.7 %	71.1 % n.s.
	Higher response rate in cartilage (81.2 %) than in bone (58.6 %) invasion		
	Median follow-up: 3.33 years; 2-year OS group 1 43.3 % and group 2 36.9 %		
Toxicity	3 pts. died during treatment; hematologic toxicity Grade 3 in 4 pts.; mucosal toxicity Grade 3 in 13 pts.; cerebrovascular event in 1 pt.		
Conclusions	Equivalent efficacy of IA chemoradiation treatment in the two groups head and neck cancer patients with and without bone or cartilage invasion		

Kovács et al. (2002) [3]

Concept	Chemoembolization of oral and oropharyngeal cancer using a high-dose cisplatin crystal suspension and degradable starch microspheres (DSM)				
N	32				
Inclusion criteria	Histology confirmed, previously untreated, primary squamous cell carcinomas				
Therapy	IA without DSM, 150 mg/m^2 cisplatin; parallel IV, 9 g/m^2 sodium thiosulfate (after a delay of 10 s)				
	IA with DSM, 150 mg/m^2 cisplatin; parallel IV, 9 g/m^2 sodium thiosulfate (after a delay of 10 s) at the end of the total amount of cisplatin minus 5 ml; 1 ml DSM (60 mg DSM) was mixed with 5 ml cisplatin (25 mg cisplatin) and 4 ml contrast medium and was administered until occlusion of the vessels				
	1 cycle of IA high-dose chemoembolization per patient (in case of PR max. 2 cycles)				
Results	Response rate was assessed 3 weeks after treatment				
		CR	**PR**	**SD**	**PD**	**T stage (*n*)**
	With DSM (*n* = 15)	5 (33.3 %)	8 (53.3 %)	2 (13.4 %)	0	T1 = 2; T2 = 5; T3 = 1; T4 = 7
	Without DSM (*n* = 17)	3 (17.6 %)	8 47.1 %)	6 (35.3 %)	0	T1 = 0; T2 = 4; T3 = 2; T4 = 11
	Overall (*n* = 32)	8 (25 %)	16 (50 %)	8 (25 %)	0	
Toxicity	Toxicity of chemoembolization: nausea (Grade I + II), 15.65 %; pain (Grade I + II), 71.9 %; leukocytosis (Grade I), 56.25 %; swelling (Grade I), 25 %				
Conclusions	Chemoembolization with DSM prolonged antitumor activity and increased overall response in squamous cell carcinoma patients				

Balm et al. (2004) [10]

Concept	High-dose intra-arterial cisplatin and radiation (RADPLAT) for stage IV patients with head and neck			
N	79			
Inclusion criteria	Functional unresectable stage IV patient			
Therapy	IA, 150 mg/m^2 cisplatin; parallel IV, 9 g/m^2/30 min; 12 g/m^2/2 h sodium thiosulfate (on days 2, 9, 16, 23) concomitantly radiotherapy; total dose, 70 Gy with 2 Gy fractions ($n=35$), one per day for 7 weeks			
Results	Median follow-up: 3.1 years			
	CR of primary tumors: 91 %			
	PR: in 3 patients			
	CR of neck node metastases: 90 %			
	1- and 2-year locoregional control rates: 82 and 69 %			
	Median OS time: 2.2 years, with 3-year OS probability of 43 %			
Toxicity	**Parameter**	**Grade 3 (%)**	**Grade 4 (%)**	**Grade 5 (%)**
	Hematologic	22	16	
	Nephrotoxic	0	0	
	Mucositis	43		
	Skin reactions	24		
	Gastrointestinal	57		
	Nausea	20		
	Ototoxicity	10		
	Treatment-related death			3.8
Conclusions	IA cisplatin and radiation is an effective organ-preserving therapy in unrespectable patients			

Kovács et al. (2004) [2]

Concept	Long-term survival of patients with resectable oral and oropharyngeal cancer treated with IA chemotherapy and surgery		
N	52		
Inclusion criteria	Histology confirmed, previously untreated, resectable, primary squamous cell carcinomas stages I–IV		
Therapy	IA, 150 mg/m^2 cisplatin; parallel IV, 9 g/m^2 sodium thiosulfate (after a delay of 10 s) 1–2 cycles of neoadjuvant IA chemotherapy followed by radical surgery		
Results	Response after first cycle: CR, 20 pts. (38 %); PR, 16 pts. (31 %); SD, 16 pts. (31 %)		
	Mean follow-up: 3 years		
	Mean survival time: 55 months		
	Mean disease-free survival time: 49 months		
		3 years	**5 years**
	Overall survival:	82 %	77 %
	Disease-free survival:	69 %	59 %
	TPI (treatment-dependent prognosis index) at 3 years survival: 63 % and at 5 years, 56 %		
Toxicity	Extremely low side effects only grades I–II		
Conclusions	Survival of patients treated with neoadjuvant IA chemotherapy was better than TPI		

