

# Intra-arterial hepatic chemotherapy for unresectable colorectal liver metastases: a review of medical devices complications in 3172 patients

Stefano Bacchetti  
 Enricomaria Pasqual  
 Elena Crozzolo  
 Alessandra Pellarin  
 Pier Paolo Cagol

Department of Surgical Sciences,  
 Faculty of Medicine and Surgery,  
 University of Udine, Italy

**Background:** Hepatic artery infusion (HAI) is indicated to treat unresectable colorectal hepatic metastases, with recent applications as a neoadjuvant or adjuvant treatment. Traditionally performed with the infusion of fluoropyrimidine-based chemotherapy, it has been now tested with oxaliplatin or irinotecan and associated with systemic chemotherapy.

**Methods:** To evaluate the impact of medical devices complications we carried out a search of the published studies on HAI in unresectable colorectal liver metastases. Complications were pooled according to the applied medical system: 1) surgical catheter, 2) radiological catheter, and 3) fully implantable pump. The surgical catheter is inserted into the hepatic artery from the gastro-duodenal artery. The radiological catheter is inserted into the hepatic artery through a percutaneous transfemoral or transaxillar access. The fully implantable pump is a totally internal medical device connected to the arterial hepatic catheter during laparotomy.

**Results:** The selection criteria were met in 47/319 studies. The complications of surgical and radiological medical devices connected to a port were found in 16 and 14 studies respectively. Meanwhile, complications with a fully implantable pump were reported in 17 studies. The total number of complications reported in studies evaluating patients with surgical or radiological catheter were 322 (322/948, 34%) and 261 (261/722, 36.1%) respectively. In studies evaluating patients with a fully implantable pump, the total number of complications was 237 (237/1502, 15.8%). In 18/319 studies the number of cycles was reported. The median number of cycles with surgically and radiologically implanted catheters was 8 and 6 respectively. The fully implantable pump allows a median number of 12 cycles.

**Conclusions:** The fully implantable pump, maintaining a continuous infusion through the system, allows the lowest risk for thrombosis and infection and the best median number of cycles of loco-regional chemotherapy in HAI.

**Keywords:** liver metastases, colorectal cancer, medical devices, loco-regional treatments, intra-arterial hepatic chemotherapy

## Introduction

Colorectal cancer is one of the most common malignancies, with one million new cases each year worldwide.<sup>1</sup> Liver metastases are detected in 40% to 60% of patients with colorectal carcinoma and in one third of the cases it is the sole site of disease.<sup>2-4</sup> If untreated, the median survival of patients with hepatic metastases is 6 to 12 months.<sup>5-7</sup> Hepatic resection is considered the best chance for long-term survival,<sup>8-16</sup> but only 10% to 25% of the patients can be resected with curative intention.<sup>17-20</sup> In patients submitted to hepatic resection 5-year survival rate is 25% to 40%.<sup>21-26</sup>

Other therapies such as cryotherapy or radiofrequency ablation have recently been increasingly used to treat unresectable hepatic metastases or in conjunction with liver resection, but defined indications and the precise role of ablative therapy are still unclear.<sup>27-33</sup> No randomized studies assessing outcome following hepatic

Correspondence: Stefano Bacchetti  
 Department of Surgical Sciences, Faculty  
 of Medicine and Surgery, University  
 of Udine, P.le Santa Maria della  
 Misericordia, 15 – 33100, Udine, Italy  
 Tel +39 0432 559303  
 Fax +39 0432 545566  
 Email stefano.bacchetti@uniud.it

resection compared with other treatments modalities have been undertaken for known resectable colorectal liver metastases.<sup>34</sup>

Over the last 40 years, systemic chemotherapy with 5-fluorouracil has been applied in patients with unresectable colorectal liver metastases. Nowadays, the fluoropyrimidine-based chemotherapy in combination with oxaliplatin or irinotecan is considered the standard treatment for patients with advanced disease and allows a median survival of 14 to 19 months.<sup>35–38</sup> An essential requirement for treatment is that all patients with advanced metastatic disease should have a good performance status in order to tolerate chemotherapy.<sup>39</sup> Nonetheless some physicians suggest more aggressive chemotherapy regimens and believe that loco-regional therapies, associated or not with systemic chemotherapy, can be an effective clinical treatment for patients with colorectal metastases confined to the liver.<sup>40–47</sup> In the past, intra-arterial chemotherapy has been associated with other treatments such as portal infusion, temporary artery occlusion, arterial infusion of degradable starch microspheres or radioactive microspheres.<sup>5,48–52</sup> In prospective controlled trials it has been clearly demonstrated a significantly higher response rate with hepatic artery infusion (HAI) when compared with systemic chemotherapy, but only a few studies showed a better survival for patients submitted to intra-arterial chemotherapy while others did not.<sup>3,42,44,53–54</sup>

Recently some physicians have applied HAI, as neoadjuvant treatment, in patients with unresectable colorectal liver metastases. This preoperative chemotherapy can offer different advantages and, after downstaging of the disease, make hepatic resection possible.<sup>56,57</sup> A recent study demonstrated that preoperative HAI may provide long-term survival comparable to that achieved in patients submitted to liver resection only.<sup>58</sup>

One of the most peculiar events with HAI is the development of frequent complications.<sup>59–62</sup> These complications, especially if occurring during the early cycles, can interfere with the planned chemotherapy, leading to the suspension and even the definitive suppression of the treatment.<sup>63</sup> The considerable number of patients who, because of the complications, did not complete the planned cycles of HAI in conjunction with patients that, for other reasons, were crossed over to systemic chemotherapy, represents a problem that does not allow definitive conclusions in the survival analysis.<sup>54,64,65</sup> Hence, up to now, many physicians have been reluctant to adopt loco-regional treatments in patients with unresectable liver metastases. To assess the complications of loco-regional chemotherapy, we analyzed the types, incidences and clinical

problems of medical device/failure following intra-arterial hepatic infusion.

