Eric Van Cutsem · Thomas J. Vogl
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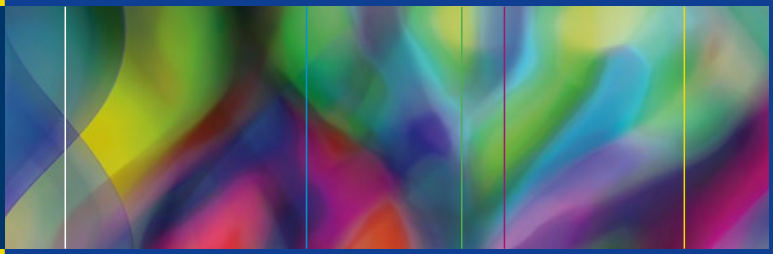

Locoregional Tumor Therapy

Second Edition

Springer

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Preface

The second edition of this booklet is an indicator for an increasing interest and broader use of the locoregional tumor therapies. According to the newest guidelines, even tumor ablation became, in addition to resection/transplantation, one of the curative approaches of the treatment of operable liver tumors. The tremendous technical progress made by interventional radiologists now allows this therapy to be performed minimally invasively. In addition to the radiofrequency and laser-based ablation systems, microwave has become another standard treatment option. Based on the accepted efficacy of the intra-arterial application of drugs in the palliation of tumors, different further developments have been established, like drug-eluting bead (DEB)- and degradable starch microspheres (DSM)-TACE. The progress includes a broader spectrum of chemotherapy agents, antibodies, mTOR inhibitors, and immunomodulators mixed with or loaded on the new embolic materials and administered to the target organ. After the failure of such a primary therapy, we are even able to change the active drug compound by keeping some of the embolic carriers, coming closer to a sequence strategy here as well. Along with this higher efficacy, the role of these therapies is changing in between the two standards of therapy consisting of surgical resection of the tumor in one side and systemic therapy on the other side. The new combinations of intra-arterial therapies with systemic administration of chemotherapy are able to prevent to some extent unfavorable outcomes related to uncontrolled extrahepatic disease. Here, we

still have to find the most optimal drug combinations, schedules, and dosages. What we have learned from systemic therapies is the importance of the release of tumor growth factors under ischemia, which has to be avoided in the locoregional therapies as well.

Another new development includes the use of organ internal radiation based on the combination of spheres loaded with radioactive agents (radioembolization). And the spectrum of these agents becomes also broader and, hopefully, more effective. Best schedules, combinations, and sequences between the different locoregional therapies have still to be found.

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 are the prerequisite for these locoregional therapies to play their important role. Also critical is their cost-effectiveness to be compared with the conventional treatments.

In this new edition, an update of the role of locoregional therapies is extensively made by experts in liver, lung, and head and neck tumors. Two additional chapters are included now—treatment of peritoneal carcinomatosis and limb perfusion. No doubt that this will allow to precise their increasing role in the larger and larger armamentarium of available treatments for malignant tumors.

Villejuif, France René Adam

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Part I
Basics of Regional Tumor Therapies

Chapter 1
Pharmacokinetic Aspects of Regional Tumor Therapy

Martin Czejka and Marie Kathrin Kitzmüller

1.1 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 1.1 gives an overview for the most relevant parameters for clinical evaluation.

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Table 1.1 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
V_d	Volume	Volume of distribution

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 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.

1.2 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 (1050 mL/min) and common hepatic artery (300 mL/min) blood flow. Therefore Q_{hep} is about 1500 mL/min (≈ 90 L/h).

1.3 Hepatic Extraction Rate (E_{hep})

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

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

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.

1.4 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, non-renal clearance by other organs (e.g., the 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 1.2).

Table 1.2 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, pk value, ionization) Metabolism (phase I and II)
Occlusion method	Means and duration of occlusion, amount of particles

Table 1.3 Pharmacokinetic parameters (after i.v. administration) of cytostatic agents that are suitable for intra-arterial administration due to their first-pass effect [4–7]

Drug	V_d [L]	Cl_{tot} [L/min]	$t_{1/2}$ [h]	Metabolism
Doxorubicin	≈1500	1.2	30	Liver
Epirubicin	≈2000	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
Paclitaxel	800	2200	50	Liver

**UF* ultrafiltrate

Despite their chemical heterogeneity, a number of different cytostatic agents can be used for regional intra-arterial treatment (see Table 1.3). 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. New investigational approaches

represent the combination of HAI irinotecan plus 5-fluorouracil, oxaliplatin, and intravenous cetuximab or bevacizumab [2, 3].

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

$$\mathrm{TA} = \frac{\dfrac{\mathrm{AUC}_{\mathrm{hep}}}{\mathrm{AUC}_{\mathrm{blood}}}\,\text{i.a.}}{\dfrac{\mathrm{AUC}_{\mathrm{hep}}}{\mathrm{AUC}_{\mathrm{blood}}}\,\text{i.v.}}$$

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

$$\mathrm{RA} = 1 + \frac{\mathrm{Cl}_{\mathrm{tot}}}{Q_{\mathrm{hep}} \times \left(1 - E_{\mathrm{hep}}\right)}$$

Regional application combines decreasing side effects and higher levels of toxicity (increased apoptosis rate) [8]. The RA gets more intense the faster the cytostatic distributes into the tissue and the higher its extraction rate from the body.

1.5 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. $\mathrm{AUC}_{\mathrm{last}}$ and C_{max} are the most suitable values for calculating the shift of the drug's concentration from the blood to the 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 [9].

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 1.4 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

Table 1.4 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	[10, 13–17]
Doxorubicin	Primary and secondary liver cancer	19	5	[18, 19]
Carmustine (BCNU)	Primary and secondary liver cancer	62	5	[11]
Fotemustine	Primary and secondary liver cancer	53	4	[20]
5-FU	Primary and secondary liver cancer	38	8	[21]
Floxuridine	Colorectal liver metastasis	34	3	[16]
Cisplatinum	Colorectal liver metastasis	38	4	[22]
Cisplatinum and sodium thiosulfate	Head and neck cancer	98	6	[23]

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 [10, 11]. Besides the chemotherapeutics given in Table 1.4, one of the most currently irinotecan is administered intra-arterial after chemoembolization as well [12]. Irinotecan (CPT-11) is a pro-drug and needs to be activated in the body. The drug shows poor affinity to the responsible enzyme (human carboxy esterase), 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.

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 1.5. 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 1.6 and 1.7. Table 1.6 gives an overview of experimental findings in animals.

Table 1.5 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	[10]
360	10	6	0.70	0.55–0.88	[13, 15]
900	5–10	11	0.61	0.47–0.80	[13, 15]
540	3	7	0.73	0.62–0.86	[15]
900	9	10	0.55	n.s.	[14]
360	10	3	0.80	n.s.	[16]
450–900	18	14	0.55	n.s.	[17]
60	20	7	No effect	n.s.	[24]

n.s. not specified

Table 1.6 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	[25]
Rat	Liver	5-FU	0.38	2.25	[26]
Rat	Liver	Doxorubicin	1.3	8.3	[27]
Rabbit	Liver	Doxorubicin	0.25	1.24	[28]
Rabbit	Liver	Doxorubicin	0.4	1.01	[29]
Rat	Liver	Tauromustine	0.47	2.16	[30]
Rabbit	Liver	Carboplatin	0.94	6.81	[31]
Rat	Lung	Carboplatin	1.19	2.11	[32]
Rat	Liver	Docetaxel	0.67	1.38	[33]

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

Table 1.7 presents data of human biopsy samples indicating that DSM leads to an increased uptake of drug into tumor tissue. Intra-arterial 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.

1.6 Further Chemoembolization Tools

Besides DSM other materials for chemoembolization have been developed recently. In transarterial 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 superadsorbent polymer microspheres (SAP, HepaSphere®, QuadraSphere®) can be loaded with a compound to become drug-eluting beads (DEB, DEBDOX, DEBIRI). In the following

Table 1.7 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 2 mCi	Secondary liver cancer	0.87 ± 0.4 (10^{-7} × CPM s/pixel) After 3 min	1.11 ± 0.5 (10^{-7} × CPM s/pixel) After 3 min	0.33 (10^{-7} × CPM s/pixel) After 3 min	0.35 (10^{-7} × CPM s/pixel) After 3 min	5	[16]
FUdR 0.15 mg/kg	Secondary liver cancer	5.9 ± 4.4 (nmol/g) After 5 min	17.1 ± 9.4 (nmol/g) After 5 min	0.16 ± 0.09 (nmol/g) After 5 min	0.63 ± 0.13 (nmol/g) After 5 min	14	[34]
DDP 25 mg/m^2	Secondary liver cancer	0.67 ± 0.5 µg/mL After 15 min	3.03 ± 1.6 µg/mL After 15 min	0.68 ± 0.6 µg/mL After 15 min	0.93 ± 0.1 µg/mL After 15 min	8	[22]
DDP 150 mg/m^2 + STS 9 g/m^2	Oral cancer	19.8 ± 4.7 µmol/L × h	89.6 ± 31.3 µmol/L × h	n.s.	n.s.	6	[23]

n.s. not specified

Table 1.8 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	[35]
	Rabbit	DEBDOX	Liver	82% after 20 min	[36]
Doxorubicin	Rabbit	QuadraSphere	Liver	54% after 10 min	[37]
Irinotecan SN-38	Sheep	DEBIRI	Lung	80% after 10 min No effect	[38]
Irinotecan SN-38	Rabbit	DEBIRI	Liver	48% from 10 to 60 min 34% after 2 h	[39]

Tables 1.8, 1.9, 1.10, and 1.11, 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 i.a. reduced systemic exposure to chemotherapy in animals and patients manifested not only in pharmacokinetic parameters but also in reduced hematological toxicity [10]. 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 neo-adjuvant medicine as evident in the following chapters.

HAI administration of superparamagnetic nanoparticles makes it possible to visualize the distribution mechanism from

Table 1.9 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 i.a. [µg/g]	Mean tumor concentration i.a. with embolization [µg/g]	Tumor/liver ratio i.a.	Tumor/liver ratio i.a. with embolization	References
Carboplatin 5 mg/kg (Embosphere)	Liver	Rabbit	4.01	20.33	1	2.5	[35]
Doxorubicin 11.25 mg (DEBDOX)	Liver	Rabbit	58	239.5	n.s.	n.s.	[36]
Doxorubicin 5 mg (DEBDOX)	Liver	Rabbit	n.s.	26.1	n.s.	17.8–16.1	[40]
Doxorubicin 4 mg (QuadraSphere)	Liver	Rabbit	153.4	196.5	n.s.	n.s.	[37]
Irinotecan 12 mg (DEBIRI) SN-38	Liver	Rabbit	0.497 0.062	0.872 0.351	n.s.	n.s.	[39]

n.s. not specified

Table 1.10 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 days (compared to conventional TACE)	[41]
Doxorubicin 25–75 mg/m^2	Drug-eluting SAP-microspheres	Unresectable HCC patients	58% after 0–3 h (compared to conventional TACE)	[42]
Oxaliplatin 25–100 mg	HepaSphere	Colorectal liver metastasis and intrahepatic cholangiocarcinoma patients	45% after 0–7 days (compared to FOLFOX)	[43]

Table 1.11 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 embolization	Control	With embolization	
Oxaliplatin 25–100 mg OEM (HepaSphere)	Colorectal liver metastasis and intrahepatic cholangiocarcinoma patients	n.s.	n.s.	1.08–1.38 (FOLFOX i.v.)	1.27–71.2	[43]
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 days	n.s.	n.s.	[44]

the blood to the liver by magnetic resonance imaging. Besides, these particles are capable of drug targeting as a drug carrier [45]. The role of Kupffer cells in drug distribution into the liver has been discussed recently [46].

Another alternative chemotherapy strategy comprises HAI plus chemoembolization plus administration of liposomal drug preparations. This has been investigated for paclitaxel [47] and fluorouracil [26] in tumor-bearing rats.

The advantage of transarterial chemoembolization (TACE) combined with drug-eluting beads (DEB) versus conventional TACE treatment has been discussed to show a lower associated toxicity, due to reduced systemic drug circulation [48].

References

1. Czejka MJ, Georgopoulos A. Pharmakokinetik. In: AKH Consilium der Medizinischen Universität Wien, Universimed Media Verlag, e-Book; 2006.
2. Lévi F, Karaboué A, Etienne-Grimaldi MC, Paintaud G, Focan C, Innominato P, Bouchahda M, Milano G, Chatelut E. Pharmacokinetics of irinotecan, oxaliplatin and 5-fluorouracil during hepatic artery chronomodulated infusion: a translational European OPTILIV study. Clin Pharmacokinet. 2017;56(2):165–77. [Epub ahead of print].
3. Said R, Kurzrock R, Naing A, Hong DS, Fu S, Piha-Paul SA, Wheler JJ, Janku F, Kee BK, Bidyasar S, Lim J, Wallace M, Tsimberidou AM. Dose-finding study of hepatic arterial infusion of irinotecan-based treatment in patients with advanced cancers metastatic to the liver. Investig New Drugs. 2015;33:911–2.
4. Austria Codex. Product information of drugs. Version 1.0-33e/2015 1048 A1PC07; 2016.
5. Ritschel W, Kearns G. Handbook of basic pharmacokinetics, including clinical application. 6th ed. Washington, DC: APhA; 2004.
6. Tsimberidou AM, Ye Y, Wheler J, Naing A, Hong D, Nwosu U, Hess KR, Wolff RA. A phase I study of hepatic arterial infusion of nab-paclitaxel in combination with intravenous gemcitabine and bevacizumab for patients with advanced cancers and predominant liver metastases. Cancer Chemother Pharmacol. 2013;71:955–63. [PubMed: 23377373].

7. Tsimberidou AM, Letourneau K, Fu S, Hong D, Naing A, Wheler J, Uehara C, McRae SE, Wen S, Kurzrock R. Phase I clinical trial of hepatic arterial infusion of paclitaxel in patients with advanced cancer and dominant liver involvement. Cancer Chemother Pharmacol. 2011;68:247–53. [PubMed: 20941597].
8. Collins JM. Pharmacologic rationale for regional drug delivery. J Clin Oncol. 1984;2:498–504.
9. Czejka MJ, Schüller J, Micksche M. In vitro interaction of interferon-alpha-2b with microspheres particles. Pharmazie. 1992;47:387.
10. Andersson M, Aronsen KF, Balch C, Domellöf L, Eksborg S, Hafström LO, Howell SB, Kåresen R, Midander J, Teder H. Pharmacokinetics of intra-arterial mitomycin C with or without degradable starch microspheres (DSM) in the treatment of non-resectable liver cancer. Acta Oncol. 1989;28:219–22.
11. Dakhil S, Ensminger W, Cho K, Niederhuber J, Doan K, Wheeler R. Improved regional selectivity of hepatic arterial BCNU with degradable microspheres. Cancer. 1982;50:631–5.
12. Morise Z, Sugioka A, Kato R, Fujita J, Hoshimoto S, Kato T. Transarterial chemoembolization with degradable starch microspheres, irinotecan, and mitomycin-C in patients with liver metastases. J Gastrointest Surg. 2006;10:249–58.
13. Ensminger WD, Gyves JW, Stetson P, Walker-Andrews S. Phase I study of hepatic arterial degradable starch microspheres and mitomycin. Cancer Res. 1985;45:4464–7.
14. Koike S, Fujimoto S, Guhji M, Shrestha RD, Kokubun M, Kobayashi K, Kiuchi S, Konno C, Okui K. Effect of degradable starch microspheres (DSM) on hepatic hemodynamics. Gan To Kagaku Ryoho. 1989;16:2818–21.
15. Gyves JW, Ensminger WD, VanHarken D, Niederhuber J, Stetson P, Walker S. Improved regional selectivity of hepatic arterial mitomycin by starch microspheres. Clin Pharmacol Ther. 1983;34:259–65.
16. Pfeifle CE, Howell SB, Ashburn WL, Barone RM, Bookstein JJ. Pharmacologic studies of intra-hepatic artery chemotherapy with degradable starch microspheres. Cancer Drug Deliv. 1986;3:1–14.
17. Czejka M, Jäger W, Schüller J, Schernthaner G. Pharmakokinetik und lokale Verfügbarkeit von Mitomycin. Einfluss von Vasokonstriktion und Chemoembolisation. Arzneimittelforschung. 1991;41:260–3.
18. Domellöf L, Andersson M, Eksborg S. Hepatic arterial chemotherapy and embolisation with degradable starch microspheres. In: Kimura K, Ota K, Carter SK, et al., editors. Cancer chemotherapy: challenges for the future. Oxford: Elsevier Science Publishers B.V.; 1989.

19. Teder H, Nilsson B, Jonsson K. Hepatic arterial administration of doxorubicin (Adriamycin) with or without degradable starch microspheres: a pharmacokinetic study in man. In: Hansen HH, editor. Antracyclines and cancer therapy. Amsterdam: Excerpta Medica; 1983.
20. Bleiberg H, Pector J, Frühling J, Parmentier N, Gerard B, Gordon B, Ings R, Solere P, Lucas C. Hepatic intra-arterial fotemustine combined with degradable starch microspheres: pharmacokinetics in a phase I-II trial. Reg Cancer Treat. 1992;4(5–6):237–43.
21. Czejka MJ, Schüller J, Jäger W, Fogl U, Weiss C, Schernthaner G. Improvement of the local bioavailability of 5-fluorouracil; I: application of biodegradable microspheres and clinical pharmacokinetics. Int J Exp Clin Chemother. 1991;4(3):161–5.
22. Civalleri D, Esposito M, Fulco RA, Vannozzi M, Balletto N, DeCian F, Percivale PL, Merlo F. Liver and tumor uptake and plasma pharmacokinetic of arterial cisplatin administered with and without starch microspheres in patients with liver metastases. Cancer. 1991;68:988–94.
23. Tegeder I, Bräutigam L, Seegel M, Al-Dam A, Turowski B, Geisslinger G, Kovács AF. Cisplatin tumor concentrations after intra-arterial cisplatin infusion or embolization in patients with oral cancer. Clin Pharmacol Ther. 2003;73:417–26.
24. Rump AFE, Woschée U, Theisohn M, Fischbach R, Heindel W, Lackner K, Klaus W. Pharmacokinetics of intra-arterial mitomycin C in the chemoembolization treatment of liver metastases with polyvinylalcohol or degradable starch microspheres. Eur J Clin Pharmacol. 2002;58:459–65.
25. Pohlen U, Reszka R, Schneider P, Buhr HJ, Berger G. Stealth liposomal 5-fluorouracil with or without degradable starch microspheres for hepatic arterial infusion in the treatment of liver metastases. An animal study in VX-2 liver tumor-bearing rabbits. Anticancer Res. 2004;24:1699–704.
26. Pohlen U, Reszka R, Buhr HJ, Berger G. Hepatic arterial infusion in the treatment of liver metastases with PEG liposomes in combination with degradable starch microspheres (DSM) increases tumor 5-FU concentration. An animal study in CC-531 liver tumor-bearing rats. Anticancer Res. 2011;31:147–52.
27. Teder H, Johansson CJ. The effect of different dosages of degradable starch microspheres (Spherex) on the distribution of doxorubicin regionally administered to the rat. Anticancer Res. 1993;13:2161–4.
28. Sigurdson ER, Ridge JA, Daly JM. Intra-arterial infusion of doxorubicin with degradable starch microspheres. Improvement of hepatic tumor drug uptake. Arch Surg. 1986;121:1277–81.

29. Thom AK, Zhang SZ, Deveney C, Daly JM. Effects of verapamil and degradable starch microspheres during hepatic artery infusion of doxorubicin. Surgery. 1990;107:552–9.
30. Teder H, Johansson CJ, d'Argy R, Lundin N, Gunnarsson PO. The effect of different dose levels of degradable starch microspheres (Spherex) on the distribution of a cytotoxic drug after regional administration to tumour-bearing rats. Eur J Cancer. 1995;31:1701–5.
31. Pohlen U, Berger G, Binnenhei M, Reszka R, Buhr HJ. Increased carboplatin concentration in liver tumors through temporary flow retardation with starch microspheres (Spherex) and gelatin powder (Gelfoam): an experimental study in liver tumor-bearing rabbits. J Surg Res. 2000;92:165–70.
32. Pohlen U, Rieger H, Meyer BT, Loddenkemper C, Buhr HJ, Heitland P, Koester HD, Schneider P. Chemoembolization of lung metastases--pharmacokinetic behaviour of carboplatin in a rat model. Anticancer Res. 2007;27:809–15.
33. Pohlen U, Buhr HJ, Berger G. Improvement of biodistribution with PEGylated liposomes containing docetaxel with degradable starch microspheres for hepatic arterial infusion in the treatment of liver metastases: a study in CC-531 liver tumor-bearing WAG RIJ rats. Anticancer Res. 2011;31:153–9.
34. Thom AK, Sigurdson ER, Bitar M, Daly JM. Regional hepatic arterial infusion of degradable starch microspheres increases fluorodeoxyuridine (FUdR) tumor uptake. Surgery. 1989;105:383–92.
35. Hong K, Kobeiter H, Georgiades CS, Torbenson MS, Geschwind J-FH. Effects of the type of embolization particles on carboplatin concentration in liver tumors after transcatheter arterial chemoembolization in a rabbit model of liver cancer. J Vasc Interv Radiol. 2005;16:1711–7.
36. Hong K, Khwaja A, Liapi E, Torbenson MS, Georgiades CS, Geschwind J-FH. New intra-arterial drug delivery system for the treatment of liver cancer: preclinical assessment in a rabbit model of liver cancer. Clin Cancer Res. 2006;12:2563–7.
37. Gupta S, Wright KC, Ensor J, van Pelt CS, Dixon KA, Kundra V. Hepatic arterial embolization with doxorubicin-loaded superabsorbent polymer microspheres in a rabbit liver tumor model. Cardiovasc Intervent Radiol. 2011;34:1021–30.
38. Baylatry M-T, Pelage J-P, Wassef M, Ghegediban H, Joly A-C, Lewis A, Lacombe P, Fernandez C, Laurent A. Pulmonary artery chemoembolization in a sheep model: evaluation of performance and safety of irinotecan eluting beads (DEB-IRI). J Biomed Mater Res B Appl Biomater. 2011;98:351–9.

39. Rao PP, Pascale F, Seck A, Auperin A, Drouard-Troalen L, Deschamps F, Teriitheau C, Paci A, Denys A, Bize P, de Baere T. Irinotecan loaded in eluting beads: preclinical assessment in a rabbit VX2 liver tumor model. Cardiovasc Intervent Radiol. 2012;35(6):1448–59.
40. Lee K-H, Liapi EA, Cornell C, Reb P, Buijs M, Vossen JA, Ventura VP, Geschwind J-FH. Doxorubicin-loaded QuadraSphere microspheres: plasma pharmacokinetics and intratumoral drug concentration in an animal model of liver cancer. Cardiovasc Intervent Radiol. 2010;33:576–82.
41. Varela M, Real MI, Burrel M, Forner A, Sala M, Brunet M, Ayuso C, Castells L, Montañá X, Llovet JM, Bruix J. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. J Hepatol. 2007;46:474–81.
42. van Malenstein H, Maleux G, Vandecaveye V, Heye S, Laleman W, van Pelt J, Vaninbroukx J, Nevens F, Verslype C. A randomized phase II study of drug-eluting beads versus transarterial chemoembolization for unresectable hepatocellular carcinoma. Onkologie. 2011;34:368–76.
43. Poggi G, Amatu A, Montagna B, Quaretti P, Minoia C, Sottani C, Villani L, Tagliaferri B, Sottotetti F, Rossi O, Pozzi E, Zappoli F, Riccardi A, Bernardo G. OEM-TACE: a new therapeutic approach in unresectable intrahepatic cholangiocarcinoma. Cardiovasc Intervent Radiol. 2009;32:1187–92.
44. Namur J, Citron SJ, Sellers MT, Dupuis MH, Wassef M, Manfait M, Laurent A. Embolization of hepatocellular carcinoma with drug-eluting beads: doxorubicin tissue concentration and distribution in patient liver explants. J Hepatol. 2011;55:1332–8.
45. Alexiou C, Jurgons R, Seliger C, Brunke O, Iro H, Odenbach S. Delivery of super-paramagnetic nanoparticles for local chemotherapy after intraarterial infusion and magnetic drug targeting. Anticancer Res. 2007;27:2019–22.
46. Ukawa M, Fujiwara Y, Ando H, Shimizu T, Ishida T. Hepatic tumor metastases cause enhanced PEGylated liposome uptake by Kupffer cells. Biol Pharm Bull. 2016;39:215–20.
47. Pohlen U, Berger G, Rieger H, Rezska R, Buhr HJ. Die Hepatisch Arterielle Infusion (HAI) mit liposomalem Taxol [3H] in Kombination mit degradierbaren Stärkemikrosphären steigert die Konzentration im CC-531 Lebertumor von WAG-Ratten. Chirurgisches Forum 2003 für experimentelle und klinische Forschung Volume 32 of the series Deutsche Gesellschaft für Chirurgie. 2003;32:165–7.
48. Angelico M. TACE versus DEB-TACE: who wins? Dig Liver Dis. 2016;48:796–7.

Chapter 2
Embolization Materials, Catheters, and Intra-Arterial Ports

Geert A. Maleux

2.1 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

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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 wash-out 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 port system, 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.

2.2 Transarterial Chemo-Infusion of Metastatic Liver Tumors [1–7]

1. *Rationale*

   (a) Liver metastases are perfused mainly by the hepatic artery, whereas normal liver tissue is primarily supplied by the portal vein.
   (b) Certain drugs have high hepatic extraction.
   (c) The liver is often the first site of metastases; eliminating liver metastases may prevent extrahepatic disease.
   (d) Many drugs have a steep dose-response disease.
   (e) Drugs with a high total body clearance are very effective.

2. *Indications*

   (a) Palliative chemotherapeutic treatment of liver-only or liver-predominant metastases, mainly as rescue for liver metastases refractory to all conventional intravenous chemotherapeutic lines.
   (b) 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.

3. *Technique*

   (a) Repeat catheterization

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

   (b) Port catheter

   - Insertion of a permanent arterial port system from the femoral or axillary artery. Before each chemotherapeutic session, patency and position of the port have to be verified. Procedure under local anesthesia.

   (c) Choice of technique depends of:

   - Experience of the interventional radiologist
   - Short interval between two sessions (<2 weeks) and many sessions foreseen (>5 sessions): port system > repeat catheterization
   - Long interval (at least 2–4 weeks) between two sessions and potentially only a few sessions foreseen: repeat catheterization > port system

4. *Which chemotherapeutic agents for which metastases?*

   (a) Mitomycin C for breast cancer-related liver metastases
   (b) Oxaliplatin for colorectal-related liver metastases
   (c) Fotemustine for ocular melanoma-related liver metastases
   (d) 5-FU + floxuridine for colorectal-related liver metastases

2.3 Chemo-Embolization of Primary and Secondary Liver Tumors [8–18]

1. *Rationale*

   (a) See chemo-infusion of metastatic liver metastases.
   (b) Addition of embolic agents:

   - Reduce the washout effect of infused chemotherapeutic agents.
   - Ischemia may induce cellular pump destruction which may lead to better uptake of cytotoxic agents by the tumoral cells.
   - Persistent ischemia may induce tumor necrosis.

2. *Indications for primary liver tumors*

   (a) First-line therapy for unresectable, liver-only hepatocellular carcinoma
   (b) Rescue therapy for cholangiocarcinoma refractory to medical management

3. *Indications for secondary liver tumors*

   (a) Rescue therapy for liver-only or liver-predominant metastases refractory to most/all conventional chemotherapeutic lines

   - Colorectal metastases
   - Neuroendocrine metastases

- Pancreatic carcinoma metastases
- Malignant melanoma metastases
- Renal cell carcinoma metastases

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

4. *Technique of chemo-embolization*

(a) Conventional chemo-embolization

- Local anesthesia
- Selective catheterization of the hepatic artery and subsequently of the feeding arteries of the tumoral lesion(s)
- Slow injection under fluoroscopic guidance of the mixture of Lipiodol (Laboratoires Guerbet, Aulnay-sous-Bois, France) and chemotherapeutic agents, like:
  - Doxorubicin
  - Cisplatinum
  - Mitomycin C
  - Combination of abovementioned agents
- 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)
    BeadBlock (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)

(b) Chemoembolization with drug-eluting beads

- Local anesthesia, except when using irinotecan-loaded microparticles (epidural or general anesthesia)
- Selective catheterization of the hepatic artery and subsequently of the feeding arteries of the tumoral lesion(s)
- Slow injection under fluoroscopic control of the mixture of drug-eluting beads and contrast medium

– HepaSphere (Merit Medical, UT, USA)

Doxorubicin
Oxaliplatin
Cisplatinum

– DC-beads (Biocompatibles, UK)

Doxorubicin
Irinotecan

– Life Pearl (Terumo, Japan)

Doxorubicin
Irinotecan

– Embozene Tandem (CeloNova, USA)

Doxorubicin
Irinotecan

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

5. *Exclusion criteria (absolute and relative contraindications)*

   (a) Absolute contraindication for chemo-embolization

   - >50% tumor involvement of the liver volume
   - Active infection
   - Liver function disturbances (bilirubin >2.5 mg/dL)
   - Macroscopic arterioportal fistula
   - Main portal vein thrombosis

   (b) Relative contraindication for chemo-embolization

   - Reduced liver function (bilirubin >1.5 > 2.5 mg/dL)
   - Child-Pugh B (drug-eluting beads are preferred)
   - Partial or distal portal vein thrombosis
   - Hepatic encephalopathy
   - ECOG >1
   - Renal insufficiency (contrast medium)

6. *Complications*

   (a) Common complications
   - Postembolization syndrome: >80%
     - Abdominal pain
     - Fever <38.5 °C
     - Nausea
     - Transient rise in liver function disturbances

   (b) Uncommon complications (<5%)

   - Liver abscess
     - Hepaticojejunostomy (Whipple operation)
     - Biliary stents

- Gallbladder necrosis
- Liver insufficiency
- Hepatorenal syndrome
- Biloma and liver necrosis with DC-beads

2.4 Radioembolization of Primary and Secondary Liver Tumors [19–25]

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.

2. *Indications*

   Primary and secondary liver tumors in patients with liver-only or liver-predominant metastatic disease:

   (a) Hepatocellular carcinoma

   - Competitive technique to chemo-embolization
   - Presence of portal vein thrombosis
   - Presence of TIPS

   (b) Metastases

   - Salvage therapy for colorectal metastases in liver-only disease
   - Salvage therapy for neuroendocrine liver metastases
   - Metastases of ocular melanoma

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"

4. *Technique*

   The yttrium-90 infusion procedure is preceded by an angiographic work-up 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-lung shunting, matching of the tumoral liver lesions and the presence or absence of extrahepatic Tc-99 uptake. In a next session, the yttrium-90 microparticles are infused through a microcatheter or an anti-reflux catheter (Surefire Medical, Westminster, CO, USA).

5. *Absolute contraindications*

   (a) Liver-lung shunt >20%
   (b) Mismatch between PET-CT and Tc-99 scintigraphy
   (c) Persistent extrahepatic TC-99 uptake
   (d) Reduced liver function (bilirubin >1.5 mg/dL)
   (e) Tumor volume >50% of the total liver volume
   (f) Significant extrahepatic disease

6. *Relative contraindications*

   (a) Liver-lung shunt >10% > 20%
   (b) Reduced liver function >1.0 > 1.5 mg/dL
   (c) Discrete extrahepatic disease

7. *Complications*

   (a) Common complications

   - Abdominal pain, fatigue (20–50%)
   - Gastroduodenal ulceration (5–10%) as a result of nontarget embolization

   (b) Uncommon complications (<5%)

   - Pancreatitis
   - Cholecystitis
   - Liver failure
   - Liver fibrosis and portal hypertension
   - Radiopneumonitis

2.5 Isolated Liver Perfusion ("Chemosaturation") [26, 27]

1. *Rationale*
   Perfusion of high concentration of chemotherapeutic agents through the liver and extraction once passed into the hepatic veins.
2. *Indications*
   Liver metastases responding to melphalan: ocular melanoma and some types of sarcoma.
3. *Technique*

   (a) General anesthesia.
   (b) 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.
   (c) Placement of a double-balloon catheter into the inferior vena cava: one balloon is placed above the inflow of the

hepatic veins, and 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. *Complications*

   (a) Device-related complications (vena cava wall dissection)
   (b) Complications related to general anesthesia
   (c) Complications related to temporary occlusion of the inferior vena cava (hypotension and related cardiac complications)
   (d) Complications related to melphalan:

   - Neutropenia
   - Thrombocytopenia
   - Anemia

   (e) Hepatic failure

2.6 Embolotherapy for Oncologic Hemorrhagic Conditions

1. *Indications*

   (a) Acute tumor-related bleeding

2. *Pathophysiology*

   (a) Intra- and peritumoral bleeding
   (b) Erosion of surrounding (large) vessel by the tumor

3. *Technique*

   (a) Distal embolization of the tumoral mass ("bland embolization") with the use of microparticles and microcoils

(b) Coil occlusion of the eroded artery
(c) Placement of a covered stent to exclude the erosion when coil embolization of the eroded vessel is not an option

- Aorta, iliac, or femoral arteries
- Subclavian, axillary, and carotid arteries
- Renal, superior mesenteric artery main branch

4. *Which tumoral lesions?*

(a) Primary and secondary liver tumors
(b) Pancreas carcinoma
(c) Renal and bladder tumor
(d) Gynecological tumors
(e) Carcinomas in head and neck region (Table 2.1)

Table 2.1 Summary of embolic agents for oncologic purposes

Embolic material	Brand name and manufacturer	Diameter of particles	Clinical indication
Non-resorbable microparticles			
Polyvinyl alcohol	Contour (Boston Scientific Corp.)	50–750 μm	Permanent occlusion adjunct for conventional chemoembolization; acute hemorrhagic conditions
Tris-acryl gelatin	PVA (Cook Medical) Embosphere—EmboGold (Merit Medical)	100–900 μm	Permanent occlusion adjunct for conventional chemoembolization; acute hemorrhagic conditions
Polyvinyl alcohol hydrogel m.	BeadBlock (Terumo)	50–900 μm	

Table 2.1 (continued)

Embolic material	Brand name and manufacturer	Diameter of particles	Clinical indication
Polyzene F-coated microspheres	Embozène (CeloNova)	50–1200 μm	
Resorbable microspheres			
Starch microspheres	EmboCept® S (PharmaCept)	35–50 μm	Mixture with chemotherapeutic drug/adjunct to conventional chemoembolization
Gelfoam	Spongostan (Ferrosan Medical Devices)		Slurry made by physician
Microspheres	Gel-bead (Vascular Solutions)		
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
	Embozene tandem (CeloNova)	40–100 μm	Chemoembolization
	LifePearl (Terumo)	100–400 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

2.7 Percutaneous, Ablative Devices and Techniques [28–38]

Most of percutaneous, ablative techniques are based on the development of heat (radio-frequency 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 needle-like 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.

1. *Indications*
2. *Radio-frequency ablation*
   (a) Primary and secondary liver tumors
   (b) Lung tumors
   (c) Kidney tumors
   (d) Bone tumors
3. *Laser ablation*
   (a) Liver tumors
4. *Irreversible electroporation*
   (a) Pancreatic tumors
   (b) Liver tumors
5. *Microwave ablation*
   (a) Liver tumors

6. *High-intensity ultrasound*
   (a) Liver tumors
   (b) Pancreatic tumors
   (c) Uterine tumors
   (d) Bone tumors

References

1. Maes T, Wildiers H, Heye S, Demey W, Maleux G, Neven P, van Oosterom AT, Paridaens R. Intra-hepatic Mitomycin C bolus infusion in the treatment of extensive liver metastases of breast cancer. Breast Cancer Res Treat. 2008;110:135–42.
2. Deschamps F, Rao P, Teriitehau C, Hakime A, Malka D, Boige V, Ducreux M, Elias D, Goere D, de Baere T. Percutaneous femoral implantation of an arterial port catheter for intraarterial chemotherapy: feasibility and predictive factors of long-term functionality. J Vasc Interv Radiol. 2010;21:1681–8.
3. Deschamps F, Elias D, Goere D, Malka D, Ducreux M, Boige V, Auperin A, de Baere T. Intra-arterial hepatic chemotherapy: a comparison of percutaneous versus surgical implantation of port-catheters. Cardiovasc Intervent Radiol. 2011;34:973–9.
4. Boige V, Malka D, Elias D, Castaing M, de Baere T, Goere D, Dromain C, Pocard M, Ducreux M. Hepatic arterial infusion of oxaliplatin and intravenous LV5FU2 in unresectable liver metastases from colorectal cancer after systemic chemotherapy failure. Ann Surg Oncol. 2008;15:219–26.
5. Kemeny N, Fata F. Hepatic-arterial chemotherapy. Lancet Oncol. 2001;2:418–28.
6. Herrmann KA, Waggershauser T, Sittek H, Reiser MF. Liver intraarterial chemotherapy: use of the femoral artery for percutaneous implantation of catheter-port systems. Radiology. 2000;215:294–9.
7. Ricke J, Hildebrandt B, Miersch A, Nicolaou A, Warschewske G, Teichgräber U, Lopez Hänninen E, Riess H, Felix R. Hepatic arterial port systems for treatment of liver metastases: factors affecting patency and adverse events. J Vasc Interv Radiol. 2004;15:825–33.