Kovács et al. (2005) [4]

Concept	Chemoembolization using cisplatin crystals as neoadjuvant treatment of oral cancer
N	103
Inclusion criteria	Histologically proven, previously untreated primary SCC of the oral cavity and anterior oropharynx T0–T4
Therapy	IA chemoembolization, 150–300 mg/m^2 highly concentrated aqueous suspension of cisplatin with precipitation of crystals; simultaneous IV, 9 g/m^2 sodium thiosulfate (after a delay of 10 s)
Results	Overall response after one procedure: CR + PR, 73 %; SD, 24 %; PD, 3 % (only T4)
	Pathological CR after one procedure: 18.5 %
Toxicity	Post-embolization syndrome: leukocytosis, 62 %; pain, 71 %; swelling, 24 %
	Acute toxicity: hypokalemia, 26 %; hyperglycemia, 26 %; hepatic enzymes, 12 %; serum creatinine, 10 %; nausea, bilirubin, LDH, serum ferrum, 7 %; hyperuremia, 5 %; no toxicity, 17 %
Conclusions	Chemoembolization of cancer in the head and neck area can be carried out regularly and safely using this method and is highly effective

Homma et al. (2005) [12]

Concept	Rapid superselective high-dose cisplatin infusion with concomitant radiotherapy for untreated advanced head and neck cancer patients		
N	43		
Inclusion criteria	Locally advanced unresectable head and neck cancer patients or patients in which neck lymph node metastases encased the carotid artery or invaded the prevertebral fascia, without distant metastases and prior treatments		
Therapy	Superselective IA, 100–120 mg/m^2 cisplatin per week for 3–4 weeks; parallel IV, 20–24 g sodium thiosulfate as described by Robbins et al. 2000; concomitant extra-beam radiotherapy, total dose 65 Gy, 26 fractions for 6.5 weeks		
Results	Median follow-up, 21 months; 3-year progression-free rate for all patients, 68.9 %, for unresectable patients, 56.4 %; 3-year overall survival for all patients, 54 %, for unresectable patients, 39.6 %		
	Response of primary disease: 81.4 % responder, 18.6 % nonresponder		
	Response of neck disease: 81 % responder, 19 % nonresponder		
Toxicity	**Parameter**	**Grade 3**	**Grade 4**
	Anemia	2	0
	Leucopenia	12	0
	Thrombocytopenia	1	0
	Fever	5	0
	Nausea/vomiting	8	0
	Dermatitis	1	2
	Mucositis	14	2
Conclusions	Superselective IA cisplatin therapy and concomitant radiotherapy are effective, even patients with unresectable disease can be cured		

Robbins et al. (2005) [8]

Concept	High-dose IA cisplatin and concurrent radiation for head and neck carcinoma (multicenter prospective) multi-RADPLAT			
N	61			
Inclusion criteria	Squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx; stage IV, T4, N 0–3, M 0; Karnofsky performance score ≥60; age ≥18 years			
Therapy	IA, 150 mg/m^2 cisplatin; parallel IV, 9 g/m^2/3–5 min sodium thiosulfate followed by 12 g/m^2/6 h sodium thiosulfate (weekly for 4 weeks); concomitant radiotherapy: 2 Gy per fraction once a day, 5 days a week; total dose, 66–74 Gy in 35 fractions during 7 weeks			
Results	CR, 85 % at primary tumors and 88 % at nodal regions; overall CR, 80 %			
	Median follow-up: 3.9 years			
	Estimated	**1 year (%)**	**2 years (%)**	
	Locoregional control	66	57	
	Survival rate	72	63	
	DFS	62	46	
Toxicity	**Parameter**	**Grade 3 (%)**	**Grade 4 (%)**	**Grade 5 (%)**
	Hematologic	31	18	2
	Nonhematologic	56	23	3
	Mucosal	48	10	0
	CNS	7	2	0
	Infection	10	2	2
	Overall worst per pts	44	39	3
Conclusions	IA cisplatin with RT was feasible and effective in the multi-institutional setting			

Bertino et al. (2007) [5]