## Materials and methods

### Search strategy

The search was carried out with computerized Medline, Embase, Ovid and Cochrane databases for studies published up to 2008 for patients with unresectable colorectal liver metastases submitted to HAI. The initial search was done using the combination of these keywords: “hepatic metastases”, “liver”, “neoplasm”, “unresectable colorectal metastases”, “large bowel cancer”, “metastatic carcinoma”, “hepatic arterial chemotherapy”, “medical devices”, “locoregional treatment”, “intra-arterial infusion” and “intra-hepatic treatment”. We then screened all the titles and the abstracts of all the articles obtained. The first step was the selection of papers referring the complications of medical devices. Bibliographies and citations from articles identified by the initial search were used to identify other articles with additional information/on the same topic.

### Inclusion and exclusion criteria

Randomized and nonrandomized studies, in which intra-arterial hepatic chemotherapy was used in patients with unresectable colorectal liver metastases, were included. Experimental studies were excluded. Studies evaluating intra-arterial therapies in patients with noncolorectal liver metastases were excluded. Studies, evaluating other modalities of locoregional therapies, were excluded. Papers were included only if they specifically reported on the complications of medical devices and no confused data were described. When 2 or more studies were reported by the same institution, the one of better quality or with more detailed data was included. In order to calculate the incidence of the different types of complications, we have distinguished catheters placed with radiological access, with surgical access and those connected to fully implantable pumps. Studies that did not clearly report the modality of application of the different implanted catheters and medical devices were evaluated as well, but often they did not make possible to estimate the separated complication rate and the average lifetime of the infusional systems.

We will briefly describe the 3 different methods of HAI. In the percutaneous method, during angiography and before catheter placement, medical radiologists occluded aberrant hepatic arteries (using coils or a mixture of cyanoacrylate and iodized oil). After several days, while the patient is kept under local anesthesia, a catheter is inserted into the hepatic artery using transfemoral or transaxillar access and the

proximal end of the catheter is connected to a port (a small nonmagnetic metal or plastic reservoir with a silicon septum that allows resealing after multiple needle sticks) that is positioned into a subcutaneous space on the anterior chest wall or on the lower abdominal wall. In the surgical method, the placement of the hepatic arterial catheter is carried out by laparotomic or laparoscopic approach under general anesthesia. The gallbladder is removed to avoid chemical cholecystitis. After isolation of the gastroduodenal artery, a transverse arteriotomy is made and the catheter is introduced in a retrograde way. Arterial collaterals supplying the stomach, duodenum and pancreas are ligated. The surgical catheter is secured with nonresorbable suture and then connected with a reservoir placed subcutaneously. After a few days, this port will be connected to an external pump that is employed during chemotherapeutical infusion. Slightly larger than a pacemaker, the fully implantable pump is placed under general anesthesia during laparotomy. The catheter is inserted into the gastroduodenal artery and arterial collaterals are ligated. Usually, a cholecystectomy is performed. At the end of the procedure, the catheter is connected to the pump that is positioned in a pocket created into the abdominal wall. An external pump is not employed after this procedure because the fully implantable pump can hold 30 to 50 mL of fluid and deliver the chemotherapeutic agent at a fixed rate.

In this review the oncological, surgical and radiological procedures had to be in agreement with the indications supplied by International or Local Ethical Committees.

## Data extraction

The following data were then extracted from every single study: first author, year of publication, study population characteristics, study design, the number of recruited patients and the type of procedure applied in the catheter positioning. Subsequently the second step was made in order to choose studies that reported number and type of complications and that reported the number of cycles of chemotherapy.

The data extraction plan was to select the complications of medical devices, considered as the primary outcome, and the cycles of chemotherapy, as the secondary outcome. To eliminate possible confusing data, time of disease progression, overall survival, chemotherapy-related toxicity, number of objective responses and quality of life achieved by different loco-regional infusional systems were not evaluated.

## Data analysis

The number of studies evaluating complications was calculated and then the number of complications was compared

with the number of patients recruited. Studies that did not clearly report the number of complications were not assumed to have reached a zero rate, but were treated as if the data were missing and therefore were not assessable in the analyses of the complications rate. Data are reported by the number of single complications and the number of patients that suffered the event and, for the cycles of chemotherapy, median value and range. Statistical comparisons between the complications of patients with surgical or radiological catheter were performed. The chi-square test was used and a *p* value less than 0.05 was considered significant. Statistical analyses were performed using computer software (StatXact version 4; Cytel Corporation, Cambridge, MA).

## Results

After exclusion, the selection criteria were met in 47/319 studies. The complications of surgical and radiological medical devices were found in 16 (Table 1) and 14 (Table 2) studies respectively. The complications of the fully implantable pump were reported in 17 studies (Table 3).

Of the 3172 patients evaluated, 948 had the catheter connected with a port by surgical and 722 by radiological access; 1502 patients had a fully implantable pump.