8. van Malenstein H, Maleux G, Vandecaveye V, Heye S, Laleman W, van Pelt J, Vaninbroukx J, Nevens F, Verslype C. A randomized phase II study of drug-eluting beads versus transarterial chemoembolization for unresectable hepatocellular carcinoma. Onkologie. 2011;34:368–76.
9. Maleux G, van Malenstein H, Vandecaveye V, Heye S, Vaninbroukx J, Nevens F, Verslype C. Transcatheter chemoembolization of unresectable hepatocellular carcinoma: current knowledge and future directions. Dig Dis. 2009;27:157–63.
10. Edelhauser G, Schicher N, Berzaczy D, Beitzke D, Höeller C, Lammer J, Funovics M. Fotemustine chemoembolization of hepatic metastases from uveal melanoma: a retrospective single-center analysis. Am J Roentgenol. 2012;199:1387–92.
11. Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, Pitton M, Sergent G, Pfammatter T, Terraz S, Benhamou Y, Avajon Y, Gruenberger T, Pomoni M, Langenberger H, Schuchmann M, Dumortier J, Mueller C, Chevallier P, Lencioni R. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol. 2010;33:41–52.
12. Martin RCG, Joshi J, Robbins K, Tomalty D, Bosnjakovik P, Derner M, Padr R, Rocek M, Scupchenko A, Tatum C. Hepatic intra-arterial injection of drug-eluting bead, irinotecan (DEBIRI) in unresectable colorectal liver metastases refractory to systemic chemotherapy: results of multi-institutional study. Ann Surg Oncol. 2011;18:192–8.
13. Lencioni R, de Baere T, Burrel M, Caridi JG, Lammer J, Malagari K, Martin RCG, O'Grady E, Real MI, Vogl TJ, Watkinson A, Geschwind J-FH. Transcatheter treatment of hepatocellular carcinoma with doxorubicin-loaded DC bead (DEBDOX): technical recommendations. Cardiovasc Intervent Radiol. 2012;35:980–5.
14. Martin RCG, Robbins K, Fagés JF, Romero FD, Rustein L, Tomalty D, Monaco R. Optimal outcomes for liver-dominant metastatic breast cancer with transarterial chemoembolization with drug-eluting beads loaded with doxorubicin. Breast Cancer Res Treat. 2012;132:753–63.
15. Burrel M, Reig M, Forner A, Barrufet M, de Lope CR, Tremosini S, Ayuso C, Llovet JM, Real MI, Bruix J. Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (TACE) using drug eluting beads. Implications for clinical practice and trial design. J Hepatol. 2012;56:1330–5.
16. Song MJ, Chun HJ, Song DS, Kim HY, Yoo SH, Park C-H, Bae SH, Choi JY, Im Chang U, Yang JM, Lee HG, Yoon SK. Comparative study between doxorubicin-eluting beads and conventional transarterial che-

moembolization for treatment of hepatocellular carcinoma. J Hepatol. 2012;57:1244–50.
17. Fiorentini G, Aliberti C, Tilli M, Mulazzani L, Graziano F, Giordani P, Mambrini A, Montagnani F, Alessandroni P, Catalano V, Coschiera P. Intra-arterial infusion of irinotecan-loaded drug-eluting beads (DEBIRI) versus intravenous therapy (FOLFIRI) for hepatic metastases from colorectal cancer: final results of a phase III study. Anticancer Res. 2012;32:1387–95.
18. Nabil M, Gruber T, Yakoub D, Ackermann H, Zangos S, Vogl TJ. Repetitive transarterial chemoembolization (TACE) of liver metastases from renal cell carcinoma: local control and survival results. Eur Radiol. 2008;18:1456–63.
19. Bonne L, Verslype C, Laenen A, Cornelissen S, Deroose C, Prenen H, Vandecaveye V, Van Cutsem E, Maleux G. Safety and efficacy of doxorubicin-eluting superabsorbent polymer microspheres for the treatment of liver metastases from neuroendocrine tumours: preliminary results. Radiol Oncol. 2017;51:74–80.
20. Tanaka T, Nishiofuku H, Hukuoka Y, Sato T, Masada T, Takano M, Gilbert C, Obayashi C, Kichikawa K. Pharmacokinetics and antitumor efficacy of chemoembolization using 40 μm irinotecan-loaded microspheres in a rabbit liver tumor model. J Vasc Interv Radiol. 2014;25:1037–44.
21. Pereira P, Plotkin S, Yu R, Sutter A, Wu Y, Sommer C, Cruise G. An in-vitro evaluation of three types of drug-eluting microspheres loaded with irinotecan. Anti Cancer Drugs. 2016;27:873–8.
22. Maleux G, Heye S, Vaninbroukx J, Deroose C. Angiographic considerations in patients undergoing liver-directed radioembolization with 90Y microspheres. Acta Gastroenterol Belg. 2010;73:489–96.
23. Hilgard P, Hamami M, Fouly AE, Scherag A, Müller S, Ertle J, Heusner T, Cicinnati VR, Paul A, Bockisch A, Gerken G, Antoch G. Radioembolization with yttrium-90 glass microspheres in hepatocellular carcinoma: European experience on safety and long-term survival. Hepatology. 2010;52:1741–9.
24. Gonsalves CF, Eschelman DJ, Sullivan KL, Anne PR, Doyle L, Sato T. Radioembolization as salvage therapy for hepatic metastasis of uveal melanoma: a single-institution experience. Am J Roentgenol. 2011;196:468–73.
25. Sangro B, Carpanese L, Cianni R, Golfieri R, Gasparini D, Ezziddin S, Paprottka PM, Fiore F, van Buskirk M, Bilbao JI, Ettorre GM, Salvatori R, Giampalma E, Geatti O, Wilhelm K, Hoffmann RT, Izzo F, Iñarrairaegui M, Maini CL, Urigo C, Cappelli A, Vit A, Ahmadzadehfar H, Jakobs TF, Lastoria S. Survival after yttrium-90 resin microsphere radioembolization

of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. Hepatology. 2011;54:868–78.
26. Mazzaferro V, Sposito C, Bhoori S, Romito R, Chiesa C, Morosi C, Maccauro M, Marchianò A, Bongini M, Lanocita R, Civelli E, Bombardieri E, Camerini T, Spreafico C. Yttrium-90 radioembolization for intermediate-advanced hepatocellular carcinoma: a phase 2 study. Hepatology. 2012;57(5):1826–37.
27. Hendlisz A, van den Eynde M, Peeters M, Maleux G, Lambert B, Vannoote J, de Keukeleire K, Verslype C, Defreyne L, van Cutsem E, Delatte P, Delaunoit T, Personeni N, Paesmans M, van Laethem J-L, Flamen P. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. J Clin Oncol. 2010;28:3687–94.
28. Cosimelli M, Golfieri R, Cagol PP, Carpanese L, Sciuto R, Maini CL, Mancini R, Sperduti I, Pizzi G, Diodoro MG, Perrone M, Giampalma E, Angelelli B, Fiore F, Lastoria S, Bacchetti S, Gasperini D, Geatti O, Izzo F. Multi-centre phase II clinical trial of yttrium-90 resin microspheres alone in unresectable, chemotherapy refractory colorectal liver metastases. Br J Cancer. 2010;103:324–31.
29. Maleux G, Deroose C, Laenen A, Verslype C, Heye S, Haustermans K, De Hertogh G, Sagaert X, Topal B, Aerts R, Prenen H, Vanbeckevoort D, Vandecaveye V, Van Cutsem E. Yttrium-90 radioembolization for the treatment of chemorefractory colorectal liver metastases: technical results, clinical outcome and factors potentially influencing survival. Acta Oncol. 2016;55:486–95.
30. Pingpank JF, Libutti SK, Chang R, Wood BJ, Neeman Z, Kam AW, Figg WD, Zhai S, Beresneva T, Seidel GD, Alexander HR. Phase I study of hepatic arterial melphalan infusion and hepatic venous hemofiltration using percutaneously placed catheters in patients with unresectable hepatic malignancies. J Clin Oncol. 2005;23:3465–74.
31. Maleux G, Monbaliu D, Verslype C, Casteleyn C, van de Velde M, Cornillie P, Hoogeveen Y, van Cutsem E. Percutaneous isolated liver perfusion with occlusion balloons and a catheter-based stent-graft-like perfusion device: an experimental study in a porcine model. Eur Radiol. 2010;20:2372–80.
32. Wijlemans JW, Bartels LW, Deckers R, Ries M, Mali WPTM, Moonen CTW, van den Bosch MAAJ. Magnetic resonance-guided high-intensity focused ultrasound (MR-HIFU) ablation of liver tumours. Cancer Imaging. 2012;12:387–94.
33. Leslie T, Ritchie R, Illing R, Ter Haar G, Phillips R, Middleton M, Bch B, Wu F, Cranston D. High-intensity focused ultrasound treatment of

liver tumours: post-treatment MRI correlates well with intra-operative estimates of treatment volume. Br J Radiol. 2012;85:1363–70.
34. Gervais DA, Arellano RS. Percutaneous tumor ablation for hepatocellular carcinoma. Am J Roentgenol. 2011;197:789–94.
35. Pathak S, Jones R, Tang JMF, Parmar C, Fenwick S, Malik H, Poston G. Ablative therapies for colorectal liver metastases: a systematic review. Color Dis. 2011;13:e252–65.
36. Hompes D, Prevoo W, Ruers T. Radiofrequency ablation as a treatment tool for liver metastases of colorectal origin. Cancer Imaging. 2011;11:23–30.
37. Lencioni R, Crocetti L. Local-regional treatment of hepatocellular carcinoma. Radiology. 2012;262:43–58.
38. Khan NA, Baerlocher MO, Owen RJT, Ho S, Kachura JR, Kee ST, Liu DM. Ablative technologies in the management of patients with primary and secondary liver cancer: an overview. Can Assoc Radiol J. 2010;61:217–22.

Part II
Intra-arterial Therapies: Liver

Chapter 3
HCC

Franco Orsi

3.1 Introduction

Hepatocellular carcinoma (HCC) ranks among the most common cancers worldwide, representing the sixth most common one, 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

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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.

3.2 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, and then a panel of experts reported, for the first time, noninvasive criteria (see Fig. 3.1) for HCC, based on a combination of imaging and laboratory findings [8]. The dynamic radiological contrast enhance-

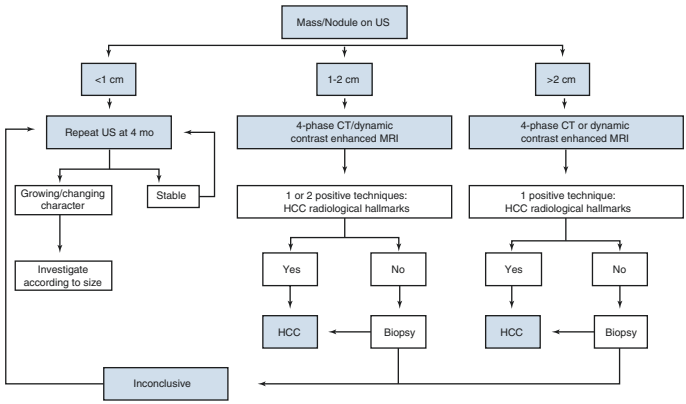

Fig. 3.1 Diagnostic algorithm for HCC in cirrhotic patients [8]

ment 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 and on the underlying liver impairment due to the cirrhosis: 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), microwaves (MWA) ablation, and transarterial embolization and chemoembolization (TACE/TAE), transarterial radioembolization (TARE), play a vital role in the management of different stages of disease and also in pre- and perioperative transplant patients.

3.3 Staging Systems

Disease staging is particularly important in the management of HCC because it helps to predict prognosis and determine appropriate treatment options. The conventional tumor-node-metastasis (TNM) classification of solid tumors, failed to be considered as reference system as in other fields, because of the two coexisting disease in the liver, even if its prognostic value could be taken in consideration, also for non-operated tumors [9, 10]. The most effective staging systems have to incorporate information about both cancer stage and liver function, which is often affected by the underlying liver disease. The Child-Turcotte-Pugh (CTP = TAB IIa/IIb) model is exclusively an assessment of liver function and is intended to predict prognosis and stratify disease severity, to facilitate transplant allocation [11]. 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 [12, 13]. MELD was originally developed at the Mayo Clinic and at that point was called the "Mayo End-stage Liver Disease" score [14]. It was derived from 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 [15–18]. 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-Clínic 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 (Fig. 3.2) [19–21]. 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). 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 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, mainly for its practical aspect and for being the only one linked to the treatment algorithm. BCLC has become the reference classification in daily clinical practice and for clinical trials in Western countries, and it is endorsed by EASL (European Associations for the Study of the Liver) and AASLD (American Association for the Study of Liver Diseases). However BCLC stage B and C include a wide range of different tumors even if only referred to TACE as the only therapeutic option. For that reason a complementary score system (NIACE) has been proposed by some experts in order to extend the indications for surgery (BCLC B) or for transarterial chemoembolization (BCLC C) [10] (Tables 3.1 and 3.2).

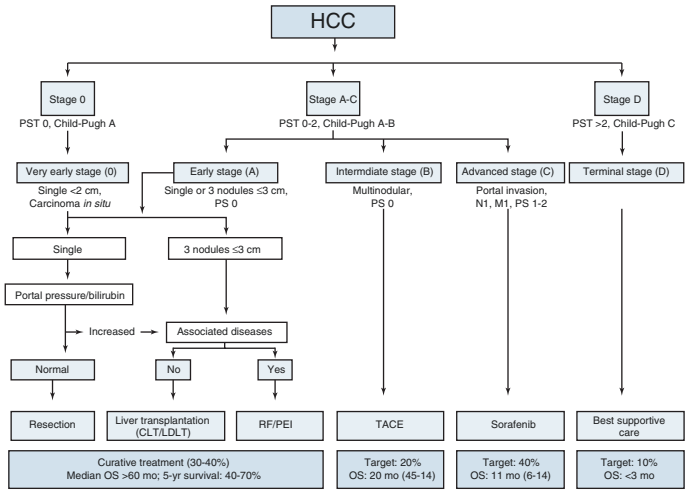

Fig. 3.2 Updated BCLC staging system and treatment strategy, 2011. Reproduced from [22]

Table 3.1 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 three indicating the most severe liver function impairment [23]

Table 3.2 Child-Pugh score classification

Points	Class	1-year survival (%)	2-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

3.4 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 well established 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-year survival expectation of 50%.

3.5 Therapy

In oncology, the benefits of treatments should be assessed through randomized controlled trials and meta-analysis. Few medical interventions have been systematically 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 therapies 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 Fig. 3.3.

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 specific clinical characteristics and imaging findings and to the international guidelines; treatment strategies should be adapted to local regulations and/or team capacities and cost-benefit strategies. The ideal treatment option, for a specific

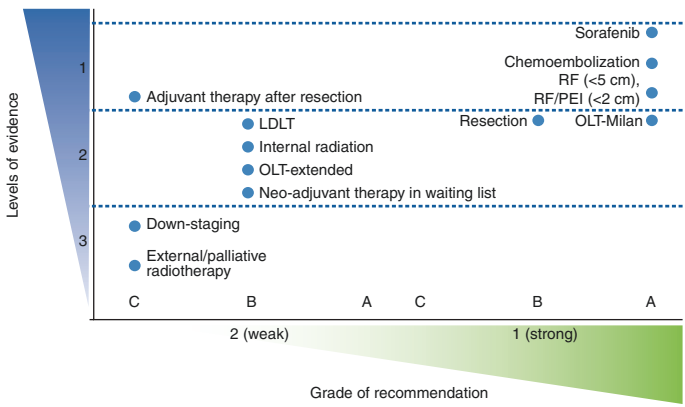

Fig 3.3 Representation of EASL–EORTC recommendations for treatment according to levels of evidence (NCI classification) and strength of recommendation (GRADE system) [24]

patient with HCC, is determined based on the burden of tumor and extent of underlying liver disease.

3.5.1 Surgical Approach

Liver resection or transplantation have been considered the best treatment options, with curative intent, for patients with HCC until the role of hepatic ablative therapies has emerged as effective curative option. A recent meta-analysis of about 8500 patients, with a 10-year perspective, showed that in patients with very early HCC and Child-Pugh class A, RFA provides similar life expectancy and quality-adjusted life year at a lower cost compared with resection [25]. However, surgical resection is still widely considered as the primary treatment in carefully selected patients with HCC. With the advances in surgical and interventional radiology techniques (such as preoperative portal vein embolization), 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 60–76%, with a perioperative mortality of 1.3–3% and blood transfusion requirements of less than 10% [26–31]. Anatomic resections, aiming at 2 cm margins, provide better survival outcome than narrow resection margins <1 cm [32] and are 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, number of microsatellites, and vascular invasion [33].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 [34]. Five-year survival rates 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. A recent meta-analysis, however, demonstrated that OS and DFS were better in hepatic resection with postoperative TACE group than in hepatic resection without postoperative TACE group. The same paper revealed not advantages in using TACE as a neoadjuvant therapy before liver resection [35].

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 [36]. Following these criteria and according to modern standards, perioperative, 1-year, 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-year survival expectation: 60–80%.

3.5.2 Systemic Therapy

Systemic chemotherapy does not play a central role in the treatment of HCC, due to the issue of a 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 (SHARP) demonstrated an advantage in the median overall survival (10.7 vs. 7.9 months) and the median time to radiological progression (5.5 vs. 2.8 months) Sorafenib group [37].

3.5.3 Minimally Invasive Locoregional Therapies

Locoregional hepatic tumor therapies include intra-arterial, percutaneous, and external therapies and the guidelines of the Liver Cancer Study Group of Japan (JSH 2014), is the only treatment algorithm including all the available local therapeutic techniques, for the wide range of clinical appearances of patients affected by HCC (Fig. 3.4).

Intra-arterial Therapies:

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

Percutaneous Therapies:

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

External Therapies:

1. External Beam Radiation Therapy (EBRT)
2. High-intensity focused ultrasound

Intra-Arterial Therapies:

Clinical conditions:

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

3.5.3.1 Hepatic Arterial Infusion (HAI)

Chemotherapeutic agents: 5-Fluorouracile, Cisplatinum/Oxaliplatin, 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 [39]. 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 blood stream. 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**); meanwhile this therapy is indicated by the guidelines of the Liver Cancer Study Group of Japan (JSH 2014) for patients with portal vein invasion at the main portal branch (Fig. 3.4) [38].

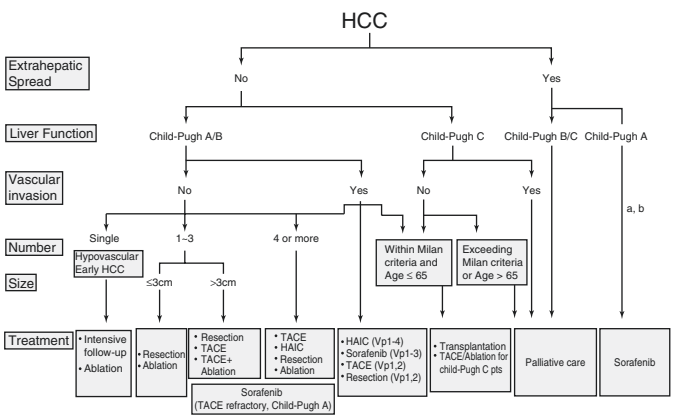

Fig. 3.4 Consensus-based treatment algorithm for hepatocellular carcinoma revised in 2014 [38]

3.5.3.2 Transarterial Chemoembolization (TACE)

Chemotherapeutic agents: Doxorubicin, Cisplatinum, Mitomycin C.

Chemoembolization is the most widely used primary treatment for unresectable HCC [34, 40, 41] and the recommended first-line therapy for patients at intermediate stage of the disease [22, 42, 43]. 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 conventional TACE (cTACE), drug-eluting beads TACE (DEBTACE), and bland embolization (TAE and micro-bland TAE).

– cTACE combines transcatheter delivery of chemotherapy emulsified 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, among supporting care, were obtained for the first time in two studies, both published in 2002 [44, 45].

Meta-analysis of some RCTs showed a beneficial survival effect of TAE/cTACE in comparison to the control group [43]. 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 [46], if the technique is not carried out with a super-selective way. There is no good evidence for which is the best chemotherapeutical agent and the optimal re-treatment strategy. Super-selective chemoembolization is recommended to minimize the ischemic insult to non-tumoral tissue, enhancing the therapeutic effect. Hepatic resection, RFA, and cTACE have been recently compared regarding the long-term survival, and it was found that a 5-year OS with cTACE was similar to the other two local treatments, in patients with single-nodule HCC of 3 cm or smaller without vascular invasion. The authors also suggested that special care should be taken to obtain a complete response when cTACE is used as an initial treatment [47]. 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 micro-catheters, a super-selective embolization of tumor-feeding arteries should 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 super-selective embolization, TACE is not without risks. Complications may range from post-embolization syndrome (of variable intensity) to liver abscesses, hepatic insufficiency, ischemic cholecystitis, or cases of death that have even been also described. The use of cone-beam CT or fluoro-CT hybrid devices during the intra-arterial techniques, also

can improve the efficacy and safety of chemoembolization, positively affecting the prognosis of HCC patients [48].

– 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 [49]. However, a randomized phase II study comparing TACE and DEBTACE reported a nonsignificant trend of better antitumoral effect [50] [295r] in the latter arm. Two recent meta-analyses comparing DEBTACE with cTACE concluded that both techniques lead to similar clinical response and tolerance [51, 52].

3.5.3.3 Transarterial Embolization (TAE)

In the majority of published studies on HCC treatment with TAE, the reported embolic agent is gelatin 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 gelatin microspheres, are available. Even if there is no evidence for a better survival benefit from DEBTACE 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 [53–56]. Few papers on HCC treatment with TAE, using very small particles, reported an interesting safety profile with local results comparable with DEBTACE/TACE series [57]. A retrospective study, comparing TAE and DEBTACE in patients waiting for liver transplantation, demonstrated no differences in outcomes of the two treatments [58]. However, based on data coming from old papers on TAE with gelatin sponge, **BCLC doesn't recommend the use of TAE for HCC.** A recent randomized clinical trial comparing TAE and DEBTACE reported no apparent difference, between the two treatment arms, in terms of response, PFS, or OS. The authors also supported the use of TAE as a reasonable therapeutic option and an alternative to the DEBTACE with doxorubicin-loaded microspheres, according to the comparable safety profile, progression rate, and survival [59].

3.5.3.4 Y90 Radio Embolization (Y90RE)

Radioembolization is defined as the infusion of very small (<40 μm) microspheres containing yttrium-90 (90Y) [60–62] 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 [61]. 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 [61–63]. Objective response rates ranged from 35 to 50% [60–62]. Around 20% of patients present liver-related toxicity and 3% treatment-related death [60]. 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. Only retrospective analyses are available, reporting approximately equivalent survivals after TACE and TARE. However, in a recent meta-analysis, the adjusted indirect comparison of DEBTACE versus TARE for hepatocellular carcinoma revealed a median overall survival longer for DEBTACE (22.6 vs. 14.7 months), with no significant difference in tumor response rate [64].

Further research trials are needed to establish a competitive efficacy role in this population **(BCLC = evidence 2A; recommendation 2B).**

3.5.3.5 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 [65]. 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 efflu-

ent 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.

3.5.4 *Study Results: Neoadjuvant Therapies (HAI/Chemoembolization)*

Author	*N*	Concept[a]	Intra-arterial therapy	RR (%)	Median survival (months)	Years survival (%)
Gerunda et al. [66]	89	TACE + LR vs. LR vs. TACE	1×: 50 mg epirubicin + Gelfoam	ND	Overall survival: TACE + LR vs. TACE/LR: $p < 0.05$	1 year: 85 vs. 71 vs. 68 5 years: 43 vs. 38 vs. 0
Graziadei et al. [67]	48	TACE + LT	70 mg epirubicin + lipiodol (+/−PVA particles) Every 6–8 weeks	CR: 30 PR: 67	ND	1 year: 98 2 years: 98 5 years: 94
Yao et al. [68]	30	TACE+/− RFA+/− PEI + LT	ND	Down staging: 70	ND	1 year: 89 2 years: 82
Bharat et al. [69]	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: significant advantage for neoadjuvant therapy	5y OS(%): 82 vs. 52 (no difference in pT0 and pT1)	ND

(continued)

(continued)

Author	*N*	Concept[a]	Intra-arterial therapy	RR (%)	Median survival (months)	Years survival (%)
Obed et al. [70]	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. [71]	48	TACE + LITT	10 mg/m^2 MMC + lipiodol + DSM 3× every 4 weeks	CR: 67 SD: 25 PD: 8	36	ND
Hoffmann et al. [72]	208	TACE +/− sorafenib + LT	4× carbo-DDP + lipiodol			
Zhou et al. [73]	108	TACE vs. control	3× 1000 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 year, 3 years, 5 years): 49, 26, 13 vs. 39, 21, 9 OS (1 year, 3 years, 5 years): 73, 40, 31 vs. 70, 32, 21 $p > 0.05$
Choi et al. [74]	16	TACE + radiation + LR	50 mg doxorubicin + lipiodol + Gelfoam Median: 3×/ patient	12 CR: 0 PR: 2 PD: 3	13	ND
Schaudt et al. [75]	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
Wang et al. [76]	MA 257	TACE + LR vs. LR	cTACE	ND	ND	5y OS = in two groups

(continued)

Author	*N*	Concept[a]	Intra-arterial therapy	RR (%)	Median survival (months)	Years survival (%)
Yu et al. [77]	MA 1347	TACE + LR vs. LR	cTACE	5y DFS > in TACE + LR	ND	ND
Si et al. [78]	MA 430	TACE + LR vs. LR	cTACE	ND	ND	5y OS = in two groups

[a]*LR* liver resection, *LT* liver transplantation, *RFA* radiofrequency ablation, *LITT* laser-induced thermotherapy, *MA* meta-analysis

3.5.5 *Study Results: Adjuvant Therapy (HAI/ Chemoembolization)*

Author	*N*	Concept	Intra-arterial therapy	Median survival (months)	Years survival/DfS (%)
Lai et al. [79]	66	LR + TACE + IV chemotherapy vs. LR (control)	3 × 10 mg cisDDP + lipiodol + 40 mg/m^2 doxorubicin IV every 2 months	ND	DfS (1, 2, 3 years): 50, 36, 18 vs. 69, 53, 48 ($p = 0.04$)
Ono et al. [80]	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/day 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 year): 37, 28 vs. 42, 26 $p = 0.324$

(continued)

(continued)

Author	*N*	Concept	Intra-arterial therapy	Median survival (months)	Years survival/DfS (%)
Wen et al. [81]	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 year: 11 3 years: 7 5 years: 5
Li et al. [82]	131	A: LR vs. B: LR + TACE vs. C: LR + TACE + PVC[a]	3 × 30 mg doxorubicin + 20 mg mitomycin +80–100 mg cis- or carbo-DDP + lipiodol	ND	DfS (1, 3, 5 year): 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. [83]	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 years): 51, 34, 22 vs. 33, 17, 9
Zhou et al. [73]	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 years): 56, 19, 18 vs. 81, 33, 23
Zhong et al. [84]	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
Cheng et al. [85]	909	(MA) LR + TACE vs. LR	Doxorubicin, epirubicin, MMC, 5-FU, carbo-DDP + lipiodol +/− Gelfoam	ND	5y OS/DFS > in TACE + LR group

[a]*PVC* portal vein chemotherapy

3.5.6 Study Results: Palliative Therapy

Llovet et al. (2002) [45]:

Concept	TAE vs. TACE vs. BSC
N	112 (37 vs. 40 vs. 35)
Therapy	TA(C)E: Gelfoam +/−75, 50 oder 25 mg/m^2 doxorubicin + Lipiodol
Frequency	Every 2 and 6 month, then every 6 month
Median survival (month)	25 vs. 29 vs. 18
	1, 2, 3 year (%): 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) [86]:

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 month
	2 year (%): 45
Toxicity (%)	pain (44), nausea (44), vomiting (22), fever (44), leucopenia (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) [87]:

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 year: 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) [88]:

Concept	(1) TACE + PEI vs. (2) PEI vs. (3) PEI after TACE vs. (4) PEI after BSC
N	101
Therapy	PEI: 96% steriler 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 year: 73%, 47% 1, 3, 5 year (%):(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× leukopenia, 1× pancytopenia, 2× dissection of A. hepatica, 1× liver failure (reversible), 1× inguinal hematoma) 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) [41]:

Concept	Prospective cohort study of TACE
N	8510
Therapy	Doxorubicin + cisDDP + lipiodol + Gelfoam
Frequency	ND
Median survival	1-, 3-, 5- und 7-Jahresüberleben (*N* = 8510): 82%, 47%, 26%, 16% Stadium T2 1-, 3- und 5-Jahresüberleben (*N* = 2934): 90%, 57%, 32% Stadium T3 1-, 3- und 5-Jahresüberleben (*N* = 2949): 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) [89]:

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 year, 2 year, 3 year: 75%, 59%, 41% OS 26 month
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) [90]:

Concept	TACE after TAE
N	13
Therapy	d1: 4–8 mg MMC + DSM followed by 1250 mg 5-FU + 25–50 mg cisDDP 125 mg FA d7: 1250 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 year (%): 100, 29, 10 Median survival (month): 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) [60]:

Concept	HAI of ^{90}Y (single-center prospective)
N	291
Therapy	1–5 dosages (100–120 Gy/therapy), glass–based device
Results	TTP: 8 months OS (BCLC B vs. Child-Pugh A): 17 vs. 14 months 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) [91]:

Concept	Comparison of TACE and HAI ^{90}Y (single-center 2 cohort experience analyses, 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 months, CR: $N = 3$, PR: $N = 8$; OS: 27.5 months
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) [50]:

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) [92]:

Concept	HAI + IFN-α (s.c.)
N	55
Therapy	d1–5, 8–12: 300 mg/mm^3/d 5-FU + 3x/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 year, 3 years (responders): 83, 31 Median survival (months): 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) [93]:

Concept	Comparison of TACE and HAI ^{90}Y (single-center 2 cohort experience analyses, 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 month, CR: *N* = 3, PR: *N* = 8; OS: 27.5 month
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) [94]:

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 year, 2 year (%): 38, 16 OS: 7 months
Toxicity (*N*)	Anorexia, nausea, fatigue, liver enzymes (grade III + IV)
Conclusion	Safe and well-tolerated therapy for this special group of patients

Gao et al. (2016) [95]:

Concept	TACE vs. TACE + HAI
N	29 TACE vs. 45 TACE + HAI
Therapy	TACE = 40 mg epirubicin; HAI = OXA + CF + 5FU
Frequency	Every 4–6 weeks
RR	TACE = ORR 45.9%; DCR 70.3% TACE + HAI = ORR 68.9%; DCR 86.7%
Survival	mPFS = 8 month (TACE + HAI) vs. 4.5 month (TACE)
Toxicity (*N*)	More common in TACE + HAI
Conclusion	TACE + HAI may be safe and more effective than TACE alone for inoperable HCC

Bonomo et al. (2010) [57]:

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 year, 2 year (%): 96, 92
Toxicity (*N*)	No/very low Post Embolization Syndrome
Conclusion	Safe and well-tolerated therapy with very high local results and survival benefits

Brown et al. (2016) [59]:

Concept	TAE vs. DC beads in HCC
N	51 pts. TAE vs. 50 pts. DC beads
Therapy	Microparticles (100–300 μm) without drug (TAE) or with doxo (DC beads)
Frequency	On demand, according to the imaging follow-up @ 3 months
Results (RECIST)	No difference between TAE and DC beads in any measure, including PFS or response rate, at any time point
Toxicity (*N*)	No difference
Conclusion	TAE should continue to be considered a reasonable therapeutic option and an alternative to embolization with doxorubicin-loaded microspheres

Ibrahim et al. (2011) [96]:

Concept	Down staging 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 months (censored) PfS: 10 months
Toxicity	Fatigue: 50%, bilirubin (grade III): $N = 1$
Conclusions	^{90}Y appears to be a feasible, safe, and effective treatment with unresectable caudate lobe HCC

Zhang et al. (2015) [97]:

Concept	TARE vs. TACE (meta-analysis)
N	(8 studies) 1499 pts.: 1048 TACE and 451 TARE for HCC
Inclusion criteria	Unresectable HCC in child A patients
Results	3 year OS better in TARE groups

Toxicity	No statistical difference between groups on any complications
Conclusions	Due to a better 3-year OS, TTP, hospitalization time, and some complications, the use of TARE (Y90) for HCC patients is to be considered promising

Lobo et al. (2016) [98]:

Concept	TARE vs. TACE (meta-analysis)
N	(5 studies) 553 pts.: 284 TACE and 269 TARE for HCC
Inclusion criteria	Unresectable HCC
Results	4 year OS no difference; CR and PR no difference
Toxicity	No difference in fever, nausea, and vomiting
Conclusions	TARE appears to be a safe alternative treatment to TACE in patients affected by unresectable HCC

References

1. IARC. Globocan Estimated cancer Incidence, Mortality, Prevalence and Disability-adjusted life years (DALYs) Worldwide in 2008. 2011. http://www-dep.iarc.fr/. Accessed 1 Nov 11.
2. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med. 1999;340:745–50.
3. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2002;55:74–108.
4. Sangiovanni A, Prati GM, Fasani P, Ronchi G, Romeo R, Manini M, Del Ninno E, Morabito A, Colombo M. The natural history of compensated cirrhosis due to hepatitis C virus: A 17-year cohort study of 214 patients. Hepatology. 2006;43:1303–10.
5. Ripoll C, Groszmann RJ, Garcia-Tsao G, Bosch J, Grace N, Burroughs A, Planas R, Escorsell A, Garcia-Pagan JC, Makuch R, Patch D, Matloff DS. Hepatic venous pressure gradient predicts development of hepatocellular carcinoma independently of severity of cirrhosis. J Hepatol. 2009;50:923–8.

6. Masuzaki R, Tateishi R, Yoshida H, Goto E, Sato T, Ohki T, Imamura J, Goto T, Kanai F, Kato N, Ikeda H, Shiina S, Kawabe T, Omata M. Prospective risk assessment for hepatocellular carcinoma development in patients with chronic hepatitis C by transient elastography. Hepatology. 2009;49:1954–61.
7. Jung KS, Kim SU, Ahn SH, Park YN, Kim DY, Park JY, Chon CY, Choi EH, Han K-H. Risk assessment of hepatitis B virus-related hepatocellular carcinoma development using liver stiffness measurement (FibroScan). Hepatology. 2011;53:885–94.
8. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E, Pagliaro L, Colombo M, Rodés J. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol. 2001;35:421–30.
9. Kee KM, Wang JH, Lee CM, Chen CL, Changchien CS, Hu TH, Cheng YF, Hsu HC, Wang CC, Chen TY, Lin CY, Lu SN. Validation of clinical AJCC/UICC TNM staging system for hepatocellular carcinoma: analysis of 5,613 cases from a medical center in southern Taiwan. Int J Cancer. 2007;120:2650–5.
10. Adhoute X, Penaranda G, Raoul JL, Le Treut P, Bollon E, Hardwigsen J, Castellani P, Perrier H, Bourlière M. Usefulness of staging systems and prognostic scores for hepatocellular carcinoma treatments. World J Hepatol. 2016;8(17):703–15.
11. Christensen E, Schlichting P, Fauerholdt L, Gluud C, Andersen PK, Juhl E, Poulsen H, Tygstrup N. Prognostic value of Child-Turcotte criteria in medically treated cirrhosis. Hepatology. 1984;4:430–5.
12. Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, Kremers W, Lake J, Howard T, Merion RM, Wolfe RA, Krom R. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology. 2003;124:91–6.
13. Ravaioli M, Grazi GL, Ballardini G, Cavrini G, Ercolani G, Cescon M, Zanello M, Cucchetti A, Tuci F, Del Gaudio M, Varotti G, Vetrone G, Trevisani F, Bolondi L, Pinna AD. Liver transplantation with the Meld system: a prospective study from a single European center. Am J Transpl. 2006;6:1572–7.
14. Mayo End-Stage Liver Disease Score. www.mayoclinic.org/meld/mayomodel6.html. Accessed 20 Mar 2013.
15. Freeman RB, Edwards EB. Liver transplant waiting time does not correlate with waiting list mortality: implications for liver allocation policy. Liver Transpl. 2000;6:543–52.

16. Institute of Medicine. Analysis of waiting times. In: Organ Procurement and Transplantation: Current Policies and the Potential Impactof the DHHS Final Rule. Washington, DC: National Academy Press; 1999.
17. Organ Procurement and Transplantation Network-HRSA. Final rule with comment period. Fed Regist. 1998;63(63):16296–338.
18. Freeman RB, Wiesner RH, Harper A, McDiarmid SV, Lake J, Edwards E, Merion R, Wolfe R, Turcotte J, Teperman L. The new liver allocation system: moving toward evidence-based transplantation policy. Liver Transpl. 2002;8:851–8.
19. Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis. 1999;19:329–38.
20. Cillo U, Vitale A, Grigoletto F, Farinati F, Brolese A, Zanus G, Neri D, Boccagni P, Srsen N, D'Amico F, Ciarleglio FA, Bridda A, D'Amico DF. Prospective validation of the Barcelona Clinic Liver Cancer staging system. J Hepatol. 2006;44:723–31.
21. Wong R, Frenette C. Updates in the management of hepatocellular carcinoma. Gastroenterol Hepatol (N Y). 2011;7:16–24.
22. Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, Sherman M, Schwartz M, Lotze M, Talwalkar J, Gores GJ. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst. 2008;100:698–711.
23. Avunduk C, Eastwood GL. Manual of gastroenterology, diagnosis and therapy. 2nd ed. Boston, MA: Little Brown and Company; 1994. p. 415–7.
24. European Association for the Study of the Liver; European Organisation for Research and Treatment of Cancer. EASL_EORT Clinical Practice Guidelines: management of hepatocellular carcinoma. J Hepatol. 2012;56(4):908–43.
25. Cucchetti A, Piscaglia F, Cescon M, Colecchia A, Ercolani G, Bolondi L, Pinna AD. Cost-effectiveness of hepatic resection versus percutaneous radiofrequency ablation for early hepatocellular carcinoma. J Hepatol. 2013;59(2):300–7.
26. Llovet JM, Bruix J. Novel advancements in the management of hepatocellular carcinoma in 2008. J Hepatol. 2008;48(Suppl 1):S20–37.
27. Roayaie S, Blume IN, Thung SN, Guido M, Fiel M-I, Hiotis S, Labow DM, Llovet JM, Schwartz ME. A system of classifying microvascular invasion to predict outcome after resection in patients with hepatocellular carcinoma. Gastroenterology. 2009;137:850–5.
28. Poon RTP, Fan ST, Lo CM, Liu CL, Lam CM, Yuen WK, Yeung C, Wong J. Extended hepatic resection for hepatocellular carcinoma in patients with cirrhosis: is it justified? Ann Surg. 2002;236:602–11.

29. Mazzaferro V, Romito R, Schiavo M, Mariani L, Camerini T, Bhoori S, Capussotti L, Calise F, Pellicci R, Belli G, Tagger A, Colombo M, Bonino F, Majno P, Llovet JM. Prevention of hepatocellular carcinoma recurrence with alpha-interferon after liver resection in HCV cirrhosis. Hepatology. 2006;44:1543–54.
30. Ishizawa T, Hasegawa K, Aoki T, Takahashi M, Inoue Y, Sano K, Imamura H, Sugawara Y, Kokudo N, Makuuchi M. Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. Gastroenterology. 2008;134:1908–16.
31. Margonis GA, Sasaki K, Andreatos N, Nishioka Y, Sugawara T, Amini N, Buettner S, Hashimoto M, Shindoh J, Pawlik TM. Prognostic impact of complications after resection of early stage hepatocellular carcinoma. Surg Oncol. 2017;15(7):791–804.
32. Shi M, Guo R-P, Lin X-J, Zhang Y-Q, Chen M-S, Zhang C-Q, Lau WY, Li J-Q. Partial hepatectomy with wide versus narrow resection margin for solitary hepatocellular carcinoma: a prospective randomized trial. Ann Surg. 2007;245:36–43.
33. Llovet JM, Schwartz M, Mazzaferro V. Resection and liver transplantation for hepatocellular carcinoma. Semin Liver Dis. 2005;25:181–200.
34. Ikai I, Arii S, Kojiro M, Ichida T, Makuuchi M, Matsuyama Y, Nakanuma Y, Okita K, Omata M, Takayasu K, Yamaoka Y. Reevaluation of prognostic factors for survival after liver resection in patients with hepatocellular carcinoma in a Japanese nationwide survey. Cancer. 2004;101:796–802.
35. Qi X, Liu L, Wang D, Li H, Su C, Guo X. Hepatic resection alone versus in combination with pre- and post-operative transarterial chemoembolization for the treatment of hepatocellular carcinoma: a systematic review and meta-analysis. Oncotarget. 2015;6(34):36838–59.
36. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996;334:693–9.
37. Rimassa L, Santoro A. Sorafenib therapy in advanced hepatocellular carcinoma: the SHARP trial. Expert Rev Anticancer Ther. 2009;9(6):739–45.
38. Kudo M, Matsui O, Izumi N, Iijima H, Kadoya M, Imai Y, Okusaka T, Miyayama S, Tsuchiya K, Ueshima K, et al. JSH Consensus-based clinical practice guidelines for the Management of Hepatocellular Carcinoma: 2014 update by the Liver Cancer Study Group of Japan. Liver Cancer. 2014;3(3–4):458–68.
39. Breedis C, Young G. The blood supply of neoplasms in the liver. Am J Pathol. 1954;30:969–77.

40. Arii S, Yamaoka Y, Futagawa S, Inoue K, Kobayashi K, Kojiro M, Makuuchi M, Nakamura Y, Okita K, Yamada R. Results of surgical and nonsurgical treatment for small-sized hepatocellular carcinomas: a retrospective and nationwide survey in Japan. The Liver Cancer Study Group of Japan. Hepatology. 2000;32:1224–9.
41. Takayasu K, Arii S, Ikai I, Omata M, Okita K, Ichida T, Matsuyama Y, Nakanuma Y, Kojiro M, Makuuchi M, Yamaoka Y. Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. Gastroenterology. 2006;131:461–9.
42. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology. 2011;53:1020–2.
43. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology. 2003;37:429–42.
44. Lo C-M, Ngan H, Tso W-K, Liu C-L, Lam C-M, Poon RT-P, Fan S-T, Wong J. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology. 2002;35:1164–71.
45. Llovet JM, Real MI, Montaña X, Planas R, Coll S, Aponte J, Ayuso C, Sala M, Muchart J, Solà R, Rodés J, Bruix J. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet. 2002;359:1734–9.
46. Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire. A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. N Engl J Med. 1995;332:1256–61.
47. Yang HJ, Lee JH, Lee DH, et al. Small single-nodule hepatocellular carcinoma: comparison of transarterial chemoembolization, radiofrequency ablation, and hepatic resection by using inverse probability weighting. Radiology. 2014;271:909–18.
48. Kim HC. Role of C-arm cone-beam CT in chemoembolization for hepatocellular carcinoma. Korean J Radiol. 2015;16(1):114–24.
49. Varela M, Real MI, Burrel M, Forner A, Sala M, Brunet M, Ayuso C, Castells L, Montañá X, Llovet JM, Bruix J. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. J Hepatol. 2007;46:474–81.
50. Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, Pitton M, Sergent G, Pfammatter T, Terraz S, Benhamou Y, Avajon Y, Gruenberger T, Pomoni M, Langenberger H, Schuchmann M, Dumortier J, Mueller C, Chevallier P, Lencioni R. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of

hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol. 2010;33:41–52.
51. Gao S, Yang Z, Zheng Z, Yao J, Deng M, Xie H, Zheng S, Zhou L. Doxorubicin-eluting bead versus conventional TACE for unresectable hepatocellular carcinoma: a meta-analysis. Hepatogastroenterology. 2013;60(124):813–20.
52. Han S, Zhang X, Zou L, Lu C, Zhang J, Li J, Li M. Does drug-eluting bead transcatheter arterial chemoembolization improve the management of patients with hepatocellular carcinoma? A meta-analysis. PLoS One. 2014;9(8):e102686.
53. Laurent A, Wassef M, Chapot R, Houdart E, Merland J-J. Location of vessel occlusion of calibrated tris-acryl gelatin microspheres for tumor and arteriovenous malformation embolization. J Vasc Interv Radiol. 2004;15:491–6.
54. Dion JE, Rankin RN, Viñuela F, Fox AJ, Wallace AC, Mervart M. Dextran microsphere embolization: experimental and clinical experience with radiologic-pathologic correlation. Work in progress. Radiology. 1986;160:717–21.
55. Pillai KM, McKeever PE, Knutsen CA, Terrio PA, Prieskorn DM, Ensminger WD. Microscopic analysis of arterial microsphere distribution in rabbit liver and hepatic VX2 tumor. Sel Cancer Ther. 1991;7:39–48.
56. Yamamoto A, Imai S, Kobatake M, Yamashita T, Tamada T, Umetani K. Evaluation of tris-acryl gelatin microsphere embolization with monochromatic X rays: comparison with polyvinyl alcohol particles. J Vasc Interv Radiol. 2006;17:1797–802.
57. Bonomo G, Pedicini V, Monfardini L, Della Vigna P, Poretti D, Orgera G, Orsi F. Bland embolization in patients with unresectable hepatocellular carcinoma using precise, tightly size-calibrated, anti-inflammatory microparticles: first clinical experience and one-year follow-up. Cardiovasc Intervent Radiol. 2010;33:552–9.
58. Kluger MD, Halazun KJ, Barroso RT, Fox AN, Olsen SK, Madoff DC, Siegel AB, Weintraub JL, Sussman J, Brown RS Jr, Cherqui D, Emond JC. Bland embolization versus chemoembolization of hepatocellular carcinoma before transplantation. Liver Transpl. 2014;20(5):536–43.
59. Brown KT, Do RK, Gonen M, Covey AM, Getrajdman GI, Sofocleous CT, Jarnagin WR, D'Angelica MI, Allen PJ, Erinjeri JP, Brody LA, O'Neill GP, Johnson KN, Garcia AR, Beattie C, Zhao B, Solomon SB, Schwartz LH, DeMatteo R, Abou-Alfa GK. Randomized trial of hepatic artery embolization for hepatocellular carcinoma using doxorubicin-eluting microspheres compared with embolization with microspheres alone. J Clin Oncol. 2016;34(17):2046–53.