Concept	IA carboplatin administration followed by surgery and/or radiotherapy for advanced head and neck cancer patients: single-center five-year results		
N	46		
Inclusion criteria	Primary untreated squamous cell carcinoma patients of the upper aerodigestive tract		
Therapy	IA, 3 × 300–350 mg/m^2 carboplatin over 10–15 min every 2 weeks; CR + PR pat. had concomitant radiotherapy, 1.8–2 Gy per fraction, 5 days a week; total dose, 66–70 Gy; resectable nonresponder underwent surgery		
Results	Response 2 weeks after IA therapy: CR, 16 pat. (35 %); PR, 20 (43 %); nonresponder, 10 pat. (22 %)		
	Response after multimodality treatment: CR, 38 pat. (83 %)		
	After 5-year follow-up: alive and disease free, 18 pat. (39 %); died of a second primary tumor, 3 pat. (6.5 %); died of disease, 25 pat. (54.5 %)		
Toxicity	**Parameter**	**Grade**	**No. of patients**
	Neutropenia	2	2
	Thrombocytopenia	1	2
	Hyperbilirubinemia	4	1
	Peripheral neuropathy	3	1
	Alopecia	1–3	1
	Stomatitis	2–3	2
	Skin rash	3	1
Conclusions	IA carboplatin chemotherapy is effective, safe, and well tolerated and discriminates between responder and nonresponder and have prognostic significance for further treatments		

Damascelli et al. (2007) [6]

Concept	Intra-arterial chemotherapy with novel nanoparticle albumin-bound paclitaxel formulation in advanced head and neck cancer patients			
N	60			
Inclusion criteria	Previously untreated patients with biopsy-proven SCC of the oral cavity, oropharynx, and hypopharynx stage T3/4			
Therapy	2–4 cycles of 230 mg/m^2 as starting dosage followed by 150 mg/m^2			
Results	3 weeks after last infusion: CR, 15 pat. (25 %); PR, 30 pat. (50 %); SD, 7 pat. (11.67 %); PD, 8 pat. (13.33 %)			
Toxicity	**Parameter**	**Grade 2**	**Grade 3**	**Grade 4**
	Neurologic	2		6
	Flu like symptoms	4	1	
	Allergy	3		
	Neutropenia	11	3	2
Conclusions	IA chemotherapy with nanoparticle albumin-bound paclitaxel resulted in promising response rates; disease was rapidly controlled with a good tolerability			

Rasch et al. (2010) [11]

Concept	Intra-arterial vs. intravenous chemoradiation for advanced head and neck cancer (randomized phase 3 trial)			
N	239			
Inclusion criteria	Functionally unresectable head and neck cancer patients			
Therapy	IA, 4 × 150 mg/m^2 cisplatin; parallel IV, 9 g/m^2/15–20 min sodium thiosulfate followed by 12 g/m^2/6 h sodium thiosulfate (on days 1, 8, 15, 22); concomitant radiotherapy, total dose 70 Gy in 35 daily fractions			
	IV: 3 × 100 mg/m^2 cisplatin (on days 1, 22, 43), with the same radiotherapeutic regime			
Results	Median follow-up: 2.75 years			
	At 3 years	**IA (%)**	**IV (%)**	***p*-value**
	Local control	76	70	0.61
	Locoregional control	63	65	0.72
	DFS	44	47	0.94
	Disease-spec. survival	69	71	0.57
	Distant metastasis FS	66	69	0.51
	Overall survival	51	47	0.41
Toxicity	Renal toxicity significantly lower in the IA arm 1 % vs. 9 %			
	Hematological toxicity >Grade 2 was 52 % IA vs. 42 % IV			
	Mucosal toxicity >Grade 2 50 % IA vs. 54 % IV			
	Ototoxicity >5 dB 53 % IA vs. 58 % IV			
	Cardiac/pulmonary >Grade 2 5 pts. IA vs. 9 pts. IV			
	Neurological >Grade 2 8 pts. IA vs. 1 pts. IV			
Conclusions	Cisplatin-based IA chemoradiation was not superior to intravenous chemoradiation for advanced stage IV head and neck cancer			

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Part IV

Thermoablation

Radiofrequency Ablation for Treating Malignant Tumors to the Liver

10

Andreas H. Mahnken and Thierry de Baère

10.1 Introduction

Radiofrequency (RF) ablation like most thermal ablation techniques was initially established for treating inoperable HCC. In the face of its technical success and ease of use, the indications for RF ablation were rapidly extended, and it is now established for treating a wide range of primary and secondary liver malignancies and its use has been described in virtually all major organs.