The most common type of vascular complications following surgically placed catheters with port was arterial thrombosis followed by catheter thrombosis and dislocation (Table 4). The most common type of vascular complications following radiologically placed catheters with port was arterial thrombosis and dislocation (Table 4). The total number of complications that were reported in studies evaluating patients with surgical or radiological catheter was 322 (322/948, 34%) and 261 (261/722, 36.1%) respectively. Various authors reported that catheter dislocation showed a variable incidence rate between 0 and 43.8% of cases. Dislocation of the surgical and radiological catheters from the gastroduodenal artery was observed in 101/703 (14.4%) and 106/670 (15.8%) patients respectively. Dislocation may be the result of fluctuations or incorrect positioning of the catheters into the hepatic artery. Infection is another frequent cause of loco-regional hepatic system failure in patients submitted to HAI. Many studies have reported an incidence of 0% to 11.7% for infective complications in patients with surgical catheter with port, while the incidence of infection with radiological catheter and with fully implantable pump was 0% to 4% and 0% to 5.9% respectively. In studies evaluating patients with fully implantable pump, the total number of complications was 237 (237/1502, 15.8%).

**Table 1** Complications of surgically implanted catheter

No. patients (Reference)	Chemotherapy	Arterial thrombosis (%)	Catheter thrombosis (%)	Catheter dislocation (%)	Catheter disconnection (%)	Infection (%)
34 <sup>106</sup>	5-FU	3 (8.8)	3 (8.8)	2 (5.9)	5 (14.7)	2 (5.9)
48 <sup>107</sup>	5-FU FUDR	19 (39.6)	7 (14.6)	21 (43.8)	0 (0)	2 (4.2)
188 <sup>108</sup>	5-FU	21 (11)	0 (0)	50 (26)	10 (5)	10 (5)
29 <sup>109</sup>	5-FU	0 (0)	6 (21)	3 (10)	0 (0)	0 (0)
52 <sup>110</sup>	5-FU	9 (17.3)	0 (0)	1 (2)	0 (0)	4 (7.6)
24 <sup>111</sup>	5-FU	0 (0)	0 (0)	1 (4)	4 (17)	1 (4)
38 <sup>112</sup>	NS <sup>a</sup>	1 (2.6)	4 (10.5)	0 (0)	0 (0)	0 (0)
91 <sup>113</sup>	FUDR CDDP	–	–	6 (6.6)	10 (11)	2 (2.2)
30 <sup>114</sup>	5-FU MITO C	8 (26.6)	6 (20)	1 (3.3)	1 (3.3)	2 (6.6)
113 <sup>63</sup>	5-FU	29 (26)	–	–	13 (12)	1 (0.8)
31 <sup>60</sup>	FUDR	–	5 (16.1)	1 (3.2)	1 (3.2)	0 (0)
75 <sup>115</sup>	5-FU MITO C	11 (19.8)	–	–	–	1 (1.3)
28 <sup>116</sup>	FUDR	1 (3.5)	1 (3.5)	0 (0)	–	–
110 <sup>72</sup>	5-FU FUDR	5 (4.5)	28 (25.5)	15 (13.6)	–	2 (1.8)
29 <sup>117</sup>	CPT-11 Oxaliplatin 5-FU	1 (3.4)	2 (6.9)	–	1 (3.4)	–
28 <sup>42</sup>	Oxaliplatin	–	5 (17.9)	–	2 (7.1)	1 (3.5)

<sup>a</sup>not stated.

For every single complication (described in Table 4), statistical analysis shows no significant difference (p value: NS) between the number of complications of patients submitted to surgical or radiological intra-arterial catheter positioning.

Concerning the number of cycles performed, the quality of data was very poor. In many studies the complete number

of cycles was not reported, either because there was no mention of these data or because the number of patients that were not submitted to HAI was not reported. In our analysis only 18/319 studies described the number of cycles allowed. Nevertheless the collected data suggest that surgically and radiologically implanted ports allow a similar median number

**Table 2** Complications of radiologically implanted catheter

No. patients (Reference)	Chemotherapy	Arterial thrombosis (%)	Catheter thrombosis (%)	Catheter dislocation (%)	Catheter disconnection (%)	Infection (%)
36 <sup>118</sup>	5-FU	0 (0)	8 (22)	2 (5)	10 (28)	0 (0)
33 <sup>119</sup>	5-FU	5 (15)	5 (15)	2 (6)	11 (33)	0 (0)
44 <sup>120</sup>	NS	1 (2.2)	5 (11.3)	4 (9)	0 (0)	2 (4)
31 <sup>121</sup>	5-FU	4 (13)	0 (0)	4 (13)	0 (0)	0 (0)
32 <sup>122</sup>	NS <sup>a</sup>	0 (0)	2 (6)	2 (6)	0 (0)	0 (0)
95 <sup>123</sup>	FUDR	4 (4)	–	16 (17)	–	1 (1)
52 <sup>63</sup>	5-FU	1 (2)	–	–	–	–
4 <sup>124</sup>	NS	0 (0)	0 (0)	0 (0)	–	–
127 <sup>125</sup>	5-FU FUDR	30 (24)	10 (8)	46 (36)	0 (0)	4 (3)
28 <sup>116</sup>	FUDR	1 (3.5)	1 (3.5)	10 (35.7)	–	–
41 <sup>100</sup>	5-FU MITO C Oxaliplatin	7 (17.9)	6 (15.4)	8 (20.5)	4 (12.8)	3 (7.7)
135 <sup>102</sup>	5-FU	25 (18.5)	1 (0.7)	11 (8.1)	2 (1.5)	–
42 <sup>101</sup>	5-FU	2 (4.7)	–	1 (2.4)	–	–
22 <sup>58</sup>	5-FU CDDP	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

<sup>a</sup>not stated.