60. Salem R, Lewandowski RJ, Mulcahy MF, Riaz A, Ryu RK, Ibrahim S, Atassi B, Baker T, Gates V, Miller FH, Sato KT, Wang E, Gupta R, Benson AB, Newman SB, Omary RA, Abecassis M, Kulik L. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. Gastroenterology. 2010;138:52–64.
61. Kulik LM, Carr BI, Mulcahy MF, Lewandowski RJ, Atassi B, Ryu RK, Sato KT, Benson A, Nemcek AA, Gates VL, Abecassis M, Omary RA, Salem R. Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. Hepatology. 2008;47:71–81.
62. Hilgard P, Hamami M, Fouly AE, Scherag A, Müller S, Ertle J, Heusner T, Cicinnati VR, Paul A, Bockisch A, Gerken G, Antoch G. Radioembolization with yttrium-90 glass microspheres in hepatocellular carcinoma: European experience on safety and long-term survival. Hepatology. 2010;52:1741–9.
63. Sangro B, Bilbao JI, Iñarrairaegui M, Rodriguez M, Garrastachu P, Martinez-Cuesta A. Treatment of hepatocellular carcinoma by radioembolization using 90Y microspheres. Dig Dis. 2009;27:164–9.
64. Ludwig JM, Zhang D, Xing M, Kim HS. Meta-analysis: adjusted indirect comparison of drug-eluting bead transarterial chemoembolization versus 90Y-radioembolization for hepatocellular carcinoma. Eur Radiol. 2017;27(5):2031–41.
65. Ku Y, Tominaga M, Iwasaki T, Fukumoto T, Muramatsu S, Kusunoki N, Sugimoto T, Suzuki Y, Kuroda Y, Saitoh Y. Efficacy of repeated percutaneous isolated liver chemoperfusion in local control of unresectable hepatocellular carcinoma. Hepatogastroenterology. 1998;45:1961–5.
66. Gerunda GE, Neri D, Merenda R, Barbazza F, Zangrandi F, Meduri F, Bisello M, Valmasoni M, Gangemi A, Faccioli AM. Role of transarterial chemoembolization before liver resection for hepatocarcinoma. Liver Transpl. 2000;6:619–26.
67. Graziadei IW, Sandmueller H, Waldenberger P, Koenigsrainer A, Nachbaur K, Jaschke W, Margreiter R, Vogel W. Chemoembolization followed by liver transplantation for hepatocellular carcinoma impedes tumor progression while on the waiting list and leads to excellent outcome. Liver Transpl. 2003;9:557–63.
68. Yao FY, Hirose R, LaBerge JM, Davern TJ, Bass NM, Kerlan RK, Merriman R, Feng S, Freise CE, Ascher NL, Roberts JP. A prospective study on downstaging of hepatocellular carcinoma prior to liver transplantation. Liver Transpl. 2005;11:1505–14.

69. Bharat A, Brown DB, Crippin JS, Gould JE, Lowell JA, Shenoy S, Desai NM, Chapman WC. Pre-liver transplantation locoregional adjuvant therapy for hepatocellular carcinoma as a strategy to improve longterm survival. J Am Coll Surg. 2006;203:411–20.
70. Obed A, Beham A, Püllmann K, Becker H, Schlitt HJ, Lorf T. Patients without hepatocellular carcinoma progression after transarterial chemoembolization benefit from liver transplantation. World J Gastroenterol. 2007;13:761–7.
71. Zangos S, Eichler K, Balzer JO, Straub R, Hammerstingl R, Herzog C, Lehnert T, Heller M, Thalhammer A, Mack MG, Vogl TJ. Large-sized hepatocellular carcinoma (HCC): a neoadjuvant treatment protocol with repetitive transarterial chemoembolization (TACE) before percutaneous MR-guided laser-induced thermotherapy (LITT). Eur Radiol. 2007;17:553–63.
72. Hoffmann K, Glimm H, Radeleff B, Richter G, Heining C, Schenkel I, Zahlten-Hinguranage A, Schirrmacher P, Schmidt J, Büchler MW, Jaeger D, Kalle C v, Schemmer P. Prospective, randomized, double-blind, multi-center, Phase III clinical study on transarterial chemoembolization (TACE) combined with Sorafenib versus TACE plus placebo in patients with hepatocellular cancer before liver transplantation—HeiLivCa [ISRCTN24081794]. BMC Cancer. 2008;8:349.
73. Zhou W-P, Lai ECH, Li A-J, Fu S-Y, Zhou J-P, Pan Z-Y, Lau WY, Wu M-C. A prospective, randomized, controlled trial of preoperative transarterial chemoembolization for resectable large hepatocellular carcinoma. Ann Surg. 2009;249:195–202.
74. Choi SB, Kim KS, Park YN, Choi JS, Lee WJ, Seong J, Han K-H, Lee JT. The efficacy of hepatic resection after neoadjuvant transarterial chemoembolization (TACE) and radiation therapy in hepatocellular carcinoma greater than 5 cm in size. J Korean Med Sci. 2009;24:242–7.
75. Schaudt A, Kriener S, Schwarz W, Wullstein C, Zangos S, Vogl T, Mehrabi A, Fonouni H, Bechstein WO, Golling M. Role of transarterial chemoembolization for hepatocellular carcinoma before liver transplantation with special consideration of tumor necrosis. Clin Transpl. 2009;23(Suppl 21):61–7.
76. Wang X, Li J, Peng Y, Dai Y, Xu W. Influence of preoperative transarterial chemoembolization on the prognosis for patients with resectable hepatocellular carcinoma: a meta-analysis of randomized trials. Hepatogastroenterology. 2011;58(107–108):869–74.
77. Yu T, Xu X, Chen B. TACE combined with liver resection versus liver resection alone in the treatment of resectable HCC: a meta-analysis. Chinese German J Clin Oncol. 2013;12:P532–6.

78. Si T, Chen Y, Ma D, Gong X, et al. Preoperative transarterial chemoembolization for resectable hepatocellular carcinoma in Asia area: a meta-analysis of random controlled trials. Scand J Gastroenterol. 2016;51(12):1512–9.
79. Lai EC, Lo CM, Fan ST, Liu CL, Wong J. Postoperative adjuvant chemotherapy after curative resection of hepatocellular carcinoma: a randomized controlled trial. Arch Surg. 1998;133:183–8.
80. Ono T, Yamanoi A, Nazmy El Assal O, Kohno H, Nagasue N. Adjuvant chemotherapy after resection of hepatocellular carcinoma causes deterioration of long-term prognosis in cirrhotic patients: metaanalysis of three randomized controlled trials. Cancer. 2001;91:2378–85.
81. Wen J, Shen W-L, Yang S-H. Adjuvant hepatic chemotherapy after resection of solitary hepatocellular carcinoma associated with hepatitis B virus cirrhosis. Hepatobiliary Pancreat Dis Int. 2006;5:224–7.
82. Li Q, Wang J, Sun Y, Cui YL, Juzi JT, Qian BY, Hao XS. Postoperative transhepatic arterial chemoembolization and portal vein chemotherapy for patients with hepatocellular carcinoma: a randomized study with 131 cases. Dig Surg. 2006;23:235–40.
83. Peng B-g, He Q, Li J-P, Zhou F. Adjuvant transcatheter arterial chemoembolization improves efficacy of hepatectomy for patients with hepatocellular carcinoma and portal vein tumor thrombus. Am J Surg. 2009;198:313–8.
84. Zhong J-H, Li L-Q. Postoperative adjuvant transarterial chemoembolization for participants with hepatocellular carcinoma: a meta-analysis. Hepatol Res. 2010;40:943–53.
85. Cheng X, Sun P, QG H, Song ZF, Xiong J, Zheng QC. Transarterial (chemo)embolization for curative resection of hepatocellular carcinoma: a systematic review and meta- analyses. J Cancer Res Clin Oncol. 2014;140:1159–70.
86. Furuse J, Ishii H, Satake M, Onaya H, Nose H, Mikami S, Sakai H, Mera K, Maru Y, Yoshino M. Pilot study of transcatheter arterial chemoembolization with degradable starch microspheres in patients with hepatocellular carcinoma. Am J Clin Oncol. 2003;26:159–64.
87. Huo T-I, Huang Y-H, Wu J-C, Chiang J-H, Lee P-C, Chang F-Y, Lee S-D. Sequential transarterial chemoembolization and percutaneous acetic acid injection therapy versus repeated percutaneous acetic acid injection for unresectable hepatocellular carcinoma: a prospective study. Ann Oncol. 2003;14:1648–53.
88. Dettmer A, Kirchhoff T-D, Gebel M, Zender L, Malek N-P, Panning B, Chavan A, Rosenthal H, Kubicka S, Krusche S, Merkesdal S, Galanski M, Manns M-P, Bleck J-S. Combination of repeated single-session percutaneous ethanol injection and transarterial chemoembolisation

compared to repeated single-session percutaneous ethanol injection in patients with non-resectable hepatocellular carcinoma. World J Gastroenterol. 2006;12:3707–15.
89. Kirchhoff TD, Bleck JS, Dettmer A, Chavan A, Rosenthal H, Merkesdal S, Frericks B, Zender L, Malek NP, Greten TF, Kubicka S, Manns MP, Galanski M. Transarterial chemoembolization using degradable starch microspheres and iodized oil in the treatment of advanced hepatocellular carcinoma: evaluation of tumor response, toxicity, and survival. Hepatobiliary Pancreat Dis Int. 2007;6:259–66.
90. Ishida K, Hirooka M, Hiraoka A, Kumagi T, Uehara T, Hiasa Y, Horiike N, Onji M. Treatment of hepatocellular carcinoma using arterial chemoembolization with degradable starch microspheres and continuous arterial infusion of 5-fluorouracil. Jpn J Clin Oncol. 2008;38:596–603.
91. Carr BI, Kondragunta V, Buch SC, Branch RA. Therapeutic equivalence in survival for hepatic arterial chemoembolization and yttrium 90 microsphere treatments in unresectable hepatocellular carcinoma: a two-cohort study. Cancer. 2010;116:1305–14.
92. Nagano H. Treatment of advanced hepatocellular carcinoma: intraarterial infusion chemotherapy combined with interferon. Oncology. 2010;78(Suppl 1):142–7.
93. Kucuk ON, Soydal C, Lacin S, Ozkan E, Bilgic S. Selective intraarterial radionuclide therapy with Yttrium-90 (Y-90) microspheres for unresectable primary and metastatic liver tumors. World J Surg Oncol. 2011;9:86.
94. Kondo M, Morimoto M, Numata K, Nozaki A, Tanaka K. Hepatic arterial infusion therapy with a fine powder formulation of cisplatin for advanced hepatocellular carcinoma with portal vein tumor thrombosis. Jpn J Clin Oncol. 2011;41:69–75.
95. Gao S, Zhang PJ, Guo JH, Chen H, HF X, et al. Chemoembolization alone vs combined chemoembolization and hepatic arterial infusion chemotherapy in inoperable hepatocellular carcinoma patients. World J Gastroenterol. 2015;21(36):10443–52.
96. Ibrahim SM, Kulik L, Baker T, Ryu RK, Mulcahy MF, Abecassis M, Salem R, Lewandowski RJ. Treating and downstaging hepatocellular carcinoma in the caudate lobe with yttrium-90 radioembolization. Cardiovasc Intervent Radiol. 2012;35:1094–101.
97. Zhang Y, Li Y, Ji H, Zhao X, Lu H. Transarterial Y90 radioembolization versus chemoembolization for patients with hepatocellular carcinoma: a meta-analysis. Biosci Trends. 2015;9(5):289–98.
98. Lobo L, Yakoub D, Picado O, Ripat C, Pendola F, et al. Unresectable hepatocellular carcinoma: radioembolization versus chemoembolization: a systematic review and meta-analysis. Cardiovasc Intervent Radiol. 2016;39(11):1580–8.

Chapter 4
Indications for Locoregional Tumor Therapies: CRC Liver Metastases

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4.1 Introduction

The liver represents the most affected site in patients affected by colorectal carcinoma (mCRC) [1]. More than half cases develop colorectal liver metastases (CLMs) during the evolution of the disease, and about one-quarter occur at the disease onset [1, 2]. To date, the standard treatment of CLM is represented by liver surgery, which has allowed to achieve interesting long-term survival rates (40–60%) [3] in reported series, while it is less than 25% for patients who do not undergo surgery [4]. Unfortunately, most patients (80%), however, are not immediately eligible for surgery [5, 6]. For these patients, surgical treatment may be administered in combination with chemotherapy regimens (+/− target agents) aiming to downsize neoplasm and to allow a surgically and oncologically radical intervention. In addition, the greater effectiveness of the abovementioned new chemotherapeutic options has allowed to revolutionize the liver resection criteria considered until recently, thus widening the proportion of patients able to obtain long-term benefit from surgery. Locoregional liver treatments (including ablative technologies and transarterial treatments) can be considered additional options able to downsize CLMs and have been shown to improve quality of life, prolonging time to local progression and overall survival [7, 8]. Of course, to achieve optimal results, it is necessary to set up a multidisciplinary team, including interventionist radiologists, able to evaluate individual cases in order to select the best therapeutic strategy for each patient.

4.1.1 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 such as chemotherapy +/− biologic agents.

4.1.2 Ablative Treatments

The ablative techniques for CLM could be divided into thermal and nonthermal. Thermal include cold ablations (cryotherapy) and the hot ablations (especially radiofrequency ablation and microwaves). RFA is a procedure that allows to obtain liver cancer cell necrosis by increasing the local temperature up to 58 °C, as limiting the involvement of the surrounding tissue as much as possible. It is the technique that presents the largest follow-up and most consistent results when compared with microwave and laser therapy. A recent analysis of Gillams et al. [9] reported a 5-year survival rate after ablation in selected patients of 31% (based on the lesion size, number, and anatomic position as well as method used) for those patients with liver-limited disease not technically operable, with poor hepatic reserve or comorbidities. The survival rised up to 50% when RFA was applied on patients with potentially operable disease. This procedure returns a significant benefit when applied to smaller size metastasis (up to 3 cm) although there is evidence demonstrating an acceptable recurrence rate from 27 to 45% for 3–5 cm lesions in favorable anatomical position [10, 11]. The use of RFA near bile vessels (<1 cm) exposes the latter at high risk of breakage. In addition, the need for a post-ablation chemotherapy increases significantly the risk of liver abscesses and cholangitis [12].

Another parameter to consider is the distance from the blood vessels, as blood flow could cool the adjacent area. RFA could therefore be an option for patients with vascular diame-

ter >3 mm taking into account the increased risk of local recurrence and therefore the need for further treatments. In some highly specialized centers, this procedure is carried out using protocols which provide for a higher power or a longer exposure of treatment [13].

Regarding the number of lesions, some centers prefer to treat up to five lesions, while others prefer to treat up to nine lesions as long as the total diameter does not exceed 4 cm, although the best long-term outcomes have been reported for solitary liver lesion [14–16].

Although the comparison between surgery and upfront thermal ablation has reported a benefit (5-year survival rate 51% vs. 48%) in favor of surgery, further RFA treatment or surgery remained valid options for patients who relapsed after RFA, helping to increase the overall survival by making surgery and RFA two equally effective treatments [17].

An important contribution to the overall outcome could derive from the use of chemotherapy before or after RFA. The use of chemotherapy before RFA, despite providing a 5-year survival rate of 34% in some series, is affected by some limits, first of all, the disappearing metastasis phenomenon. In addition, chemotherapy could render more difficult lesion visualization because of the steatohepatitis, requiring a careful liver study through MRI with specific contrast medium [18–20]. The use of chemotherapy (5-FU) in the adjuvant phase showed a trend toward a benefit ($p = 0.058$) in a pooled analysis of two randomized studies that resulted in a median overall survival of 62 vs. 47 months [21]. It was also evaluated the perioperative regimen with FOLFOX (six cycles before and six cycles after ablation). The authors reported a benefit in terms of PFS after more than 8 years of follow-up that has allowed to recommend this regimen despite it not resulted in an overall survival gain [21]. Neoadjuvant combination of transarterial chemoembolization prior to RFA resulted in a 2-year overall survival rate of 88%, with low toxicity [22].

In conclusion, the strength of the available evidences does not allow to generate unique recommendations about the use of RFA as part of a multimodal strategy. A recent analysis of Sartori et al. [23] emphasizes a lack of trials designed to answer this question because of poor accrual, due mostly to the impossibility to obtain a homogeneous patient's cohort. This condition resulted in a weakening of the trial outcomes and with a loss of important information to provide a global strategy as effective as possible [24]. Microwaves (MWA) in recent years have become a new option in the treatment of CLM [25]. MWA uses frequencies ranging from 900 to 2450 MHZ able to shake water molecules and produce more heat (about 65 °C) compared to other techniques such as RFA, causing tissue coagulative necrosis [26]. In addition, it can be used in larger lesions (up to 6 cm), as more rapid procedure and potentially less painful. MWA are often administered percutaneously under ultrasound guidance, and the most reported side effects are pain, fever, pleural effusion, ascites, and breakage of the bile ducts [27, 28].

Most of the data on this procedure are retrospective and often involve non-colorectal liver metastases.

In an experience, Lorentzen et al. reported a technical success rate of 100% and local recurrence in 9.6% of patients (CRC, breast, carcinoid tumor, and GIST) showing how this method is safe and effective in the treatment of liver lesions.

Moreover, in a retrospective series of patients treated with MWA with or without liver surgery and selective regional and systemic therapy (48.3%), researchers reported a median 4-year OS rate of 58.3%, noting that recurrences were reported mostly for lesions which diameter was >3 cm and for those located nearby the vessels [29].

Furthermore, MWA was compared with surgery in a randomized trial of mCRC patients with potentially resectable liver metastases with survival rates at 1, 2, and 3 years similar to those of the cohort who underwent surgery and had a median OS of 27 months [30]. More randomized trials are needed to assess the efficacy of MWA in the treatment of CLMs.

4.1.3 Hepatic Arterial Treatments

Hepatic arterial treatments can be divided in embolic and non-embolic procedures. The most common type of embolic technique used in the treatment of CLM is the transarterial chemoembolization (TACE), while others such as hepatoarterial infusion (HAI), transarterial embolotherapy (TAE), and radioembolization using yttrium-90 are less commonly used. The rationale comes out that normally the liver parenchyma is mainly vascularized by the portal circuit, while the malignant parenchyma is vascularized from the arterial circuit. Therefore, using TACE, it may be possible to increase the concentration of chemotherapeutic agents nearby the tumor, sparing healthy parenchyma through a selective catheterization and the use of embolic particles. The cytotoxic effect is due to the drug cytotoxicity with the contribution of ischemia [31]. The treatment also is responsible for a decrease of clearance of chemotherapy and tumor perfusion [32].

A literature overview shows that the use of TACE is reserved after surgery failure and/or systemic therapy reporting median OS >28 months. When used over the second line, while some authors report a significant OS benefit for TACE, others underline its futility because it is not able to influence the extrahepatic recurrence compared to palliation [33–37]. In addition, no study to date has shown what kind of TACE (cTACE, DEB-TACE, or DSM-TACE) is more oncologically effective on CLM. Therefore, the abovementioned results would seem to recommend the use of TACE at an early stage of the disease in association with systemic treatments rather than as a palliative treatment as heretofore indicated. Toxicities of this procedure seem acceptable, and for this reason, several studies assessed the possibility to evaluate TACE in combination with surgery or chemotherapy. There are few data regarding the association with surgery. An outdated study had evaluated the efficacy of TACE prior to sur-

gery showing a benefit in terms of 1-year recurrence rate and OS although the study was not randomized [38]. Vogl et al. evaluated a protocol of repeated TACE with mitomycin alone, mitomycin and irinotecan, or mitomycin and gemcitabine for downstaging of CLM before MR-guided laser-induced interstitial thermotherapy (LITT) and found that the size of the target lesions was reduced by 21.4%, with no significant difference concerning the applied chemotherapeutic [39, 40]. The DEB-TACE procedure (DEBIRI), which uses new embolizing agents such as polymer-based microparticles (DC) loaded with irinotecan, would appear with greater efficiency due to prolonged shedding of intratumoral drug [41–44]. Two studies evaluated DEBIRI before surgical treatment bringing a complete pathological response of treated lesions and a partial response on those not directly treated, providing a rationale about the possible activity of TACE on not target micrometastases, although this procedure in combination with surgery still cannot be recommended [45]. About combination with chemotherapy, Akinwande et al. have evaluated the efficacy of DEBIRI in combination with capecitabine alone compared to DEBIRI, bringing a different but not significant survival (22 vs. 13 months) in favor of combination schedule [46]. DEBIRI was also compared with the systemic FOLFIRI in a cohort of 74 patients demonstrating a significant benefit in terms of OS (22 vs. 15 months) and PFS (7 vs. 4 months), although DEBIRI has been burdened by a higher early ≥G3 toxicity rate (70% vs. 25%) providing a rationale for the use of DEBIRI instead of standard chemotherapy [47]. A recent randomized trial with 70 patients also evaluated DEBIRI + FOLFOX versus the same chemotherapy regimen (FOLFOX) plus a target therapy (bevacizumab). The containing DEBIRI arm had more patients with ECOG performance status 1 or 2 (57% vs. 31%) and extrahepatic disease (56% vs. 32%) but nevertheless showed both higher early (2 months, 78% vs. 54%) and late (6 months, 76% vs. 60%) response rates and a greater PFS (15.3 vs. 7.6 months),

although wider studies are required to define DEBIRI utility in this disease setting [48].

Radioembolization (selective internal radiation therapy—SIRT) is the more recent embolic therapeutic option. This procedure consists in the selective intra-arterial injection of yttrium-90 (Y90), beta-radioactive particles—alone or in combination with chemotherapy—incorporated in glass or resin microspheres [49]. With this technique, it is possible to spread about 100 Gy in liver cancer lesions, avoiding the damage of the surrounding healthy liver tissue [50, 51]. Some studies' results have guaranteed the approval of radioembolization for the treatment of liver lesions using SIR-Spheres (20–60 μm), improving clinical outcomes (PFS, RR, CEA value) both when used in the first and last therapeutic lines, with acceptable toxicity when associated with FUDR (floxuridine) compared to FUDR alone, although the study was discontinued before the OS was evaluated [52–54]. The use of SIRT + chemotherapy has been evaluated in a randomized trial, where combination therapy has been shown to double the PFS compared with chemotherapy alone. In addition, the recent phase III study SIRFLOX evaluated the combination of FOLFOX (+/− bevacizumab) + SIRT versus FOLFOX (+/− bevacizumab) in mCRC liver-dominant patients reporting a delay in liver disease progression without significantly improving any-site PFS (10.7 vs. 10.2 months) [55]. A recent meta-analysis by Townsend et al., which pooled the four randomized trials using SIRT in mCRC patients, showed no benefit in terms of PFS and life expectancy for patients undergoing SIRT (OS values of individual studies are still awaited for pooled data analysis) [56]. In another study, SIRT was found to be a safe treatment, but outcomes depend on performance status, liver function, and previous treatment [57]. Some researchers have suggested that the quality of the microspheres may affect the effectiveness of the therapy. In this regard, the EPOCH study is currently investigating whether the use of glass TheraSphere is more effective as it is less embolic and therefore can improve

tissue oxygenation (since the damage is mediated by free oxygen radicals) (NCT01483027).

Hepatic arterial infusion (HAI) is the most common non-embolic procedure. This is often used in combination with chemotherapy (more systemic HAIC-oxaliplatin 5-FU and cetuximab or HAIC-FUDR plus systemic oxaliplatin/irinotecan) to increase overall response rates and overall survival. In particular, recent retrospective studies have shown that HAIC is able to produce R0 conversion surgery in more than 40% of cases in chemotherapy-naive patients and 20% in heavily pretreated patients, finally prolonging DFS ($p < 0.0001$) if compared with intravenous chemotherapy in adjuvant post-metastasectomy setting, although multicenter randomized trials in this patient setting are currently ongoing. The overall result of a six-trial meta-analysis suggests that there is probably no solid benefit in reducing death risk in the use of this procedure, which is also heavily complicated and is therefore reserved for highly specialized centers (because of arterial thrombosis, extrahepatic perfusion, hemorrhage, and hepatotoxic toxicity) [58–65].

4.1.4 Conclusion

The treatment of CLM expects different options. The only curative is represented by surgery, mainly due to the new techniques that have led to a thorough review of the up to now considered resectability criteria. Results have demonstrated long-term (5 years) survival rates of up to 40–60%, in this setting. Even when supported by chemotherapy with the purpose of debulking, modern targeted agents have helped to generate better outcomes, improving the response chances. In all other situations, where the intent of radicality is compromised, RHT allows local control of the disease, improving the quality of life and overall survival of these patients. In the near future, results of clinical trials with homogenous features are needed to better understand

the peculiarities of each local technique, especially if associated with new molecular target therapies or even more with immune-checkpoint blockade agents.

4.2 Study Results

4.2.1 Neoadjuvant Regional Therapy

Tanaka K et al. (2003) [18]:

Concept	Role of neoadjuvant chemotherapy in the treatment of multiple colorectal metastases to the liver
N	71
Inclusion criteria	Five or more bilobar liver metastases, all surgically treated patients received adjuvant CT
Therapy	1. Neoadjuvant CT 2. No neoadjuvant CT
Results ($N = 10$)	3-year survival rate: 67.0% vs. 51.8% S 5-year survival rate: 38.9% vs. 20.7% S
Toxicity	No differences in surgery complication rate (20%)
Conclusions	In patients with bilateral multiple colorectal liver metastases, neoadjuvant chemotherapy before hepatectomy was associated with improved survival and enabled complete resection with fewer extended hepatectomies

Yamakado K et al. (2017) [22]:

Concept	Role of neoadjuvant DSM-MMC TACE in combination with RFA in the treatment of colorectal liver metastases
N	25
Inclusion criteria	Three or fewer liver tumors of ≤3 cm or a single tumor of ≤5 cm
Therapy	Percutaneous RFA immediately after chemoembolization with degradable starch microspheres and mitomycin C

Results	2-year recurrence-free survival: 63.3% 2-year overall survival: 88.0%
Toxicity	Fever in 2 patients (8%)
Conclusions	The combination of RFA with DSM-TACE is a safe therapy, exhibiting strong anticancer effects on CRC metastases in the liver

4.2.2 Palliative Regional Therapies

Gray B et al. (2001) [54]**:**

Concept	SIR-Spheres plus chemotherapy (SIRT) vs. chemotherapy alone for CLM		
N	70		
Inclusion criteria	Unresectable liver metastases, systemic therapy allowed, bilobar involvement		
Therapy	1. SIRT plus HAC (12-day cycles of continuous infusion floxuridine at 0.3 mg/kg of body weight/day) 2. HAC (12-day cycles of continuous infusion floxuridine at 0.3 mg/kg of body weight/day)		
Results	RR: 44% vs. 17.6% S Hepatic PFS: 15.9 vs. 9.7 mos S 5-year survival rate: 3.5% vs. 0% NS		
Toxicity G4–G4	Parameter %	1	2
	AST	35	15
	Alk phos	14	41
Conclusions	The combination of SIR-Spheres plus HAC is substantially more effective in increasing tumor responses and progression-free survival than the same regimen of HAC alone		

Fiorentini G et al. (2007) [41]**:**

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 mets from CRC

Reuter NP et al. (2009) [17]**:**

Concept	Radiofrequency ablation vs resection for hepatic colorectal metastasis: therapeutically equivalent		
N	192		
Inclusion criteria	Single lobar involvement, resection, or RFA was determined by the surgeon at his discretion		
Therapy	1. RFA 2. Resection		
Results	Time to recurrence: 12.2 vs. 31.1 mos S Recurrence at the ablation–resection site: 17% vs. 2% S Distant recurrence in the liver: 33% vs. 14% S mOS: 27.0 vs. 36.4 mos NS		
Toxicity	Parameter %	1	2
	Blood transfusion	3%	21%
	Length of hospital stay	6.6%	9.8%
	Major complication	10%	29%
Conclusions	Surgical resection is associated with a lower chance of recurrence and a longer disease-free interval than RFA and should remain the treatment of choice in resectable CLM		

Vogl T et al. (2009) [40]**:**

Concept	Repeated chemoembolization
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 + 1000 mg/m^2 gemcitabin (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 the start of TACE), 14 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	DSM-TACE as a minimally invasive therapy option for palliative treatment of liver metastases of CRC

Parameter	MMC	MMC +gemcitabin	MMC + irinotecan
RR (%)	13,6	11,1	19,4
OS (mo)	14,0	13,9	14,0

Ruers T et al. (2011) [15]**:**

Concept	Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC intergroup phase II study (EORTC 40004)
N	119
Inclusion criteria	Unresectable liver metastases, LLD, <n°10 lesions, DT max. 4 cm (if treated with RFA)

Therapy	1. Oxaliplatin 85 mg/m^2, LV 200 mg/m^2, and 5-FU bolus 400 mg/m^2 followed by 600 mg/m^2 22-h infusion, every 14 days, or oxaliplatin 85 mg/m^2, folinic acid 175 mg, and 5-FU bolus 400 mg/m^2 followed by 2400 mg/m^2 46-h infusion every 14 days or oxaliplatin 85 mg/m^2 every 14 days and weekly LV 200 mg/m^2 and 5-FU 2600 mg/m^2 24-h infusion, for 6 weeks followed by 1 week of rest. Bevacizumab was administered at 5 mg/kg body weight, once every 2 weeks 2. CT as above reported + RFA		
Results	30-month OS rate > 38%: 61.7% vs. 57.6% mOS: 45.3 vs. 40.5 mos (HR 0.74 NS) mPFS: 16.8 vs. 9.9 mos (HR 0.63 S) QoL > 20 points: 10 NS		
Toxicity (grade III + IV)	Parameter %	1	2
	Neutropenia	27.5	20.3
	Diarrhea	19.6	16.9
	Neuropathy	17.6	13.6
	Fatigue	13.7	6.8
	Nausea	13.7	10.2
Conclusions	The study met the primary end point on 30-month OS; however, the results in the control arm were in the same range. RFA plus systemic treatment resulted in significant longer PFS. At present, the ultimate effect of RFA on OS remains uncertain		

Fiorentini G et al. (2012) [47]**:**

Concept	Comparison between DEBIRI and FOLFIRI (prospective)
N	74
Inclusion criteria	Unresectable liver metastases, no extrahepatic disease, after systemic chemotherapy failure, liver involvement <50%
Therapy	1. DEBIRI (drug-eluting beads 100–300 μm) 2. FOLFIRI (irinotecan at 180 mg/m^2 on day 1 with folinic acid at 100 mg/m^2 as a 2-h infusion, followed by bolus of fluorouracil at 400 mg/m^2 and fluorouracil 600 mg/m^2 as 22-h infusion on days 1 and 2 every 2 weeks)

Results	OS: 22 vs. 15 mos S PFS: 7.0 vs. 4.0 mos S RR: 68.6% vs. 20% S		
Toxicity	Parameter %	1	2
	Pain	30	0
	Diarrhea	2	35
	Asthenia	20	50
	Leukopenia	5	35
	Anemia	5	35
	Alopecia	5	35
Conclusions	Results suggest a benefit of DEBIRI treatment over standard chemotherapy		

Stintzing S et al. (2013) [28]**:**

Concept	Comparison between single session robotic radiosurgery (RRS) and percutaneous radiofrequency ablation (RFA)		
N	60		
Inclusion criteria	Heavily pretreated colorectal patients, unresectable liver lesions		
Therapy	1. RSS 2. RFA		
Results	1-year local control rate: 85% vs. 65% NS 2-year local control rate: 80% vs. 61% NS Local PFS: 34.4 vs. 6.0 mos S OS: 34.4 vs. 52.3 mos NS		
Toxicity	Parameter %	1	2
	Nausea	0	13
Conclusions	Single session RRS is a safe and effective method to treat colorectal liver metastases. In this analysis, a trend toward longer DFS was seen in patients treated with RRS when compared to RFA		

Riemsma RP et al. (2013) [33]**:**

Concept	Transarterial chemoembolization versus no intervention or placebo intervention for liver metastases
N	61
Inclusion criteria	Unresectable liver metastases, most synchronous metastases
Therapy	1. Hepatic artery embolization 2. No intervention
Results	Mortality rate: 86% vs. 95% NS OS: 7.0 vs. 7.9 mos NS Extrahepatic disease: RR 1.64
Toxicity	82% post-embolic syndrome (hepatic artery embolization group)
Conclusions	Transarterial (chemo)embolization cannot be recommended outside randomized clinical trials

Allard MA et al. (2014) [65]**:**

Concept	A comparison between oxaliplatin systemic and arterial infusion about complete pathological response (cPR) and severe oxaliplatin-related lesions (SOxL)(prospective)
N	68
Inclusion criteria	Unresectable liver metastases, mostly bilobar
Therapy	1. HAI (HAI bolus of oxaliplatin 100 mg/m^2, intravenous administration of 200 mg/m^2 leucovorin and 400 mg/m^2 5-fluorouracil (5-FU) over a 2-h period, IV infusion of 2400 mg/m^2 5-FU over a 2-day period (modified LV5-FU2)) 2. Oxaliplatin (FOLFOX4 or FOLFOX6 protocol)
Results	cPR: 33% vs. 10% S SOxL: 66% vs. 20% S cPR OS: 114 vs. 42 mos S
Toxicity	N/A
Conclusions	HAI of oxaliplatin increases the likelihood of a CPR at the cost of a higher incidence of SOxL in patients with initially unresectable CLM

Ruers T et al. (2015) [24]**:**

Concept	Combining systemic chemotherapy (CT) with local tumor destruction by RFA		
N	119		
Inclusion criteria	Unresectable liver metastases, <10 lesions, no extrahepatic disease		
Therapy	1. CT (FOLFOX +/− bevacizumab) + RFA 2. CT (FOLFOX +/− bevacizumab)		
Results	30-mo OS rate: 61.7% vs. 57.6% OS: 45.6 vs. 40.5 mos S		
Toxicity	Parameter %	1	2
	Neutropenia	27.5	20.3
	Diarrhea	19.6	16.9
	Neuropathy	17.6	13.6
	Fatigue	13.7	6.8
	Nausea	13.7	10.2
Conclusions	RFA + CT was associated with improved long-term OS compared to CT alone		

Martin RCG et al. (2015) [48]**:**

Concept	A comparison between FOLFOX(+/− bevacizumab) + DEBIRI and FOLFOX + bevacizumab (prospective)		
N	70		
Inclusion criteria	Unresectable liver metastases, no prior chemotherapy		
Therapy	1. FOLFOX (+/− bevacizumab) (dose set at 85 mg/m^2) + DEBIRI 2. FOLFOX + bevacizumab		
Results	6-month RR: 76% vs. 60% S PFS: 15.3 vs. 7.6 mos S		
Toxicity G3–G4	Parameter %	1	2
	Neutropenia	13	21
	Abdominal pain	13	3
	Procedure hypertension	13	0
	Hypertension	13	7

Conclusions	The simultaneous administration of mFOLFOX6 (with or without bevacizumab) and DEBIRI (FOLFOX–DEBIRI) is safe. This strategy leads to improved overall response rates and overall progression-free survival in patients downsized to resection

Van Hazel GA et al. (2016) [55]:

Concept	A comparison between FOLFOX + bevacizumab +/− SIRT		
N	530		
Inclusion criteria	Unresectable synchronous or metachronous liver metastases (involvement of 3 or 4 segments, inadequate liver remnant, or involvement of essential intrahepatic vascular structures)		
Therapy	1. mFOLFOX6 + bevacizumab 2. mFOLFOX6 + bevacizumab + SIRT		
Results	PFS: 10.2 vs. 10.7 mos NS Liver PFS: 12.6 vs. 20.5 mos S RR: 68.8% vs. 78.7% S		
Toxicity G3–G4	Parameter %	1	2
	Neutropenia	28.5	40.7
	Febrile neutropenia	6.1	1.9
	Thrombocytopenia	2.6	9.8
	Fatigue	4.8	10.6
	Nausea/vomit	4.1	8.1
	Abdominal pain	2.6	7.7
Conclusions	The addition of SIRT to systemic chemotherapy does not improve overall PFS but delivers significantly liver PFS		

References

1. Garden OJ, Rees M, Poston GJ, et al. Guidelines for resection of colorectal cancer liver metastases. Gut. 2006;55(Suppl 3):iii1–8. https://doi.org/10.1136/gut.2006.098053.

2. Bengtsson G, Carlsson G, Hafström L, et al. Natural history of patients with untreated liver metastases from colorectal cancer. Am J Surg. 1981;141(5):586–9.
3. Scheele J, Stangl R, Altendorf-Hofmann A. Hepatic metastases from colorectal carcinoma: impact of surgical resection on the natural history. Br J Surg. 1990;77(11):1241–6.
4. Choti MA, Sitzmann JV, Tiburi MF, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg. 2002;235(6):759–66.
5. Poston GJ, Figueras J, Giuliante F, et al. Urgent need for a new staging system in advanced colorectal cancer. J Clin Oncol. 2008;26(29):4828–33. https://doi.org/10.1200/JCO.2008.17.6453.
6. van den Eynde M, Hendlisz A. Treatment of colorectal liver metastases: a review. Rev Recent Clin Trials. 2009;4(1):56–62.
7. Ksienski D, Woods R, Speers C, et al. Patterns of referral and resection among patients with liver-only metastatic colorectal cancer (MCRC). Ann Surg Oncol. 2010;17(12):3085–93. https://doi.org/10.1245/s10434-010-1304-9.
8. Chiappa A, Makuuchi M, Lygidakis NJ, et al. The management of colorectal liver metastases: expanding the role of hepatic resection in the age of multimodal therapy. Crit Rev Oncol Hematol. 2009;72(1):65–75. https://doi.org/10.1016/j.critrevonc.2008.11.003.
9. Gillams A, Goldberg N, Ahmed M, et al. Thermal ablation of colorectal liver metastases: a position paper by an international panel of ablation experts. The Interventional Oncology Sans Frontières Meeting 2013. Eur Radiol. 2015;25(12):3438–54. https://doi.org/10.1007/s00330-015-3779-z.
10. Nielsen K, van Tilborg AAJM, Meijerink MR, et al. Incidence and treatment of local site recurrences following RFA of colorectal liver metastases. World J Surg. 2013;37(6):1340–7. https://doi.org/10.1007/s00268-013-1997-6.
11. Hammill CW, Billingsley KG, Cassera MA, et al. Outcome after laparoscopic radiofrequency ablation of technically resectable colorectal liver metastases. Ann Surg Oncol. 2011;18(7):1947–54. https://doi.org/10.1245/s10434-010-1535-9.
12. Marchal F, Elias D, Rauch P, et al. Biliary lesions during radiofrequency ablation in liver. Study on the pig. Eur Surg Res. 2004;36(2):88–94. https://doi.org/10.1159/000076648.
13. Kingham TP, Karkar AM, D'Angelica MI, et al. Ablation of perivascular hepatic malignant tumors with irreversible electroporation. J Am Coll Surg. 2012;215(3):379–87. https://doi.org/10.1016/j.jamcollsurg.2012.04.029.

14. Gillams AR, Lees WR. Five-year survival following radiofrequency ablation of small, solitary, hepatic colorectal metastases. J Vasc Interv Radiol. 2008;19(5):712–7. https://doi.org/10.1016/j.jvir.2008.01.016.
15. Ruers T, Punt C, van Coevorden F, et al. Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC Intergroup phase II study (EORTC 40004). Ann Oncol. 2012;23(10):2619–26. https://doi.org/10.1093/annonc/mds053.
16. Gillams AR, Lees WR. Radiofrequency ablation of colorectal liver metastases. Abdom Imaging. 2005;30(4):419–26. https://doi.org/10.1007/s00261-004-0256-6.
17. Reuter NP, Woodall CE, Scoggins CR, et al. Radiofrequency ablation vs. resection for hepatic colorectal metastasis: therapeutically equivalent? J Gastrointest Surg. 2009;13(3):486–91. https://doi.org/10.1007/s11605-008-0727-0.
18. Tanaka K, Adam R, Shimada H, et al. Role of neoadjuvant chemotherapy in the treatment of multiple colorectal metastases to the liver. Br J Surg. 2003;90(8):963–9. https://doi.org/10.1002/bjs.4160.
19. Adam R, Vibert E, Pitombo M. Chimiothérapie d'induction et chirurgie des métastases hépatiques du cancer colorectal (induction chemotherapy and surgery of colorectal liver metastases). Bull Cancer. 2006;93(Suppl 1):S45–9.
20. Knudsen AR, Kannerup A-S, Mortensen FV, et al. Radiofrequency ablation of colorectal liver metastases downstaged by chemotherapy. Acta Radiol. 2009;50(7):716–21. https://doi.org/10.1080/02841850902991634.
21. Mitry E, Fields ALA, Bleiberg H, et al. Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials. J Clin Oncol. 2008;26(30):4906–11. https://doi.org/10.1200/JCO.2008.17.3781.
22. Yamakado K, Inaba Y, Sato Y, et al. Radiofrequency ablation combined with hepatic arterial chemoembolization using degradable starch microsphere mixed with Mitomycin C for the treatment of liver metastasis from colorectal cancer: a prospective multicenter study. Cardiovasc Intervent Radiol. 2017;40(4):560–7. https://doi.org/10.1007/s00270-016-1547-3.
23. Sartori S, Tombesi P, Di Vece F. Thermal ablation in colorectal liver metastases: lack of evidence or lack of capability to prove the evidence? World J Gastroenterol. 2016;22(13):3511–5. https://doi.org/10.3748/wjg.v22.i13.3511.
24. Ruers T, Punt CJA, van Coevorden F, et al. O-018 * Radiofrequency ablation (RFA) combined with chemotherapy for unresectable colorec-

tal liver metastases (CRC LM): long-term survival results of a randomised phase II study of the EORTC-NCRI CCSG-ALM intergroup 40004 (CLOCC). Ann Oncol. 2015;26(suppl 4):iv114–5. https://doi.org/10.1093/annonc/mdv235.17.