10.1.1 HCC

RF ablation is an established competitor for surgery in the treatment of small hepatocellular carcinomas (HCC), and it is accepted for bridging the time to liver transplantation. Guidelines recommend the use of RF ablation for treating up to 3 HCC foci measuring up to 3 cm in case of contraindication to surgery [1]. RF ablation has been proven to be superior to percutaneous ethanol injection therapy [2]. The most important predictor of long-term survival is an initially complete ablation with an adequate safety margin [3]. There is some conflicting data from randomized controlled trials comparing RF ablation to surgery in small HCC [4–6]. The overall survival rates after RF ablation are quite similar to those of surgery [4, 5], but the disease-free survival is longer after resection. With overall survival being the most relevant parameter in HCC, RF ablation appears to be more or less equal to surgery in HCC tumors within the Milan criteria.

As stated above, the comparative data on RF ablation vs. resection is conflicting. A current meta-analysis comparing RF ablation and resection for HCC within the Milan criteria including 877 patients concluded that resection appears to be superior to RF ablation [7]. However, the study was based on only six studies, while other studies which should have qualified for this analysis were not included. In contrast, a recent systematic review on the same topic identified eight studies, including two prospective trials, fulfilling

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the same inclusion criteria [8]. In this systematic review, there were no differences in 1-, 3-, and 5-year overall survival in patients inside the Milan criteria [9–16], while some studies with patients outside the Milan criteria showed surgery to be superior to RF ablation alone [17, 18]. Thus, RF ablation is likely to provide similar results to surgery in patients inside the Milan criteria if performed in expert hands (Table 10.1).

In HCC the combination of RF ablation and transarterial chemoembolization (TACE) is particularly useful. There are three randomized controlled trials indicating the combination of RF ablation and TACE to be superior to RF ablation alone, although only one of these trials found a significant advantage in overall survival for the combination of RF ablation plus TACE. These findings are supported by two retrospective studies comparing RF ablation plus TACE with RF ablation alone. The same is true for recurrent HCC. In a prospective randomized trial, the sequential combination of RF ablation plus TACE was shown to result in a significantly longer overall survival, when compared to RF ablation alone in recurrent HCC [19, 20]. So far there is only limited data on the combination of TACE plus RF ablation in comparison to resection. These retrospective studies, however, indicated that the survival after a combination of embolization and RF ablation is not different from surgery, even in patients outside the Milan criteria [21–23] (Table 10.2).

10.1.2 Metastatic Liver Disease

Resection offers the best long-term survival in colorectal liver metastases with 5-year overall survival rates of about 50 % [24]. In contrast even the most recent chemotherapeutic regimen only provides a median survival of up to 22 months [25]. With only 25 % of liver metastases being resectable, thermal ablation was evaluated for treating secondary liver disease. While there is only very limited data of mostly poor quality on microwave ablation, cryoablation, and laser-induced thermal therapy, there is a huge body of data on RF ablation for treating liver metastases. Two prospective studies on RF ablation in colorectal liver metastases resulted in a median survival of 24 (percutaneous approach) and 39 months (open and percutaneous approach), respectively [26, 27]. However, there were marked differences in patient selection limiting comparability of results. In general, RF ablation results in higher local recurrence rates when compared with surgery, while survival data varies (Table 10.3). A recent meta-analysis indicated a better survival for patients undergoing resection when compared to RF ablation, but the data needs to be interpreted carefully as the raw data was only of limited quality [28]. For RF ablation, major complication rates around 7 % and local recurrence rates of 14–33 % have been reported. So far, there is almost no data on the combination of embolization and local ablation in colorectal liver metastases. A recent case series indicate this approach to be safe and worthwhile considering a 3-year survival rate of 50 % in patients deemed unresectable [29].

There is a variety of case series on thermal ablation in liver metastases from a broad variety of different tumor entities. These studies, however, are of limited value as the natural course of the different tumor entities varies significantly. Nevertheless, the available data indicates the potential benefit achievable by interventional treatment in patients who are otherwise considered unfit for surgery (Table 10.4).

Liver metastases from neuroendocrine tumors (NET) are a separate topic. In these patients cytoreductive liver surgery is well established in symptomatic patients in order to improve the quality of life [30]. This goal can also be achieved by local ablation as a less invasive approach. Consequently, encouraging results have been reported from local ablation with a median survival after ablation ranging from 29 to 72 months and relief from symptoms in more than 90 % of patients (Table 10.4).