**Table 3** Complications of fully implantable pump

No. patients (Reference)	Chemotherapy	Catheter/arterial thrombosis (%)	Catheter break up (%)	Infection (%)	Pocket hematoma/seroma (%)	Pump malfunction (%)
50 <sup>126</sup>	FUDR	0 (0)	1 (2)	1 (2)	–	0 (0)
26 <sup>127</sup>	FUDR	0 (0)	0 (0)	0 (0)	3 (12)	0 (0)
21 <sup>128</sup>	FUDR	0 (0)	1 (5)	1 (5)	1 (5)	0 (0)
93 <sup>129</sup>	FUDR	3 (3)	1 (1)	1 (1)	2 (2)	0 (0)
30 <sup>130</sup>	FUDR MITO C BCNU	0 (0)	2 (7)	1 (3)	6 (20)	0 (0)
62 <sup>131</sup>	FUDR	0 (0)	0 (0)	0 (0)	–	0 (0)
110 <sup>132</sup>	FUDR	0 (0)	0 (0)	0 (0)	–	0 (0)
143 <sup>133</sup>	5-FU	16 (11.2)	21 (14.7)	1 (0.7)	19 (13.3)	2 (1.4)
44 <sup>113</sup>	FUDR CDDP	6 (13.6)	0 (0)	2 (4.5)	9 (21)	1 (2.3)
24 <sup>134</sup>	FUDR	–	–	–	–	–
67 <sup>135</sup>	FUDR	–	9 (13.4)	1 (1.5)	–	–
33 <sup>136</sup>	FUDR	5 (15)	–	2 (6)	–	2 (6)
40 <sup>137</sup>	FUDR	–	–	–	–	–
81 <sup>138</sup>	FUDR	10 (12)	1 (1.2)	–	12 (15)	–
64 <sup>60</sup>	FUDR	2 (3.1)	–	3 (4.7)	4 (6.3)	2 (3.1)
70 <sup>72</sup>	5-FU FUDR	5 (7.1)	–	4 (5.7)	–	5 (7.1)
544 <sup>99</sup>	FUDR	44 (8)	4 (0.7)	14 (2.6)	1 (0.2)	6 (1.1)

of cycles of locoregional chemotherapy: the former 8 and the latter 6 cycles. The median number of cycles with the fully implantable pump was 12 (Table 5).

## Discussion

In patients with unresectable colorectal liver metastases, HAI achieves objective responses in 35%–83% of cases and allows an improvement in the quality of life.<sup>64,66–73</sup> It has been recently suggested that intra-arterial or systemic chemotherapy may be utilized as a neoadjuvant treatment in order to obtain the down-staging of the disease and as adjuvant treatment aimed at the reduction of the local recurrence rate after hepatic resection.<sup>4,18,20,58,74–83</sup> Rational bases

of loco-regional treatments are based on clinical and experimental demonstration that colorectal liver metastases depend heavily on the hepatic artery for most of their blood supply, whereas the normal liver parenchyma relies mainly on portal blood flow.<sup>84–88</sup> In order to increase the drug concentrations within the tumour and, at the same time, to reduce drug concentration within normal liver tissue, various drugs, different infusion modality<sup>72,84–87,89,90</sup> and different dosages were proposed.<sup>91–93</sup> Randomized clinical studies have confirmed a significant statistical difference in terms of objective responses achieved by intra-arterial hepatic infusion compared to systemic chemotherapy, but meta-analyses are contradictory for an evident survival advantage.<sup>68,94–96</sup>

**Table 4** Complication rate of surgical catheter, radiological catheter and fully implantable pump

Complication	Surgical catheter complications/patients	Radiological catheter complications/patients	Fully implantable pump complications/patients
Arterial thrombosis	79/798	80/722	91/1371
Catheter thrombosis	67/669	38/533	
Catheter dislocation	101/703	106/670	–
Catheter disconnection	47/735	27/501	–
Infection	28/891	10/461	31/1357
Pocket hematoma/seroma	–	–	57/1046
Pump malfunction	–	–	18/1290

**Table 5** Cycles of chemotherapy achievable by intra-arterial medical devices

Type of access	No. of cycles	
	Median	Range
Surgical implanted catheter	8	0–34
Radiological implanted catheter	6	0–19
Fully implantable pump	12	0–46

A crucial point in loco-regional chemotherapy is the high complication rate of medical devices. In many studies, complications may be difficult to assess because data on infusional medical devices are poor and only a small number of studies included the separate analysis of surgical catheters, radiological catheters and implantable infusional pumps. A careful description of the type and number of complications was infrequent. Frequently there was an inadequate description of procedures applied. Hence, after careful data extraction, only a part of all data could be used for this review. To better clarify the role and incidence of complications in loco-regional chemotherapy we adopted a separate analysis of surgical or radiological catheters and fully implantable pumps. In surgically placed devices, complications are reported in 1.8% to 43.8% of cases. The dysfunction of early medical devices has negatively influenced the outcome of patients randomized in two recent studies where loco-regional intra-arterial chemotherapy has been applied in patients with unresectable hepatic metastases.<sup>55,97</sup> The number of these complications can be reduced only if fully implantable pumps are employed.<sup>60,62,98,99</sup>

Radiologic placing of a catheter-port system is described to be an easier and safer procedure than surgical implantation and appears to offer technical advantages compared to the surgical approach.<sup>100</sup> In recent studies, different methods of side-hole catheter placement, like the distal fixation method or the modified fixed method, have been applied. Medical radiologists have been suggested these techniques as an alternative to the more used surgical approach.<sup>101,102</sup> Nevertheless, most of the radiological papers failed to summarize the study population, the inclusion criteria and the technical procedures in satisfactory detail. In patients submitted to percutaneous catheter placing, complications have an incidence rate of 1% to 36% of patients. In regard to the five most common complications reported in studies including surgically or percutaneously treated patients, it was not possible to clearly assess that a different risk for complications existed between these two implanted systems.