25. Solbiati L, Ahmed M, Cova L, et al. Small liver colorectal metastases treated with percutaneous radiofrequency ablation: local response rate and long-term survival with up to 10-year follow-up. Radiology. 2012;265(3):958–68. https://doi.org/10.1148/radiol.12111851.
26. Simon CJ, Dupuy DE, Mayo-Smith WW. Microwave ablation: principles and applications. Radiographics. 2005;25(Suppl 1):S69–83. https://doi.org/10.1148/rg.25si055501.
27. Babawale SN, Jensen TM, Frøkjær JB. Long-term survival following radiofrequency ablation of colorectal liver metastases: a retrospective study. World J Gastrointest Surg. 2015;7(3):33–8. https://doi.org/10.4240/wjgs.v7.i3.33.
28. Stintzing S, Grothe A, Hendrich S, et al. Percutaneous radiofrequency ablation (RFA) or robotic radiosurgery (RRS) for salvage treatment of colorectal liver metastases. Acta Oncol. 2013;52(5):971–7. https://doi.org/10.3109/0284186X.2013.766362.
29. Leung U, Kuk D, D'Angelica MI, et al. Long-term outcomes following microwave ablation for liver malignancies. Br J Surg. 2015;102(1):85–91. https://doi.org/10.1002/bjs.9649.
30. Shibata T, Niinobu T, Ogata N, et al. Microwave coagulation therapy for multiple hepatic metastases from colorectal carcinoma. Cancer. 2000;89(2):276–84.
31. Breedis C, Young G. The blood supply of neoplasms in the liver. Am J Pathol. 1954;30(5):969–77.
32. Wallace S, Carrasco CH, Charnsangavej C, et al. Hepatic artery infusion and chemoembolization in the management of liver metastases. Cardiovasc Intervent Radiol. 1990;13(3):153–60.
33. Riemsma RP, Bala MM, Wolff R, et al. Transarterial (chemo)embolisation versus no intervention or placebo intervention for liver metastases. Cochrane Database Syst Rev. 2013;4:CD009498. https://doi.org/10.1002/14651858.CD009498.pub3.
34. Richardson AJ, Laurence JM, Lam VWT. Transarterial chemoembolization with irinotecan beads in the treatment of colorectal liver metastases: systematic review. J Vasc Interv Radiol. 2013;24(8):1209–17. https://doi.org/10.1016/j.jvir.2013.05.055.
35. Pellerin O, Geschwind J-F. Traitement intra-artériel des métastases hépatiques de cancer colorectal (Intra-arterial treatment of liver metastases from colorectal carcinoma). J Radiol. 2011;92(9):835–41. https://doi.org/10.1016/j.jradio.2011.07.008.

36. Liu DM, Thakor AS, Baerlocher M, et al. A review of conventional and drug-eluting chemoembolization in the treatment of colorectal liver metastases: principles and proof. Future Oncol. 2015;11(9):1421–8. https://doi.org/10.2217/fon.15.3.
37. Clark TWI. Chemoembolization for colorectal liver metastases after FOLFOX failure. J Vasc Interv Radiol. 2013;24(1):66–7. https://doi.org/10.1016/j.jvir.2012.10.014.
38. Ceelen W, Praet M, Villeirs G, et al. Initial experience with the use of preoperative transarterial chemoembolization in the treatment of liver metastasis. Acta Chir Belg. 1996;96(1):37–40.
39. Vogl TJ, Jost A, Nour-Eldin NA, et al. Repeated transarterial chemoembolisation using different chemotherapeutic drug combinations followed by MR-guided laser-induced thermotherapy in patients with liver metastases of colorectal carcinoma. Br J Cancer. 2012;106(7):1274–9. https://doi.org/10.1038/bjc.2012.69.
40. Vogl TJ, Gruber T, Balzer JO, et al. Repeated transarterial chemoembolization in the treatment of liver metastases of colorectal cancer: prospective study. Radiology. 2009;250(1):281–9. https://doi.org/10.1148/radiol.2501080295.
41. Fiorentini G, Aliberti C, Turrisi G, et al. Intraarterial hepatic chemoembolization of liver metastases from colorectal cancer adopting irinotecan-eluting beads: results of a phase II clinical study. In Vivo. 2007;21(6):1085–91.
42. Martin RCG, Joshi J, Robbins K, et al. Hepatic intra-arterial injection of drug-eluting bead, irinotecan (DEBIRI) in unresectable colorectal liver metastases refractory to systemic chemotherapy: results of multi-institutional study. Ann Surg Oncol. 2011;18(1):192–8. https://doi.org/10.1245/s10434-010-1288-5.
43. Aliberti C, Benea G, Tilli M, et al. Chemoembolization (TACE) of unresectable intrahepatic cholangiocarcinoma with slow-release doxorubicin-eluting beads: preliminary results. Cardiovasc Intervent Radiol. 2008;31(5):883–8. https://doi.org/10.1007/s00270-008-9336-2.
44. Martin RCG, Scoggins CR, Tomalty D, et al. Irinotecan drug-eluting beads in the treatment of chemo-naive unresectable colorectal liver metastasis with concomitant systemic fluorouracil and oxaliplatin: results of pharmacokinetics and phase I trial. J Gastrointest Surg. 2012;16(8):1531–8. https://doi.org/10.1007/s11605-012-1892-8.
45. Jones RP, Dunne D, Sutton P, et al. Segmental and lobar administration of drug-eluting beads delivering irinotecan leads to tumour destruction: a case-control series. HPB (Oxford). 2013;15(1):71–7. https://doi.org/10.1111/j.1477-2574.2012.00587.x.
46. Akinwande O, Miller A, Hayes D, et al. Concomitant capecitabine with hepatic delivery of drug eluting beads in metastatic colorectal cancer. Anticancer Res. 2014;34(12):7239–45.

47. Fiorentini G, Aliberti C, Tilli M, et al. Intra-arterial infusion of irinotecan-loaded drug-eluting beads (DEBIRI) versus intravenous therapy (FOLFIRI) for hepatic metastases from colorectal cancer: final results of a phase III study. Anticancer Res. 2012;32(4):1387–95.
48. Martin RCG, Scoggins CR, Schreeder M, et al. Randomized controlled trial of irinotecan drug-eluting beads with simultaneous FOLFOX and bevacizumab for patients with unresectable colorectal liver-limited metastasis. Cancer. 2015;121(20):3649–58. https://doi.org/10.1002/cncr.29534.
49. Khodjibekova M, Szyszko T, Khan S, et al. Selective internal radiation therapy with Yttrium-90 for unresectable liver tumours. Rev Recent Clin Trials. 2007;2(3):212–6.
50. Kennedy AS, Coldwell D, Nutting C, et al. Resin 90Y-microsphere brachytherapy for unresectable colorectal liver metastases: modern USA experience. Int J Radiat Oncol Biol Phys. 2006;65(2):412–25. https://doi.org/10.1016/j.ijrobp.2005.12.051.
51. Kennedy A. Radioembolization of hepatic tumors. J Gastrointest Oncol. 2014;5(3):178–89. https://doi.org/10.3978/j.issn.2078-6891.2014.037.
52. Atassi B, Bangash AK, Lewandowski RJ, et al. Biliary sequelae following radioembolization with Yttrium-90 microspheres. J Vasc Interv Radiol. 2008;19(5):691–7. https://doi.org/10.1016/j.jvir.2008.01.003.
53. Sag AA, Savin MA, Lal NR, et al. Yttrium-90 radioembolization of malignant tumors of the liver: gallbladder effects. Am J Roentgenol. 2014;202(5):1130–5. https://doi.org/10.2214/AJR.13.10548.
54. Gray B, van Hazel G, Hope M, et al. Randomised trial of SIR-Spheres plus chemotherapy vs. chemotherapy alone for treating patients with liver metastases from primary large bowel cancer. Ann Oncol. 2001;12(12):1711–20.
55. van Hazel GA, Heinemann V, Sharma NK, et al. SIRFLOX: randomized phase III trial comparing first-line mFOLFOX6 (plus or minus Bevacizumab) versus mFOLFOX6 (plus or minus Bevacizumab) plus selective internal radiation therapy in patients with metastatic colorectal cancer. J Clin Oncol. 2016;34(15):1723–31. https://doi.org/10.1200/JCO.2015.66.1181.
56. Townsend AR, Chong LC, Karapetis C, et al. Selective internal radiation therapy for liver metastases from colorectal cancer. Cancer Treat Rev. 2016;50:148–54. https://doi.org/10.1016/j.ctrv.2016.09.007.
57. Lewandowski RJ, Memon K, Mulcahy MF, et al. Twelve-year experience of radioembolization for colorectal hepatic metastases in 214 patients: survival by era and chemotherapy. Eur J Nucl Med Mol Imaging. 2014;41(10):1861–9. https://doi.org/10.1007/s00259-014-2799-2.
58. Chan DL, Alzahrani NA, Morris DL, et al. Systematic review and meta-analysis of hepatic arterial infusion chemotherapy as bridging

therapy for colorectal liver metastases. Surg Oncol. 2015;24(3):162–71. https://doi.org/10.1016/j.suronc.2015.06.014.
59. Allard M-A, Malka D. Place of hepatic intra-arterial chemotherapy in the treatment of colorectal liver metastases. J Visc Surg. 2014;151(Suppl 1):S21–4. https://doi.org/10.1016/j.jviscsurg.2013.12.003.
60. Kemeny N, Fata F. Arterial, portal, or systemic chemotherapy for patients with hepatic metastasis of colorectal carcinoma. J Hepatobiliary Pancreat Surg. 1999;6(1):39–49.
61. Lévi FA, Boige V, Hebbar M, et al. Conversion to resection of liver metastases from colorectal cancer with hepatic artery infusion of combined chemotherapy and systemic cetuximab in multicenter trial OPTILIV. Ann Oncol. 2016;27(2):267–74. https://doi.org/10.1093/annonc/mdv548.
62. Malka D, Paris E, Caramella C, et al. Hepatic arterial infusion (HAI) of oxaliplatin plus intravenous (iv) fluorouracil (FU), leucovorin (LV), and cetuximab for first-line treatment of unresectable colorectal liver metastases (CRLM) (CHOICE): a multicenter phase II study. J Clin Oncol. 2010;28(15_suppl):3558. https://doi.org/10.1200/jco.2010.28.15_suppl.3558.
63. Boige V, Malka D, Elias D, et al. Hepatic arterial infusion of oxaliplatin and intravenous LV5FU2 in unresectable liver metastases from colorectal cancer after systemic chemotherapy failure. Ann Surg Oncol. 2008;15(1):219–26. https://doi.org/10.1245/s10434-007-9581-7.
64. Kemeny NE, Melendez FDH, Capanu M, et al. Conversion to resectability using hepatic artery infusion plus systemic chemotherapy for the treatment of unresectable liver metastases from colorectal carcinoma. J Clin Oncol. 2009;27(21):3465–71. https://doi.org/10.1200/JCO.2008.20.1301.
65. Allard MA, Sebagh M, Baillie G, et al. Comparison of complete pathologic response and hepatic injuries between hepatic arterial infusion and systemic administration of oxaliplatin in patients with colorectal liver metastases. Ann Surg Oncol. 2015;22(6):1925–32. https://doi.org/10.1245/s10434-014-4272-7.

Chapter 5
Liver Metastases of Neuroendocrine Tumors and CCC

Thomas J. Ettrich and Thomas Seufferlein

5.1 Liver Metastases of Neuroendocrine Tumors

5.1.1 Introduction

With an incidence of about 5/100.000, neuroendocrine tumors (NETs) are relatively rare tumors [1]. They originate from different types of neuroendocrine cells located not only in endocrine glands like the thyroid but in almost every tissue. NETs can arise in almost every part of the body, but the lung (about 30% of all NETs) and the gastro-entero-pancreatic 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 advanced tumor stage (UICC IV) exhibiting liver metastases. There are two different groups of GEP-NETs—hormonally inactive (70%) and hormon-

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ally 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.

There are different classification systems for the classification of NETs. Most frequently used 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 are well-differentiated types: neuroendocrine tumor (NET G1) with low mitotic activity (ki67 $\leq$2%) and NET G2 with moderate mitotic activity (ki67 3–20%). The third category is a poorly differentiated tumor type called neuroendocrine carcinoma (NEC) G3 with a high mitotic activity (ki67 >20%).

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

Metastasized, poorly differentiated NEC G3 tumors, independently of their primary localization, should be treated with systemic chemotherapy. A common combination in this situation is cisplatin or carboplatin plus etoposide. The carboplatin/etoposide combination 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, 5]. Other combinations like fluoropyrimidines plus oxaliplatin (RR 23%) are also an option [6].

There are several systemic and locoregional treatment options particularly for well-differentiated advanced G1 and G2 GEP-NETs. Somatostatin analogues (SSA) like lanreotide or octreotide are widely used and recommended as first therapeutic agents especially in GEP-NETs [5]. 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 peptide hormones that cause clinical syndromes and thereby reduce the symptom burden and improve quality of life. In addition, SSAs also exhibit an antiproliferative effect especially in midgut and pancreatic NETs, even if they are nonfunctioning. It could be demonstrated that SSAs prolong the time to progression (TTP) of these tumors compared to placebo (PROMID trial, 14.3 months vs. 6 months; CLARINET trial, median not yet reached vs. 18 months) [7, 8].

The site of the primary tumor can also define the choice of treatment. NETs of the small intestine and colon are not very sensitive to systemic chemotherapy, whereas pancreatic NETs do respond well to systemic treatment. In pancreatic NETs systemic chemotherapy with streptozotocin + 5-FU or doxorubicin reduces hormonal symptoms and results in an objective tumor response in 20–35% of patients [5]. An exceptionally high and durable response rate of metastatic NETs of the pancreas but also other organs has been reported in retrospective studies for the combination of capecitabine and temozolomide [9–12]. Taken together, systemic therapy is a validated and well-tolerated therapeutic option in pancreatic NETs.

In the recent years, novel targeted drugs like everolimus, a mTor inhibitor (in GEP-NETs and lung NETs) [13, 14], or sunitinib, a multi-tyrosine kinase inhibitor (in pancreatic NETS) [15] alone (phase III trials) or sometimes in combination with SSAs (only retrospective analysis) [16] improved TTP (sunitinib vs. placebo, 11.4 vs. 5.5 months; everolimus vs. placebo, 11 vs. 3.9 months (RADIANT4 trial), respectively) in well-differentiated NETs in randomized, controlled phase 3 trials.

Finally, peptide radio receptor therapy (PRRT) with radiolabeled somatostatin analogues is a novel systemic therapeutic

option in somatostatin receptor-positive metastatic NETs (as determined by SSA scintigraphy or Ga68 DOTATOC PET-CT scan) progressing on a SSA treatment. Results from the NETTER-1 trial, the first phase III, randomized, controlled trial evaluating PRRT vs. octreotide LAR in patients with inoperable, progressive, somatostatin receptor-positive midgut NETs, show that the median PFS was not reached for PRRT (×4 administrations) and was 8.4 months with 60 mg octreotide LAR (p <0.0001, HR 0.21). The number of complete and partial remissions was 18.8% in the PRRT group and 3% in the octreotide LAR 60 mg group (p <0.0004) [17].

5.1.1.2 Options for Regional Tumor Therapy

There are various situations where regional tumor therapies like transarterial embolization/transarterial chemoembolization (TAE/TACE), radiofrequency ablation (RFA)/microwave ablation, and selective internal radiation therapy (SIRT) are used in the treatment of NETs, particularly in case of liver-only metastases of functional NETs. Here, reducing the tumor burden in the liver is paramount to reduce symptoms 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. As demonstrated by the trials listed 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 [18–26]. Even combinations of SIRT and PRRT have been investigated [22, 27]. In general, for oligonodular metastatic deposits in the liver, local resection or RFA/microwave ablation is recommended (size limit for RFA/microwave ablation about 4 cm). In multinodular disease with higher tumor load, TACE,

TAE, or SIRT is the treatment of choice. However, long-time data for SIRT are still pending. In conclusion, regional tumor therapy is an important part of the multidisciplinary treatment of NET patients, especially in case of well-differentiated NETs of the gastro-entero-pancreatic system.

5.1.2 Study Results: Liver Metastases of Neuroendocrine Tumors

McStay et al. (2005) [27]

Concept	HAI of yttrium 90 (^{90}Y)-tetraazacyclododecane tetraacetic acid (DOTA)-lanreotide, phase II trial
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 year: 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

Fiorentini et al. (2004) [19]

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 month

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

Kress et al. (2003) [23]

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 month (after TACE), 54 month (after diagnosis) 5 year survival rate (%): 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

Touzios JG et al. (2005) [25]

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 patients (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 + mitomycin C			
Survival	Parameter	Not aggressive	Aggressive treatment	
		R/A	TACE +/−R/A	
	Morbidity (%)	25	42	28
	Symptomatic improvement (%)	42	95*	88*
	Median OS (months)	20	>96*	50*
	5-OS rate (%)	25	72*	50*
Conclusion	Aggressive management improves survival of the patients, and chemoembolization improves the success rate of this strategy			

*$p < 0.05$

Gupta et al. (2005) [20]

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 months PFS: 23 months 1 year, 2 years, 5 years: 95, 69, 29% Median survival for patients with islet cell carcinoma: 23 months PfS: 16 months 1 year, 2 years, 5 years: 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

Osborne et al. (2006) [24]

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 months (after TAE). 44 months (carcinoid), 31 months (pancreatic endocrine tm), 15 months (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) [21]

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 applications 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 months 1 year, 2 years, 3 years, 4 years, 5 years: 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

Christante et al. (2008) [18]

Concept	HAI + TACE for liver metastases + octreotide (retrospective analysis)
N	77 (61 carcinoid, 16 islet cell carcinomas)
Therapy	HAI (3 × 4 monthly): 5 FU, followed by TACE, 100 mg cisDDP + 30 mg doxorubicin + 15 mg MMC + Lipiodol (4 monthly between applications in both lobs)
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 HAI or TACE: 36–44 months (total), 31–80 months (carcinoid), 20–23s (islet cell carcinoma) HAI + TACE: 39 months (total), 51 months (carcinoid), 29 (islet cell carcinoma) 1 year, 5 years (total): 78%, 27% PFS (total): 19 months
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) [28]

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 months PFS (total): 19 months 1 year, 5 year rate (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 are safe and produce high response rates, even with extensive tumor replacement of normal liver and/or heavy pretreatment

Kratochwil et al. (2010) [22]

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 severalfold higher after Selective i.a. Administration in comparison with i.v. 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

5.2 Cholangiocarcinoma (CCC)

5.2.1 Introduction

Cholangiocarcinoma (CCC) originates in the bile duct system. CCC is a rare type of adenocarcinoma with an annual incidence of 1–2/100.000 [29].

CCC is considered to be an incurable malignancy unless the tumor is surgically resectable. However, most patients, in particular those with intrahepatic CCCs, present with an advanced disease stage at 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 alone as demonstrated by a randomized, controlled phase 3 trial (OS 11.7 vs. 8.1 months) [30]. To prevent tumor complications like malignant bile duct obstruction with resulting cholestasis and cholangitis, regional tumor therapies like ERCP-based stenting are regularly used. 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) [31, 32].

Other regional tumor therapies like TAE, TACE, RFTA, or SIRT are currently not the standard of care for the treatment of CCC. However, as shown below, especially TACE with drugs like gemcitabine and/or cisplatin shows promising results in preliminary studies (OS: i.a. gemcitabine + cisplatin vs. systemic gemcitabine alone: 14 vs. 6 months) [33]. Additionally retrospective analyses on SIRT in unresectable intrahepatic cholangiocarcinoma report positive results. Thirty-three patients were treated with yttrium-90 microspheres resulting in a disease control rate of 85%, a time to progression of 9.8 months, and median overall survival of 22 months [34].

Nevertheless, at the moment there is too few data for this type of regional therapy to become a standard of care. In individual situations like in case of intolerable toxicity of or contraindications for systemic chemotherapy, regional therapeutic strategies such as TACE or SIRT may be a valuable treatment option for patients with inoperable CCC.

5.2.2 Study Results: CCC

Ortner et al. (2003) [28]

Concept	Stenting plus subsequent photodynamic therapy vs. stenting alone, phase II trial
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 non-resectable CCC

Kirchhoff et al. (2005) [35]

Concept	Combination of systemic and regional chemotherapy, phase II trial
N	8
Therapy	IV: 1000 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 months
Survival	12 months
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 not resectable CCC

Cantore et al. (2005) [36]

Concept	Combination of systemic and regional chemotherapy, phase II trial
N	30 (25 intrahepatic cholangiocarcinoma, 5 gallbladder carcinoma)
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 months
Survival	Median survival: 13 months 1 year, 2 year rate: 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) [37]

Concept	TACE with Doxorubicin-eluting beads, phase II trial
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 months
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) [32]

Concept	Stenting plus subsequent photodynamic therapy vs. stenting alone, randomized phase II trial
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) [38]

Concept	Dose finding study for intra-arterial application of Gemcitabine −/+ DSM
N	24
Therapy	HAI, 1000 mg/m^2 (d1 + 8); dose step, 200 mg/m^2 (3 patients/group)—till MTD TACE: starting at 1400 mg/m^2 + DSM; dose step 200 mg/m^2—till MTD
Response rates	HAI: MTD: 1400 mg/m^2 SD: *N* = 9/12 (75%) TtP: 4 months TACE: MTD: 1800 mg/m^2 SD: *N* = 11/12 (92%) TTP: 7 months
Survival	HAI, 13 months; TACE, 20 months
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 1000 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) [39]

Concept	Combination of oral and regional chemotherapy, phase II trial
N	20
Therapy	Oral: 1000 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 months
Survival	Median survival: 18 months 1 year: 74%
Toxicity	Cumulative Grade III: 35%; (neutropenia, nausea/emesis, mucositis, alopecia)
Conclusions	This combined locoregional and oral chemotherapeutic therapeutic approach seems to be active and safe with a good survival response

Herber et al. (2007) [40]

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 months 1 year, 2 years, 3 years: 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 i.v. 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) [41]

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 months 1 year, 2 year, 3 year: 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) [42]

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 months
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) [33]

Concept	Gemcitabine-based TACE (retrospective analysis)
N	42
Therapy	1250 mg/m^2 up to 2250 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 months Gemcitabine + cisDDP vs. Gemcitabine alone: 14 vs. 6 months
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

Hoffmann et al. (2012) [34]

Concept	SIRT with (90)Y resin microspheres, retrospective analysis
N	33
Therapy	Selective intra-arterial radiotherapy with (90)Y resin microspheres, assessed at 3-month intervals
Response rates	36%, partial response; 52%, stable disease; 15%, progressive disease after 3 months
Survival	The median OS was 22 months posttreatment and 43.7 months postdiagnosis
Conclusions	Radioembolization is an effective and safe option for patients with unresectable ICC. Predictors for prolonged survival are performance status, tumor burden, and RECIST response

Poggi et al. (2009) [43]

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 + 1000 mg/m^2 Gemcitabine (2–4 weeks after TACE) vs. IV: 85 mg/m^2 Oxaliplatin + 1000 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 months IV: 3 months Median survival: TACE+: 13 months IV: 30 months
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

References

1. Yao JC, Hassan M, Phan A, et al. One hundred years after “carcinoid”: epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008;26:3063–72.
2. Mitry E, Baudin E, Ducreux M, et al. Treatment of poorly differentiated neuroendocrine tumours with etoposide and cisplatin. Br J Cancer. 1999;81:1351–5.
3. Moertel CG, Kvols LK, O'Connell MJ, et al. Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin. Evidence of major therapeutic activity in the anaplastic variants of these neoplasms. Cancer. 1991;68:227–32.
4. Eriksson B, Annibale B, Bajetta E, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: chemotherapy in patients with neuroendocrine tumors. Neuroendocrinology. 2009;90:214–9.
5. Garcia-Carbonero R, Sorbye H, Baudin E, et al. ENETS Consensus Guidelines for high-grade gastroenteropancreatic neuroendocrine tumors and neuroendocrine carcinomas. Neuroendocrinology. 2016;103:186–94.
6. Bajetta E, Catena L, Procopio G, et al. Are capecitabine and oxaliplatin (XELOX) suitable treatments for progressing low-grade and high-grade neuroendocrine tumours? Cancer Chemother Pharmacol. 2007;59:637–42.
7. Caplin ME, Pavel M, Cwikla JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med. 2014;371:224–33.

8. Rinke A, Muller HH, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol. 2009;27:4656–63.
9. Crespo G, Jimenez-Fonseca P, Custodio A, et al. Capecitabine and temozolomide in grade 1/2 neuroendocrine tumors: a Spanish multicenter experience. Future Oncol. 2016;13:615–24.
10. Kotteas EA, Syrigos KN, Saif MW. Profile of capecitabine/temozolomide combination in the treatment of well-differentiated neuroendocrine tumors. Onco Targets Ther. 2016;9:699–704.
11. Peixoto RD, Noonan KL, Pavlovich P, et al. Outcomes of patients treated with capecitabine and temozolomide for advanced pancreatic neuroendocrine tumors (PNETs) and non-PNETs. J Gastrointest Oncol. 2014;5:247–52.
12. Strosberg JR, Fine RL, Choi J, et al. First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. Cancer. 2011;117:268–75.
13. Yao JC, Fazio N, Singh S, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet. 2016;387:968–77.
14. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med. 2011;364:514–23.
15. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med. 2011;364:501–13.
16. Capdevila J, Sevilla I, Alonso V, et al. Evaluation of the efficacy and safety of lanreotide in combination with targeted therapies in patients with neuroendocrine tumours in clinical practice: a retrospective cross-sectional analysis. BMC Cancer. 2015;15:495.
17. Strosberg JR, Wolin EM, Chasen B, et al. NETTER-1 phase III: progression-free survival, radiographic response, and preliminary overall survival results in patients with midgut neuroendocrine tumors treated with 177-Lu-Dotatate. J Clin Oncol. 2016;2016(suppl 4S; abstr 194):34.
18. Christante D, Pommier S, Givi B, et al. Hepatic artery chemoinfusion with chemoembolization for neuroendocrine cancer with progressive hepatic metastases despite octreotide therapy. Surgery. 2008;144:885–93. discussion 893–4.
19. Fiorentini G, Rossi S, Bonechi F, et al. Intra-arterial hepatic chemoembolization in liver metastases from neuroendocrine tumors: a phase II study. J Chemother. 2004;16:293–7.

20. Gupta S, Johnson MM, Murthy R, et al. Hepatic arterial embolization and chemoembolization for the treatment of patients with metastatic neuroendocrine tumors: variables affecting response rates and survival. Cancer. 2005;104:1590–602.
21. Ho AS, Picus J, Darcy MD, et al. Long-term outcome after chemoembolization and embolization of hepatic metastatic lesions from neuroendocrine tumors. Am J Roentgenol. 2007;188:1201–7.
22. Kratochwil C, Giesel FL, Lopez-Benitez R, et al. Intraindividual comparison of selective arterial versus venous 68Ga-DOTATOC PET/CT in patients with gastroenteropancreatic neuroendocrine tumors. Clin Cancer Res. 2010;16:2899–905.
23. Kress O, Wagner HJ, Wied M, et al. Transarterial chemoembolization of advanced liver metastases of neuroendocrine tumors—a retrospective single-center analysis. Digestion. 2003;68:94–101.
24. Osborne DA, Zervos EE, Strosberg J, et al. Improved outcome with cytoreduction versus embolization for symptomatic hepatic metastases of carcinoid and neuroendocrine tumors. Ann Surg Oncol. 2006;13:572–81.
25. Touzios JG, Kiely JM, Pitt SC, et al. Neuroendocrine hepatic metastases: does aggressive management improve survival? Ann Surg. 2005;241:776–83. discussion 783–5.
26. Vogl TJ, Naguib NN, Zangos S, et al. Liver metastases of neuroendocrine carcinomas: interventional treatment via transarterial embolization, chemoembolization and thermal ablation. Eur J Radiol. 2009;72:517–28.
27. McStay MK, Maudgil D, Williams M, et al. Large-volume liver metastases from neuroendocrine tumors: hepatic intraarterial 90Y-DOTA-lanreotide as effective palliative therapy. Radiology. 2005;237:718–26.
28. Kennedy AS, Dezarn WA, McNeillie P, et al. Radioembolization for unresectable neuroendocrine hepatic metastases using resin 90Y-microspheres: early results in 148 patients. Am J Clin Oncol. 2008;31:271–9.
29. Landis SH, Murray T, Bolden S, et al. Cancer statistics, 1998. CA Cancer J Clin. 1998;48:6–29.
30. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010;362:1273–81.
31. Ortner ME, Caca K, Berr F, et al. Successful photodynamic therapy for nonresectable cholangiocarcinoma: a randomized prospective study. Gastroenterology. 2003;125:1355–63.
32. Zoepf T, Jakobs R, Arnold JC, et al. Palliation of nonresectable bile duct cancer: improved survival after photodynamic therapy. Am J Gastroenterol. 2005;100:2426–30.

33. Gusani NJ, Balaa FK, Steel JL, et al. Treatment of unresectable cholangiocarcinoma with gemcitabine-based transcatheter arterial chemoembolization (TACE): a single-institution experience. J Gastrointest Surg. 2008;12:129–37.
34. Hoffmann RT, Paprottka PM, Schon A, et al. Transarterial hepatic yttrium-90 radioembolization in patients with unresectable intrahepatic cholangiocarcinoma: factors associated with prolonged survival. Cardiovasc Intervent Radiol. 2012;35:105–16.
35. Kirchhoff T, Zender L, Merkesdal S, et al. Initial experience from a combination of systemic and regional chemotherapy in the treatment of patients with nonresectable cholangiocellular carcinoma in the liver. World J Gastroenterol. 2005;11:1091–5.
36. Cantore M, Mambrini A, Fiorentini G, et al. Phase II study of hepatic intraarterial epirubicin and cisplatin, with systemic 5-fluorouracil in patients with unresectable biliary tract tumors. Cancer. 2005;103: 1402–7.
37. Burger I, Hong K, Schulick R, et al. Transcatheter arterial chemoembolization in unresectable cholangiocarcinoma: initial experience in a single institution. J Vasc Interv Radiol. 2005;16:353–61.
38. Vogl TJ, Schwarz W, Eichler K, et al. Hepatic intraarterial chemotherapy with gemcitabine in patients with unresectable cholangiocarcinomas and liver metastases of pancreatic cancer: a clinical study on maximum tolerable dose and treatment efficacy. J Cancer Res Clin Oncol. 2006;132:745–55.
39. Mambrini A, Guglielmi A, Pacetti P, et al. Capecitabine plus hepatic intra-arterial epirubicin and cisplatin in unresectable biliary cancer: a phase II study. Anticancer Res. 2007;27:3009–13.
40. Herber S, Otto G, Schneider J, et al. Transarterial chemoembolization (TACE) for inoperable intrahepatic cholangiocarcinoma. Cardiovasc Intervent Radiol. 2007;30:1156–65.
41. Kim JH, Yoon HK, Sung KB, et al. Transcatheter arterial chemoembolization or chemoinfusion for unresectable intrahepatic cholangiocarcinoma: clinical efficacy and factors influencing outcomes. Cancer. 2008;113:1614–22.
42. Aliberti C, Benea G, Tilli M, et al. Chemoembolization (TACE) of unresectable intrahepatic cholangiocarcinoma with slow-release doxorubicin-eluting beads: preliminary results. Cardiovasc Intervent Radiol. 2008;31:883–8.
43. Poggi G, Amatu A, Montagna B, et al. OEM-TACE: a new therapeutic approach in unresectable intrahepatic cholangiocarcinoma. Cardiovasc Intervent Radiol. 2009;32:1187–92.

Chapter 6
Liver Metastases of Other Indications

Michel Ducreux

6.1 Introduction

Locoregional treatment of liver metastases has been developed especially for tumors that give liver-limited metastases. For all the tumor types and especially for 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.

Another potential interest of locoregional treatment of liver metastases seems to develop more active medical treatments in rather orphan tumors such as pancreatic cancer.

Even in diseases sensitive to several drugs or drug regimens, locoregional treatment could also prevent the appearance of resistance to systemic treatment (pancreatic carcinoma, breast cancer).

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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

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.

6.2 Liver Metastases of Pancreatic Adenocarcinoma

6.2.1 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%
Occurrence of hepatic metastases	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
Occurrence of hepatic metastases	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 (nonrandomized)
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 months vs. 13.4 months NS
Occurrence of hepatic metastases	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

6.2.2 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 year, 2 years, 3 years: 67, 31, 14% Median survival: 16 months
Toxicity	Cytopenia (grade 2): $N = 11$, 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

Vogl et al. (2006) [5]

Concept	Intra-arterial dose finding of gemcitabine +/− starch microspheres
N	24
Access	Catheter into A. femoralis placed in the truncus coeliacus
Therapy	HAI: Initial dose, 1000 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: 1600 mg/m^2 TACE: 1800 mg/m^2
Time to progression	HAI: 4 months TACE: 7 months
Survival	Median survival: 9.1 months HAI: 14 months TACE: 20 months
Toxicity	Myelosuppression (grade 3)
Conclusion	This clinical study indicates that the intra-arterial application of gemcitabine with doses higher than the recommended 1000 mg/m^2 is well tolerated if combined with microspheres and yields respectable results in patients who do not respond to systemic chemotherapy

Heinrich et al. (2013) [6]

Concept	HAI + IV therapy
N	17
Access	Catheter into A. femoralis placed in the truncus coeliacus
Therapy	HAI: mitomycin C 8.5 mg/m^2 and gemcitabine 500 mg/m^2 d1, d22 IV: gemcitabine 500 mg/m^2 d8, d15
Response rates	24%
Survival	Median survival: 9.1 months Median progression-free survival: 4.6 months
Toxicity	Grade 3–4 hematological toxicity: 48.6% of the cycles
Conclusion	IV and IA treatment with gemcitabine combined with IA treatment with mitomycin C gives interesting treatment in refractory patients
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: 1000 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 3), *N* = 8; thrombocytopenia, *N* = 6; non-hematologic (grade 3), *N* = 5
Conclusion	For patients with advanced pancreatic cancer, HAI with systemic chemotherapy appeared to be effective and may prolong survival

6.2.2.1 Randomized Studies

Cantore et al. (2003) [8]

Concept	Intra-arterial chemotherapy vs. IV gemcitabine
N	71 vs. 67
Access	Catheter via A. femoralis in truncus coeliacus
Therapy	5FU 1000 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%, nausea/vomiting 4%

6.2.2.2 TACE

Azizi et al. (2011) [9]

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 + 1000 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 months (SD, 20 months; PD, 5 months)
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

6.2.3 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.

6.3 Liver Metastases of Melanoma

6.3.1 Hepatic Arterial Infusion

Becker et al. (2002) [10]

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 months (HAI vs. IV: 369 vs. 349 d)
Toxicity	Thrombocytopenia, leucopenia (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) [11]

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 months
Survival	Median survival: 15 months 1 year, 2 years, 3 years: 67, 29, 12%
Toxicity	Grades 3 and 4, 11% (mainly hematoxicity); grade 2, the grade toxicities seen in these patients were related to hematologic toxicity 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) [12]

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 months
Survival	Median survival: 14 months 1 year, 2 years, 3 years: 67, 29, 12%
Toxicity	≥ grade 3 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) [13]

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) [14]

Concept	HAI
N	23
Inclusion criteria	Patients after treatment failure of systemic therapy for hepatic metastases from melanoma (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 (PR + SD): 72%
Survival	Median PFS: 6.2 months Median survival: 21 months
Toxicity	No grade 4 toxicity Grade 3: 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) [15]

Concept	HAI (retrospective analysis)
N	61
Inclusion criteria	Liver and extrahepatic metastases
Therapy	Melphalan or melphalan + fotemustine, dacarbazine, MMC, doxorubicin, or gemcitabine Every 4 weeks
Response rates	At four sessions: PR, 30%; SD, 15%; PD, 55% At six sessions: PR, 19%; SD, 57%; PD, 24%
Survival	Median survival: 10 months Extrahepatic vs. hepatic metastases only: 6 vs. 14 months ≤ vs. >9 metastases: 17 vs. 9 months
Toxicity	Liver failure in one patient (0.4%), thrombocytopenia (20%), leucopenia (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

6.3.2 TACE

6.3.2.1 Standard TACE

Mavligit et al. (1988) [16]

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 months
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) [17]

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 months
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) [18]

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 months
Toxicity	Mild. MTD was not reached up to the dose level of 2000 mg, 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) [19]

Concept	TACE
N	25
Inclusion criteria	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 months
Toxicity	No grade 4 toxicity Grade 3: 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

Gupta et al. (2010) [20]

Concept	TACE
N	125
Inclusion criteria	Liver metastases of uveal melanoma
Therapy	Chemoembolization
Response rates	Partial response: 27%
	Disease stabilization: 65%
Survival	Median overall survival: 6.7 months
	Median disease-free survival: 3.8 months
	Multivariate analysis: >75% liver involvement and high lactate dehydrogenase levels were associated with short overall survival
	Median survival >75%: 2.4 months
Toxicity	???
Conclusions	TACE is an active treatment of liver metastases of uveal melanoma

Huppert et al. (2010) [21]

Concept	TACE
N	14
Inclusion criteria	Liver metastases of uveal melanoma
Therapy	Chemoembolization with continuous infusion of cisplatin

Response rates	Partial response: 57% Disease stabilization: 29%
Survival	Median overall survival: 11.5 months Median time to progression: 8.5 months <25% liver involvement: median overall survival 17 months
Toxicity	???
Conclusions	TACE of liver metastases from uveal melanoma is well tolerated and may prolong survival in patients with limited tumor extension

Ahrar et al. (2011) [22]

Concept	TACE
N	42
Inclusion criteria	Liver metastases of cutaneous melanoma
Therapy	Chemoembolization
Response rates	Partial response: 38.9% Disease stabilization: 47.2%
Survival	Median overall survival: 7 months Median disease-free survival: 6 months Significant predictors of OS: patient's age, LDH levels, type of treatment, number of extrahepatic metastatic sites, and response to therapy
Toxicity	
Conclusions	TACE is an active treatment of liver metastases of cutaneous melanoma

Edelhauser et al. (2012) [23]

Concept	TACE
N	21
Inclusion criteria	Patients with liver metastases from uveal melanoma
Therapy	50 mg/m^2 fotemustine + Lipiodol every 6–8 weeks
Response rates	RR: 14% Disease control rate (PR + SD): 72%
Survival	Median survival: 28.7 months

Toxicity	Minor side effects: postembolization syndrome with fever 19%, pain 14%, nausea 24%
Conclusions	TACE with fotemustine of hepatic metastases from uveal melanoma with fotemustine was well tolerated and gave interesting results in terms of response rate and overall survival

Valsecchi et al. (2015) [24]

Concept	Embolization with or without granulocyte-macrophage colony-stimulating factor (GM-CSF) (immunoembolization)
N	Randomized phase II trial Immunoembolization = 25 (IE) Bland embolization = 27 (BE)
Inclusion criteria	Patients with liver metastases from uveal melanoma
Therapy	GM-CSF 2000 μg + Lipiodol or normal saline solution + Lipiodol Followed by embolization with gelatin sponge
Response rates	RR: 21% IE group versus 17% BE group Disease control rate (PR + SD): 68% IE group vs. 81% BE group
Survival	Median survival: 21.5 months IE group, 17.2 BE group
Toxicity	No difference between the two groups. Most common side effects: transient increases of hepatic enzyme levels and liver pain
Conclusions	Immunoembolization induced more robust inflammatory responses, which correlated with the delayed progression of extrahepatic metastases

6.3.2.2 TACE with New Embolization Vectors

Firorentini et al. (2009) [25]

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 had one procedure, 5 patients had 2 procedures
Response rates	Three patient reduction of 90%, three patient reduction of 80%, four patient 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

Valpione et al. (2015) [26]

Concept	TACE with DC beads loaded with irinotecan (DEBIRI) Retrospective analysis of a prospectively maintained database
N	58
Inclusion criteria	Liver metastases of uveal melanoma. First-line therapy
Therapy	DC beads loaded with irinotecan (DEBIRI) Every 4 weeks
Survival	Median survival TACE with DC beads:16.5 months Historical control: 12.2 months Better benefit in patients with liver involvement >50%
Toxicity	No severe toxicity
Conclusions	TACE using DC beads loaded with irinotecan is effective in liver metastases from uveal melanoma

6.3.3 Radioembolization

Gonsalves et al. (2010) [27]

Concept	Radioembolization with ^{90}Y spheres
N	32
Inclusion criteria	Liver metastases of uveal melanoma. Refractory patients
Therapy	^{90}Y spheres (SIRTEX)
Response rates	CR: 3% PR: 3% SD: 56%
Survival	Median overall survival: 10 months Progression-free survival: 4.7 months
Toxicity	Grade 3–4 hepatic toxicity, 12.5%; systemic toxicity, 28% grades 1–2
Conclusions	Interesting ratio efficacy/toxicity of radioembolization in refractory uveal melanoma

6.3.4 High-Dose Hepatic Arterial Infusion and Hemofiltration

Pingpank et al. (2005) [28]

Concept	High-dose liver infusion of melphalan + hemofiltration (PHP), 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 (Delcath® system). 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

Hughes et al. (2016) [29]

Concept	High-dose liver infusion of melphalan + hemofiltration, phase III
N	44: percutaneous hepatic perfusion (PHP) 49: best alternative care (BAC), 28 crossovers to PHP
Inclusion criteria	Liver metastases of cutaneous and uveal melanoma
Therapy	Double-balloon inferior vena cava (IVC) catheter system. Infusion of melphalan (30 min) and hemoperfusion of the liver effluent with drug filtration cartridges (Delcath® system). Melphalan 3 mg/kg. Treatment every 4–8 weeks
Response rates	RR PHP: 36%
Survival	Median hepatic progression-free survival: 7.0 months PHP vs. 1.6 months BAC. Median overall progression-free survival: 5.4 months vs. 1.6 months Median overall survival: 10.6 months PHP vs. 10.0 months, NS
Toxicity	Any adverse events: 90%. 17.1% febrile neutropenia. Procedure-associated hypotension routinely noted
Conclusions	PHP with melphalan is a new treatment option for unresectable metastatic melanoma in the liver

6.3.5 Recommendations

Uveal melanoma metastases occur most commonly in the liver. Even if recent treatments have 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. In this specific population, the role of immunotherapy seems less clear, and surgery remains the first choice in the treatment of these lesions. But surgery 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 and PHP with high-dose melphalan, but there are less data to support this kind of treatment.