10.2 Study Results

Table 10.1 Summary of comparative studies on RF ablation vs. resection in HCC

Author	Method	Patients (*n*)	Tumor size (cm)	Overall survival			*p*
				1 y (%)	3 y (%)	5 y (%)	
Vivarelli (2004) [17]	Surgery	79	n.a.	83	65	n.a.	0.002
	RFA	79	n.a.	78	33	n.a.	
Hong (2005) [16]	Surgery	93	2.5 ± 0.8	97.9	83.9	n.a.	0.240
	RFA	55	2.4 ± 0.6	100	72.7	n.a.	
Montorosi (2005) [31]	Surgery	40	n.a.	84	73	n.a.	0.139
	RFA	58	n.a.	85	61	n.a.	
Cho (2005) [9]	Surgery	61	3.4 ± 1	98.3	77.4	n.a.	0.77
	RFA	99	3.1 ± 0.8	95.8	80.0	n.a.	
Ogihara (2005) [32]	Surgery	47	7.4 ± 5.2	75	65	31	n.s.
	RFA	40	4.6 ± 2.9	78	58	39	
Lü (2006) [5]	Surgery	54	n.a.	91.3	86.4	n.a.	0.808
	RFA	51	n.a.	93.5	87.1	n.a.	
Chen (2006)[a] [4]	Surgery	90	n.a.	93.3	73.4	n.a.	n.s.
	RFA	90	n.a.	94.4	68.6	n.a.	
Lupo (2007) [15]	Surgery	42	4 (3–5)	91	57	43	0.824
	RFA	60	3.65 (3–5)	96	53	32	
Takahashi (2007) [12]	Surgery	53	2.5 (1–5)	n.a.	n.a.	70.4	0.561
	RFA	171	2.1 (0.7–4.8)	n.a.	n.a.	76.8	

(continued)

Table 10.1 (continued)

Author	Method	Patients (*n*)	Tumor size (cm)	Overall survival			*p*
				1 y (%)	3 y (%)	5 y (%)	
Guglielmi (2008) [18]	Surgery	91	n.a.	84	64	48	0.01
	RFA	109	n.a.	83	42	20	
Abu-Hilal (2008) [33]	Surgery	34	3.8 (1.3–5.0)	91	n.a.	56	0.302
	RFA	34	3 (2–5)	83	n.a.	57	
Hiraoka (2008) [10]	Surgery	59	2.27 ± 0.55	98.1	91.4	59.4	n.s.
	RFA	105	1.98 ± 0.52	95.1	87.8	59.3	
Huang (2010)[a] [6]	Surgery	115	n.a.	98.3	92.2	75.5	0.001
	RFA	115	n.a.	87	69.6	54.8	
Kobayashi (2009) [11]	Surgery	199	2 (0.9–3.0)	96.9	90.3	79	n.s.
	RFA	209	1.8 (0.8–3.0)	99	87.4	74.8	
Ueno (2009) [14]	Surgery	123	2.7 ± 0.1	99	92	80	0.06
	RFA	155	2.0 ± 0.1	98	92	63	
Santambrogio (2009)[a] [13]	Surgery	78	2.87 ± 1.21	93	85	54	0.163
	RFA	74	2.66 ± 1.06	88	66	41	
Nanashima (2010) [34]	Surgery	144	n.a.	n.a.	77	57	n.a.
	RFA	56	n.a.	n.a.	59	51	
Nishikawa (2011) [35]	Surgery	69	2.68 ± 0.49	100	81.4	75.6	0.259
	RFA	162	1.99 ± 0.62	95.4	79.6	63.1	
Hung (2011) [36]	Surgery	229	2.88 ± 1.06	97.3	88.2	79.3	0.009
	RFA	190	2.37 ± 0.92	96.6	77.3	67.4	

Wang (2012) [37]	Surgery	52	Very early stage	98	98	91.5	0.298
	RFA	91		96.7	89.3	72	
Wang (2012) [37]	Surgery	208	Early stage	96.1	87.8	77.2	0.088
	RFA	254		91.6	73.5	57.4	
Feng (2012)[a] [38]	Surgery	84	2.6 ± 0.8	96	87.6	74.8	0.342
	RFA	84	2.4 ± 0.6	93.1	83.1	67.2	
Peng (2012) [39]	Surgery	74	1.1 ± 0.5	90.5	70.9	62.1	0.048
	RFA	71	1.2 ± 0.6	98.5	87.7	71.9	

[a]Prospective study
y year, *n.a.* not available, *n.s.* not significant

Table 10.2 Summary of comparative studies on RF ablation in combination with embolization vs. resection in HCC