From a technical point of view, it is possible that the main characteristics of the catheter in terms of material or

diameter, the different site of implantation (gastroduodenal artery or other branches of hepatic artery) and the different type of fixation techniques can modify the complication rate. It is possible also that the type of chemotherapeutic agent can change the overall complication rate of medical devices used for HAI. We must underline that, in most of the studies evaluated in this review, different dosages and association of different chemotherapeutic agents were used. We did not find randomized controlled studies in which these different technical or pharmacological variables were evaluated and it is very difficult to assess the impact of these aspects on the complication rate or on the number of cycles.

The greater part of complications can be avoided through meticulous care in positioning and with appropriate handling of the device;<sup>103</sup> therefore the incidence of complications decreases as the experience of the medical team increases and with a careful medical manipulation.<sup>60,104</sup> A high number of complications are reported with the use of catheters and external medical devices, but, when fully implantable systems are placed, the only problem is related to the pump pocket management. Complications, like fluid collection, seromas or hematomas, can be easily treated by drainage.<sup>105</sup> Our study showed that the surgical and radiological implanted catheter with port allows a median of 8 and 6 cycles respectively. The median number of cycles of the HAI with the fully implantable pump was 12. Some studies suggest that surgical or percutaneous access with reservoir has inferior performance compared to the fully implantable pump.<sup>63,72</sup> This is probably due to the fact that a totally implantable system allows continuous perfusion. However, for implantation of a fully implantable pump, a laparotomy under general anesthesia is required. Some physicians state that the implantation of the surgical catheter with port or the fully implantable pump can preferably be done at the time of colorectal resection and that the best indication for the radiological implantation of the hepatic arterial catheter could be the presence of metachronous unresectable colorectal liver metastases.

## Conclusions

One of the most frequent problems in patients submitted to loco-regional hepatic chemotherapy is the morbidity related to complications due to medical devices. Several patients in which these techniques have been applied suffered from complications producing frequent interruptions and early failure of the system. If the number of complications is high, the number of cycles of chemotherapy is unsatisfactory.

Fully implantable pumps are the systems of choice for long-term infusion, because of better performances of these medical devices compared to surgical or radiological catheter with port. Fully implantable systems for continuous infusion allow the lowest risk for thrombosis, system malfunction and infection. If these medical devices are appropriately managed and complications are avoided, a good quality of life and an acceptable tolerance are achievable. In patients with colorectal liver metastases, the severe prognosis and the poor benefit caused by technical failure of medical devices underlines the main concept that loco-regional hepatic chemotherapy is a delicate procedure that must be employed only by trained medical staff in order to reduce the risk of the vast majority of potential complications.

## Acknowledgments

We thank Mrs Maria Luisa Ciattei (University of Udine) for English language revision.

## Disclosures

The authors have no conflicts of interest to disclose.