6.4 Liver Metastases of Breast Cancer

6.4.1 HAI

Cocconi et al. (2005) [30]

Concept	HAI
N	10
Inclusion criteria	Liver metastases under systemic chemotherapy
Therapies	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 months
Toxicity	Hematological (grade 3), $N = 6$; non-hematological (grade 3), $N = 2$ (pain, asthenia)
Conclusions	The administration of docetaxel via the hepatic artery is feasible with a highly interesting response

Zhang et al. (2013) [31]

Concept	HAI
N	28
Inclusion criteria	Liver metastases
Therapy	Docetaxel 75 mg/m^2 and epiadriamycin 50 mg/m^2 every 3 weeks
Toxicity	No serious complications
Response rates	CR: 4% RR: 82%
Survival	None reported. 3 R0 liver surgery
Conclusion	Intra-arterial chemoinfusion is a safe and effective therapy, achieving downstaging in a relatively short period for locally advanced breast cancer

6.4.2 TACE

Giroux et al. (2004) [32]

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 months (from primary diagnosis); 20 months (from liver metastasis diagnosis); 6 months (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) [33]

Concept	TACE vs. systemic chemotherapy (retrospective comparison)
N	48 (28, 20)
Inclusion criteria	Liver metastases under systemic chemotherapy
Therapy	TACE: 1000 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 months 1 year, 2 years, 3 years (%): 63, 30, 13 vs. 34, 11, 0
Toxicity	TACE: leuko-/thrombocytopenia (grades 1–2), elevation of liver enzymes (grades 1–2) IV: leuko−/thrombocytopenia (grades 1–4), elevation of liver enzymes (grades 1–2)
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. (2010) [34]

Concept	TACE with two different schedules of chemotherapy
N	208
Inclusion criteria	Liver metastases
Therapy	8 mg/m^2 MMC + Lipiodol (n = 76) 1000 mg/m^2 gemcitabine + Lipiodol (n = 21) 8 mg/m^2 MMC + 1000 mg/m^2 gemcitabine + Lipiodol (n = 111) Embolization with starch microspheres
Response rates	RR 13% Stable disease: 36.5%

Survival	1 year, 2 years, 3 years survival of the whole group: 69, 40, 33% Median survival MMC: 13.3 months Gemcitabine: 11 months MMC + gemcitabine: 24.8 months
Conclusion	TACE is an optional therapy for treatment of liver metastases in breast cancer patients with better results from the combined chemotherapy protocol

Vogl et al. (2011) [35]

Concept	TACE 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 + 1000 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 months (5–101) 1 year, 2 years, 3 years, 5 years (%): 89, 56, 37, 13% MMC: 45 months (5–101) MMC + gemcitabine: 26 months (5–63) TtP: MMC vs. MMC + gemcitabine, 8 vs. 11 months
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

Duan et al. (2011) [36]

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 months (42 vs. 26 months) $p = 0.027$ 1 year, 2 years, 3 years (%): 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 group of patients
Conclusions	The combined treatment of TACE and systemic chemotherapy may prolong survival for liver metastases in breast cancer after mastectomy

Eichler et al. (2013) [37]

Concept	TACE with gemcitabine
N	43
Inclusion criteria	Liver metastases
Therapy	Suspension of gemcitabine 1.200 mg/m^2, 2–10 mL/m^{2}of Lipiodol, and 5 mL of degradable starch microsphere (EmboCept) administered intra-arterially up to three times with a 4-week interval (n = 111)
Toxicity	Mild hematological toxicity: 20%. Grade 1/2 nausea/vomiting: 51%/5%. One case of Lipiodol encapsulation in the stomach. Full recovery in 1 day

Response rates	RR 7% Stable disease: 37%
Survival	Median progression-free survival: 3.3 months Median overall survival: 10.2 months
Conclusion	Transarterial chemoembolization with gemcitabine is well tolerated and provides an alternative treatment method for patients with liver metastases of breast cancer

6.4.3 TACE with New Vectors

Martin et al. (2012) [38]

Concept	TACE with doxorubicin-loaded drug-eluting beads (DEBDOX). Multicenter, prospective, open, noncontrolled repeat treatment registry
N	40 patients, 75 procedures
Inclusion criteria	Liver metastases under systemic chemotherapy
Therapy	Doxorubicin-loaded drug-eluting beads (DEBDOX)
Response rates	???
Survival	Median progression-free survival: 26 months Median overall survival: 47 months
Toxicity	13 grade 1 and 2 adverse events (17% of the procedures)
Conclusions	The treatment of hepatic metastasis from MBC using DEBDOX is an effective local therapy with very high response rates and a very safe toxicity profile

6.4.4 Radioembolization with (90)Y-Labeled Microspheres

Cianni et al. (2013) [39]

Concept	Radioembolization with (90)Y-labeled resin microspheres
N	52
Inclusion criteria	Inoperable and chemotherapy-refractory hepatic metastases

Therapy	(90)Y-labeled resin microspheres: median dose 1.9 GBq (range 0.33–2.71)
Response rates	RR: 56% SD: 35%
Survival	Median survival: 11.5 months 14.3 months in patients without extrahepatic disease, ECOG PS less than 1, less than 25% of hepatic involvement
Toxicity	Mild abdominal pain and nausea in 12% of the patients. Mild cholecystitis: 10%. 7% grade 2 and 3 gastritis. Two hepatic failures in patients with >50% liver involvement
Conclusions	The combined treatment of TACE and systemic chemotherapy may prolong survival for liver metastases in breast cancer after mastectomy

6.4.5 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 very selected patient; experience of HAI is very scarce and no conclusion can be given.

6.5 Liver Metastases of Kidney Cancer

Nabil et al. (2008) [40]

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 1000–2000 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 months (from start of TACE) no statistical difference between therapy concepts (MMC vs. MMC + gemcitabine)
Toxicity	Postembolization 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) [41]

Concept	Radioembolization with ^{90}Y
N	6
Inclusion criteria	Chemorefractory liver-dominant metastases from RCC
Therapy	Bi-lobar 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	Grade 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

6.5.1 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.

The conclusion of this chapter is quite similar to the conclusion of a recent overview of intra-arterial treatment on non-colorectal liver metastases [42]: Despite many years of clinical use and documented efficacy on intra-arterial treatments of the

liver, there are still only a few prospective multicenter trials with many different protocols. Further large randomized trials and transparent guidelines need to be established.

References

1. Beger HG, Gansauge F, Buchler MW, Link KH. Intraarterial adjuvant chemotherapy after pancreaticoduodenectomy for pancreatic cancer: significant reduction in occurrence of liver metastasis. World J Surg. 1999;23:946–9.
2. Cantore M, Serio G, Pederzoli P, Mambrini A, Iacono C, Pulica C, Capelli P, Lombardi M, Torri T, Pacetti P, Pagani M, Fiorentini G. Adjuvant intra-arterial 5-fluoruracil, leucovorin, epirubicin and carboplatin with or without systemic gemcitabine after curative resection for pancreatic adenocarcinoma. Cancer Chemother Pharmacol. 2006;58:504–8.
3. Hayashibe A, Kameyama M, Shinbo M, Makimoto S. Clinical results on intra-arterial adjuvant chemotherapy for prevention of liver metastasis following curative resection of pancreatic cancer. Ann Surg Oncol. 2007;14:190–4.
4. Homma H, Niitsu Y. A new regional arterial infusion chemotherapy for patients with advanced pancreatic cancer. Gan To Kagaku Ryoho. 2002;29:383–9.
5. Vogl TJ, Schwarz W, Eichler K, Hochmuth K, Hammerstingl R, Jacob U, Scheller A, Zangos S, Heller M. Hepatic intraarterial chemotherapy with gemcitabine in patients with unresectable cholangiocarcinomas and liver metastases of pancreatic cancer: a clinical study on maximum tolerable dose and treatment efficacy. J Cancer Res Clin Oncol. 2006;132:745–55.
6. Heinrich S, Kraft D, Staib-Sebler E, Schwarz W, Gog C, Vogl T, Lorenz M. Phase II study on combined intravenous and intra-arterial chemotherapy with gemcitabine and mitomycin C in patients with advanced pancreatic cancer. Hepato-Gastroenterology. 2013;60:1492–6.
7. Ikeda O, Tamura Y, Nakasone Y, Shiraishi S, Kawanaka K, Tomiguchi S, Yamashita Y, Takamori H, Kanemitsu K, Baba H. Comparison of intrahepatic and pancreatic perfusion on fusion images using a combined SPECT/CT system and assessment of efficacy of combined

continuous arterial infusion and systemic chemotherapy in advanced pancreatic carcinoma. Cardiovasc Intervent Radiol. 2007;30: 912–21.
8. Cantore M, Fiorentini G, Luppi G, Rosati G, Caudana R, Piazza E, Comella G, Ceravolo C, Miserocchi L, Mambrini A, Del Freo A, Zamagni D, Aitini E, Marangolo M. Randomised trial of gemcitabine versus flec regimen given intra-arterially for patients with unresectable pancreatic cancer. J Exp Clin Cancer Res. 2003;22:51–7.
9. Azizi A, Naguib NN, Mbalisike E, Farshid P, Emami AH, Vogl TJ. Liver metastases of pancreatic cancer: role of repetitive transarterial chemoembolization (TACE) on tumor response and survival. Pancreas. 2011;40:1271–5.
10. Becker JC, Terheyden P, Kampgen E, Wagner S, Neumann C, Schadendorf D, Steinmann A, Wittenberg G, Lieb W, Brocker EB. Treatment of disseminated ocular melanoma with sequential fotemustine, interferon alpha, and interleukin 2. Br J Cancer. 2002;87:840–5.
11. Peters S, Voelter V, Zografos L, Pampallona S, Popescu R, Gillet M, Bosshard W, Fiorentini G, Lotem M, Weitzen R, Keilholz U, Humblet Y, Piperno-Neumann S, Stupp R, Leyvraz S. Intra-arterial hepatic fotemustine for the treatment of liver metastases from uveal melanoma: experience in 101 patients. Ann Oncol. 2006;17:578–83.
12. Siegel R, Hauschild A, Kettelhack C, Kahler KC, Bembenek A, Schlag PM. Hepatic arterial Fotemustine chemotherapy in patients with liver metastases from cutaneous melanoma is as effective as in ocular melanoma. Eur J Surg Oncol. 2007;33:627–32.
13. Voelter V, Schalenbourg A, Pampallona S, Peters S, Halkic N, Denys A, Goitein G, Zografos L, Leyvraz S. Adjuvant intra-arterial hepatic fotemustine for high-risk uveal melanoma patients. Melanoma Res. 2008;18:220–4.
14. Farolfi A, Ridolfi L, Guidoboni M, Milandri C, Calzolari F, Scarpi E, Amadori D, Ridolfi R. Liver metastases from melanoma: hepatic intra-arterial chemotherapy. A retrospective study. J Chemother. 2011;23:300–5.
15. Heusner TA, Antoch G, Wittkowski-Sterczewski A, Ladd SC, Forsting M, Verhagen R, Scheulen M. Transarterial hepatic chemoperfusion of uveal melanoma metastases: survival and response to treatment. Rofo. 2011;183:1151–60.
16. Mavligit GM, Charnsangavej C, Carrasco CH, Patt YZ, Benjamin RS, Wallace S. Regression of ocular melanoma metastatic to the liver after hepatic arterial chemoembolization with cisplatin and polyvinyl sponge. JAMA. 1988;260:974–6.

17. Patel K, Sullivan K, Berd D, Mastrangelo MJ, Shields CL, Shields JA, Sato T. Chemoembolization of the hepatic artery with BCNU for metastatic uveal melanoma: results of a phase II study. Melanoma Res. 2005;15:297–304.
18. Sato T, Eschelman DJ, Gonsalves CF, Terai M, Chervoneva I, McCue PA, Shields JA, Shields CL, Yamamoto A, Berd D, Mastrangelo MJ, Sullivan KL. Immunoembolization of malignant liver tumors, including uveal melanoma, using granulocyte-macrophage colony-stimulating factor. J Clin Oncol. 2008;26:5436–42.
19. Schuster R, Lindner M, Wacker F, Krossin M, Bechrakis N, Foerster MH, Thiel E, Keilholz U, Schmittel A. Transarterial chemoembolization of liver metastases from uveal melanoma after failure of systemic therapy: toxicity and outcome. Melanoma Res. 2010;20:191–6.
20. Gupta S, Bedikian AY, Ahrar J, Ensor J, Ahrar K, Madoff DC, Wallace MJ, Murthy R, Tam A, Hwu P. Hepatic artery chemoembolization in patients with ocular melanoma metastatic to the liver: response, survival, and prognostic factors. Am J Clin Oncol. 2010;33:474–80.
21. Huppert PE, Fierlbeck G, Pereira P, Schanz S, Duda SH, Wietholtz H, Rozeik C, Claussen CD. Transarterial chemoembolization of liver metastases in patients with uveal melanoma. Eur J Radiol. 2010;74:e38–44.
22. Ahrar J, Gupta S, Ensor J, Ahrar K, Madoff DC, Wallace MJ, Murthy R, Tam A, Hwu P, Bedikian AY. Response, survival, and prognostic factors after hepatic arterial chemoembolization in patients with liver metastases from cutaneous melanoma. Cancer Investig. 2011;29:49–55.
23. Edelhauser G, Schicher N, Berzaczy D, Beitzke D, Hoeller C, Lammer J, Funovics M. Fotemustine chemoembolization of hepatic metastases from uveal melanoma: a retrospective single-center analysis. Am J Roentgenol. 2012;199:1387–92.
24. Valsecchi ME, Terai M, Eschelman DJ, Gonsalves CF, Chervoneva I, Shields JA, Shields CL, Yamamoto A, Sullivan KL, Laudadio M, Berd D, Mastrangelo MJ, Sato T. Double-blinded, randomized phase II study using embolization with or without granulocyte-macrophage colony-stimulating factor in uveal melanoma with hepatic metastases. J Vasc Interv Radiol. 2015;26:523–32.
25. Fiorentini G, Aliberti C, Del Conte A, Tilli M, Rossi S, Ballardini P, Turrisi G, Benea G. Intra-arterial hepatic chemoembolization (TACE) of liver metastases from ocular melanoma with slow-release irinotecan-eluting beads. Early results of a phase II clinical study. In Vivo. 2009;23:131–7.

26. Valpione S, Aliberti C, Parrozzani R, Bazzi M, Pigozzo J, Midena E, Pilati P, Campana LG, Chiarion-Sileni V. A retrospective analysis of 141 patients with liver metastases from uveal melanoma: a two-cohort study comparing transarterial chemoembolization with CPT-11 charged microbeads and historical treatments. Melanoma Res. 2015;25:164–8.
27. Gonsalves CF, Eschelman DJ, Sullivan KL, Anne PR, Doyle L, Sato T. Radioembolization as salvage therapy for hepatic metastasis of uveal melanoma: a single-institution experience. Am J Roentgenol. 2011;196:468–73.
28. Pingpank JF, Libutti SK, Chang R, Wood BJ, Neeman Z, Kam AW, Figg WD, Zhai S, Beresneva T, Seidel GD, Alexander HR. Phase I study of hepatic arterial melphalan infusion and hepatic venous hemofiltration using percutaneously placed catheters in patients with unresectable hepatic malignancies. J Clin Oncol. 2005;23:3465–74.
29. Hughes MS, Zager J, Faries M, Alexander HR, Royal RE, Wood B, Choi J, McCluskey K, Whitman E, Agarwala S, Siskin G, Nutting C, Toomey MA, Webb C, Beresnev T, Pingpank JF. Results of a randomized controlled multicenter phase III trial of percutaneous hepatic perfusion compared with best available care for patients with melanoma liver metastases. Ann Surg Oncol. 2016;23:1309–19.
30. Cocconi G, Gamboni A, Gasparro D, Leonardi F, Salvagni S, Vasini G, Larini P, Marcato C, Camisa R, Cascinu S. Hepatic artery administration of docetaxel in liver metastases from breast carcinoma: a feasibility study. Tumori. 2005;91:121–5.
31. Zhang W, Liu R, Wang Y, Qian S, Wang J, Yan Z, Zhang H. Efficacy of intraarterial chemoinfusion therapy for locally advanced breast cancer patients: a retrospective analysis of 28 cases. Onco Targets Ther. 2013;6:761–5.
32. Giroux MF, Baum RA, Soulen MC. Chemoembolization of liver metastasis from breast carcinoma. J Vasc Interv Radiol. 2004;15:289–91.
33. Li XP, Meng ZQ, Guo WJ, Li J. Treatment for liver metastases from breast cancer: results and prognostic factors. World J Gastroenterol. 2005;11:3782–7.
34. Vogl TJ, Naguib NN, Nour-Eldin NE, Eichler K, Zangos S, Gruber-Rouh T. Transarterial chemoembolization (TACE) with mitomycin C and gemcitabine for liver metastases in breast cancer. Eur Radiol. 2010;20:173–80.
35. Vogl TJ, Naguib NN, Nour-Eldin NE, Mack MG, Zangos S, Abskharon JE, Jost A. Repeated chemoembolization followed by laser-induced thermotherapy for liver metastasis of breast cancer. Am J Roentgenol. 2011;196:W66–72.

36. Duan XF, Dong NN, Zhang T, Li Q. Treatment outcome of patients with liver-only metastases from breast cancer after mastectomy: a retrospective analysis. J Cancer Res Clin Oncol. 2011;137:1363–70.
37. Eichler K, Jakobi S, Gruber-Rouh T, Hammerstingl R, Vogl TJ, Zangos S. Transarterial chemoembolisation (TACE) with gemcitabine: phase II study in patients with liver metastases of breast cancer. Eur J Radiol. 2013;82:e816–22.
38. Martin RC, Robbins K, Fages JF, Romero FD, Rustein L, Tomalty D, Monaco R. Optimal outcomes for liver-dominant metastatic breast cancer with transarterial chemoembolization with drug-eluting beads loaded with doxorubicin. Breast Cancer Res Treat. 2012;132:753–63.
39. Cianni R, Pelle G, Notarianni E, Saltarelli A, Rabuffi P, Bagni O, Filippi L, Cortesi E. Radioembolisation with (90)Y-labelled resin microspheres in the treatment of liver metastasis from breast cancer. Eur Radiol. 2013;23:182–9.
40. Nabil M, Gruber T, Yakoub D, Ackermann H, Zangos S, Vogl TJ. Repetitive transarterial chemoembolization (TACE) of liver metastases from renal cell carcinoma: local control and survival results. Eur Radiol. 2008;18:1456–63.
41. Abdelmaksoud MH, Louie JD, Hwang GL, Kothary N, Minor DR, Sze DY. Yttrium-90 radioembolization of renal cell carcinoma metastatic to the liver. J Vasc Interv Radiol. 2012;23:323–30.
42. Puippe G, Pfammatter T, Schaefer N. Arterial therapies of non-colorectal liver metastases. Viszeralmedizin. 2015;31:414–22.

Part III
Intra-arterial Therapies: Lung, Head and Neck

Chapter 7
Chemoperfusion and Chemoembolization of Malignant Pulmonary Tumors

Thomas J. Vogl

7.1 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 2014, 224,210 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

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carcinoma, resection offers the best chance for long-term survival [4–7], but only 25 to 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 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.

7.1.1 Bronchial Arterial Infusion (BAI) Chemotherapy

Bronchial arterial infusion (BAI) chemotherapy was first introduced by Kahn et al. [39] in 1965, where a transfemoral 5-French catheter was guided into a bronchial artery under angiographic guidance. This technique was described to be more useful in organs with dual blood supply, especially when the tumor is perfused preferentially different from the primary organ [40].

The use of a coaxial microcatheter for superselective catheterization can be done, followed by injection of chemotherapeutic regime in the form of either mono- or combination therapy. The treatment sessions can be repeated every 2–4 weeks.

The BAI chemotherapy technique is used for the treatment of primary lung cancer either as a single treatment or in adjuvant or neoadjuvant context [39, 41–48]. The technique has also been reported to be used in combination with radiotherapy [49] and with pulmonary artery perfusion [50].

BAI was used but in very limited manner in treatment of lung metastases, namely, colorectal cancer [51, 52], and for local delivery of immunotherapy in a case of pulmonary metastases of HCC [53]. Its combination with systemic chemotherapy and radiotherapy to treat a case of recurrent thymic large cell carcinoma was also described [54].

The outcome of BAI in four articles with a total of 162 patients was reported to be “good” with only minor or no complications [41, 43, 45, 48].

Multiarterial infusion chemotherapy has been performed when there are multiple feeding arteries other than the bronchial artery with good response and without significant toxicity [55]. In a study of 32 patients with NSCLC who underwent intra-arterial chemotherapy, the response rate was 53%, and the precise identification of the feeding arteries and the degree of

tumor opacification by contrast were the most important determinants of efficient treatment [56].

Despite the high safety profile of the technique, there are some rare but potential serious complications of the technique like spinal injury [57], bronchial or esophageal ulceration, and also bronchoesophageal fistula formation [58].

7.1.2 Mesothelioma Perfusion

Intra-aortic infusion of chemotherapy was used long time ago for regional delivery of chemotherapy as close as possible to the target tumor with intention to improve efficiency and reduce complications, mainly with palliative setting, not only for lung tumors [59] but also for tumors in other body parts [60–62].

According to the general equation proposed by Collins, J. M. [63] to calculate the theoretical advantage of intra-arterial (IA) chemotherapy compared with systemic chemotherapy, infusion of drugs with high total body clearance into vessels with low flow rate that supply the tumor can maximize the advantage of IA chemotherapy. Also, higher drug infusion rates were shown in animal studies to result in increased drug concentration and sufficient distribution into the tumor tissues, and thus better clinical results could be achieved [64].

Despite the lack of sufficiently specific evidence that supports the advantage of intra-aortic chemoperfusion over the systemic intravenous chemotherapy regarding the drug concentrations in the tumor tissues and the pharmacokinetic aspects of the injected drugs [65, 66], the intra-arterial chemoperfusion was reintroduced in recent years by many oncological groups in the treatment of various tumor types with relatively good objective and subjective response rate [66–71].

In a recent study by Vogl, T. J. et al. [66], 39 patients with unresectable or recurrent pleural mesothelioma were treated with nonselective transarterial chemoperfusion using

mitomycin C, cisplatin, and gemcitabine in a palliative intention. Because of the multiarterial supply, selective catheterization of each artery would be difficult and not practical, not only because of the long procedure time but also because of the bad condition of the patients.

According to the tumor location, the infusion catheter was placed within the aorta at the level of the origin of the feeding vessel, and the chemotherapeutic agents were injected through maximum hand pressure. For tumors supplied by multiple intercostal arteries, the catheter was placed proximal to the most cephalad tumor-supplying artery.

A good response rate was obtained in the form of 36% partial regression (PR), 49% stable disease (SD), and mean survival time 14.2 months (range, 2.1–33.1 months) from the start of treatment. Mean time to disease progression was 2.6 months (1.5 months for SD and 1.3 months for PD). A low incidence of side effects after treatment in comparison to usual systemic chemotherapy was noted. However, further studies to evaluate the pharmacokinetics of used drugs were suggested and also to investigate the improved response and low incidence of complications in cases that previously failed to respond to systemic chemotherapy.

7.1.3 Technique: C-Arm

Flat-panel detector *CT* (*FDCT*) has revolutionized the interventional and intraoperative imaging using C-arm systems by providing immediate intra- and periprocedural soft-tissue CT control imaging without moving the patient, which was not possible before [72].

FDCT can provide not only parenchymal images (DynaCT) but also three-dimensional morphological and hemodynamic functional imaging, e.g., perfusion maps, through combining one or more C-arm rotations [73].

FDCT is used during TPCE to obtain 3D–CTA surveys of the pulmonary vascular tree before the injection of the chemoembolic agents to exclude any arteriovenous shunts and to find the best possible position for the application [74].

CT perfusion characteristics of lung tumors are a significant predictor of early tumor response and overall survival, with more treatment responsiveness among tumors with higher perfusion than with lower perfusion [75–77].

Periprocedural evaluation of parenchymal blood volume (PBV), one of the perfusion parameters, using C-arm CT and its potential values were previously explored in other organs [78, 79], namely, the brain and liver, and recently its potential value as predictor of early tumor response was evaluated by Vogl, T. J., et al. [74] during transpulmonary chemoperfusion and chemoembolization in primary and secondary lung tumors. In this study, PBV expressed a stronger response, to TPCE treatment, than diameter measurements and statistically significant correlation between the functional and imaging responses ($p \leq 0.05$).

The highest pretreatment PBV values were measured in decreasing tumors (206.93 mL/L) and the lowest values in increasing tumors (60.17 mL/L; $p > 0.05$). Also lung cancer expressed lower values (53.02 mL/L) compared to metastasis from uterine leiomyosarcoma (103.31 mL/L) or renal cell cancer (113.14 mL/L; $p \leq 0.05$).

C-arm CT imaging and assessment of PBV C-arm CT were performed on a multi-axis flat-detector angiographic system after placing the diagnostic catheter into the corresponding artery supplying the tumor (pulmonary artery, descending aorta, or the internal thoracic artery). The acquisition consisted of an initial mask run followed by a second fill run. The injection of 9 mL of contrast medium diluted to 25% at a rate of 3 mL/s was started immediately after the mask run had been finished using a power injector, then the C-arm rotated back to start the fill run. The 5 s for back-rotation allowed the contrast to distribute

through the vessels and fill the lung tumor in an approximately steady state.

PBV post-processing is performed using a dedicated workstation where the mask and the fill run were reconstructed and subtracted and the arterial input function value calculated from an automated histogram analysis of the vascular tree was then applied as a scaling factor to obtain the quantitative PBV map that could be visualized with a color map [74].

7.1.4 Combination TPCE + Ablation

The application of local thermal ablative therapies in the management of primary or secondary lung cancer is growing exponentially nowadays. The thermal effect of these modalities is affected largely by unique characteristics of the ablated tumor and its surroundings.

The major limitation regarding local ablation remains the tumor size. The inhomogeneity of tumor tissues together with the lower thermal conductivity of the aerated lung can limit adequate ablation at tumor margins [80]. In NSCLC a safety margin up to 8 mm is required to cover 95% of microscopic disease [81]. Tumors larger than 5 cm in diameter cannot be effectively handled, and even with the recent advancements in the ablation technologies, the local control of tumors larger than 3 cm is still very limited [82–85].

Many strategies and periprocedural techniques were evaluated, mainly in animals, to improve the efficiency of thermal ablation. These techniques included either changing the tumor microenvironment through local injection of various drugs, e.g., DDMC-p53 gene therapy or Lipiodol [86, 87], reducing tissue impedance through local NaCl solution infusion [88, 89], or reducing heat loss caused by ventilation and perfusion through bronchial or pulmonary artery occlusion [90]. Another strategy is the combination with other oncological treatments like radio-

therapy [91, 92] and systemic [93, 94], liposomal [95–97], or regional [85, 98, 99] chemotherapy.

Heat sink effects caused by either blood or air flow are particularly important in lung ablation, because these inherent characteristics of normal aerated lung are known to increase heat dispersion in the vicinity of the ablation zone and may represent a major limitation to both the extent and homogeneity of the intended ablation [100]. Several attempts were done to overcome perfusion and ventilation heat sinks with significant increase in the volume of ablation. Perfusion limiting techniques such as pulmonary artery occlusion were shown to have greater effect than ventilation limiting techniques, e.g., bronchial balloon occlusion [90, 100–102].

In normal porcine lungs, pulmonary artery embolization with degradable starch microspheres resulted in significantly larger volumes of coagulation necrosis after RF ablation. Because it was noted that tumor recurrence after ablation is more common at the periphery than in the center of the tumor, extending the ablation margin in the peritumoral normal lung can allow for adequate safety margin and decrease the risk of local recurrence [103].

Various occlusion materials and techniques can be used for pulmonary arterial flow blockage. Embolizing particles have the advantages of distal embolization, thus reducing collateral flow. Also it can be mixed or loaded with chemotherapy with more therapeutic effect [103, 104]. It was histologically proven that transient embolization with DSMs did not induce parenchymal ischemic damage [103], and that correlates well with the concept that pulmonary parenchymal cells can survive for up to 4 h after complete cessation of circulation by direct respiration across the alveolar walls, if O_2 ventilation is provided [105].

The clinical benefit of combined MW ablation and systemic chemotherapy was evaluated by Wei, Z., et al. [93, 94] in patients with advanced NSCLC, with a significant prolongation in progression-free survival (PFS) and overall survival (OS)

over chemotherapy alone. In another study by Gadaleta, C. D., et al. [85], the treatment of unresectable lung tumors using RF ablation 48 h after regional chemotherapy (in the form of transpulmonary chemoembolization using DEB) was shown to be technically feasible and well tolerated and represent an advantage over RF ablation alone.

In conclusion, optimization of thermal ablation through combination with TPCE, bland embolization, and vein/artery occlusion could allow patients with larger lesions and higher tumor burden to be treated [98, 99]. The macroscopic parts can be ablated, while microscopic perilesional infiltrations and satellites are managed by either regional or systemic chemotherapy [15, 94, 106]. TPCE as a method of regional chemotherapy application with iodized oil and DSMs has the potential advantages of being a well-tolerated treatment with higher safety profile [98, 99]. However, further preclinical and clinical studies are still required to define the best combination mode of these treatment modalities to achieve best clinical results.

7.2 Study Results

7.2.1 Experimental Data

Schneider et al. (2002) [107]

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 case 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 a symptom of early toxicity could not be detected even with additional application of carboplatin

Schneider et al. (2002) [34]

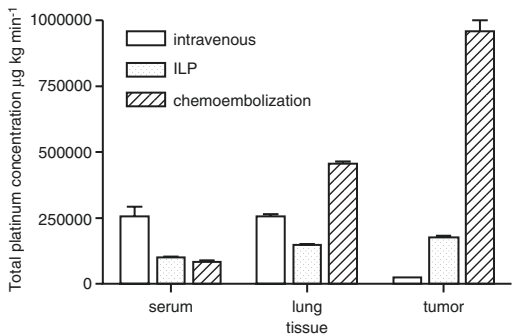
Tumor model	Lung tumor model (adenocarcinoma), rats
N	25 (5 × 5)
Objective	Tumor control in lung metastases
Comparisons	1. ILP[a] with buffered starch solution 2. DSM mono 3. carboDDP i.v. 4. ILP with carboDDP 5. DSM + carboDDP
Embolization	Amilomer (DSM)
Results	Tumor volumes after 7 days after therapy (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

[a]*ILP* isolated lung perfusion

Pohlen et al. (2007) [108]

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 carboDDP)
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

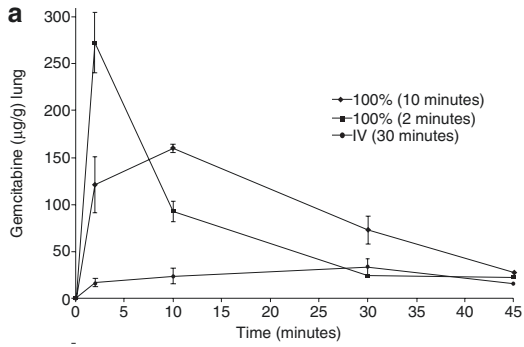
Pohlen et al. (2007) [109]

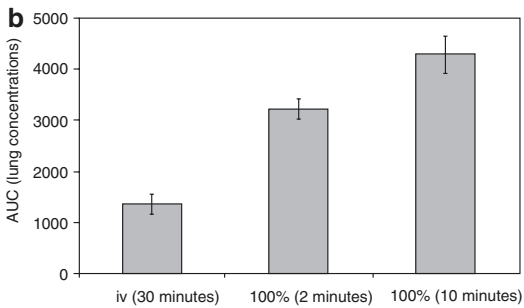
Model	TACE of lung, pig
N	6
Objective	Safety and effectiveness of this method in a large animal model
Method	Puncture of the femoral vein, selective exploration of the tumor-supplying pulmonary arteries; chemoembolization with DSM and carboplatin, documentation of survival, hemodynamic parameters, ventilation 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) [110]

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 significant different lung and serum AUC compared with SPAP without flow reduction
Toxicity	Histologic 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

Baylatry et al. (2011) [104]

Concept	To evaluate and compare plasma pharmacokinetics, lung tissue concentration, and the potential toxicity of drug-eluting beads loaded with irinotecan (DEB-IRI) in a sheep pulmonary artery chemoembolization (PACE) model
Number	24
Technique	Pulmonary artery chemoembolization with DEB-IRI loaded with different doses (0, 20, 50, or 100 mg) and direct pulmonary artery injections of irinotecan at two doses (50 or 100 mg) were performed Irinotecan was quantified in plasma and lung tissues, and pathological examination of lungs was performed 4 days and 4 weeks after PACE
Inclusion criteria	
Therapy interval	Once per week for 4 weeks
Result	Irinotecan was detected in the systemic circulation few minutes after PACE and for several hours in DEB-IRI 20 and DEB-IRI 50 groups and for 24 h for DEB-IRI 100. Both C_{max} and AUC values increased significantly with dose after PACE. C_{max} and AUC values were significantly reduced after PACE versus after direct PA injection. Irinotecan was not detected in tissue 4 days after PACE
Toxicity	Limited hemorrhagic angionecrosis seen 4 days after embolization with DEB-IRI 100. Inflammatory response was moderate in all DEB-IRI groups
Conclusion	Transpulmonary embolization by DEB loaded with irinotecan at doses up to 100 mg is a well-tolerated treatment and can be further evaluated in patients' trials

Hohenforst-Schmidt et al. (2015) [86]

Concept	Enhancement of intratumoral chemotherapy with cisplatin with or without microwave ablation and Lipiodol
Number	160

Technique	BALBC mice with Lewis lung carcinoma cell lines were divided into eight groups, (a) control, (b) cisplatin, (c) microwave, (d) microwave and Lipiodol, (e) cisplatin and Lipiodol, (f) microwave and cisplatin, (g) Lipiodol, and (h) Lipiodol, cisplatin, and microwave, and MRI follow-up was done
Inclusion criteria	
Therapy interval	Once per week for 4 weeks
Result	Efficient tumor apoptosis for the groups b, c, d, e, and f Group h developed severe toxicity and no available follow-up after the second week of therapy
Toxicity	Hemorrhage apart from necrosis was observed inside the tumors (mainly group h)
Conclusion	Lipiodol in its current form does not assist in a more efficient way the distribution of cisplatin, as well as the microwave apoptotic effect Combination of drug and microwave ablation is possible

Hohenforst-Schmidt et al. (2015) [87]

Concept	Role of local treatment using 2-diethylaminoethyl-dextran methyl methacrylate copolymer with p53 (DDMC-p53) with or without cisplatin and/or microwave ablation in enhancing the disease control in BALBC mice with lung carcinoma inoculate
Number	140
Technique	Mice were divided into the following seven groups: control, cisplatin, microwave ablation, DDMC-p53, DDMC-p53 plus cisplatin, DDMC-p53 plus microwave, and DDMC-p53 plus cisplatin plus microwave. Microwave ablation energy was administered at 20 W for 10 min. Cisplatin was administered at 1 mL/mg, and the DDMC-p53 complex delivered was 0.5 mL
Inclusion criteria	
Therapy interval	Once per week for 4 weeks

Result	Efficient tumor apoptosis for the groups b, c, d, e, and f Group h developed severe toxicity and no available follow-up after the second week of therapy
Toxicity	Increased toxicity was observed in the group receiving DDMC-p53 plus cisplatin plus microwave followed by the group receiving DDMC-p53 plus cisplatin. Infection after repeated treatment administration was a major issue
Conclusion	A combination of gene therapy using DDMC-p53 with or without cisplatin and microwave is an alternative method that may improve local disease control. More experiments are required to identify the appropriate dosage

7.2.2 Clinical Data

7.2.2.1 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—therapy.

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.)