Author	Method	Patients (*n*)	Tumor size (cm)	Overall survival			*p*
				1 y (%)	3 y (%)	5 y (%)	
Maluccio (2005) [21]	Surgery	40	4.6 (1.8–7)	97	77	56	0.200
	RFA & TACE	33	4 (1.7–7)	81	70	58	
Yamakado (2008) [22]	Surgery	62	2.7 ± 1.1	97	93	81	0.870
	RFA & TACE	104	2.5 ± 0.8	98	94	75	
Kagawa (2010) [40]	Surgery	55	2.8 (1–5)	92.5	82.7	76.9	0.788
	RFA & TACE	62	2.4 (0.8–5)	100	94.8	64.6	
Tashiro (2011) [41]	Surgery	199	2.1 ± 0.63	95.6	90.9	76	0.11
	RFA & TACE	87 (69 TACE)	1.8 ± 0.52	97.6	81.4	71	

Table 10.3 Summary of studies of RF ablation in colorectal liver metastases

Author	Method	Patients (*n*)	Tumor size (cm)	Overall survival			*p*	Median survival
				2 y (%)	3 y (%)	5 y (%)		
Orshowo (2003) [42]	Surgery	20	4 (2–7)	n.a.	55.4	n.a.	n.s.	41
	RFA	25	3 (1–10)	n.a.	52.6	n.a.		37
Abdalla (2004) [43]	Surgery	190	n.a.	n.a.	73	58	0.0001	n.a.
	Surgery + RFA	101	n.a.	n.a.	43	n.a.		n.a.
	RFA	57	2.5	n.a.	37	n.a.		n.a.
Aloia (2006) [44]	Surgery	150	3 (1–7)	n.a.	79	71	0.001	n.a.
	RFA	30		n.a.	57	27		n.a.
Park (2008) [45]	Surgery	59	3.1 (0.5–8)	n.a.	n.a.	48	0.0002	56
	RFA	30	2 (0.6–4)	n.a.	n.a.	19		36
White (2007) [19]	Surgery	30	2.7 (1–5)	100	82	65	n.a.	80
	RFA	22	2.4 (1–5)	100	28	0		31
Berber (2008) [46]	Surgery	90	3.8 ± 0.2	n.a.	n.a.	40	0.35	n.a.
	RFA	68	3.7 ± 0.2	n.a.	n.a.	30		n.a.
Lee (2008) [47]	Surgery	116	3.29 (0.5–18)	n.a.	n.a.	65.7	0.227	44.7
	RFA	37	2.25 (0.8–5.0)	n.a.	n.a.	48.5		40
Hur (2009) [48]	Surgery	42	2.8 (0.6–8)	n.a.	70	60	0.026	60
	RFA	25	2.5 (0.8–3.6)	n.a.	50.1	25.5		41
Reuter (2009) [49]	Surgery	192	n.a.	n.a.	n.a.	23	n.s.	n.a.
	RFA	66	n.a.	n.a.	n.a.	21		n.a.
McKay (2009) [50]	Surgery	58	4.1 (1–14.5)	n.a.	n.a.	43	0.021	45.6
	RFA	43	3 (1–7.5)	n.a.	n.a.	23		27.6

(continued)

Table 10.3 (continued)

Author	Method	Patients (*n*)	Tumor size (cm)	Overall survival			*p*	Median survival
				2 y (%)	3 y (%)	5 y (%)		
Otto (2010)[a] [51]	Surgery	28	5 (1–14)	n.a.	67	51[a]	0.721	n.a.
	RFA	82	3 (1–5)	n.a.	60	48[a]		n.a.
Schiffman (2010) [52]	Surgery	94	5.6	92[a]	81[a]	65[a]	0.005	n.a.
	RFA	46	3.9	81[a]	64[a]	42[a]		n.a.
Lee (2012) [53]	Surgery	25	4	n.a.	n.a.	n.a.	0.017	41
	RFA	28	2.05	n.a.	n.a.	n.a.		24

[a]Prospective study

n.a. not available, *n.s.* not significant

Table 10.4 Summary of studies on RF ablation in liver metastases other than colorectal cancer