## References

- Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. *CA Cancer J Clin.* 2005;55:74–108.
- Kemeny N, Eid A, Stockman J, et al. Hepatic arterial infusion of floxuridine and dexamethasone plus high-dose Mitomycin C for patients with unresectable hepatic metastases from colorectal carcinoma. *J Surg Oncol.* 2005;91:97–101.
- Homsy J, Garrett CR. Hepatic arterial infusion of chemotherapy for hepatic metastases from colorectal cancer. *Cancer Control.* 2006;13:42–47.
- Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet.* 2008;371:1007–1016.
- Hunt TM, Flowerdew AD, Birch S, et al. Prospective randomized controlled trial of hepatic arterial embolization or infusion chemotherapy with 5-fluorouracil and degradable starch microspheres for colorectal liver metastases. *Br J Surg.* 1990;77:779–782.
- Rougier P, Milan C, Lazorthes F, et al. Prospective study of prognostic factors in patients with unresected hepatic metastases from colorectal cancer. *Br J Surg.* 1995;82:1397–1400.
- Rothbarth J, van de Velde CJ. Treatment of liver metastases of colorectal cancer. *Ann Oncol.* 2005;16:144–149.
- Cady B, Stone MD, McDermott WV, et al. Technical and biological factors in disease-free survival after hepatic resection for colorectal cancer metastasis. *Arch Surg.* 1992;127:561–569.
- Taylor I. Colorectal cancer and the liver. *Ann R Surg Engl.* 1997;79:315–318.
- Lehnert T, Pfitzenmaier J, Hinz U, et al. Surgery for local recurrence or distant metastases in patients aged 75 years or older. *Eur J Surg Oncol.* 1998;24:418–422.
- Fong Y, Salo J. Surgical therapy of hepatic colorectal metastasis. *Semin Oncol.* 1999;26:514–523.
- Jarnagin WR, Gonen M, Fong Y, et al. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. *Ann Surg.* 2002;236:397–406.
- Poston GJ, Adam R, Alberts S, et al. OncoSurge: a strategy for improving resectability with curative intent in metastatic colorectal cancer. *J Clin Oncol.* 2005;23:7125–134.
- Simmonds PC, Primrose JN, Colquitt JL, et al. Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. *Br J Cancer.* 2006;94:982–999.
- Malik HZ, Prasad KR, Halazun KJ, et al. Preoperative prognostic score for predicting survival after hepatic resection for colorectal liver metastases. *Ann Surg.* 2007;246:806–814.
- Zakaria S, Donohue JH, Que FG, et al. Hepatic resection for colorectal metastases: value for risk scoring systems? *Ann Surg.* 2007;246:183–191.
- Van Ooijen B, Wiggers T, Meijer S, et al. Hepatic resections for colorectal metastases in The Netherlands. A multiinstitutional 10-year study. *Cancer.* 1992;70:28–34.
- Bismuth H, Adam R, Levi F, et al. Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. *Ann Surg.* 1996;224:509–520.
- Beard SM, Holmes M, Price C, et al. Hepatic resection for colorectal liver metastases: a cost-effectiveness analysis. *Ann Surg.* 2000;232:763–776.
- Andres A, Majno PE, Morel P, et al. Improved long-term outcome of surgery for advanced colorectal liver metastases: reasons and implications for management on the basis of a severity score. *Ann Surg Oncol.* 2008;15:134–143.
- Rosen CB, Nagorney DM, Taswell HF, et al. Perioperative blood transfusion and determinants of survival after liver resection for metastatic colorectal carcinoma. *Ann Surg.* 1992;216:493–504.
- Gayowski T, Iwatsuki S, Madariaga JR, et al. Experience in hepatic resection for metastatic colorectal cancer: analysis of clinical and pathologic risk factors. *Surgery.* 1994;116:703–711.
- Scheele J, Stang R, Altendorf-Hofmann A, et al. Resection of colorectal liver metastases. *World J Surg.* 1995;19:59–71.
- Choti MA, Sitzmann JV, Tiburi MF, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. *Ann Surg.* 2002;235:759–766.
- Rees M, Tekkis PP, Welsh FK, et al. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. *Ann Surg.* 2008;247:125–135.
- Pawlik TM, Schulick RD, Choti MA. Expanding criteria for resectability of colorectal liver metastases. *Oncologist.* 2008;3:51–64.
- Polk W, Fong Y, Karpeh M, Blumgart L. A technique for the use of cryosurgery to assist hepatic resection. *J Am Coll Surg.* 1995;180:171–176.
- Adam R, Akpınar E, Johann M, et al. Place of cryosurgery in the treatment of malignant liver tumors. *Ann Surg.* 1997;225:39–50.
- Seifert J, Morris DL. Prognostic factors after cryotherapy for hepatic metastases from colorectal cancer. *Ann Surg.* 1998;228:201–208.
- Solbiati L, Livraghi T, Goldberg SN, et al. Percutaneous radio-frequency ablation of hepatic metastases from colorectal cancer: long-term results in 117 patients. *Radiology.* 2001;221:159–166.
- McKay A, Dixon E, Taylor M. Current role of radiofrequency ablation for the treatment of colorectal liver metastases. *Br J Surg.* 2006;93:1192–1201.
- Ruers TJ, Joosten JJ, Wiering B, et al. Comparison between local ablative therapy and chemotherapy for non-resectable colorectal liver metastases: a prospective study. *Ann Surg Oncol.* 2007;14:1161–1169.
- McGrane S, McSweeney SE, Maher MM. Which patients will benefit from percutaneous radiofrequency ablation of colorectal liver metastases? Critically appraised topic. *Abdom Imaging.* 2008;33:48–53.
- Garden OJ, Rees M, Poston GJ, et al. Guidelines for resection of colorectal cancer liver metastases. *Gut.* 2006;55:1–8.
- de Gramont A, Figuer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol.* 2000;18:2938–2947.
- Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet.* 2000;25:1041–1047.