(continued)

(continued)

Treatment phase	Action
Postprocedural (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

7.2.2.2 Study Results

Isolated Lung Perfusion (ILP)

Schröder et al. (2002) [111]

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 one 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 in (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) [99]

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) [112]

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 be 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 of this technology; thus, treatment of pulmonary metastases remains a major clinical challenge

Vogl et al. (2008) [113]

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, 1–21), six 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

Transarterial Chemoperfusion (TACP)

Tsuchiya et al. (2009) [70]

Concept	Evaluation of the effectiveness of combined chemotherapy by oral enteric-coated tegafur/uracil with intra-arterial docetaxel, cisplatin (CDDP), and UFT-E for lung metastases of HCC
Number	1
Technique	400 mg/d oral UFT-E Intra-arterial delivery of docetaxel (80 mg/body initially, followed by 40 mg/body) and CDDP (50 mg/body initially, followed by 20 mg/body) into the aorta just before the bronchial arteries
Inclusion criteria	A case of lung metastases of HCC
Therapy interval	Every 2 weeks for 2 months
Result	Serum level of PIVKA-II decreased after 1 month and normalized in 4 month CR after 2 months
Toxicity	Grade 3 leukocytopenia, grade 2 fatigue and anorexia, and grade 1 alopecia according to common terminology criteria for adverse events v3.0
Conclusion	This report is the second to document the effectiveness of combined chemotherapy with docetaxel, CDDP, and UFT-E for lung metastasis of HCCs. It is uncertain whether docetaxel is the key drug and whether repeated doses via the intra-arterial route improved the outcome for this patient

Vogl et al. (2013) [66]

Concept	To evaluate tumor response, survival, and changes in patient symptoms after palliative regional nonselective transarterial chemoperfusion of unresectable or recurrent pleural mesothelioma
Number	39
Technique	Repetitive nonselective transarterial chemoperfusion using mitomycin C, cisplatin, and gemcitabine is done intra-aortic proximal to the most predominant tumor-supplying artery
Inclusion criteria	Unresectable and/or recurrent pleural mesothelioma with no response to previous chemotherapy or radiation therapy with adequate performance status
Therapy interval	4-week intervals
Result	Mean survival time was 14.2 months (range, 2.1–33.1 months) from the start of treatment PR = 36% (mean survival = 15 months) SD = 49% PD = 15% Mean specific growth rate = 0.00158% per day Mean time to disease progression = 2.6 months (1.5 months for SD and 1.3 months for PD)
Toxicity	Patients showed complications, such as chest pain (74%), gastrointestinal disorders (18%), and dysphagia (15%), that lasted 2–3 days after treatment. No major complications were observed
Conclusion	Transarterial chemoperfusion may have the potential to yield positive results and response in the treatment of recurrent and/or unresectable pleural mesothelioma

C-Arm CT

Vogl et al. (2016) [74]

Concept	Assessment of the role of parenchymal blood volume (PBV) measurements using a C-arm CT in detecting early functional response to transpulmonary chemoembolization (TPCE) in primary and secondary pulmonary malignancies and its clinical practicability
Number	21
Technique	During transarterial chemoperfusion and chemoembolization, a 5-F pigtail catheter was placed into the pulmonary artery supplying the tumor, the descending aorta, or the internal thoracic artery, and 3D–CTA surveys of the tumor-supplying vessels were obtained and immediately processed before application of the therapeutic regimen
Inclusion criteria	
Therapy interval	4-week intervals
Result	Correlation between functional and imaging response per tumor was statistically significant ($p \leq 0.05$) Median diameter increases of 18.18% ($p > 0.05$) PBV reduction 39.62% ($p > 0.05$) Highest pretreatment PBV values were measured in decreasing tumors (206.93 mL/L) Lowest values in increasing tumors (60.17 mL/L; $p > 0.05$) Lowest values also in lung cancer (53.02 mL/L)
Toxicity	
Conclusion	Assessment of PBV maps by using 3D–CTA image data is feasible in the clinical routine. PBV shows a stronger response to TPCE treatment than measurement in diameter and should be considered as a response parameter for early detection

Combined Ablation and TPCE

Gadaleta et al. (2013) [85]

Concept	Evaluation of the feasibility, safety, and effectiveness of combining segmental pulmonary arterial chemoembolization (SPACE) and percutaneous radiofrequency ablation in patients with unresectable lung neoplasms or patients with resectable neoplasms who refused surgery
Number	17 (20 nodules)
Technique	Antineoplastic agents loaded on 50–100-μm microspheres were selectively infused into specific pulmonary arteries. Percutaneous CT-guided RF ablation of lung nodules was performed after 48 hours
Inclusion criteria	Primary and metastatic lung cancer
Therapy interval	
Result	Technical success was achieved in 100% of cases LTP rate was 21% (3 of 14 nodules) in 3–5-cm-diameter tumors and 0% (0 of 6 nodules) in tumors less than 3 cm CR = 65% (11 of 17) of patients at minimum follow-up of 6 months Treatment was well tolerated with no significant changes in lung function
Toxicity	Pneumothorax in 5 of 19 sessions (26%) Bronchopleural fistula in 1 of 19 (5%)
Conclusion	Combination therapy with RF ablation after SPACE to treat unresectable lung tumors is technically feasible, safe, and effective and may represent an advantage over RF ablation alone

Vogl et al. (2011) [114]

Concept	To evaluate the safety and efficacy of microwave ablation therapy of unresectable pulmonary metastases
Number	80 (130 lesions)
Technique	Computed tomography-guided percutaneous microwave ablation of pulmonary metastatic lesions with power settings at 35–45 W and a mean ablation time of 15 min (range, 10–30 min)
Inclusion criteria	Unresectable and/or recurrent pulmonary metastases, poor candidates for surgery with five lesions or less, that are 5 cm or smaller in maximal axial diameter
Therapy interval	1–2 weeks between sessions (30 patients underwent 2 ablation sessions, and 10 patients underwent 3 ablation sessions)
Result	Complete, successful ablation was achieved in 73.1% of lesions. Successful tumor ablation was significantly more frequent for lesions with a maximal axial diameter of 3 cm or smaller than for larger lesions and for peripheral lesions than for central lesions Histopathologic type of the metastasis did not significantly correlate with the ablation result The 12- and 24-month survival rates were 91.3% and 75%, respectively, with higher rates of survival in patients with tumor-free states after successful ablation than in patients with failed ablation
Toxicity	Pneumothorax (8.5%), one case of severe pneumothorax required intercostal chest tube insertion (0.8%) Intraparenchymal pulmonary hemorrhage (6.2%) and hemoptysis (4.6%) A focal grade 3 skin burn at the site of puncture in one session (0.8%)
Conclusion	Microwave ablation therapy may be safely and effectively used as a therapeutic tool for treatment of pulmonary metastases. The efficacy of the treatment is primarily determined by preablation tumor size and location in relation to the hilum

References

1. Zutić H. Karcinom bronha—pregled. Med Arh. 1999;53:27–31.
2. American Cancer Society. Cancer facts & figures 2002. Atlanta, GA: American Cancer Society; 2002.
3. Weiss W, Boucot KR, Cooper DA. The Philadelphia pulmonary neoplasm research project. Survival factors in bronchogenic carcinoma. JAMA. 1971;216(13):2119–23.
4. Frommhold W, Gerhardt P. Klinisch-radiologisches Seminar. Band 17, Tumoren der Lunge. New York/Stuttgard: Georg-Thiemeverlag; 1987.
5. McCormack P. Surgical resection of pulmonary metastases. Semin Surg Oncol. 1990;6(5):297–302.
6. Plickova K, et al. Patient survival analysis in surgery of bronchogenic carcinoma from 1986 to 1997. Rozhl Chir. 2003;82(6):293–9.
7. Müller M. Chirurgie für Studium und Praxis: unter Berücksichtigung des Gegenstandskataloges und der münlichen Examinain der ärzlichen Prüfung 2002/03. Markus Müller und Mitarbeiter. -6. Aufl.-Breisach/Rh, Med Verl.- und Informationsdienste; 2001. p. 101.
8. American Cancer Society. Cancer facts & figures 2004. Atlanta, GA: American Cancer Society; 2004.
9. Hendriks JM, et al. Isolated lung perfusion with melphalan for resectable lung metastases: a phase I clinical trial. Ann Thorac Surg. 2004;78(6):1919–26. discussion 1926-7.
10. Vogt-Moykopf I, et al. Results in surgery of pulmonary metastases. Chirurgie. 1992;118(5):263–71.
11. Hendriks JM, et al. Long-term results of surgical resection of lung metastases. Acta Chir Belg. 2001;101(6):267–72.
12. Abecasis N, et al. Surgical treatment of lung metastases: prognostic factors for long-term survival. J Surg Oncol. 1999;72(4):193–8.
13. Lanza LA, et al. Response to chemotherapy does not predict survival after resection of sarcomatous pulmonary metastases. Ann Thorac Surg. 1991;51(2):219–24.
14. Casson AG, et al. Five-year survival after pulmonary metastasectomy for adult soft tissue sarcoma. Cancer. 1992;69(3):662–8.
15. Ueda T, et al. Aggressive pulmonary metastasectomy for soft tissue sarcomas. Cancer. 1993;72(6):1919–25.
16. Weksler B, et al. Isolated single-lung perfusion with doxorubicin is pharmacokinetically superior to intravenous injection. Ann Thorac Surg. 1993;56(2):209–14.

17. Friedl G, Pastorino U, Buyse M. Resection of lung metastases: long-term results and prognostic analyses based on 5.206 cases—the International Registry of Lung Metastases. Zentralblatt fur Chirurgie. 1999;124:96–103.
18. Mentzer SJ, et al. Selected benefits of thoracotomy and chemotherapy for sarcoma metastatic to the lung. J Surg Oncol. 1993;53(1):54–9.
19. Greenall MJ, et al. Chemotherapy for soft tissue sarcoma. Surg Gynecol Obstet. 1986;162(2):193–8.
20. Dirix LY, Van Oosterom AT. Diagnosis and treatment of soft tissue sarcomas in adults. Curr Opin Oncol. 1994;6(4):372–83.
21. Van Schil PE. Surgical treatment for pulmonary metastases. Acta Clin Belg. 2002;57(6):333–9.
22. Pan Y, et al. Evaluation of tumour vascularisation in two rat sarcoma models for studying isolated lung perfusion. Injection route determines the origin of tumour vessels. Eur Surg Res. 2005;37(2):92–9.
23. Van Putte BP, et al. Isolated lung perfusion for the treatment of pulmonary metastases current mini-review of work in progress. Surg Oncol. 2003;12(3):187–93.
24. Romijn S, et al. Anterograde versus retrograde isolated lung perfusion with melphalan in the WAG-Rij rat. Eur J Cardiothorac Surg. 2005;27(6):1083–5.
25. Hendriks JM, et al. Isolated lung perfusion for the treatment of pulmonary metastatic disease: a review. Acta Chir Belg. 2005;105(4):338–43.
26. Muller H, Hilger R. Curative and palliative aspects of regional chemotherapy in combination with surgery. Support Care Cancer. 2003;11(1):1–10.
27. Van Putte BP, et al. Single-pass isolated lung perfusion versus recirculating isolated lung perfusion with melphalan in a rat model. Ann Thorac Surg. 2002;74(3):893–8; discussion 898.
28. Romijn S, et al. Regional differences of melphalan lung levels after isolated lung perfusion in the rat. J Surg Res. 2005;125(2):157–60.
29. Franke UF, et al. Evaluation of isolated lung perfusion as neoadjuvant therapy of lung metastases using a novel in vivo pig model: I. Influence of perfusion pressure and hyperthermia on functional and morphological lung integrity. Eur J Cardiothorac Surg. 2004;26(4):792–9.
30. Demmy TL, Wagner-Mann C, Allen A. Isolated lung chemotherapeutic infusions for treatment of pulmonary metastases: a pilot study. J Biomed Sci. 2002;9(4):334–8.

31. Burt ME, et al. Isolated lung perfusion for patients with unresectable metastases from sarcoma: a phase I trial. Ann Thorac Surg. 2000;69(5):1542–9.
32. Johnston MR, Minchen RF, Dawson CA. Lung perfusion with chemotherapy in patients with unresectable metastatic sarcoma to the lung or diffuse bronchioloalveolar carcinoma. J Thorac Cardiovasc Surg. 1995;110(2):368–73.
33. Pass HI, et al. Isolated lung perfusion with tumor necrosis factor for pulmonary metastases. Ann Thorac Surg. 1996;61(6):1609–17.
34. Schneider P, et al. Chemoembolization of the lung improves tumor control in a rat model. Clin Cancer Res. 2002;8(7):2463–8.
35. Ratto GB, et al. Isolated lung perfusion with platinum in the treatment of pulmonary metastases from soft tissue sarcomas. J Thorac Cardiovasc Surg. 1996;112(3):614–22.
36. Vogl TJ, et al. Transarterial chemoembolization for hepatocellular carcinoma: volumetric and morphologic CT criteria for assessment of prognosis and therapeutic success-results from a liver transplantation center. Radiology. 2000;214(2):349–57.
37. Miller BJ, Rosenbaum AS. The vascular supply to metastatic tumors of the lung. Surg Gynecol Obstet. 1967;125:1009–12.
38. Huppert PE, et al. Chemoembolisation des hepatozellulären Karzinoms: Computertomographische Befunde und klinische Resultate bei prospektiv repetitiver Therapie. Fortschr Röntgenstr. 1994;160(05):425–32.
39. Kahn PC, Paul RE, Rheinlander HF. Selective bronchial arteriography and intra-arterial chemotherapy in carcinoma of the lung. J Thorac Cardiovasc Surg. 1965;50(5):640–5.
40. Jiang GM, et al. Blood supply of pulmonary metastases and its clinical significance. Ai Zheng. 2006;25(7):885–7.
41. Osaki T, et al. Bronchial arterial infusion is an effective therapeutic modality for centrally located early-stage lung cancer: results of a pilot study. Chest. 1999;115(5):1424–8.
42. So T, et al. Carinal resection after induction bronchial arterial infusion for locally advanced non-small cell lung cancer. Jpn J Thorac Cardiovasc Surg. 2004;52(3):143–7.
43. Liu CL, Wang YD, Jin XJ. Clinical observation on treatment of non-small cell lung cancer with Chinese herbal medicine combined with bronchial arterial infusion chemotherapy. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2001;21(8):579–81.
44. Koshiishi H, et al. Evaluation of bronchial arterial infusion (BAI) for lung cancer with brain metastasis. Gan To Kagaku Ryoho. 2006;33(12):1860–2.

45. Koshiishi H, et al. Evaluation of bronchial arterial infusion (BAI) for high risk lung cancer. Gan To Kagaku Ryoho. 2000;27(12):1907–10.
46. Oura S, et al. Recurrent squamous-cell lung cancer treated with bronchial-arterial infusion of docetaxel—case report. Gan To Kagaku Ryoho. 1998;25(13):2109–13.
47. Neyazaki T, et al. Bronchial artery infusion therapy for lung cancer. Cancer. 1969;24(5):912–22.
48. Watanabe Y, et al. Reappraisal of bronchial arterial infusion therapy for advanced lung cancer. Jpn J Surg. 1990;20(1):27–35.
49. Wang G, et al. Prospective trial of combined hyperfractionated radiotherapy and bronchial arterial infusion of chemotherapy for locally advanced nonsmall cell lung cancer. Int J Radiat Oncol Biol Phys. 1996;34(2):309–13.
50. Shi W, Zhang S, Zhang X. Treatment of non-small-cell lung cancer by dual (bronchial and pulmonary) arterial drug infusion. Zhonghua Zhong Liu Za Zhi. 1995;17(2):146–8.
51. Koshiishi H, et al. Evaluation of bronchial arterial infusion (BAI) for metastatic lung tumor from colorectal cancer. Gan To Kagaku Ryoho. 2004;31(11):1838–41.
52. Kitai T, et al. Clinical benefit of bronchial arterial infusion chemotherapy to pulmonary metastasis from colorectal cancer—report of two cases. Gan To Kagaku Ryoho. 2003;30(13):2125–8.
53. Sheng S, et al. Complete remission of multiple lung metastases after ablation of hepatocellular carcinoma by transarterial infusion with the p53 gene. Anti-Cancer Drugs. 2015;26(2):227–31.
54. Kaseda S, et al. Bronchial arterial infusion with cisplatin followed by irradiation successfully treats recurrent stage IVb thymic large cell carcinoma. Eur J Cardiothorac Surg. 1999;16(4):471–4.
55. Nakanishi M, et al. Effective use of multi-arterial infusion chemotherapy for advanced non-small cell lung cancer patients: four clinical specified cases. Lung Cancer. 2007;55(2):241–7.
56. Nakanishi M, et al. Multi-arterial infusion chemotherapy for non-small cell lung carcinoma—significance of detecting feeding arteries and tumor staining. Lung Cancer. 2008;61(2):227–34.
57. Brown AC, Ray CE. Anterior spinal cord infarction following bronchial artery embolization. Semin Interv Radiol. 2012;29(3):241–4.
58. Mallick R, Demmy T. Regional lung chemotherapy techniques. Innovations (Phila). 2011;6(1):1–9.
59. Freckman HA, et al. Chemotherapy for lung cancer by intra-aortic infusion. JAMA. 1966;196(1):5–10.

60. Miura T, Ishida M, Hatano S. Combination cancer chemotherapy by regional intra-arterial or intra-aortic infusion of 5-fluorouracil and mitomycin-C with or without irradiation. Jpn J Surg. 1971;1(2):133–45.
61. Kitamura M, et al. Intra-aortic infusion therapy with sequential methotrexate (MTX) and 5-FU in advanced gastric carcinoma. Gan To Kagaku Ryoho. 1986;13(5):1927–33.
62. Yoshikawa K. Ten years' experience with intra-aortic infusion chemotherapy for gastrointestinal malignant tumors. Jpn J Clin Oncol. 1981;11(2):391–8.
63. Collins JM. Pharmacologic rationale for regional drug delivery. J Clin Oncol. 1984;2(5):498–504.
64. Takeda N, Diksic M. Relationship between drug delivery and the intra-arterial infusion rate of SarCNU in C6 rat brain tumor model. J Neurooncol. 1999;41(3):235–46.
65. Maruyama M, Nagahama T, Maruyama S. MTX-CDDP-5-FU double modulation intra aortic chemotherapy for advanced and metastatic gastric cancer—a comparison with an intra venous route. Gan To Kagaku Ryoho. 2006;33(12):1814–6.
66. Vogl TJ, et al. Nonselective transarterial chemoperfusion: a palliative treatment for malignant pleural mesothelioma. Radiology. 2013;266(2):649–56.
67. Shimada Y, et al. Two cases of advanced gallbadder cancer with para-aortic lymph node metastasis responding to intra-aortic infusion of gemcitabine and low-dose CDDP/5-FU. Gan To Kagaku Ryoho. 2005;32(9):1347–50.
68. Sheen MC, et al. Advanced penile verrucous carcinoma treated with intra-aortic infusion chemotherapy. J Urol. 2010;183(5): 1830–5.
69. Sheen MC, et al. Penile verrucous carcinoma successfully treated by intra-aortic infusion with methotrexate. Urology. 2003;61(6): 1216–20.
70. Tsuchiya A, et al. Successful treatment of multiple lung metastases of hepatocellular carcinoma by combined chemotherapy with docetaxel, cisplatin and tegafur/uracil. World J Gastroenterol. 2009;15(14):1779–81.
71. Vogl TJ, et al. Transarterial chemoperfusion of the pelvis—results in symptomatic locally recurrent tumors and lymph node metastases. Rofo. 2007;179(11):1174–80.
72. Kyriakou Y, et al. Basic principles of flat detector computed tomography (FD-CT). Radiologe. 2009;49(9):811–9.

73. Hung S-C, et al. Toward the era of a one-stop imaging service using an angiography suite for neurovascular disorders. Biomed Res Int. 2013;2013:873614.
74. Vogl TJ, et al. Feasibility of assessing pulmonary blood volume using C-arm CT during transpulmonary chemoperfusion and chemoembolization in primary and secondary lung tumours. Br J Radiol. 2016;89(1062):20150244.
75. Wang J, et al. Tumor response in patients with advanced non-small cell lung cancer: perfusion CT evaluation of chemotherapy and radiation therapy. Am J Roentgenol. 2009;193(4):1090–6.
76. Li XS, et al. Value of whole-tumor dual-input perfusion CT in predicting the effect of multiarterial infusion chemotherapy on advanced non-small cell lung cancer. Am J Roentgenol. 2014;203(5):W497–505.
77. Wang JW, Wu N, Song Y. Application of perfusion CT scan in assessing the treatment and predicting prognosis for lung cancer before and after chemotherapy/radiotherapy. Zhonghua Zhong Liu Za Zhi. 2009;31(1):54–7.
78. Lin CJ, et al. In-room assessment of cerebral blood volume for guidance during intra-arterial thrombolytic therapy. Interv Neuroradiol. 2012;18(4):463–8.
79. Syha R, et al. C-arm computed tomography parenchymal blood volume measurement in evaluation of hepatocellular carcinoma before transarterial chemoembolization with drug eluting beads. Cancer Imaging. 2015;15:22.
80. Ponder E. The coefficient of thermal conductivity of blood and of various tissues. J Gen Physiol. 1962;45(3):545–51.
81. Ambrogi MC, et al. Biologic effects of radiofrequency thermal ablation on non-small cell lung cancer: results of a pilot study. J Thorac Cardiovasc Surg. 2006;131(5):1002–6.
82. Palussiere J, et al. Percutaneous lung thermal ablation of non-surgical clinical N0 non-small cell lung cancer: results of eight years' experience in 87 patients from two centers. Cardiovasc Intervent Radiol. 2015;38(1):160–6.
83. Andreetti C, et al. Resolution of a life-threatening complication after lung radiofrequency ablation. Eur J Cardiothorac Surg. 2014;46(4):e56–8.
84. Akeboshi M, et al. Percutaneous radiofrequency ablation of lung neoplasms: initial therapeutic response. J Vasc Interv Radiol. 2004;15(5):463–70.
85. Gadaleta CD, et al. Unresectable lung malignancy: combination therapy with segmental pulmonary arterial chemoembolization

with drug-eluting microspheres and radiofrequency ablation in 17 patients. Radiology. 2013;267(2):627–37.
86. Hohenforst-Schmidt W, et al. Enhancement of Intratumoral chemotherapy with Cisplatin with or without microwave ablation and Lipiodol. Future concept for local treatment in lung cancer. J Cancer. 2015;6(3):218–26.
87. Hohenforst-Schmidt W, et al. DDMC-p53 gene therapy with or without cisplatin and microwave ablation. Onco Targets Ther. 2015;8:1165–73.
88. Lee JM, et al. Radio-frequency thermal ablation with hypertonic saline solution injection of the lung: ex vivo and in vivo feasibility studies. Eur Radiol. 2003;13(11):2540–7.
89. Gananadha S, Morris DL. Saline infusion markedly reduces impedance and improves efficacy of pulmonary radiofrequency ablation. Cardiovasc Intervent Radiol. 2004;27(4):361–5.
90. Oshima F, et al. Lung radiofrequency ablation with and without bronchial occlusion: experimental study in porcine lungs. J Vasc Interv Radiol. 2004;15(12):1451–6.
91. Horkan C, et al. Reduced tumor growth with combined radiofrequency ablation and radiation therapy in a rat breast tumor model. Radiology. 2005;235(1):81–8.
92. Dupuy DE, et al. Radiofrequency ablation followed by conventional radiotherapy for medically inoperable stage I non-small cell lung cancer. Chest. 2006;129(3):738–45.
93. Wei Z, et al. Microwave ablation plus chemotherapy improved progression-free survival of advanced non-small cell lung cancer compared to chemotherapy alone. Med Oncol. 2015; 32(2):464.
94. Wei Z, et al. Microwave ablation in combination with chemotherapy for the treatment of advanced non-small cell lung cancer. Cardiovasc Intervent Radiol. 2015;38(1):135–42.
95. Solazzo SA, et al. Liposomal doxorubicin increases radiofrequency ablation-induced tumor destruction by increasing cellular oxidative and nitrative stress and accelerating apoptotic pathways. Radiology. 2010;255(1):62–74.
96. Goldberg SN, et al. Radiofrequency ablation of hepatic tumors: increased tumor destruction with adjuvant liposomal doxorubicin therapy. Am J Roentgenol. 2002;179(1):93–101.
97. Ahmed M, et al. Combined radiofrequency ablation and adjuvant liposomal chemotherapy: effect of chemotherapeutic agent, nanoparticle size, and circulation time. J Vasc Interv Radiol. 2005;16(10):1365–71.

98. Vogl TJ, et al. Regional chemotherapy of the lung: transpulmonary chemoembolization in malignant lung tumors. Semin Intervent Radiol. 2013;30(2):176–84.
99. Vogl TJ, et al. Treatment of unresectable lung metastases with transpulmonary chemoembolization: preliminary experience. Radiology. 2005;234(3):917–22.
100. Sonntag PD, et al. Thermal ablation of lung tumors. Surg Oncol Clin N Am. 2011;20(2):369–87. ix
101. Johansen B, et al. Time course and pattern of pulmonary flow distribution following unilateral airway occlusion in sheep. Clin Sci (Lond). 1998;94(4):453–60.
102. Anai H, et al. Effects of blood flow and/or ventilation restriction on radiofrequency coagulation size in the lung: an experimental study in swine. Cardiovasc Intervent Radiol. 2006;29(5):838–45.
103. Hiraki T, et al. Radiofrequency ablation of normal lungs after pulmonary artery embolization with use of degradable starch microspheres: results in a porcine model. J Vasc Interv Radiol. 2006;17(12):1991–8.
104. Baylatry MT, et al. Pulmonary artery chemoembolization in a sheep model: evaluation of performance and safety of irinotecan eluting beads (DEB-IRI). J Biomed Mater Res B Appl Biomater. 2011;98((2):351–9.
105. Lechner JF, Stoner GD, Yoakum GH, et al. In vitro carcinogenesis studies with tracheobronchial tissues and cells. In: Schiff LJ, editor. In vitro models of respiratory epithelium. Boca Raton: CRC; 1986. p. 143–59.
106. Wagner W, et al. Neoadjuvant radiochemotherapy in locally advanced non-small cell bronchial carcinoma. Initial results of a prospective multicenter study. Strahlenther Onkol. 1995;171(7):390–7.
107. Schneider P, et al. Temporary unilateral microembolization of the lung-a new approach to regional chemotherapy for pulmonary metastases. J Surg Res. 2002;107(2):159–66.
108. Pohlen U, et al. Chemoembolization of lung metastases—pharmacokinetic behaviour of carboplatin in a rat model. Anticancer Res. 2007;27(2):809–15.
109. Pohlen U, et al. Chemoembolization with carboplatin of the lung. Feasibility and toxicity in a pig model. Anticancer Res. 2007;27(3B):1503–8.
110. van Putte BP, et al. Pharmacokinetics of gemcitabine when delivered by selective pulmonary artery perfusion for the treatment of lung cancer. Drug Metab Dispos. 2008;36(4):676–81.

111. Schroder C, et al. Technique and results of hyperthermic (41 degrees C) isolated lung perfusion with high-doses of cisplatin for the treatment of surgically relapsing or unresectable lung sarcoma metastasis. Eur J Cardiothorac Surg. 2002;22(1):41–6.
112. Lindemayr S, et al. Transpulmonary chemoembolization: a novel approach for the treatment of unresectable lung tumors. Tech Vasc Interv Radiol. 2007;10(2):114–9.
113. Vogl TJ, et al. Transpulmonary chemoembolization (TPCE) as a treatment for unresectable lung metastases. Eur Radiol. 2008;18(11):2449–55.
114. Vogl TJ, et al. Microwave ablation therapy: clinical utility in treatment of pulmonary metastases. Radiology. 2011;261(2):643–51.

Chapter 8
Head and Neck

Adorján F. Kovács

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 chemo-

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therapy 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 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 and twenty-two eligible subjects were randomized 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 ($P = 0.048$) 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). A new preparation and effect format of cisplatin was introduced by using a highly concentrated aqueous crystal suspension with microembolizing properties, and this method alone is compared to a combination using degradable starch microspheres (DSM) in the treatment of oral and oropharyngeal squamous cell carcinomas. DSM were chosen because occlusion of the vessels endures only maximum

1–2 h [3]. As an alternative procedure for TACE, the authors were using the suspension of cisplatin crystals alone [4].

The most comprehensive trial sequence of *intra-arterial chemoradiation* was conducted by Robbins and coworkers. 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 [5]. Having started as treatment for unresectable patients, IA chemoradiation was developed as a regimen for organ preservation. Other study groups confirmed these favorable results. Based on these promising results, a randomized trial was conducted in the Netherlands comparing RADPLAT with IV chemoradiation therapy [6]. 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. (Other studies seemed to support this result [7].) 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 and comparable results. 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. It is a pity that quality-of-life issues are neglected in such cases.

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 variations of the prototypic Robbins method with higher doses of cisplatin [8] and new combinations and agents, e.g., [8, 9]. New radiation techniques are also evaluated in combination with IA chemotherapy [9].

Too often, the fundamental pharmacologic principles of IA therapy have been ignored, and response rates and survival rates 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.

8.1 Study Results

Kovács and Turowski (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) were mixed with 5 mL cisplatin (25 mg cisplatin)and 4 mL contrast medium and were administered until occlusion of the vessels One cycle of IA high-dose chemoembolization per patient (in case of PR max. Two 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				

Kovács (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 stage I–IV
Therapy	IA, 150 mg/m^2 cisplatin; parallel IV, 9 g/m^2 sodium thiosulfate (after a delay of 10 s) One to two 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 of survival, 63%, and at 5 years, 56%		
Toxicity	Extremely low side effects only grade III		
Conclusions	Survival of patients treated with neoadjuvant IA chemotherapy was better than TPI		

Kovács (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

Robbins et al. (2005) [5]

Concept	High-dose IA cisplatin and concurrent radiation for head and neck carcinoma (multicenter prospectively) multi-RADPLAT			
N	61			
Inclusion criteria	Squamous cell carcinoma of oral cavity, oropharynx, hypopharynx, or larynx stage IV, T4, N0–3, M0; 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); concomitantly radiotherapy, 2 Gy per fraction once a day, 5 days a week; total dose of 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			

Rasch et al. (2010) [6]

Concept	Intra-arterial versus 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); concomitantly radiotherapy, total dose of 70 Gy in 35 daily fractions IV, 3 × 100 mg/m^2 cisplatin (on days 1, 22, 43); with the same radiotherapeutic regimen			
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 significant 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			

Mendenhall et al. (2010) [7]

Concept	Altered fractionation and adjuvant chemotherapy for head and neck squamous cell carcinoma (meta-analysis, review)
N	App. 10,000 (RT), app. 40,000 (adjuvant chemotherapy)
Inclusion criteria	Previously untreated patients with stage III–stage IVA and/or IVB HNSCCs (nonmetastatic)
Therapy	Hyperfractionated RT (HFRT) vs. accelerated fractionated RT (AFRT) compared with conventionally fractionated RT (CFRT); adjuvant chemotherapy

Results	1. HFRT is more efficacious than either CFRT or AFRT 2. Concomitant chemoradiation is more efficacious than RT alone 3. Concomitant chemotherapy is more effective than induction or maintenance chemotherapy 4. Intra-arterial chemotherapy is no more effective than intravenous chemotherapy 5. Monochemotherapy is as effective as polychemotherapy 6. The most effective chemotherapeutic agents are fluorouracil, cisplatin, and cetuximab 7. The role of induction chemotherapy followed by concomitant chemoradiation remains unproven
Conclusions	Altered fractionation and/or concomitant chemotherapy results in improved outcomes compared with conventionally fractionated definitive RT alone for stage III–stage IV HNSCCs. The optimal combination of RT fractionation and chemotherapy remains unclear

Nishio et al. (2011) [8]

Concept	Intra-arterial chemoradiation therapy for oropharyngeal carcinoma with high-dose cisplatin (retrospective study)
N	21
Inclusion criteria	Oropharyngeal carcinoma, stages II–IVB
Therapy	d1 and 35: 300 mg/m^2 (<70 years); 200 mg/m^2 (≥70 years) cisplatin IA d2-ff: radiation (2 Gy per day; max. 60 Gy) d1–4 and 8–11: 1000 mg/m^2 5-FU IV
Results	2-year overall survival: 71.3% 2-year locoregional control and disease-free survival rate: 95.0% and 67.7%

Toxicity	Mucositis (grade II): all patients except for one with grade III Hematological toxicity (grade III): one patient Dysphagia (grade III): one patient Nephrotoxicity: six patients (three had grade I and three had grade III) No intra-arterial-intervention-related complications
Conclusions	Selective intra-arterial high-dose cisplatin chemotherapy with concomitant radiation therapy is well tolerated. It can achieve good results in patients with oropharyngeal carcinoma

Takayama et al. (2016) [9]

Concept	Alternating chemoradiotherapy followed by proton beam therapy boost combined with intra-arterial infusion chemotherapy (prospective study)
N	33
Inclusion criteria	Tongue cancer (stage III–IVB)
Therapy	d1–5: 700 mg/m^2 5-FU d6: 110 mg/m^2 nedaplatin Week 1–5: radiation (36 Gy in 20 fractions) Proton beam therapy 28.6–39.6 Gy in 13–18 fractions From week 7: 20–40 mg/m^2 cisplatin IA (weekly 4–6×)
Results	24 patients (72.7%) completed the course CR: 28 patients (84.8%) PR: 5 (15.2%) Median period to recurrence: 6 months (range 5–31) Relapse rate: 8 patients (2 at the primary site, 3 at the cervical lymph node, 1 at the primary site and the cervical lymph node, 1 at the primary site and distant metastasis, 1 at the cervical lymph node and distant metastasis) Three-year OS, PFS, LC, and RC rates: 87.0%, 74.1%, 86.6%, 83.9%

Toxicity	Major acute adverse events (>grade 3): mucositis in 26 (79%) patients, neutropenia in 17 (51%), and dermatitis in 11 (33%) Neutropenic sepsis (involving catheter-related infection): six patients (18%)
Conclusions	PBT-IACT for stage III–IVB tongue cancer has an acceptable toxicity profile and shows good treatment results. This protocol could be considered as a treatment option for locally advanced tongue cancer

References

1. Richard JM, Kramar A, Molinari R, Lefebvre JL, Blanchet F, Jortay A, et al. Randomised EORTC head and neck cooperative group trial of preoperative intraarterial chemotherapy in oral cavity and oropharynx carcinoma. Eur J Cancer. 1991;27(7):821–7.
2. Kovács AF. Intra-arterial induction high-dose chemotherapy with cisplatin for oral and oropharyngeal cancer: long-term results. Br J Cancer. 2004;90(7):1323–8.
3. Kovács AF, Turowski B. Chemoembolization of oral and oropharyngeal cancer using a high-dose cisplatin crystal suspension and degradable starch microspheres. Oral Oncol. 2002;38(1):87–95.
4. Kovács AF. Chemoembolization using cisplatin crystals as neoadjuvant treatment of oral cancer. Cancer Biother Radiopharm. 2005;20(3):267–79.
5. Robbins KT, Kumar P, Harris J, McCulloch T, Cmelak A, Sofferman R, et al. Supradose intra-arterial cisplatin and concurrent radiation therapy for the treatment of stage IV head and neck squamous cell carcinoma is feasible and efficacious in a multiinstitutional setting: results of Radiation Therapy Oncology Group Trial 9615. J Clin Oncol. 2005;23(7):1447–54.
6. Rasch CRN, Hauptmann M, Schornagel J, Wijers O, Buter J, Gregor T, et al. Intraarterial versus intravenous chemoradiation for advanced head and neck cancer: results of a randomized phase 3 trial. Cancer. 2010;116(9):2159–65.

7. Mendenhall WM, Riggs CE, Vaysberg M, Amdur RJ, Werning JW. Altered fractionation and adjuvant chemotherapy for head and neck squamous cell carcinoma. Head Neck. 2010 Jul;32(7):939–45.
8. Nishio R, Saito K, Ito H, Yoshida T, Kitamura K, Shimizu A, Kanesaka N, Mikami R, Hasegawa D, Suzuki M, Tokuuye K. Selective intraarterial chemoradiation therapy for oropharyngeal carcinoma with high-dose cisplatin. Jpn J Radiol. 2011 Oct;29(8):570–5.
9. Takayama K, Nakamura T, Takada A, Makita C, Suzuki M, Azami Y, Kato T, Hayashi Y, Ono T, Toyomasu Y, Hareyama M, Kikuchi Y, Daimon T, Mitsudo K, Tohnai I, Fuwa N. Treatment results of alternating chemoradiotherapy followed by proton beam therapy boost combined with intra-arterial infusion chemotherapy for stage III-IVB tongue cancer. J Cancer Res Clin Oncol. 2016 Mar;142(3):659–67.

Part IV
Thermoablation

Chapter 9
Thermal Ablation for Treating Malignant Tumors to the Liver

Andreas H. Mahnken and Thierry de Baère

9.1 Introduction

Most thermal ablation techniques were initially established for treating inoperable hepatocellular carcinomas (HCC). In the face of the technical success, ease of use, and relatively low complication rates, the indications for local ablation were rapidly extended and are now established for treating a wide range of primary and secondary liver malignancies. Moreover, its use has been described in virtually all major organs. Several thermal ablation techniques are currently in clinical use, including radiofrequency (RF) ablation, microwave ablation (MWA), and cryoablation.

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Nowadays new promising nonthermal ablation techniques such as irreversible electroporation are under investigation, but due to the lack of clinical data still have to be considered experimental. Most clinical data deals with radiofrequency (RF) ablation. Therefore this chapter will focus on RF ablation.

9.2 Ablation Techniques

9.2.1 Radiofrequency Ablation

RF ablation requires a closed-loop circuit created with an RF generator, an active tip electrode inside the target lesion, neutral electrodes placed on the patients' skin, or less commonly another electrode inside the target lesion (multipolar ablation). High-frequency alternating currents (360–480 KHz) applied via the electrodes cause heat to form due to ionic agitation within the target tissue. The resultant ionic agitation creates frictional heat which spreads via conduction, leading to cell death from coagulative necrosis. In order to achieve reliable tumor destruction, the target needs to be treated with >60 °C. Temperatures higher than 100 °C can cause gas formation (vaporization) and carbonization. These effects are known to reduce ablation effectiveness. Effectiveness can be improved by various probe designs (e.g., internal cooling, umbrella, etc.), use of multiple probes, current modulation, and energy output of the generator.

9.2.2 Microwave Ablation

For MWA a high-frequency oscillating electromagnetic field (915 MHz or 2.45 GHz) is delivered to the target lesion via an active antenna. This high-frequency oscillating electromag-

netic field induces rapid realignment of water molecules in the target lesion. This results in friction and subsequent tissue heating. Tissues with a high concentration of water are particularly susceptible to microwave heating. The antenna design and active length is limited due to physical dependencies between frequency and active tip length. Microwave ablation is known to create higher temperatures and bigger lesions in less time than RF ablation. Like in RF ablation, MWA creates coagulative necrosis. The use of multiple probes, different cooling systems, and higher energy output can enhance lesion size.

9.2.3 Cryoablation

Cryoablation utilizes the Joule–Thomson effect. It works by passing high-pressure argon gas through a thin probe. Rapid expansion of the gas in an expansion chamber at the tip of the probe results in cooling of the metal of the probe down to −180 °C and less. As the probe cools, surrounding tissues are also cooled, creating a visible iceball. For thawing helium gas is then forced through the probe causing warming of the probe and of the adjacent tissues. A different technique using fluid nitrogen for creating an iceball is much less effective and outdated. The cooling and subsequent thawing of the probe results in cell death caused by several processes. Firstly, cooling results in intracellular ice crystal formation, leading to cell membrane damage and cell death. Secondly, larger ice crystals form during slow thawing, resulting in a shearing effect triggering a different mechanism of cell death. Thirdly, ice crystal formations in small blood vessels cause ischemia. The lethal isotherm for cryoablation is somewhere between −40 and −20 °C, well inside the visible iceball, which marks the 0 °C isotherm. The use of multiple probes with different active lengths allows to individually tailor the size of the iceball.

9.3 Outcomes

9.3.1 HCC

RF ablation is an established competitor for surgery in the treatment of small 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 [5, 6], 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 versus 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, this meta-analysis 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 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 9.1).

Table 9.1 Summary of comparative studies on thermal ablation vs. resection in HCC

				Overall survival			
Author	Method	Patients (*n*)	Tumor size (cm)	1 year (%)	3 years (%)	5 years (%)	*p*
Vivarelli (2004) [18]	Surgery	79	n.a.	83	65	n.a.	0.002
	RFA	79	n.a.	78	33	n.a.	
Hong (2005) [9]	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.	
Montorsi (2005) [35]	Surgery	40	n.a.	84	73	n.a.	0.139
	RFA	58	n.a.	85	61	n.a.	
Cho (2005) [16]	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) [36]	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] [6]	Surgery	90	n.a.	93.3	73.4	n.a.	n.s.
	RFA	90	n.a.	94.4	68.6	n.a.	
Lupo (2007) [10]	Surgery	42	4 (3–5)	91	57	43	0.824
	RFA	60	3.65 (3–5)	96	53	32	
Takahashi (2007) [13]	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	
Guglielmi (2008) [17]	Surgery	91	n.a.	84	64	48	0.01
	RFA	109	n.a.	83	42	20	
Abu-Hilal (2008) [37]	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) [15]	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] [4]	Surgery	115	n.a.	98.3	92.2	75.5	0.001
	RFA	115	n.a.	87	69.6	54.8	
Kobayashi (2009) [14]	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) [11]	Surgery	123	2.7 ± 0.1	99	92	80	0.06
	RFA	155	2.0 ± 0.1	98	92	63	

(continued)

Table 9.1 (continued)

Author	Method	Patients (*n*)	Tumor size (cm)	Overall survival 1 year (%)	3 years (%)	5 years (%)	*p*
Santambrogio (2009)[a] [12]	Surgery	78	2.87 ± 1.21	93	85	54	0.163
	RFA	74	2.66 ± 1.06	88	66	41	
Nanashima (2010) [38]	Surgery	144	n.a.	n.a.	77	57	n.a.
	RFA	56	n.a.	n.a.	59	51	
Nishikawa (2011) [39]	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) [40]	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) [41]	Surgery	52	Very early stage	98	98	91.5	0.298
	RFA	91		96.7	89.3	72	
Wang (2012) [41]	Surgery	208	Early stage	96.1	87.8	77.2	0.088
	RFA	254		91.6	73.5	57.4	
Feng (2012)[a] [42]	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) [43]	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	
Zhang (2016) [44]	Surgery	122	2.7 ± 0.4	98.4	93.6	55.2	0.153
	MWA	68	2.7 ± 0.3	97.1	87.7	51.0	
Zhang (2016) [45]	Surgery	73	Small	95.2	71.4	38.1	n.s.
	MWA			96.7	53.3	43.3	

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

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. Most of these studies 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]; the only prospective study, however, favored surgery over locoregional treatments (Table 9.2).

Table 9.2 Summary of comparative studies on RF ablation in combination with embolization vs. resection in HCC

				Overall survival			
Author	Method	Patients (*n*)	Tumor size (cm)	1 year (%)	3 years (%)	5 years (%)	*p*
Maluccio (2005) [23]	Surgery	40	4.6 (1.8–7)	97	77	56	0.200
	RFA and TACE	33	4 (1.7–7)	81	70	58	
Yamakado (2008) [22]	Surgery	62	2.7 ± 1.1	97	93	81	0.870
	RFA and TACE	104	2.5 ± 0.8	98	94	75	
Kagawa (2010) [46]	Surgery	55	2.8 (1–5)	92.5	82.7	76.9	0.788
	RFA and TACE	62	2.4 (0.8–5)	100	94.8	64.6	
Tashiro (2011) [47]	Surgery	199	2.1 ± 0.63	95.6	90.9	76	0.11
	RFA and TACE	87 (69 TACE)	1.8 ± 0.52	97.6	81.4	71	
Liu (2016) [50][a]	Surgery	100	3 (0.6–5)	97.0	83.7	61.9	0.007
	RFA and TACE	100	2.8 (0.6–5)	96.0	67.2	45.7	
Bholee (2017) [52]	Surgery	782	3 ± 1.1	94.6	75.1	55.3	0.488
	RFA and TACE	74	2.9 ± 1.1	91.2	64.4	47.7	

[a]Prospective study

While RF ablation was the dominant ablative technique for treating small HCC, there is now a growing body of evidence on the use of MWA in HCC (Table 9.1). The data is promising, but there still is no relevant prospective randomized trial comparing MWA and surgery. Several studies compared RF ablation and MWA. While there is no statistically significant difference between both techniques, there is a trend toward better outcomes after MWA [24]. Data on cryoablation of liver tumors is scarce, and the only meta-analysis on HCC indicates RF ablation to be superior to cryoablation, particularly in terms of safety [25].