Author	Patients/lesions (*n*)	Entity	Lesion size (cm)	Overall survival			Median survival [months]
				1 y (%)	3 y (%)	5 y (%)	
Livraghi (2001) [54]	24/64	Breast	1.9 (1–6.6)	n.a.	n.a.	n.a.	n.a.
Lawes (2006) [55]	19/46	Breast	3 (1.4–7.3)	n.a.	n.a.	n.a.	n.a.
Sofocleous (2007) [56]	12/14	Breast	n.a.	n.a.	70	30	60
Gunabushanam (2007) [57]	14/16	Breast	1.9 (1.1–4)	64	n.a.	n.a.	n.r.
Jakobs (2009) [58]	43/111	Breast	2.1 (0.5–8.5)	95	68	48	58.6
Meloni (2009) [59]	52/87	Breast	2.5 (0.7–5)	68	43	27	29.9
Gillams (2005) [60]	25/189	NET	3.5 (1–9)	92	80	72	29
Mazzaglia (2007) [61]	63/384	NET	2.3 (0.5–10)	91	n.a.	48	47
Akyildiz (2010) [62]	89/547	NET	3.6 (1–10)	n.a.	n.a.	57	72
Yamakado (2005) [63]	7/16	Gastric	2.4 (2, 3)	86	n.a.	n.a.	16.5
Kim (2010) [64]	20/29	Gastric	5.1 ± 2.2	66.8	40.1	16.1	30.7
Mylona (2009) [65]	22/36	CUP	2.7 (1.1–4.8)	n.a.	n.a.	n.a.	10.9
Gervais (2006) [66]	6/6	Ovarian	2.7 (1.5–5.3)	83	n.a.	n.a.	n.r.

Of note, there were no prospective studies available
n.a. not available, *n.r.* not reached, *NET* neuroendocrine tumor, *CUP* cancer of unknown primacy

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Radiofrequency Ablation for Treating Malignant Tumors to the Lungs

11

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11.1 Introduction

Starting in 2000, a reasonable body of data on the use of RF ablation in lung tumors has evolved. Unfortunately, the quality of the data is limited with only very few prospective studies and often inhomogeneous patient populations. There is only very limited data on other thermal ablation techniques for treating lung lesions. Thus, interpretation of available data on pulmonary ablation is difficult. The following sections are designed to provide an overview on the available clinical data, based on a selective literature review. Experimental data and studies including mixed populations with primary lung cancer and metastatic disease were excluded. As the only prospective trials cover a mixture of primary and secondary lung malignancies, they were excluded from the summary tables [1, 2].

11.1.1 Bronchial Carcinoma

Small-cell lung cancer (SLC) is usually treated with systemic chemotherapy with only few patients being eligible for local treatment as salvage therapy. In contrast early non-small-cell lung cancer (NSCLC) is known to respond well to local therapy, and surgery is often performed in curative intent. In selected patients thermal ablation such as RF ablation is an alternative to surgical resection. This includes patients with a single lung after pneumonectomy, patients with very limited lung capacity, or patients otherwise unfit for surgery. It may be indicated as a salvage therapy with promising results being reported for this indication. Outcomes are favorable in early stages of disease (stage Ia/Ib) and deteriorate rapidly in stage III and IV (Table 11.1). Ideally tumor size is below 3–3.5 cm. Additional systemic therapy appears to favorably add to the prognosis. The most common complication is

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pneumothorax, which may occur in up to 63 % of patients [3], with most of these patients requiring further treatment for pneumothorax. Major complications are reported in about 2–10 % of patients with pleuritis, pneumonia and abscess being the most common complications. A case series with 1,000 RF ablations reported a major complication rate of 9.8 % with previous chemotherapy or radiation therapy being significant risk factors for pleuritis or pneumonia [4]. So far, it is hard to estimate the clinical value of RF ablation in NSCLC as comparative data are scarce (Table 11.2).

11.1.2 Metastatic Lung Disease

The acceptance of resecting lung metastases dates back to 1997, when an international registry reported actuarial 5-, 10-, and 15-year survival rates of 36, 26, and 22 %, respectively [5]. Despite several reports indicating difference in survival depending on the primary tumor's histology [6], evidence for surgical metastasectomy remains weak and is discussed controversial [7]. Overall survival after RF ablation of lung metastases appears to be very similar to surgery, where 5-year survival rates of 50.3 % in lung metastases from colorectal carcinoma, 21.7 % for sarcoma, 25 % in malignant melanoma, and 41.4 % in renal cell carcinoma were reported (Table 11.3) [6]. However, there might be a selection bias as RF ablation is typically limited to no more than 6 lesions (3 per lung) with a diameter of 3–3.5 cm. An obvious advantage of RF ablation over surgery is its potential to easily perform repeated ablations during the course of the disease.