37. Goldberg RM, Sargent DJ, Morton RF, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol.* 2004;1:23–30.
38. Zuckerman DS, Clark JW. Systemic therapy for metastatic colorectal cancer: current questions. *Cancer.* 2008;112:1879–1891.
39. Chari RS, Helton WS, Marsh RD. Chemotherapy and regional therapy of hepatic colorectal metastases: expert consensus statement by Bartlett et al. *Ann Surg Oncol.* 2006;13:1293–1295.
40. Kohnoe S, Endo K, Yamamoto M, et al. Protracted hepatic arterial infusion with low-dose cisplatin plus 5-fluorouracil for unresectable liver metastases from colorectal cancer. *Surgery.* 2002;131(1):128–134.
41. Zelek L, Bugat R, Cherqui D, et al. Multimodal therapy with intravenous biweekly leucovorin, 5-fluorouracil and irinotecan combined with hepatic arterial infusion pirarubicin in non-resectable hepatic metastases from colorectal cancer (a European Association for Research in Oncology trial). *Ann Oncol.* 2003;14:1537–1542.
42. Ducreux M, Ychou M, Laplanche A, et al. Hepatic arterial oxaliplatin infusion plus intravenous chemotherapy in colorectal cancer with inoperable hepatic metastases: a trial of the gastrointestinal group of the Federation Nationale des Centres de Lutte Contre le Cancer. *J Clin Oncol.* 2005;23:4881–4887.
43. Ensminger WD. A role for hepatic-directed chemotherapy in colorectal liver metastases. *J Clin Oncol.* 2005;23:4815–4817.
44. Kemeny NE, Niedzwiecki D, Hollis DR, et al. Hepatic arterial infusion versus systemic therapy for hepatic metastases from colorectal cancer: a randomized trial of efficacy, quality of life, and molecular markers (CALGB 9481). *J Clin Oncol.* 2006;24:1395–1403.
45. Fiorentini G, Cantore M, Rossi S, et al. Hepatic arterial chemotherapy in combination with systemic chemotherapy compared with hepatic arterial chemotherapy alone for liver metastases from colorectal cancer: results of a multi-centric randomized study. *In Vivo.* 2006;20:707–709.
46. Carnaghi C, Santoro A, Rimassa L, et al. The efficacy of hybrid chemotherapy with intravenous oxaliplatin and folinic acid and intra-hepatic infusion of 5-fluorouracil in patients with colorectal liver metastases: a phase II study. *Invest New Drugs.* 2007;25:479–485.
47. 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;15:219–226.
48. Hafstrom L, Engaras B, Holmberg SB, et al. Treatment of liver metastases from colorectal cancer with hepatic artery occlusion, intraportal 5-fluorouracil infusion, and oral allopurinol. A randomized clinical trial. *Cancer.* 1994;74:2749–2756.
49. Laffer UT, Metzger U. Intraportal chemotherapy for colorectal hepatic metastases. *World J Surg.* 1995;19:246–251.
50. Allen-Mersh TG, Glover C, Fordy C, et al. Randomized trial of regional plus systemic fluorinated pyrimidine compared with systemic fluorinated pyrimidine in treatment of colorectal liver metastases. *Eur J Surg Oncol.* 2000;26:468–473.
51. 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;12:1711–1720.
52. Piedbois P, Zelek L and Cherqui D. Chemotherapy of nonoperable colorectal liver metastases. *Hepatogastroenterology.* 2001;48:711–714.
53. Kemeny N, Ron I. Hepatic arterial chemotherapy in metastatic colorectal patients. *Semin Oncol.* 1999a;26:524–535.
54. Skitzki JJ, Chang AE. Hepatic artery chemotherapy for colorectal liver metastases: technical considerations and review of clinical trials. *Surg Oncol.* 2002;11:123–135.
55. Kerr DJ, McArdle CS, Ledermann J, et al. Intrahepatic arterial versus intravenous fluorouracil and folinic acid for colorectal cancer liver metastases: a multicentre randomised trial. *Lancet.* 2003;361:368–373.
56. Clavien PA, Selzner N, Morse M, et al. Downstaging of hepatocellular carcinoma and liver metastases from colorectal cancer by selective intra-arterial chemotherapy. *Surgery.* 2002;131:433–442.
57. Selzner N, Pestalozzi BC, Kadry Z, et al. Downstaging colorectal liver metastases by concomitant unilateral portal vein ligation and selective intra-arterial chemotherapy. *Br J Surg.* 2006;93:587–592.
58. Tanaka K, Shimada H, Ueda M, et al. Perioperative complications after hepatectomy with or without intra-arterial chemotherapy for bilobar colorectal cancer liver metastases. *Surgery.* 2006;139:599–607.
59. Campbell KA, Burns RC, Sitzmann JV, et al. Regional chemotherapy devices: effect of experience and anatomy on complications. *J Clin Oncol.* 1993;11:822–826.
60. Fordy C, Burke D, Earlam S, et al. Treatment interruptions and complications with two continuous hepatic artery floxuridine infusion systems in colorectal liver metastases. *Br J Cancer.* 1995;72:1023–1025.
61. Doughty JC, Keogh G, Mc Ardle S. Methods of replacing blocked hepatic artery catheters. *Br J Surg.* 1997;84:618–619.
62. Civalleri D, DeCian F, Pellicci R, et al. Differential device performances for hepatic arterial chemotherapy: a technical report on totally implantable pumps and ports for both continuous and bolus infusion. *Eur Surg Res.* 1998;30:26–33.
63. Van Riel JM, Groening CJ, Albers S, et al. Hepatic arterial 5-fluorouracil in patients with liver metastases of colorectal cancer: single-centre experience in 145 patients. *Ann Oncol.* 2000;11:1563–1570.
64. O'Connell MJ, Nagorney DM, Bernath AM, et al. Sequential intrahepatic fluorodeoxyuridine and systemic fluorouracil plus leucovorin for the treatment of metastatic colorectal cancer confined to the liver. *J Clin Oncol.* 1998;16:2528–2533.
65. Bonetti A. Hepatic artery infusion for liver metastases from colorectal cancer. *Lancet.* 2003;361:358–359.
66. Allen-Mersh TG, Earlam S, Fordy C, et al. Quality of life and survival with continuous hepatic-artery floxuridine infusion for colorectal liver metastases. *Lancet.* 1994;334:1255–1260.
67. Kemeny N, Conti JA, Cohen A, et al. Phase II study of hepatic arterial floxuridine, leucovorin and dexamethasone for unresectable liver metastases from colorectal carcinoma. *J Clin Oncol.* 1994;12:2288–2295.
68. Buyse M. Meta-Analysis Group in Cancer. Reappraisal of hepatic arterial infusion in the treatment of nonresectable liver metastases from colorectal cancer. *J Nat Cancer Inst.* 1996;88:252–258.
69. Earlam S, Glover C, Davies M, et al. Effect of regional and systemic fluorinated pyrimidine chemotherapy on quality of life in colorectal liver metastasis patients. *J Clin Oncol.* 1997;15:2022–2029.
70. Durand-Zaleski I, Roche B, Buyse M, et al. Economic implications of hepatic arterial infusion chemotherapy in treatment of nonresectable colorectal liver metastases. *J Natl Cancer Inst.* 1997;4:790–795.
71. Link K, Sunelaitis E, Kornmann M, et al. Regional chemotherapy of nonresectable colorectal liver metastases with mitoxantrone, 5-fluorouracil, folinic acid and mitomycin C may prolong survival. *Cancer.* 2001;92:2746–2753.
72. Heinrich S, Petrowsky H, Schwinnen I, et al. Technical complications of continuous intra-arterial chemotherapy with 5-fluorodeoxyuridine and 5-fluorouracil for colorectal liver metastases. *Surgery.* 2003;133:40–48.
73. Bartlett DL, Berlin J, Lauwers GY, et al. Chemotherapy and regional therapy of hepatic colorectal metastases: expert consensus statement. *Ann Surg Oncol.* 2006;13:1284–1292.
74. Nonami T, Takeuchi Y, Yasui M, et al. Regional adjuvant chemotherapy after partial hepatectomy for metastatic colorectal carcinoma. *Semin Oncol.* 1997;24:130–134.
75. Kemeny N, Huang Y, Cohen A, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N Engl J Med.* 1999b;341:2039–2048.
76. Tono T, Hasuike Y, Ohzato H, et al. Limited but definite efficacy of prophylactic hepatic arterial infusion chemotherapy after curative resection of colorectal liver metastases: A randomized study. *Cancer.* 2000;88:1549–1556.
77. Shankar A, Leonard P, Renaut AJ, et al. Neo-adjuvant therapy improves resectability rates for colorectal liver metastases. *Ann R Coll Surg Engl.* 2001;83:85–88.