9.3.2 Metastatic Liver Disease

Resection offers the best long-term survival in colorectal liver metastases with 5-year overall survival rates of about 50% [26]. In contrast even the most recent chemotherapeutic regimen only provides a median survival of up to 22 months [27]. 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 [28, 29]. 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 9.3). A recent meta-analysis indicated a better survival for patients undergoing resection when compared to RF ablation, but the

Table 9.3 Summary of studies on RF ablation in colorectal liver metastases

				Overall survival				
Author	Method	Patients (*n*)	Tumor size (cm)	2 years (%)	3 years (%)	5 years (%)	*p*	Median survival
Oshowo (2003) [48]	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) [49]	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) [51]	Surgery	150	3 (1–7)	n.a.	79	71	0.001	n.a.
	RFA	30		n.a.	57	27		n.a.
Park (2008) [53]	Surgery	59	3.1 (0.5–8)	n.a.	n.a.	48	0.000256	
	RFA	30	2 (0.6–4)	n.a.	n.a.	19		36
White (2007) [20]	Surgery	30	2.7 (1–5)	100	82	65	n.a.	80
	RFA	22	2.4 (1–5)	100	28	0		31
Berber (2008) [54]	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) [55]	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) [56]	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) [57]	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) [58]	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
Otto (2010)[a] [59]	Surgery	28	5 (1–14)	n.a.	67	51*	0.721	n.a.
	RFA	82	3 (1–5)	n.a.	60	48*		n.a.
Schiffman (2010) [60]	Surgery	94	5.6	92*	81*	65*	0.005	n.a.
	RFA	46	3.9	81*	64*	42*		n.a.

(continued)

Table 9.3 (continued)

Author	Method	Patients (*n*)	Tumor size (cm)	Overall survival 2 years (%)	3 years (%)	5 years (%)	*p*	Median survival
Lee (2012) [61]	Surgery	25	4	n.a.	n.a.	n.a.	0.017	41
	RFA	28	2.05	n.a.	n.a.	n.a.		24
Ko (2014) [62]	Surgery	12	3.59	n.a.	n.a.	66.7	0.29	n.a.
	RFA	17	2.02	n.a.	n.a.	37.8		n.a.
Lee (2015) [63]	Surgery	102	1.7		73.9	55.2	0.194	n.a.
	RFA	51	1.8		62.4	48.2		n.a.

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

data needs to be interpreted carefully as the raw data was only of limited quality [30]. In addition, the lower complication rate for RF ablation has to be acknowledged. For RF ablation major complication rates are about 4.5% with a mortality of 0.15%. Local recurrence rates of 9–33% have been reported.

While there are no prospective randomized controlled trials comparing RF ablation with surgery, there is a single prospective randomized controlled trial comparing chemotherapy alone with chemotherapy plus RF ablation [31]. This study suffered several shortcomings in the study design and patient accrual. While the primary end point was met with a 30-month overall survival rate of 61.7% for combined treatment, overall survival of systemic treatment alone was much better than expected (57.6% at 30 months). Median overall survival in the combination arm was better (45.3 months) than with chemotherapy alone (40.5 months), but failed to reach significance ($P = 0.22$). Progression-free survival, however, was significantly better in the combination arm (16.8 vs. 9.9 months; $p = 0.025$). Long-

term analysis may reveal if this translates in a better overall survival.

Unlike in the treatment of HCC, there are only few case series on the combination of embolization and local ablation in liver metastases. Most patients in these reports were poor candidates for ablation, and the combination treatment was thought to improve outcome [33]. The most recent case series on the combination of TACE and ablation in colorectal liver metastases indicates this approach to be safe and worthwhile considering a 3-year survival rate of 50% in patients deemed unresectable [32].

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 9.4). For MWA and cryoablation, there are only case series including a variety of primary tumors; therefore, this data is very difficult to interpret, as tumor biology varies.

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 [34]. 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 9.4).

9.4 Study Results

Table 9.4 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 year (%)	3 years (%)	5 years (%)	
Livraghi (2001) [64]	24/64	Breast	1.9 [1–6.6]	n.a.	n.a.	n.a.	n.a.
Lawes (2006) [65]	19/46	Breast	3 [1.4–7.3]	n.a.	n.a.	n.a.	n.a.
Sofocleous (2007) [66]	12/14	Breast	n.a.	n.a.	70	30	60
Gunabushanam (2007) [67]	14/16	Breast	1.9 [1.1–4]	64	n.a.	n.a.	n.r.
Jakobs (2009) [68]	43/111	Breast	2.1 [0.5–8.5]	95	68	48	58.6
Meloni (2009) [69]	52/87	Breast	2.5 [0.7–5]	68	43	27	29.9
Gillams (2005) [70]	25/189	NET	3.5 [1–9]	92	80	72	29
Mazzaglia (2007) [71]	63/384	NET	2.3 [0.5–10]	91	n.a.	48	47
Akyildiz (2010) [72]	89/547	NET	3.6 [1–10]	n.a.	n.a.	57	72
Yamakado (2005) [73]	7/16	Gastric	2.4 [2–3]	86	n.a.	n.a.	16.5
Kim (2010) [74]	20/29	Gastric	5.1 ± 2.2	66.8	40.1	16.1	30.7
Mylona (2009) [75]	22/36	CUP	2.7 [1.1–4.8]	n.a.	n.a.	n.a.	10.9
Gervais (2006) [76]	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

References

1. Llovet JM, Di Bisceglie AM, Bruix J, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst. 2008;100(10):698–711. https://doi.org/10.1093/jnci/djn134.
2. Cho YK, Kim JK, Kim MY, et al. Systematic review of randomized trials for hepatocellular carcinoma treated with percutaneous ablation therapies. Hepatology. 2009;49(2):453–9. https://doi.org/10.1002/hep.22648.
3. Nakazawa T, Kokubu S, Shibuya A, et al. Radiofrequency ablation of hepatocellular carcinoma: correlation between local tumor progression after ablation and ablative margin. Am J Roentgenol. 2007;188(2):480–8. https://doi.org/10.2214/AJR.05.2079.
4. Huang J, Yan L, Cheng Z, et al. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. Ann Surg. 2010;252(6):903–12. https://doi.org/10.1097/SLA.0b013e3181efc656.
5. M-D L, Kuang M, Liang L-J, et al. Surgical resection versus percutaneous thermal ablation for early-stage hepatocellular carcinoma: a randomized clinical trial. Zhonghua Yi Xue Za Zhi. 2006;86(12):801–5.
6. Chen M-S, Li J-Q, Zheng Y, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg. 2006;243(3):321–8. https://doi.org/10.1097/01.sla.0000201480.65519.b8.
7. Li L, Zhang J, Liu X, et al. Clinical outcomes of radiofrequency ablation and surgical resection for small hepatocellular carcinoma: a meta-analysis. J Gastroenterol Hepatol. 2012;27(1):51–8. https://doi.org/10.1111/j.1440-1746.2011.06947.x.
8. Tiong L, Maddern GJ. Systematic review and meta-analysis of survival and disease recurrence after radiofrequency ablation for hepatocellular carcinoma. Br J Surg. 2011;98(9):1210–24. https://doi.org/10.1002/bjs.7669.
9. Hong SN, Lee S-Y, Choi MS, et al. Comparing the outcomes of radiofrequency ablation and surgery in patients with a single small hepatocellular carcinoma and well-preserved hepatic function. J Clin Gastroenterol. 2005;39(3):247–52.
10. Lupo L, Panzera P, Giannelli G, et al. Single hepatocellular carcinoma ranging from 3 to 5 cm: radiofrequency ablation or resection? HPB (Oxford). 2007;9(6):429–34. https://doi.org/10.1080/13651820701713758.
11. Ueno S, Sakoda M, Kubo F, et al. Surgical resection versus radiofrequency ablation for small hepatocellular carcinomas within the Milan

criteria. J Hepatobiliary Pancreat Surg. 2009;16(3):359–66. https://doi.org/10.1007/s00534-009-0069-7.
12. Santambrogio R, Opocher E, Zuin M, et al. Surgical resection versus laparoscopic radiofrequency ablation in patients with hepatocellular carcinoma and Child-Pugh class a liver cirrhosis. Ann Surg Oncol. 2009;16(12):3289–98. https://doi.org/10.1245/s10434-009-0678-z.
13. Takahashi S, Kudo M, Chung H, et al. Outcomes of nontransplant potentially curative therapy for early-stage hepatocellular carcinoma in Child-Pugh stage A cirrhosis is comparable with liver transplantation. Dig Dis. 2007;25(4):303–9. https://doi.org/10.1159/000106909.
14. Kobayashi M, Ikeda K, Kawamura Y, et al. High serum des-gamma-carboxy prothrombin level predicts poor prognosis after radiofrequency ablation of hepatocellular carcinoma. Cancer. 2009;115(3):571–80. https://doi.org/10.1002/cncr.24031.
15. Hiraoka A, Horiike N, Yamashita Y, et al. Efficacy of radiofrequency ablation therapy compared to surgical resection in 164 patients in Japan with single hepatocellular carcinoma smaller than 3 cm, along with report of complications. Hepato-Gastroenterology. 2008;55(88):2171–4.
16. Cho CM, Tak W-Y, Kweon Y-O, et al. The comparative results of radiofrequency ablation versus surgical resection for the treatment of hepatocellular carcinoma. Korean J Hepatol. 2005;11(1):59–71.
17. Guglielmi A, Ruzzenente A, Valdegamberi A, et al. Radiofrequency ablation versus surgical resection for the treatment of hepatocellular carcinoma in cirrhosis. J Gastrointest Surg. 2008;12(1):192–8. https://doi.org/10.1007/s11605-007-0392-8.
18. Vivarelli M, Guglielmi A, Ruzzenente A, et al. Surgical resection versus percutaneous radiofrequency ablation in the treatment of hepatocellular carcinoma on cirrhotic liver. Ann Surg. 2004;240(1):102–7.
19. Peng Z-W, Zhang Y-J, Chen M-S, et al. Radiofrequency ablation with or without transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma: a prospective randomized trial. J Clin Oncol. 2013;31(4):426–32. https://doi.org/10.1200/JCO.2012.42.9936.
20. White RR, Avital I, Sofocleous CT, et al. Rates and patterns of recurrence for percutaneous radiofrequency ablation and open wedge resection for solitary colorectal liver metastasis. J Gastrointest Surg. 2007;11(3):256–63. https://doi.org/10.1007/s11605-007-0100-8.
21. Yamagiwa K, Shiraki K, Yamakado K, et al. Survival rates according to the Cancer of the Liver Italian Program scores of 345 hepatocellular carcinoma patients after multimodality treatments during a 10-year period in a retrospective study. J Gastroenterol Hepatol. 2008;23(3):482–90. https://doi.org/10.1111/j.1440-1746.2007.05262.x.

22. Yamakado K, Nakatsuka A, Takaki H, et al. Early-stage hepatocellular carcinoma: radiofrequency ablation combined with chemoembolization versus hepatectomy. Radiology. 2008;247(1):260–6. https://doi.org/10.1148/radiol.2471070818.
23. Maluccio M, Covey AM, Gandhi R, et al. Comparison of survival rates after bland arterial embolization and ablation versus surgical resection for treating solitary hepatocellular carcinoma up to 7 cm. J Vasc Interv Radiol. 2005;16(7):955–61. https://doi.org/10.1097/01.RVI.0000161377.33557.20.
24. Facciorusso A, Di Maso M, Muscatiello N. Microwave ablation versus radiofrequency ablation for the treatment of hepatocellular carcinoma: A systematic review and meta-analysis. Int J Hyperth. 2016;32(3):339–44. https://doi.org/10.3109/02656736.2015.1127434.
25. Huang Y-Z, Zhou S-C, Zhou H, et al. Radiofrequency ablation versus cryosurgery ablation for hepatocellular carcinoma: a meta-analysis. Hepato-Gastroenterology. 2013;60(125):1131–5. https://doi.org/10.5754/hge121142.
26. Wei AC, Greig PD, Grant D, et al. Survival after hepatic resection for colorectal metastases: a 10-year experience. Ann Surg Oncol. 2006;13(5):668–76. https://doi.org/10.1245/ASO.2006.05.039.
27. Gallagher DJ, Kemeny N. Metastatic colorectal cancer: from improved survival to potential cure. Oncology. 2010;78(3–4):237–48. https://doi.org/10.1159/000315730.
28. Abitabile P, Hartl U, Lange J, et al. Radiofrequency ablation permits an effective treatment for colorectal liver metastasis. Eur J Surg Oncol. 2007;33(1):67–71. https://doi.org/10.1016/j.ejso.2006.10.040.
29. Sgouros J, Cast J, Garadi KK, et al. Chemotherapy plus percutaneous radiofrequency ablation in patients with inoperable colorectal liver metastases. World J Gastrointest Oncol. 2011;3(4):60–6. https://doi.org/10.4251/wjgo.v3.i4.60.
30. Han Y, Yan D, Xu F, et al. Radiofrequency Ablation versus Liver Resection for Colorectal Cancer Liver Metastasis: An Updated Systematic Review and Meta-analysis. Chin Med J. 2016;129(24):2983–90. https://doi.org/10.4103/0366-6999.195470.
31. Ruers T, Punt C, van Coevorden F, et al. Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC Intergroup phase II study (EORTC 40004). Ann Oncol. 2012;23(10):2619–26. https://doi.org/10.1093/annonc/mds053.
32. Fong ZV, Palazzo F, Needleman L, et al. Combined hepatic arterial embolization and hepatic ablation for unresectable colorectal metastases to the liver. Am Surg. 2012;78(11):1243–8.

33. Xu C, Lv P-H, Huang X-E, et al. Radiofrequency Ablation for Liver Metastases after Transarterial Chemoembolization: A Systemic Analysis. Asian Pac J Cancer Prev. 2015;16(12):5101–6.
34. Sarmiento JM, Heywood G, Rubin J, et al. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. J Am Coll Surg. 2003;197(1):29–37. https://doi.org/10.1016/S1072-7515(03)00230-8.
35. Montorsi M, Santambrogio R, Bianchi P, et al. Survival and recurrences after hepatic resection or radiofrequency for hepatocellular carcinoma in cirrhotic patients: a multivariate analysis. J Gastrointest Surg. 2005;9(1):62. https://doi.org/10.1016/j.gassur.2004.10.003.
36. Ogihara M, Wong LL, Machi J. Radiofrequency ablation versus surgical resection for single nodule hepatocellular carcinoma: long-term outcomes. HPB (Oxford). 2005;7(3):214–21. https://doi.org/10.1080/13651820510028846.
37. Abu-Hilal M, Primrose JN, Casaril A, et al. Surgical resection versus radiofrequency ablation in the treatment of small unifocal hepatocellular carcinoma. J Gastrointest Surg. 2008;12(9):1521–6. https://doi.org/10.1007/s11605-008-0553-4.
38. Nanashima A, Tobinaga S, Masuda J, et al. Selecting treatment for hepatocellular carcinoma based on the results of hepatic resection and local ablation therapy. J Surg Oncol. 2010;101(6):481–5. https://doi.org/10.1002/jso.21523.
39. Nishikawa H, Inuzuka T, Takeda H, et al. Comparison of percutaneous radiofrequency thermal ablation and surgical resection for small hepatocellular carcinoma. BMC Gastroenterol. 2011;11:143. https://doi.org/10.1186/1471-230X-11-143.
40. Hung H-H, Chiou Y-Y, Hsia C-Y, et al. Survival rates are comparable after radiofrequency ablation or surgery in patients with small hepatocellular carcinomas. Clin Gastroenterol Hepatol. 2011;9(1):79–86. https://doi.org/10.1016/j.cgh.2010.08.018.
41. Wang J-H, Wang C-C, Hung C-H, et al. Survival comparison between surgical resection and radiofrequency ablation for patients in BCLC very early/early stage hepatocellular carcinoma. J Hepatol. 2012;56(2):412–8. https://doi.org/10.1016/j.jhep.2011.05.020.
42. Feng K, Yan J, Li X, et al. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. J Hepatol. 2012;57(4):794–802. https://doi.org/10.1016/j.jhep.2012.05.007.
43. Peng Z-W, Lin X-J, Zhang Y-J, et al. Radiofrequency ablation versus hepatic resection for the treatment of hepatocellular carcinomas 2 cm

or smaller: a retrospective comparative study. Radiology. 2012;262(3):1022–33. https://doi.org/10.1148/radiol.11110817.
44. Zhang E-L, Yang F, Wu Z-B, et al. Therapeutic efficacy of percutaneous microwave coagulation versus liver resection for single hepatocellular carcinoma </=3 cm with Child-Pugh A cirrhosis. Eur J Surg Oncol. 2016;42(5):690–7. https://doi.org/10.1016/j.ejso.2016.02.251.
45. Zhang Q-B, Zhang X-G, Jiang R-D, et al. Microwave ablation versus hepatic resection for the treatment of hepatocellular carcinoma and oesophageal variceal bleeding in cirrhotic patients. Int J Hyperth. 2016;33(3):255–62. https://doi.org/10.1080/02656736.2016.1257824.
46. Kagawa T, Koizumi J, Kojima S-I, et al. Transcatheter arterial chemoembolization plus radiofrequency ablation therapy for early stage hepatocellular carcinoma: comparison with surgical resection. Cancer. 2010;116(15):3638–44. https://doi.org/10.1002/cncr.25142.
47. Tashiro H, Aikata H, Waki K, et al. Treatment strategy for early hepatocellular carcinomas: comparison of radiofrequency ablation with or without transcatheter arterial chemoembolization and surgical resection. J Surg Oncol. 2011;104(1):3–9. https://doi.org/10.1002/jso.21745.
48. Oshowo A, Gillams A, Harrison E, et al. Comparison of resection and radiofrequency ablation for treatment of solitary colorectal liver metastases. Br J Surg. 2003;90(10):1240–3. https://doi.org/10.1002/bjs.4264.
49. Abdalla EK, Vauthey J-N, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg. 2004;239(6):818.
50. Liu H, Wang Z-G, S-Y F, et al. Randomized clinical trial of chemoembolization plus radiofrequency ablation versus partial hepatectomy for hepatocellular carcinoma within the Milan criteria. Br J Surg. 2016;103(4):348–56. https://doi.org/10.1002/bjs.10061.
51. Aloia TA, Vauthey J-N, Loyer EM, et al. Solitary colorectal liver metastasis: resection determines outcome. Arch Surg. 2006;141(5):460. https://doi.org/10.1001/archsurg.141.5.460.
52. Bholee AK, Peng K, Zhou Z, et al. Radiofrequency ablation combined with transarterial chemoembolization versus hepatectomy for patients with hepatocellular carcinoma within Milan criteria: a retrospective case-control study. Clin Transl Oncol. 2017;19(7):844–52. https://doi.org/10.1007/s12094-016-1611-0.
53. Park IJ, Kim HC, CS Y, et al. Radiofrequency ablation for metachronous liver metastasis from colorectal cancer after curative surgery. Ann Surg Oncol. 2008;15(1):227–32. https://doi.org/10.1245/s10434-007-9625-z.

54. Berber E, Tsinberg M, Tellioglu G, et al. Resection versus laparoscopic radiofrequency thermal ablation of solitary colorectal liver metastasis. J Gastrointest Surg. 2008;12(11):1967–72. https://doi.org/10.1007/s11605-008-0622-8.
55. Lee W-S, Yun SH, Chun H-K, et al. Clinical outcomes of hepatic resection and radiofrequency ablation in patients with solitary colorectal liver metastasis. J Clin Gastroenterol. 2008;42(8):945–9. https://doi.org/10.1097/MCG.0b013e318064e752.
56. Hur H, Ko YT, Min BS, et al. Comparative study of resection and radiofrequency ablation in the treatment of solitary colorectal liver metastases. Am J Surg. 2009;197(6):728–36. https://doi.org/10.1016/j.amjsurg.2008.04.013.
57. Reuter NP, Woodall CE, Scoggins CR, et al. Radiofrequency ablation vs. resection for hepatic colorectal metastasis: therapeutically equivalent? J Gastrointest Surg. 2009;13(3):486–91. https://doi.org/10.1007/s11605-008-0727-0.
58. McKay A, Fradette K, Lipschitz J. Long-term outcomes following hepatic resection and radiofrequency ablation of colorectal liver metastases. HPB Surg. 2009;2009:346863. https://doi.org/10.1155/2009/346863.
59. Otto G, Düber C, Hoppe-Lotichius M, et al. Radiofrequency ablation as first-line treatment in patients with early colorectal liver metastases amenable to surgery. Ann Surg. 2010;251(5):796–803. https://doi.org/10.1097/SLA.0b013e3181bc9fae.
60. Schiffman SC, Bower M, Brown RE, et al. Hepatectomy is superior to thermal ablation for patients with a solitary colorectal liver metastasis. J Gastrointest Surg. 2010;14(12):1881. https://doi.org/10.1007/s11605-010-1339-z.
61. Lee KH, Kim HO, Yoo CH, et al. Comparison of radiofrequency ablation and resection for hepatic metastasis from colorectal cancer. Korean J Gastroenterol. 2012;59(3):218–23.
62. Ko S, Jo H, Yun S, et al. Comparative analysis of radiofrequency ablation and resection for resectable colorectal liver metastases. World J Gastroenterol. 2014;20(2):525–31. https://doi.org/10.3748/wjg.v20.i2.525.
63. Lee H, Heo JS, Cho YB, et al. Hepatectomy vs radiofrequency ablation for colorectal liver metastasis: a propensity score analysis. World J Gastroenterol. 2015;21(11):3300–7. https://doi.org/10.3748/wjg.v21.i11.3300.
64. Livraghi T, Goldberg SN, Solbiati L, et al. Percutaneous radio-frequency ablation of liver metastases from breast cancer: initial experience in 24 patients. Radiology. 2001;220(1):145–9.

65. Lawes D, Chopada A, Gillams A, et al. Radiofrequency ablation (RFA) as a cytoreductive strategy for hepatic metastasis from breast cancer. Ann R Coll Surg Engl. 2006;88(7):639–42. https://doi.org/10.1308/003588406X149129.
66. Sofocleous CT, Nascimento RG, Gonen M, et al. Radiofrequency ablation in the management of liver metastases from breast cancer. Am J Roentgenol. 2007;189(4):883–9. https://doi.org/10.2214/AJR.07.2198.
67. Gunabushanam G, Sharma S, Thulkar S, et al. Radiofrequency ablation of liver metastases from breast cancer: results in 14 patients. J Vasc Interv Radiol. 2007;18(1 Pt 1):67–72. https://doi.org/10.1016/j.jvir.2006.10.014.
68. Jakobs TF, Hoffmann R-T, Schrader A, et al. CT-guided radiofrequency ablation in patients with hepatic metastases from breast cancer. Cardiovasc Intervent Radiol. 2009;32(1):38–46. https://doi.org/10.1007/s00270-008-9384-7.
69. Meloni MF, Andreano A, Laeseke PF, et al. Breast cancer liver metastases: US-guided percutaneous radiofrequency ablation--intermediate and long-term survival rates. Radiology. 2009;253(3):861–9. https://doi.org/10.1148/radiol.2533081968.
70. Gillams A, Cassoni A, Conway G, et al. Radiofrequency ablation of neuroendocrine liver metastases: the Middlesex experience. Abdom Imaging. 2005;30(4):435–41. https://doi.org/10.1007/s00261-004-0258-4.
71. Mazzaglia PJ, Berber E, Milas M, et al. Laparoscopic radiofrequency ablation of neuroendocrine liver metastases: a 10-year experience evaluating predictors of survival. Surgery. 2007;142(1):10–9. https://doi.org/10.1016/j.surg.2007.01.036.
72. Akyildiz HY, Mitchell J, Milas M, et al. Laparoscopic radiofrequency thermal ablation of neuroendocrine hepatic metastases: long-term follow-up. Surgery. 2010;148(6):1288. https://doi.org/10.1016/j.surg.2010.09.014.
73. Yamakado K, Nakatsuka A, Takaki H, et al. Prospective study of arterial infusion chemotherapy followed by radiofrequency ablation for the treatment of liver metastasis of gastric cancer. J Vasc Interv Radiol. 2005;16(12):1747–51. https://doi.org/10.1097/01.RVI.0000188738.84911.3B.
74. Kim HR, Cheon SH, Lee K-H, et al. Efficacy and feasibility of radiofrequency ablation for liver metastases from gastric adenocarcinoma. Int J Hyperth. 2010;26(4):305–15. https://doi.org/10.3109/02656730903555696.
75. Mylona S, Stroumpouli E, Pomoni M, et al. Radiofrequency ablation of liver metastases from cancer of unknown primary site. Diagn Interv

Radiol. 2009;15(4):297–302. https://doi.org/10.4261/1305-3825.DIR.1714-08.1.

76. Gervais DA, Arellano RS, Mueller PR. Percutaneous radiofrequency ablation of ovarian cancer metastasis to the liver: indications, outcomes, and role in patient management. Am J Roentgenol. 2006;187(3):746–50. https://doi.org/10.2214/AJR.05.1106.

Chapter 10
Radiofrequency Ablation for Treating Malignant Tumors to the Lungs

Thierry de Baère and Andreas H. Mahnken

10.1 Introduction

Even if the clinical use of RF ablation in lung tumors started in 2000 [1], the quality of the data available today is limited with inhomogeneous patient populations in early studies mixing primary and metastatic disease. More recently a few prospective studies with larger volume of patient with more homogeneous disease became available. No randomized study versus competitive local treatment such as surgery or stereotaxic body radiation is available. There is only very limited data on other thermal ablation techniques for treating lung lesions such as microwaves, cryoablation [2, 3], and irrevers-

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ible electroporation [4]. The pathological proof of local efficacy of lung RFA has been obtained in an ablation-resection study where nine of the nine treated metastases show 100% necrosis after percutaneous RFA when treating metastases up to 3 cm [5]. Oversizing the ablation zone has been reported in many study as a key for obtaining local control [6, 7]. The following sections are designed to provide an overview on the available clinical data, based on a selective literature review. Studies including mixed populations with primary lung cancer and metastatic disease are excluded.

Major complications are reported in about 2–10% of patients with a case series of 1403 lung tumors who underwent 1000 RFA sessions reporting a major complication rate of 9.8% including 4 deaths with 3 related to pneumonia and 1 to hemorrhage. Frequent major complications were aseptic pleuritis (2.3%), pneumonia (1.8%), lung abscess (1.6%), bleeding requiring blood transfusion (1.6%), pneumothorax requiring pleural sclerosis (2.0%), brachial nerve injury (0.3%), and tumor seeding (0.1%). Previous external beam radiotherapy and age were significant risk factors for pneumonia, emphysema being a risk factor for lung abscess, and pneumothorax requiring pleural sclerosis [8].

Pneumothorax occurs in up to 63% of patients, with roughly 20% of patients requiring chest tube for a short period of time. Pneumothorax should not be considered as a complication unless long-term drainage or more aggressive treatment is needed.

10.1.1 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. Outcomes are favorable in early stages of disease (Stage Ia/Ib). Ideally tumor size is below 3–3.5 cm. Additional

systemic therapy appears to favorably add to the prognosis. So far it is hard to estimate the clinical value of RF ablation in NSCLC as comparative data are scarce (Table 10.1). RFA for NSCLC is usually performed in nonsurgical patients with severe comorbidities, and it is noteworthy to notice that most of reported deaths in NSCLC RFA series are not related to cancer progression but comorbidities. For Simon et al., Cox regressions showed that an increasing Charlson comorbidity index score was significantly associated with an increased risk of death (HR 1.3, 95% CI 25.5, 58.2) with a score ≥5 (OS = 10.43 months—95% CI 7.61, 19.85), a score of 3–4 (OS = 36.62 months—95% CI 25.54, 58.29), and a score of 1–2 (OS = 55.5 months—95% CI 39.46, 64.02) [9].

10.1.2 Metastatic Lung Disease

The acceptance of resecting of 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 [10]. Despite several reports evidence for surgical metastasectomy remains weak and is discussed controversial [11]. Overall survival after RF ablation of lung metastases appears to be very similar to s surgical metastasectomy. A systematic review of lung metastasectomy in colorectal lung metastases looked at 2925 patients with a 5-year overall survival in between 27 and 68% [12]. RF ablation is typically limited to no more than 5–6 lesions, ideally less than 3, with a maximum diameter of 3–3.5 cm. An obvious advantage of RF ablation over surgery is its potential to easily preform repeated ablations during the course of disease. OS rate after RFA of lung metastases is within the range of the best results obtained by surgical resection with very similar predictive factors of OS than RFA. Indeed complete resection, location of primary disease, DFI, number of metastases, and positive lymph nodes at pathology have been reported as predictive factors in meta-analysis of lung metastasectomies [10, 12]. The size of metastases, number of metastases, extrapulmonary disease, and DFI have been reported as predictive as predictive factors in lung radiofrequency ablation [13, 14] (Table 10.2).

Table 10.1 Summary of studies on RF ablation in NSCLC

Author	Patients/ lesions	Ablations [*n*]	Tumor stage	Lesion size [mm]	Follow-up [months]	Overall survival 1 year [%]	3 year [%]	5 year [%]	Median survival [months]	Local recurrence/ progression [%]	Major complications [%]
Fernando (2005) [15]	18/21		I–IV	28 (12–45)	14 (3–25)	80			n.r.	38	1 death
Beland (2010) [16]	79/79		I–IV	26 (10–55)	17 (1–72)				n.a.	38	
Hiraki (2011) [17]	50/52	52	I	21 (7–60)	37 (2–88)	94	74		67	31	6
Ambrogi (2011) [18]	57/59	80	I	26 (11–50)	46 (12–82)	83	40	25	33	41	5
Lanuti (2012) [19]	45/?	55	I	23 (7–45)	32 (2–75)		67	31	44	38	n.a.
Kodama (2012) [20]	44/51	55	I–IV	17 (6–40)	29 (1–98)	98	73	56		11	5.5
Simon (2012) [9]	82	–	IA–IB	–	–	77	50	20	36.6	–	–
Palussiere (2015) [21]	87/97	–	I–IIA	21 (10–54)	31 (17–51)	91.9	77.5	58.1		21.1	3.4

10.2 Study Results

Table 10.2 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 1 year [%]	3 year [%]	5 year [%]	Median survival [months]	Local recurrence/ progression [%]	Major complications [%]
Yan (2006) [22]	55/n.a.	70	CRC	21±11	24 (6–40)	85	46	n.a.	33 (4–40)	38	17
Yamakado (2007) [23]	71/155	n.a.	CRC	24±13	19 (4–42)	84	46	n.a.	31	47	20
Hamada (2012) [24]	84/141	n.a.	CRC	23±14	27 (14–93)	91	45	21	34.9	28	2.2
Soga (2009) [25]	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	
Palussiere (2011) [26]	29/47	n.a.	Sarcoma	9 (4–40)	50 (28–72)	92	65	n.a.	n.a.	11	59
Chua (2010) [27]	148	188	Mixed	40	29 (2–103)		60	45	51	4	
Gillams (2013) [13]	122/398	256	CRC	17 (5–40)	18 (6–102)		57		41	19	4
Matsui (2015) [28]	84/172	113	CRC		37.5	95	65	52		14	1.8
De Baere (2015) [3]	40/60	48 cryo	Mixed	14 (3–32)	Min 12					6	6
De Baere (2015) [14]	566/1037	642	Mixed 188 CRC	15 (4–70)	36 (20–53)	92	68	52	62	11	–

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

References

1. Dupuy DE, Zagoria RJ, Akerley W, et al. Percutaneous radiofrequency ablation of malignancies in the lung. Am J Roentgenol. 2000;174:57–9.
2. Inoue M, Nakatsuka S, Jinzaki M. Cryoablation of early-stage primary lung cancer. Biomed Res Int. 2014;2014:521691.
3. de Baere T, Tselikas L, Woodrum D, et al. Evaluating cryoablation of metastatic lung tumors in patients—safety and efficacy: the ECLIPSE trial—interim analysis at 1-year. J Thorac Oncol. 2015;10(10): 1468–74.
4. Ricke J, Jurgens JH, Deschamps F, et al. Irreversible electroporation (IRE) fails to demonstrate efficacy in a prospective multicenter phase II trial on lung malignancies: the ALICE trial. Cardiovasc Intervent Radiol. 2015;38:401–8.
5. Jaskolka JD, Kachura JR, Hwang DM, et al. Pathologic assessment of radiofrequency ablation of pulmonary metastases. J Vasc Interv Radiol. 2010;21:1689–96.
6. de Baere T, Palussiere J, Auperin A, et al. Mid-term local efficacy and survival after radiofrequency ablation of lung tumors with a minimum follow-up of 1 year : prospective evaluation. Radiology. 2006;240:587–96.
7. Ihara H, Gobara H, Hiraki T, et al. Radiofrequency ablation of lung tumors using a multitined expandable electrode: impact of the electrode array diameter on local tumor progression. J Vasc Interv Radiol. 2016;27:87–95.
8. Kashima M, Yamakado K, Takaki H, et al. Complications after 1000 lung radiofrequency ablation sessions in 420 patients: a single center's experiences. Am J Roentgenol. 2011;197:W576–80.
9. Simon TG, Beland MD, Machan JT, Dipetrillo T, Dupuy DE. Charlson Comorbidity Index predicts patient outcome, in cases of inoperable non-small cell lung cancer treated with radiofrequency ablation. Eur J Radiol. 2012;81(12):4167–72.
10. Pastorino U, Buyse M, Friedel G, et al. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. J Thorac Cardiovasc Surg. 1997;113:37–49.
11. Treasure T, Milosevic M, Fiorentino F, Macbeth F. Pulmonary metastasectomy: what is the practice and where is the evidence for effectiveness? Thorax. 2014;69:946–9.
12. Gonzalez M, Poncet A, Combescure C, et al. Risk factors for survival after lung metastasectomy in colorectal cancer patients: a systematic review and meta-analysis. Ann Surg Oncol. 2013;20:572–9.

13. Gillams A, Khan Z, Osborn P, Lees W. Survival after radiofrequency ablation in 122 patients with inoperable colorectal lung metastases. Cardiovasc Intervent Radiol. 2013;36(3):724–30.
14. de Baere T, Auperin A, Deschamps F, et al. Radiofrequency ablation is a valid treatment option for lung metastases: experience in 566 patients with 1037 metastases. Ann Oncol. 2015;26(5):987–91.
15. Fernando HC, De Hoyos A, Landreneau RJ, et al. Radiofrequency ablation for the treatment of non-small cell lung cancer in marginal surgical candidates. J Thorac Cardiovasc Surg. 2005;129:639–44.
16. Beland MD, Wasser EJ, Mayo-Smith WW, Dupuy DE. Primary non-small cell lung cancer: review of frequency, location, and time of recurrence after radiofrequency ablation. Radiology. 2010;254:301–7.
17. Hiraki T, Gobara H, Mimura H, et al. Percutaneous radiofrequency ablation of clinical stage I non-small cell lung cancer. J Thorac Cardiovasc Surg. 2011;142:24–30.
18. Ambrogi MC, Fanucchi O, Cioni R, et al. Long-term results of radiofrequency ablation treatment of stage I non-small cell lung cancer: a prospective intention-to-treat study. J Thorac Oncol. 2011;6:2044–51.
19. Lanuti M, Sharma A, Willers H, et al. Radiofrequency ablation for stage I non-small cell lung cancer: management of locoregional recurrence. Ann Thorac Surg. 2012;93:921–7. discussion 927-988.
20. Kodama H, Yamakado K, Takaki H, et al. Lung radiofrequency ablation for the treatment of unresectable recurrent non-small-cell lung cancer after surgical intervention. Cardiovasc Intervent Radiol. 2012;35:563–9.
21. Palussiere J, Lagarde P, Auperin A, et al. Percutaneous lung thermal ablation of non-surgical clinical N0 non-small cell lung cancer: results of eight years' experience in 87 patients from two centers. Cardiovasc Intervent Radiol. 2015;38:160–6.
22. Yan TD, King J, Sjarif A, et al. Percutaneous radiofrequency ablation of pulmonary metastases from colorectal carcinoma: prognostic determinants for survival. Ann Surg Oncol. 2006;13:1529–37.
23. Yamakado K, Hase S, Matsuoka T, et al. Radiofrequency ablation for the treatment of unresectable lung metastases in patients with colorectal cancer: a multicenter study in Japan. J Vasc Interv Radiol. 2007;18:393–8.
24. Hamada A, Yamakado K, Nakatsuka A, et al. Radiofrequency ablation for colorectal liver metastases: prognostic factors in non-surgical candidates. Jpn J Radiol. 2012;30:567–74.
25. Soga N, Yamakado K, Gohara H, et al. Percutaneous radiofrequency ablation for unresectable pulmonary metastases from renal cell carcinoma. BJU Int. 2009;104(6):790–4.

26. Palussiere J, Italiano A, Descat E, et al. Sarcoma lung metastases treated with percutaneous radiofrequency ablation: results from 29 patients. Ann Surg Oncol. 2011;18:3771–7.
27. Chua TC, Sarkar A, Saxena A, et al. Long-term outcome of image-guided percutaneous radiofrequency ablation of lung metastases: an open-labeled prospective trial of 148 patients. Ann Oncol. 2010;21:2017–22.
28. Matsui Y, Hiraki T, Gobara H, et al. Long-term survival following percutaneous radiofrequency ablation of colorectal lung metastases. J Vasc Interv Radiol. 2015;26:303–10. quiz 311.

Part V
Other locoregional Tumor Therapies

Chapter 11
Treatment of Peritoneal Carcinomatosis

M. Hornung and H.J. Schlitt

11.1 Introduction

Peritoneal carcinomatosis is defined as a metastatic spread of a malignant tumor into the peritoneal cavity. Previously, patients suffering from this kind of malignant peritoneal dissemination were supposed to have a very poor prognosis [1]. However, this situation has improved over the last decade due to the implementation of new systemic and surgical treatment strategies.

Based on histopathology, peritoneal carcinomatosis is divided into primary and secondary neoplasms. In the majority of cases, peritoneal carcinomatosis originates as secondary neoplasms from metastatic lesions of gastrointestinal and ovarian cancer. Pseudomyxoma peritonei, however, represents a special entity. Derived from mucinous neoplasms of the appendix, this malignancy is characterized by an accumulation of mucus in the

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peritoneal cavity [2]. Unlike the term carcinomatosis indicates, primary malignant tumors of the peritoneum, such as peritoneal mesothelioma and primary peritoneal carcinoma, are usually included in this clinical picture.

In the past, the standard of care for patients with peritoneal carcinomatosis mainly consisted of palliative systemic chemotherapy if possible and palliative surgery if required [1]. However, over the last decade, cytoreductive surgery (CRS) in combination with hyperthermic intraperitoneal chemotherapy (HIPEC) was introduced as a new treatment strategy. Accumulation of experiences with this new treatment approach until now suggests that five main tumor entities are an eligible target for CRS/HIPEC. The following chapter gives a brief description of the CRS/HIPEC procedure as well as the indication for the treatment of peritoneal carcinomatosis in context of the different tumor entities.

11.2 Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

11.2.1 CRS

The CRS and HIPEC procedure is carried out with curative intention and includes the surgical resection of tumor lesions in the abdominal cavity followed by hyperthermic intraperitoneal chemotherapy. The aim of the surgical procedure should be the complete removal of all macroscopic visible tumor lesions. Therefore, the extent of the surgical intervention varies from removal of single tumor spots up to multiple visceral resections depending on the volume of the respective peritoneal carcinomatosis, technical feasibility, and oncological benefit. Since there is

no possibility for a histopathological classification, the Gilly classification and the more detailed peritoneal cancer index (PCI) were introduced to estimate and, in consequence, to compare the extent of peritoneal carcinomatosis (Fig. 11.1) [3, 4].

11.2.2 HIPEC

Intraperitoneal chemotherapy has been already applied in the 1980s and early 1990s of the last century in the case of ovarian and gastrointestinal cancer overall with little success [6–9]. Subsequently, the intraperitoneal chemotherapy was heated in order to enhance the cytotoxic effect of the chemotherapeutic drugs and therefore established as hyperthermic intraperitoneal chemotherapy [10–12].

Regions	Lesion Seize
0 Central	
1 Right Upper	
2 Epigastrium	
3 Left Upper	
4 Left Flank	
5 Left Lower	
6 Pelvis	
7 Right Lower	
8 Right Flang	
9 Upper Jejunum	
10 Lower Jejunum	
11 Upper Ileum	
12 Lower Ileum	
PCI	

Lesion Seize Score	
LS 0	No tumor seen
LS 1	Tumor up to 0.5 cm
LS 2	Tumor up to 5.0 cm
LS 3	Tumor > 5.0 cm or confluence

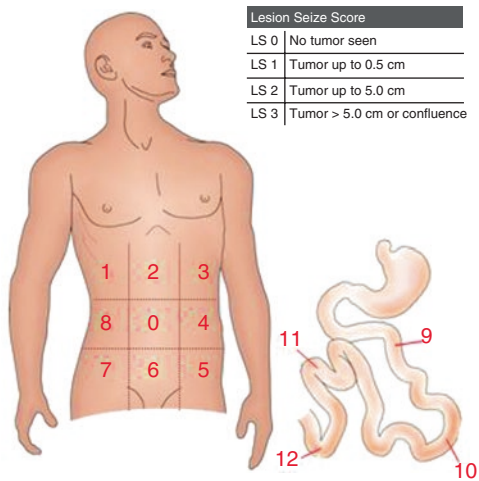

Fig. 11.1 Peritoneal cancer index: size and regions of peritoneal lesions to quantify tumor volume [4, 5]

Table 11.1 HIPEC regimens recommended by the authors

Tumor entity	Cytostatic drug	Dosage[a] (mg/m²)	Duration (min)
Colorectal and appendix cancer	5-fluorouracil i.v.	400	30
	Leucovorin i.v.	20	
	Oxaliplatin i.p.	300	
Pseudomyxoma peritonei	5-fluorouracil i.v.	400	30
	Leucovorin i.v.	20	
	Oxaliplatin i.p.	300	
Peritoneal mesothelioma	Cisplatin i.p.	75	60
	Doxorubicin i.p.	15	
Gastric cancer	Cisplatin i.p.	75	60
	Doxorubicin i.p.	15	
Ovarian cancer	Cisplatin i.p.	75	60
	Doxorubicin i.p.	15	

[a]Dosage per m² body surface area

Usually, at the end of the CRS procedure, special drainages are put in place and the HIPEC is applied directly. Sterile solution containing the respective chemotherapy is heated up to 42 °C and then circulated in the abdomen using a special pumping device for 30 or 60 min depending on the treatment algorithm. The choice of the respective chemotherapeutic agent thereby depends on the tumor entity. Most frequently used cytostatic drugs are mitomycin C, oxaliplatin, cisplatin, doxorubicin, and irinotecan for intraperitoneal application (i.p.) as well as 5-fluorouracil and leucovorin intravenously (i.v.) in the bidirectional setting (Table 11.1).