11.2 Study Results

Table 11.1 Summary of studies on RF ablation in NSCLC

Author	Patients/ lesions	Ablations (*n*)	Tumor stage	Lesion size (mm)	Follow-up (months)	Overall survival			Median survival (months)	Local recurrence/ progression (%)	Major complications (%)
						1 y (%)	3 y (%)	5 y (%)			
						1 y (%)	3 y (%)	5 y (%)			
Fernando (2005) [8]	18/21		I–IV	28 (12–45)	14 (3–25)	80			n.r.	38	1 death
Pennathur (2007) [3]	19/n.a.		I	26 (16–38)	29 (9–52)	95			n.r.	42	63 %
Hiraki (2007) [9]	20/?	23	I	24 (13–60)	22 (2–52)	90	74		n.r.	35	6 %
Beland (2010)[a] [10]	79/79		I–IV	26 (10–55)	17 (1–72)				n.a.	38	
Hiraki (2011) [11]	50/52	52	I	21 (7–60)	37 (2–88)	94	74		67	31	6 %
Ambrogi (2011) [12]	57/59	80	I	26 (11–50)	46 (12–82)	83	40	25	33	41	5 %
Lanuti (2012) [13]	45/?	55	I	23 (7–45)	32 (2–75)		67	31	44	38	n.a.
Kodama (2012) [14]	44/51	55	I–IV	17 (6–40)	29 (1–98)	98	73	56		11	5.5

n.a. not available, *n.r.* not reached, *y* year

[a]Additional therapies brachytherapy 11 % and external beam radiation 24 %

Table 11.2 Summary of studies comparing RF ablation to surgery or chemotherapy in NSCLC

Author	Method	Patients (*n*)	Tumor stage	Lesion size (mm)	Overall survival			*p*	Median survival (months)	Local recurrence/ progression (%)	Major complications (%)
					1 y (%)	3 y (%)	5 y (%)				
Zemlyak (2010) [15]	Surgery	25	I	n.a.	n.a.	87	n.a.	>0.05	n.r.	12	0
	RFA	12		n.a.	n.a.	88	n.a.		n.r.	33	n.a.
	Cryo	27		n.a.	n.a.	77	n.a.		n.r.	11	n.a.
Kim (2012) [16]	Surgery	8	I	36±5	93	n.a.	67	0.054	28	29	n.a.
	RFA	14		30±4	88	n.a.	25		n.r.	50	0
Lee (2012) [17]	Surgery	13	I–II	38±22	86	n.a.	0	0.426	33.8	n.a.	Death *n*=1
	RFA	16		38±15	100	n.a.	19		28.2	n.a.	15
	Chemotherapy	18		52±3	78	n.a.	0	0.031	29	n.a.	n.a.
	RFA+chemo	12		46±16	100	n.a.	0		42	n.a.	15

n.a. not available, *n.r.* not reached

Table 11.3 Summary of studies on RF ablation in lung metastases from cancer of different origins

Author	Patients/ lesions	Ablations (*n*)	Entity	Lesion size (mm)	Follow-up (months)	Overall survival			Median survival (months)	Local recurrence/ progression (%)	Major complications (%)
						1 y (%)	3 y (%)	5 y (%)			
Yan (2006) [18]	55/n.a.	70	CRC	21 ± 11	24 (6–40)	85	46	n.a.	33 (4–40)	38	17
Yan (2007) [19]	30/n.a.	n.a.	CRC	n.a.	23 (5–50)	75	45	n.a.	32 (5–50)	43	13
Yamakado (2007) [20]	71/155	n.a.	CRC	24 ± 13	19 (4–42)	84	46	n.a.	31	47	20
Chua (2010) [21]	100/n.a.	n.a.	CRC	n.a.	23 (1–96)	87	50	30	36	49	23
Hamada (2012) [22]	84/141	n.a.	CRC	23 ± 14	27 (14–93)	91	45	21	34.9	28	2.2
Kim (2003) [23]	3/4	5	HCC	22 ± 5	17 (12–35)	100		n.a.	n.r.	0	n.a.
Hiraki (2011) [24]	32/83	65	HCC	14	21 (4–98)	87	57	n.a.	37.7	7	25
Shu Yan Huo (2009) [25]	9/23	25	RCC	19 (3–57)	19 (7–55)	n.a.	n.a.	n.a.	21	36	12
Soga (2009) [26]	15/26	n.a.	RCC	22 ± 14	25 (1–70)	100	100	100	n.r.	13	7
	24/109	n.a.		25 ± 15	29 (1–70)	90	52	52	n.r.	46	
Ding (2009) [27]	4/6	n.a.	Sarcoma	45 (30–50)	53 (37–83)	100	100	25	46.5 (37–83)	0	0
Palussiere (2011) [28]	29/47	n.a.	Sarcoma	9 (4–40)	50 (28–72)	92	65	n.a.	n.a.	11	59

The relatively high major complication rate is almost completely based on cases requiring chest tube due to pneumothorax after ablation

n.a. not available, *n.r.* not reached, *RCC* renal cell carcinoma

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