11.3 Patient Selection

The indication of CRS/HIPEC should always consider the oncological outcome with respect to the underlying malignancy and the disease stage. Usually, the CRS/HIPEC procedure is only

performed if there is no sign of extraabdominal metastasis and complete cytoreduction can be achieved. However, in the case of peritoneal carcinomatosis derived from a colorectal carcinoma, even the presence of liver metastasis represents no contraindication for CRS/HIPEC if they are removable with a limited liver resection. In addition, the Peritoneal Surface Disease Severity Score (PSDSS: 2–22 points) can help regarding preoperative selection of patients who might benefit from CRS/HIPEC [13]. In this context diagnostic laparoscopy should be considered to estimate the volume of peritoneal carcinomatosis.

Surgical feasibility of complete cytoreduction depends largely on peritoneal tumor dissemination. Especially miliary tumor nodules in the mesenteric and enteric peritoneum of the small bowel make a complete cytoreduction impossible even with a low PCI.

Furthermore, HIPEC alone without complete cytoreduction can be useful in single cases of palliative therapy of extensive ascites [14, 15]. Finally, the volume of residual tumor postoperative should be standardly recorded by using the completeness of cytoreduction (CC) score (Table 11.2) [16].

On principle, patients with peritoneal carcinomatosis and indication for CRS/HIPEC should be discussed in a multidisciplinary tumor board since the procedure of CRS/HIPEC itself represents only one part of multimodality treatment concepts for these patients. Despite oncological benefits, the indication for CRS/HIPEC should also consider distinct morbidity and even mortality of the procedure. Although studies report divergent

Table 11.2 Completeness of cytoreduction (CC) score [16]

Score	Residual tumor
CC-0	No visible tumor
CC-1	Up to 2.5 mm
CC-2	Between 2.5 mm and 2.5 cm
CC-3	>2.5 cm

data, there is a significant risk of surgical complications. Most of them are anastomosis leakage, intra-abdominal abscess, fistula, and ileus [17].

11.4 Tumor Entities

11.4.1 Colorectal and Appendix Cancer

Peritoneal metastasis derived from primary colorectal carcinoma including the appendix represents a high number of neoplasms in the abdominal cavity. Up to 28% of patients with colorectal carcinoma develop peritoneal carcinomatosis [18] with an average survival time of about 6 months [1, 19]. Several studies including the prospective randomized Dutch trial (12.6 vs. 22.3 months) [20], case control (23.9 vs. 62.7 months) [21], and meta-analysis [22] showed significantly prolonged overall survival in patients undergoing CRS/HIPEC compared to systemic chemotherapy alone. An additional benefit for overall survival can be achieved using bidirectional HIPEC. Therefore, 5-fluorouracil and leucovorin are given as i.v. drugs simultaneously with the respective intraperitoneal application [23]. Furthermore, the appendix as the origin of peritoneal carcinomatosis has a much better prognosis than other sites of the colon [24].

11.4.2 Pseudomyxoma Peritonei

Pseudomyxoma peritonei is a rare tumor manifestation with a rather small number of mucus-producing cells, which lead to an extensive accumulation of mucus in the abdominal cavity. Two

subtypes can be classified by histology, disseminated peritoneal adenomucinosis (DPAM) and peritoneal mucinous carcinomatosis (PMCA) [25]. Patients suffering from PMCA have a poorer prognosis, and additional systemic chemotherapy is recommended [26]. In the majority of cases, the mucus-producing cells are derived from a tumor of the appendix.

Large non-randomized studies reported that patients treated with CRS/HIPEC have a 5-year and a 10-year overall survival of about 75% and 63%, respectively, whereas in patients treated without HIPEC, the 10-year overall survival is reduced to 21–32% [27, 28]. Further studies confirmed these data or even showed a 5-year overall survival of 97% [29, 30].

11.4.3 Peritoneal Mesothelioma

Peritoneal mesothelioma is a malignant neoplasia of the peritoneum itself. The prognosis is depending on the histological subtype and worsens from the epithelial over the biphasic to the sarcomatoid subtype. In a retrospective analysis of 49 patients who underwent CRS/HIPEC, a median survival of 92 months was reported [31]. However, Yan et al. showed in a multicenter study including a total of 401 participants a median survival of 53 months for the patients that received CRS/HIPEC [32]. In comparison, treatment with systemic chemotherapy combined with palliative surgery resulted in a median survival of 12.5 months [33].

11.4.4 Gastric Cancer

For gastric cancer with peritoneal carcinomatosis, it is in particular recommended to consider the extent of peritoneal metastasis. Basically, two studies showed a significant

median survival benefit in the case of local peritoneal carcinomatosis derived from gastric cancer comparing gastrectomy with CRS/HIPEC to gastrectomy or CRS alone (10–11 vs. 5–6.5 months) [34, 35].

However, patients with peritoneal cancer index (PCI) above 12 do not benefit from the CRS/HIPEC procedure [36].

11.4.5 Ovarian Cancer

Ovarian cancer is unfortunately often diagnosed at later disease stages, and although it shows a good response to surgical cytoreduction followed by systemic chemotherapy, long-term survival is still poor with only about 20–25% 5-year survival rate [37].

Only non-randomized studies analyzed CRS/HIPEC regarding peritoneal carcinomatosis due to spread from ovarian cancer, and results are somewhat heterogeneous. Piso et al. showed that complete cytoreduction surgery combined with HIPEC could improve survival in selected patients [38]. In another study, patients with advanced disease stages or recurrent disease treated by CRS/HIPEC reached a median survival of 24–64 months or 23–49 months, respectively [39].

Furthermore, multiple studies looking at intraperitoneal in combination with intravenous chemotherapy showed significant benefits in overall survival compared to intravenous chemotherapy alone (49–66 vs. 41–49 months) [40–42].

Taken together, there is some evidence indicating that patients with peritoneal carcinomatosis from ovarian cancer might benefit from intraperitoneal chemotherapy in addition to cytoreductive surgery.

11.5 Study Results

11.5.1 Colorectal and Appendix Cancer

Verwaal et al. (2003) [20]

Concept	CRS and HIPEC vs. systemic chemotherapy and palliative surgery (randomized trial)
N	105
Therapy	– CRS and HIPEC (mitomycin C) – Systemic chemotherapy (fluorouracil-leucovorin) with or without palliative surgery
Median survival	22.3 vs. 12.6 months
Toxicity	Grade III: leukopenia 15%, heart failure 8% Grade IV: GI fistula 15%, hemorrhage 8% Fatal: 8%
Conclusion	CRS and HIPEC improve survival in patients with peritoneal carcinomatosis of colorectal origin

Elias et al. (2009) [21]

Concept	Case control study CRS and HIPEC (prospectively) vs. palliative chemotherapy (retrospectively)
N	48 in each group
Therapy	– CRS and HIPEC (bidirectional: oxaliplatin i.p., fluorouracil-leucovorin i.v.) – Divers paliative chemotherapy regimens (i.e., fluorouracil, capecitabine, leucovorin, oxaliplatin, irinotecan)
Median survival	62.7 vs. 23.9 months
Toxicity	Not reported
Conclusion	CRS and HIPEC are able to prolong median survival in patients with resectable peritoneal carcinomatosis

Cao et al. (2009) [22]

Concept	Meta-analysis CRS with perioperative intraperitoneal chemotherapy
N	4 comparative and 43 observational studies
Therapy	CRS and hyperthermic intraperitoneal chemotherapy (HIPEC) and/or early postoperative intraperitoneal chemotherapy (EPIC)
Median survival	Significant improvement in survival for patients treated with CRS and perioperative intraoperative chemotherapy
Toxicity	Perioperative morbidity 14.8–76% and mortality 0–12%
Conclusion	CRS combined with perioperative intraperitoneal chemotherapy has a significant survival benefit vs. control groups

Hompes et al. (2012) [23]

Concept	Treatment of peritoneal carcinomatosis with CRS and HIPEC with oxaliplatin (multicenter prospective phase II study)
N	48
Therapy	CRS and HIPEC (bidirectional: oxaliplatin i.p., fluorouracil-leucovorin i.v.)
Survival	Overall survival: 97.9% 1 year, 88.7% 2 years Disease-free survival: 65.8% 1 year, 45.5% 2 years
Toxicity	Complication rate 52.1% (anastomotic leakage 10.4%, bleeding 6.3%, bowel perforation 2.1%)
Conclusion	CRS and HIPEC with oxaliplatin can achieve long-term OS and DFS with acceptable morbidity

11.5.2 Pseudomyxoma Peritonei

Deraco et al. (2004) [29]

Concept	CRS and HIPEC: survival, morbidity, toxicity, mortality (prospective multicenter phase II study)
N	33

Therapy	CRS and HIPEC (cisplatin, mitomycin C)
Overall survival	97% 5 years
Toxicity	Grade II 15% Grade III 18% Fatal: 3%
Conclusion	CRS and HIPEC improve significantly long-term survival with acceptable morbidity and mortality

Sugarbaker (2006) [30]

Concept	Comparison of different treatment strategies (review)
N	350 vs. 88 vs. 56 vs. 46
Therapy	CRS and HIPEC vs. serial debulking and perioperative intraperitoneal chemotherapy
Overall survival	About 70% (20 years) after CRS and HIPEC vs. < 30% after serial debulking and intraperitoneal chemotherapy
Toxicity	Morbidity 12–55% Mortality 0–12%
Conclusion	Complete cytoreduction improves significantly long-term survival compared to serial debulking

11.5.3 Peritoneal Mesothelioma

Feldman et al. (2003) [31]

Concept	Outcome in patients after CRS and HIPEC (retrospective)
N	49
Therapy	CRS and HIPEC (cisplatin i.p. and cisplatin i.v.), 35 patients received additionally fluorouracil and paclitaxel i.p. on days 7 and 10 postoperative
Survival	Median survival 92 months Progression-free survival 17 months
Toxicity	Operative morbidity 25% Chemotherapy-related complications grade III–IV (neutropenia 13%, creatinine 15%, bilirubin 21%, transaminases 19%)
Conclusion	CRS and HIPEC result in a prolonged survival in patients with peritoneal mesothelioma

Yan et al. (2009) [32]

Concept	Analysis of CRS and HIPEC for diffuse malignant peritoneal mesothelioma (multi-institutional registry study)
N	405
Therapy	CRS and HIPEC (cisplatin + doxorubicin, cisplatin + mitomycin C, cisplatin or mitomycin C alone) with or without early postoperative intraperitoneal chemotherapy
Survival	Median survival 53 months Overall survival 60% 3 years, 47% 5 years
Toxicity	Grade III–IV 31% Fatal 2%
Conclusion	Data suggest that CRS and HIPEC provide a benefit in long-term survival

11.5.4 Gastric Cancer

Zhu et al. (2006) [34]

Concept	Comparison of gastrectomy with HIPEC and gastrectomy alone in patients with gastric cancer stage T3 or T4 with and without peritoneal carcinomatosis (PC)
N	118
Therapy	Gastrectomy and HIPEC (cisplatin + mitomycin C) (52) Gastrectomy alone (66)
Median survival	Without PC 60.85 months (HIPEC) vs. 42.9 months (without HIPEC) With PC 10 months (HIPEC) vs. 5 months (without HIPEC)
Toxicity	Postoperative 23.08% (HIPEC) vs. 12.12% (without HIPEC) Significance only in renal dysfunction 13.46% vs. 4.03%
Conclusion	In selected patients additional therapy with HIPEC prolongs survival

Yang et al. (2011) [35]

Concept	Comparison between CRS alone and CRS with HIPEC (prospective randomized phase III study)
N	68
Therapy	CRS vs. CRS and HIPEC (cisplatin + mitomycin C)
Median survival	6.5 vs. 11 months
Toxicity	Severe adverse events (wound infection, sepsis, respiratory failure, gastrointestinal bleeding, severe bone marrow suppression, intestinal obstruction) 4 (CRS) vs. 5 (CRS + HIPEC)
Conclusion	Prognosis is still poor but HIPEC may improve survival

11.5.5 Ovarian Cancer

Piso et al. (2004) [38]

Concept	CRS and HIPEC in patients with primary and recurrent ovarian cancer (retrospective)
N	19
Therapy	CRS and HIPEC (cisplatin or mitoxantrone)
Survival	Mean survival 33 months Overall survival 15% 5 years
Toxicity	Anastomotic leakage 11%, intra-abdominal abscess formation 11% Fatal 5%
Conclusion	CRS and HIPEC are feasible with reasonable morbidity and mortality and may increase survival

Armstrong et al. (2006) [40]

Concept	Analysis of intravenous with intraperitoneal chemotherapy vs. intravenous chemotherapy alone after surgical resection (no residual mass > 1 cm) (prospective randomized)
N	429
Therapy	Intravenous chemotherapy (paclitaxel + cisplatin) Intravenous + intraperitoneal chemotherapy (paclitaxel i.v. + cisplatin i.p. + paclitaxel i.p.)

Median survival	65.6 (i.v. + i.p.) vs. 49.7 months (i.v. alone)
Toxicity	Grade III–IV (pain, fatigue, and hematologic, gastrointestinal, metabolic, neurologic toxic effects) significantly higher in the i.v. + i.p. group
Conclusion	In patients with optimal surgical cytoreduction, intraperitoneal chemotherapy improves survival

References

1. Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J, Fontaumard E, Brachet A, Caillot JL, Faure JL, Porcheron J, Peix JL, Francois Y, Vignal J, Gilly FN. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. Cancer. 2000;88(2):358–63.
2. Carr NJ, Cecil TD, Mohamed F, Sobin LH, Sugarbaker PH, Gonzalez-Moreno S, Taflampas P, Chapman S, Moran BJ. A consensus for classification and pathologic reporting of pseudomyxoma peritonei and associated appendiceal neoplasia: the results of the Peritoneal Surface Oncology Group International (PSOGI) modified Delphi process. Am J Surg Pathol. 2016;40(1):14–26.
3. Sugarbaker PH. Management of peritoneal-surface malignancy: the surgeon's role. Langenbeck's Arch Surg. 1999;384(6):576–87.
4. Piso P, Glockzin G, von Breitenbuch P, Sulaiman T, Popp F, Dahlke M, Esquivel J, Schlitt HJ. Patient selection for a curative approach to carcinomatosis. Cancer J. 2009;15(3):236–42.
5. Glehen O, Gilly FN. Quantitative prognostic indicators of peritoneal surface malignancy: carcinomatosis, sarcomatosis, and peritoneal mesothelioma. Surg Oncol Clin N Am. 2003;12(3):649–71.
6. Ozols RF, Young RC, Speyer JL, Sugarbaker PH, Greene R, Jenkins J, Myers CE. Phase I and pharmacological studies of adriamycin administered intraperitoneally to patients with ovarian cancer. Cancer Res. 1982;42(10):4265–9.
7. Sugarbaker PH, Gianola FJ, Barofsky I, Hancock SL, Wesley R. 5-Fluorouracil chemotherapy and pelvic radiation in the treatment of large bowel cancer. Decreased toxicity in combined treatment with 5-fluorouracil administration through the intraperitoneal route. Cancer. 1986;58(4):826–31.

8. Sugarbaker PH, Graves T, DeBruijn EA, Cunliffe WJ, Mullins RE, Hull WE, Oliff L, Schlag P. Early postoperative intraperitoneal chemotherapy as an adjuvant therapy to surgery for peritoneal carcinomatosis from gastrointestinal cancer: pharmacological studies. Cancer Res. 1990;50(18):5790–4.
9. WS Y, Sugarbaker PH. Early postoperative intraperitoneal chemotherapy for gastric cancer. Cancer Treat Res. 1991;55:265–75.
10. Fernandez-Trigo V, Stuart OA, Stephens AD, Hoover LD, Sugarbaker PH. Surgically directed chemotherapy: heated intraperitoneal lavage with mitomycin C. Cancer Treat Res. 1996;81:51–61.
11. Barlogie B, Corry PM, Drewinko B. In vitro thermochemotherapy of human colon cancer cells with cis-dichlorodiammineplatinum(II) and mitomycin C. Cancer Res. 1980;40(4):1165–8.
12. Wallner KE, Li GC. effect of drug exposure duration and sequencing on hyperthermic potentiation of mitomycin-C and cisplatin. Cancer Res. 1987;47(2):493–5.
13. Pelz JO, Stojadinovic A, Nissan A, Hohenberger W, Esquivel J. Evaluation of a peritoneal surface disease severity score in patients with colon cancer with peritoneal carcinomatosis. J Surg Oncol. 2009;99(1):9–15.
14. Sangisetty SL, Miner TJ. Malignant ascites: a review of prognostic factors, pathophysiology and therapeutic measures. World J Gastrointest Surg. 2012;4(4):87–95.
15. Randle RW, Swett KR, Swords DS, Shen P, Stewart JH, Levine EA, Votanopoulos KI. Efficacy of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in the management of malignant ascites. Ann Surg Oncol. 2014;21(5):1474–9.
16. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. Cancer Treat Res. 1996;82:359–74.
17. Chua TC, Yan TD, Saxena A, Morris DL. Should the treatment of peritoneal carcinomatosis by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy still be regarded as a highly morbid procedure?: a systematic review of morbidity and mortality. Ann Surg. 2009;249(6):900–7.
18. Koppe MJ, Boerman OC, Oyen WJ, Bleichrodt RP. Peritoneal carcinomatosis of colorectal origin: incidence and current treatment strategies. Ann Surg. 2006;243(2):212–22.
19. Chu DZ, Lang NP, Thompson C, Osteen PK, Westbrook KC. Peritoneal carcinomatosis in nongynecologic malignancy. A prospective study of prognostic factors. Cancer. 1989;63(2):364–7.

20. Verwaal VJ, van RS, de BE, van Sloothen GW, van TH, Boot H, Zoetmulder FA. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol. 2003;21(20):3737–43.
21. Elias D, Lefevre JH, Chevalier J, Brouquet A, Marchal F, Classe JM, Ferron G, Guilloit JM, Meeus P, Goere D, Bonastre J. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. J Clin Oncol. 2009;27(5):681–5.
22. Cao C, Yan TD, Black D, Morris DL. A systematic review and meta-analysis of cytoreductive surgery with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis of colorectal origin. Ann Surg Oncol. 2009;16(8):2152–65.
23. Hompes D, D'Hoore A, Van CE, Fieuws S, Ceelen W, Peeters M, Van Der Speeten K, Bertrand C, Legendre H, Kerger J. The treatment of peritoneal carcinomatosis of colorectal cancer with complete cytoreductive surgery and hyperthermic intraperitoneal peroperative chemotherapy (HIPEC) with oxaliplatin: a Belgian multicentre prospective phase II clinical study. Ann Surg Oncol. 2012;19(7):2186–94.
24. Elias D, Glehen O, Pocard M, Quenet F, Goere D, Arvieux C, Rat P, Gilly F. A comparative study of complete cytoreductive surgery plus intraperitoneal chemotherapy to treat peritoneal dissemination from colon, rectum, small bowel, and nonpseudomyxoma appendix. Ann Surg. 2010;251(5):896–901.
25. Bradley RF, Stewart JH, Russell GB, Levine EA, Geisinger KR. Pseudomyxoma peritonei of appendiceal origin: a clinicopathologic analysis of 101 patients uniformly treated at a single institution, with literature review. Am J Surg Pathol. 2006;30(5):551–9.
26. Chua TC, Moran BJ, Sugarbaker PH, Levine EA, Glehen O, Gilly FN, Baratti D, Deraco M, Elias D, Sardi A, Liauw W, Yan TD, Barrios P, Gomez PA, de Hingh IH, Ceelen WP, Pelz JO, Piso P, Gonzalez-Moreno S, Van Der Speeten K, Morris DL. Early- and long-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. J Clin Oncol. 2012;30(20):2449–56.
27. Miner TJ, Shia J, Jaques DP, Klimstra DS, Brennan MF, Coit DG. Long-term survival following treatment of pseudomyxoma peritonei: an analysis of surgical therapy. Ann Surg. 2005;241(2):300–8.
28. Gough DB, Donohue JH, Schutt AJ, Gonchoroff N, Goellner JR, Wilson TO, Naessens JM, O'Brien PC, van Heerden JA. Pseudomyxoma

peritonei. Long-term patient survival with an aggressive regional approach. Ann Surg. 1994;219(2):112–9.
29. Deraco M, Baratti D, Inglese MG, Allaria B, Andreola S, Gavazzi C, Kusamura S. Peritonectomy and intraperitoneal hyperthermic perfusion (IPHP): a strategy that has confirmed its efficacy in patients with pseudomyxoma peritonei. Ann Surg Oncol. 2004;11(4):393–8.
30. Sugarbaker PH. New standard of care for appendiceal epithelial neoplasms and pseudomyxoma peritonei syndrome? Lancet Oncol. 2006;7(1):69–76.
31. Feldman AL, Libutti SK, Pingpank JF, Bartlett DL, Beresnev TH, Mavroukakis SM, Steinberg SM, Liewehr DJ, Kleiner DE, Alexander HR. Analysis of factors associated with outcome in patients with malignant peritoneal mesothelioma undergoing surgical debulking and intraperitoneal chemotherapy. J Clin Oncol. 2003;21(24):4560–7.
32. Yan TD, Deraco M, Baratti D, Kusamura S, Elias D, Glehen O, Gilly FN, Levine EA, Shen P, Mohamed F, Moran BJ, Morris DL, Chua TC, Piso P, Sugarbaker PH. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: multi-institutional experience. J Clin Oncol. 2009;27(36):6237–42.
33. Eltabbakh GH, Piver MS, Hempling RE, Recio FO, Intengen ME. Clinical picture, response to therapy, and survival of women with diffuse malignant peritoneal mesothelioma. J Surg Oncol. 1999;70(1):6–12.
34. Zhu ZG, Tang R, Yan M, Chen J, Yang QM, Li C, Yao XX, Zhang J, Yin HR, Lin YZ. Efficacy and safety of intraoperative peritoneal hyperthermic chemotherapy for advanced gastric cancer patients with serosal invasion. A long-term follow-up study. Dig Surg. 2006;23(1–2):93–102.
35. Yang XJ, Huang CQ, Suo T, Mei LJ, Yang GL, Cheng FL, Zhou YF, Xiong B, Yonemura Y, Li Y. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from gastric cancer: final results of a phase III randomized clinical trial. Ann Surg Oncol. 2011;18(6):1575–81.
36. Glehen O, Gilly FN, Arvieux C, Cotte E, Boutitie F, Mansvelt B, Bereder JM, Lorimier G, Quenet F, Elias D. Peritoneal carcinomatosis from gastric cancer: a multi-institutional study of 159 patients treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. Ann Surg Oncol. 2010;17(9):2370–7.
37. Ozols RF. Treatment goals in ovarian cancer. Int J Gynecol Cancer. 2005;15(Suppl 1):3–11.

38. Piso P, Dahlke MH, Loss M, Schlitt HJ. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in peritoneal carcinomatosis from ovarian cancer. World J Surg Oncol. 2004;2:21.
39. Chan DL, Morris DL, Rao A, Chua TC. Intraperitoneal chemotherapy in ovarian cancer: a review of tolerance and efficacy. Cancer Manag Res. 2012;4:413–22.
40. Armstrong DK, Bundy B, Wenzel L, Huang HQ, Baergen R, Lele S, Copeland LJ, Walker JL, Burger RA. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med. 2006;354(1):34–43.
41. Markman M, Bundy BN, Alberts DS, Fowler JM, Clark-Pearson DL, Carson LF, Wadler S, Sickel J. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. J Clin Oncol. 2001;19(4):1001–7.
42. Alberts DS, Liu PY, Hannigan EV, O'Toole R, Williams SD, Young JA, Franklin EW, Clarke-Pearson DL, Malviya VK, DuBeshter B. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. N Engl J Med. 1996;335(26):1950–5.

Chapter 12
Melanoma

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12.1 Introduction

Locoregional disease for melanoma encompasses the following disease presentations:

- Primary disease
- Local recurrence (in the scar of the primary)
- Satellite metastases (adjacent to the scar, but within 2 cm distance)
- In-transit metastases (ITM), beyond 2 cm from the scar, but not beyond the regional node basin
- Regional lymph node recurrence in the draining lymph node basin (which can be multiple in case of a melanoma of the trunk)

Everything beyond the draining lymph node basin is considered a distant metastasis and will not be discussed here.

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The 2 cm cutoff for satellite versus in-transit metastasis has been arbitrarily chosen and is oftentimes interchanged with each other. For this chapter, we shall refer to satellite and/or in-transit metastases as ITM. Furthermore, treatment of regional lymph node metastases will also not be discussed here, since basically the only treatment option is surgical resection.

ITM are a heterogeneous patient group in itself; they can present as cutaneous or subcutaneous lesions. ITM can be solitary or multiple and/or bulky. The incidence of ITM is not exactly known, because patients from institutional databases might have undergone a resection of a simple solitary lesion by a peripheral doctor, without the center knowing this. Cancer registries are also likely to underestimate the incidence. However, from some large prospective trials, it is known that the incidence is around 4–8% of the prevalent melanoma cases, depending on the median Breslow thickness and amount of ulceration seen in the population but also depending on the median duration of follow-up [1, 2].

ITM are considered in the TNM staging system as N2c (without any lymph node involvement) or N3 (in case of concurrent or previous lymph node involvement). This automatically makes patients at least AJCC stage IIIB or IIIC. Stage IIIB melanoma was defined according to the AJCC criteria as in-transit metastases with a non-ulcerated primary tumor and no nodal involvement (pT1-4aN2cM0). Stage IIIC was defined as in-transit metastases with an ulcerated primary tumor (pT1-4bN2cM0), nodal involvement (pT1-4aN3M0), or both.

Five-year survival rates according to the 2009 AJCC Balch et al. paper were 69% for stage IIIB and 46% for stage IIIC [3]. Read et al. reported on 11,614 from the Melanoma Institute Australia (MIA) and found 505 patients with ITM (4.3%) had a 5-year survival rate of 32.8% [1]. This differed for non-ulcerated limb lesions with a 5-year survival rate of 47.9% to 13.6% for ulcerated trunk lesions [1].

12.2 Therapy

12.2.1 Surgery

Surgery can usually be performed on solitary cutaneous and/or subcutaneous ITM. Due to the superficial nature of the disease, it is usually technically quite simple to perform a radical excision and primary closure. The biology of the disease dictates if surgery fails in due course, when the lesions become numerous or bulky or when the interval becomes increasingly shorter.

12.2.2 Isolated Limb Perfusion (ILP)

This technique was developed in 1958 by Creech and Krementz [4]. In short the technique is as follows: surgical access to the main artery and main vein of a limb is made by a surgical wound. The vein is clamped and cannulated first; thereafter the artery is clamped and cannulated. The cannules are connected to an oxygenated extracorporeal circuit. Collateral vessels may be ligated to prevent leakage. A tourniquet is applied proximal to the tips of the cannules. Leakage is checked by using a precordial scintillation probe to detect radiolabeled albumin, which is injected into the perfusion circuit after first checking a low background dose systemically. Once the limb has reached the correct temperature (normothermic (37–38 °C) or hyperthermic (38–40 °C)), the first drug is given through the perfusion circuit. Most frequently melphalan (L-phenylalanine mustard (L-PAM)) is used. Also, the combination with tumor necrosis factor-alpha (TNF-alpha) is well recognized. Elsewhere actinomycin D is used. This technique allows for tenfold higher concentrations of chemotherapy in a limb than that would be possible if given through a peripheral I.V.

12.2.3 Isolated Limb Infusion (ILI)

This less invasive technique was developed at the Melanoma Institute Australia (MIA) in the 1990s. The objective was to keep the benefits of an ILP, but reduce the major disadvantages, such as general anesthesia and a surgical arteriotomy by performing a simplified and minimally invasive alternative.

12.2.4 Talimogene Laherparepvec (T-VEC)

Talimogene laherparepvec (T-VEC) is a new form of locoregional oncolytic immunotherapy. It is derived from herpes simplex type 1 and altered with some insertions and deletion in the DNA to selective replicate within melanoma tumors and produce granulocyte-macrophage colony-stimulating factor (GM-CSF). It is injected directly into cutaneous, subcutaneous, and/or nodal deposits. It had two effects: The first is a direct effect of lysis of melanoma cells. The second is an indirect effect of GM-CSF and tumor-derived antigen (TDA) leading to an enhancement of systemic antitumor immune response.

The pivotal phase 3 randomized controlled trial (OPTiM) analyzed intratumoral injection of T-VEC every 2 weeks to subcutaneous GM-CSF daily for 14 days in 28-day cycles. 436 patients were randomized 2:1 for T-VEC vs. GM-CSF. The primary end-point was durable response rate (DRR), which was defined as an objective response lasting ≥6 months.

DRR was significantly higher with T-VEC 16.3% compared to GM-CSF 2.1 ($P < 0.001$) [5]. Overall response rate was also higher for T-VEC at 26.4% vs. 5.7% [5]. Median overall survival (OS) was 23 months for T-VEC compared to 18.9 months for GM-CSF ($P = 0.051$) [5]. Toxicity was very acceptable, with the only grade 3/4 toxicity ≥2% being cellulitis at 2.3% [5].

Importantly, Harrington et al. have reported the results for stage IIIB/C and IV M1a patients from the OPTiM study. 249 patients randomized 2:1 for T-VEC vs. GM-CSF demonstrated a DRR of 25% vs. 1.2% ($P < 0.001$) [6]. Objective response rate

(ORR) was also higher at 40.5% for T-VEC vs. 2.3% for GM-CSF [6]. Median OS was 41.1 months vs. 21.5 months for this subgroup of the OPTiM study [6].

12.2.5 Miscellaneous/Others

There are many other locoregional treatment options for melanoma. However, the response rates and duration of response are usually less than ILP/ILI or T-VEC. Therefore, they are considered as palliative options.

12.2.5.1 PV-10

Rose bengal disodium (RB) is a dye. PV-10 is a sterile, nonpyrogenic 10% solution of RB in 0.9% saline. PV-10 can be administered intralesionally for the locoregional treatment of cutaneous or subcutaneous melanoma ITM. A phase 2 study by Thompson et al. examined intralesional injections of up to 20 lesions at week 0, which could be repeated at weeks 8, 12, and 16 for remaining or new lesions. This study demonstrated a best overall response rate of 51% in 62 stage III and 18 stage IV patients [7]. However, the median duration of response was only 4.0 months [7]. Median time until a first response was 1.9 months [7], with 8% of patients achieving a disease-free status after 52 weeks [7].

12.2.5.2 CO_2 Laser

Carbon dioxide (CO_2) laser is another technique to treat cutaneous ITM. A single-center series by van Jarwaarde et al. demonstrated in 22 patients a median duration of regional control of 14 weeks with limited morbidity [8].

12.2.5.3 Electrochemotherapy

Electrochemotherapy (ECT) is a technique which uses electroporation with high-intensity electric pulses to facilitate the

intracellular delivery of cytotoxic drugs (chemotherapy) administered intravenously or by intralesional injections [9–11]. Most frequently used drug includes bleomycin or cisplatin. A study in 127 patients (108 evaluable) demonstrated an overall response rate of 88% and a complete response rate of 72% [9].

12.2.6 Systemic Therapy

Systemic therapy for melanoma has changed enormously since 2010/2011 with the parallel discoveries of targeted therapy (TT) of the MAP kinase pathway in BRAF- or NRAS-mutated melanomas with selective BRAF and MEK inhibitors and at the same time the identification of immune checkpoint inhibitors, such as anti-CTLA-4 and anti-PD-(L)1 [12–27]. Response rates of immune checkpoint inhibitors are lower (20–50%), but they have the potential of durable responses, whereas TT has a higher response rate (50–75%) but will lead to resistance in due course. Studies have focused on stage IV (M+) disease, but most protocols allow for unresectable stage IIIC disease to be included too. There is no evidence yet which therapy is preferred in these cases (locoregional therapy versus systemic therapy), and it is also unclear in which order these therapies should be given (systemic first and locoregional after? Or vice versa?). Interestingly, combination of a locoregional therapy with a systemic therapy might improve both response rates and the duration of response and is under investigation.

The first data shows that the combination of T-VEC with anti-CTLA-4 (ipilimumab) has a tolerable safety profile and appeared to have a greater efficacy than either T-VEC or ipilimumab monotherapy with an objective response rate of 50% and 44% having a durable response (≥6 months) [28].

Currently, a phase 3 study (Masterkey-265) is examining pembrolizumab (anti-PD-1) + placebo versus pembrolizumab + T-VEC.

12.3 Study Results

Study	Year	Design	Treatment	*N*	ORR	CR	PR	Wieberdink	Systemic grade 3/4	DFS	OS
Lienard [29]	1992	Retrospective, single center	M + TNF	19	100%	89.5%	10.5%	84.2% II 15.8% III	10.5%	70% 1-year	76% 1-year
Lienard [30]	1994	Retrospective, multicenter	M + TNF	53	100%	90%	10%		2%		Med 28 months
Vaglini [31, 32]	1994	Retrospective, single center	M + TNF	22	69%	55%	14%	79% II 14% III 7% IV	1 pt grade 5	Med 3–4 months	
Fraker	1996	Retrospective, single center	M + TNF	36	94%	64%	30%	6% IV/V	46%		
Bartlett [33]	1997	Retrospective, single center	M + TNF	17	94%	65%	29%	47% II 6% III 6% V	6 (35%)	Med 6 months (2–24+)	
Lienard [34]	1999	RCT, multicenter	M+TNF	64	95%	73%	22%			Med 11 months	Med 29 months
Fraker [35]	2002	RCT, multicenter	M vs. M + TNF	103	96% M 81% M + TNF	58% M 72% M + TNF				Med 14 (M)—12 (M+TNF) months	56% 3-year

(continued)

(continued)

Study	Year	Design	Treatment	*N*	ORR	CR	PR	Wieberdink	Systemic grade 3/4	DFS	OS
Noorda [36]	2004	Retrospective, multicenter	M vs. M + TNF	130	77%	55%	22%	73% II 24% III 3% IV			29% 5-year
Grunhagen [37]	2004	Retrospective, single center	M + TNF	100	95%	69%	26%	69% I/II 27% III 3% IV 1% V	7%	Med 16 months	32% 5-year
Cornett [38]	2006	RCT, multicenter	M vs. M + TNF	124	62% M 69% M + TNF	25% M 26% M + TNF			38% vs. 48%		
Deroose [39]	2012	Retrospective, single center	M + TNF	118	93%	68%	25%	71% I/II 25% III 3% IV 1% V		Med 13 months	27% 5-year
Madu [40]	2017	Retrospective, single center	M vs. M + TNF	88	81%	47%		28% I 67% II 2% III 2% IV	9%		38% 5-year

References

1. Read RL, Haydu L, Saw RP, et al. In-transit melanoma metastases: incidence, prognosis, and the role of lymphadenectomy. Ann Surg Oncol. 2015;22:475–81.
2. Morton DL, Thompson JF, Cochran AJ, et al. Sentinel-node biopsy or nodal observation in melanoma. N Engl J Med. 2006;355:1307–17.
3. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol. 2009;27:6199–206.
4. Creech O Jr, Krementz ET, Ryan RF, et al. Chemotherapy of cancer: regional perfusion utilizing an extracorporeal circuit. Ann Surg. 1958;148:616–32.
5. Andtbacka RH, Kaufman HL, Collichio F, et al. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. J Clin Oncol. 2015;33:2780–8.
6. Harrington KJ, Andtbacka RH, Collichio F, et al. Efficacy and safety of talimogene laherparepvec versus granulocyte-macrophage colony-stimulating factor in patients with stage IIIB/C and IVM1a melanoma: subanalysis of the Phase III OPTiM trial. Onco Targets Ther. 2016;9:7081–93.
7. Thompson JF, Agarwala SS, Smithers BM, et al. Phase 2 study of intralesional PV-10 in refractory metastatic melanoma. Ann Surg Oncol. 2015;22:2135–42.
8. van Jarwaarde JA, Wessels R, Nieweg OE, et al. CO_2 laser treatment for regional cutaneous malignant melanoma metastases. Dermatol Surg. 2015;41:78–82.
9. Testori A, Faries MB, Thompson JF, et al. Local and intralesional therapy of in-transit melanoma metastases. J Surg Oncol. 2011;104:391–6.
10. Campana LG, Mocellin S, Basso M, et al. Bleomycin-based electrochemotherapy: clinical outcome from a single institution's experience with 52 patients. Ann Surg Oncol. 2009;16:191–9.
11. Mir LM, Glass LF, Sersa G, et al. Effective treatment of cutaneous and subcutaneous malignant tumours by electrochemotherapy. Br J Cancer. 1998;77:2336–42.
12. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364:2507–16.
13. Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med. 2012;367:1694–703.

14. Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med. 2012;367:107–14.
15. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2012;380:358–65.
16. Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med. 2014;371:1877–88.
17. Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med. 2015;372:30–9.
18. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015;372:320–30.
19. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363:711–23.
20. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med. 2015;373:23–34.
21. Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med. 2015;372:2006–17.
22. Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol. 2015;16:908–18.
23. Robert C, Ribas A, Wolchok JD, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. Lancet. 2014;384:1109–17.
24. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med. 2015;372:2521–32.
25. Schadendorf D, Hodi FS, Robert C, et al. Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in unresectable or metastatic melanoma. J Clin Oncol. 2015;33:1889–94.
26. Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med. 2013;369:122–33.
27. Daud A, Ribas A, Robert C, et al. Long-term efficacy of pembrolizumab (pembro; MK-3475) in a pooled analysis of 655 patients (pts) with advanced melanoma (MEL) enrolled in KEYNOTE-001. J Clin Oncol. 2015;33(15 suppl):abstr 9005.

28. Puzanov I, Milhem MM, Minor D, et al. Talimogene laherparepvec in combination with ipilimumab in previously untreated, unresectable stage IIIB-IV melanoma. J Clin Oncol. 2016;34:2619–26.
29. Lienard D, Ewalenko P, Delmotte JJ, et al. High-dose recombinant tumor necrosis factor alpha in combination with interferon gamma and melphalan in isolation perfusion of the limbs for melanoma and sarcoma. J Clin Oncol. 1992;10:52–60.
30. Lienard D, Eggermont AM, Schraffordt Koops H, et al. Isolated perfusion of the limb with high-dose tumour necrosis factor-alpha (TNF-alpha), interferon-gamma (IFN-gamma) and melphalan for melanoma stage III. Results of a multi-centre pilot study. Melanoma Res. 1994;(4 Suppl 1):21–6.
31. Vaglini M, Belli F, Ammatuna M, et al. Treatment of primary or relapsing limb cancer by isolation perfusion with high-dose alpha-tumor necrosis factor, gamma-interferon, and melphalan. Cancer. 1994;73:483–92.
32. Vaglini M, Santinami M, Manzi R, et al. Treatment of in-transit metastases from cutaneous melanoma by isolation perfusion with tumour necrosis factor-alpha (TNF-alpha), melphalan and interferon-gamma (IFN-gamma). Dose-finding experience at the National Cancer Institute of Milan. Melanoma Res. 1994;(4 Suppl 1):35–8.
33. Bartlett DL, Ma G, Alexander HR, et al. Isolated limb reperfusion with tumor necrosis factor and melphalan in patients with extremity melanoma after failure of isolated limb perfusion with chemotherapeutics. Cancer. 1997;80:2084–90.
34. Lienard D, Eggermont AM, Koops HS, et al. Isolated limb perfusion with tumour necrosis factor-alpha and melphalan with or without interferon-gamma for the treatment of in-transit melanoma metastases: a multicentre randomized phase II study. Melanoma Res. 1999;9:491–502.
35. Fraker DL, Alexander HR, Ross M, et al. A phase III trial of isolated limb perfusion for extremity melanoma comparing melphalan alone versus melphalan plus tumor necrosis factor (TNF) plus interferon-gamma (IFN). Ann Surg Oncol. 2002;9:S8.
36. Noorda EM, Vrouenraets BC, Nieweg OE, et al. Isolated limb perfusion for unresectable melanoma of the extremities. Arch Surg. 2004;139:1237–42.
37. Grunhagen DJ, Brunstein F, ten Hagen TL, et al. TNF-based isolated limb perfusion: a decade of experience with antivascular therapy in the management of locally advanced extremity soft tissue sarcomas. Cancer Treat Res. 2004;120:65–79.

38. Cornett WR, McCall LM, Petersen RP, et al. Randomized multicenter trial of hyperthermic isolated limb perfusion with melphalan alone compared with melphalan plus tumor necrosis factor: American College of Surgeons Oncology Group Trial Z0020. J Clin Oncol. 2006;24:4196–201.
39. Deroose JP, Grunhagen DJ, van Geel AN, et al. Long-term outcome of isolated limb perfusion with tumour necrosis factor-alpha for patients with melanoma in-transit metastases. Br J Surg. 2011;98:1573–80.
40. Madu M, Deken MM, Van der Hage JA, et al. Isolated limb perfusion for melanoma is safe and effective in elderly patients. Ann Surg Oncol. 2017;24(7):1997–2005.