78. Khushalani NI, McKinley BP, Gibbs JF, et al. Regional chemotherapy is indicated after surgical resection of colorectal metastases to the liver: a debate. *J Surg Oncol.* 2003;82:65–72.
79. Karoui M, Penna C, Amin-Hashem M, et al. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. *Ann Surg.* 2006;243:1–7.
80. Elias D, Goere D, Boige V, et al. Outcome of posthepatectomy-missing colorectal liver metastases after complete response to chemotherapy: impact of adjuvant intra-arterial hepatic oxaliplatin. *Ann Surg Oncol.* 2007;14:3188–3194.
81. Xu J, Zhong Y, Weixin N, Xinyu Q, et al. Preoperative hepatic and regional arterial chemotherapy in the prevention of liver metastasis after colorectal cancer surgery. *Ann Surg.* 2007;245:583–590.
82. Morris-Stiff G, Tan YM, Vauthey JN. Hepatic complications following preoperative chemotherapy with oxaliplatin or irinotecan for hepatic colorectal metastases. *Eur J Surg Oncol.* 2008;34:609–614.
83. White RR, Schwartz LH, Munoz JA, et al. Assessing the optimal duration of chemotherapy in patients with colorectal liver metastases. *J Surg Oncol.* 2008;97:601–604.
84. Goey SH, Eggermont AM, Oskam R, et al. Prolonged continuous hepatic artery infusion with interleukin-2 in unresectable liver metastases of colorectal cancer: a phase I study. *Ann Oncol.* 1996;7:317–319.
85. Howell JD, Warren HW, Anderson JH, et al. Intra-arterial 5-fluorouracil and intravenous folinic acid in the treatment of liver metastases from colorectal cancer. *Eur J Surg.* 1999;165:652–658.
86. Okuno K, Yasutomi M, Kon M, et al. Intrahepatic interleukin-2 with chemotherapy for unresectable liver metastases: a randomized multicenter trial. *Hepatogastroenterology.* 1999;46:1116–1121.
87. Burke D, Davies MM, Zweit J, et al. Continuous angiotensin II infusion increases tumour normal blood flow ratio in colo-rectal liver metastases. *Br J Cancer.* 2001;85:1640–1645.
88. Cagol PP, Pasqual E, Bacchetti S. Potential advantages of loco-regional intra-arterial chemotherapy. *In Vivo.* 2006;20:777–779.
89. Bacchetti S, Pasqual E, Cagol PP. Epirubicin and its metabolites levels in experimental liver metastases after different administration routes. *J Exp Clin Cancer Res.* 2003;22:181–185.
90. Pasqual E, Bacchetti S, Cagol PP. Epidryamicin concentration in experimental hepatic metastases after bolus or continuous infusion through systemic or locoregional routes. *J Exp Clin Cancer Res.* 2003;22:229–232.
91. Kerr DJ, Ledermann JA, McArdle CS, et al. Phase I clinical and pharmacokinetic study of leucovorin and infusional hepatic arterial fluorouracil. *J Clin Oncol.* 1995;13:2968–2972.
92. Arai Y, Inaba Y, Takeuchi Y, et al. Intermittent hepatic arterial infusion of high-dose 5-FU on a weekly schedule for liver metastases from colorectal cancer. *Cancer Chemother Pharmacol.* 1997;40:526–530.
93. Shankar A, Loizidou M, Burnstock G, et al. Noradrenaline improves the tumour to normal blood flow ratio and drug delivery in a model of liver metastases. *Br J Surg.* 1999;86:453–457.
94. Harmantas A, Rotstein L, Langer B. Regional versus systemic chemotherapy in the treatment of colorectal carcinoma metastatic to the liver. Is there a survival difference? Meta-analysis of the published literature. *Cancer.* 1996;78:1639–1645.
95. Thirion P, Wolmark N, Haddad E, et al. Survival impact of chemotherapy in patients with colorectal metastases confined to the liver: a re-analysis of 1458 non-operable patients randomised in 22 trials and 4 meta-analyses. Meta-Analysis Group in Cancer. *Ann Oncol.* 1999;10:1317–1320.
96. Mocellin S, Pilati P, Lise M, et al. Meta-analysis of hepatic arterial infusion for unresectable liver metastases from colorectal cancer: the end of an era? *J Clin Oncol.* 2007;25:5649–5654.
97. Lorenz M, Muller H. Randomized multicenter trial of fluorouracil plus leucovorin administered either via hepatic arterial or intravenous infusion versus fluorodeoxyuridine administered via hepatic arterial infusion in patients with nonresectable liver metastases from colorectal carcinoma. *J Clin Oncol.* 2000;18:243–254.
98. Kemeny M. The surgical aspects of the totally implantable hepatic artery infusion pump. *Arch Surg.* 2001;136:348–352.
99. Allen PJ, Nissan A, Picon AI, et al. Technical complications and durability of hepatic artery infusion pumps for unresectable colorectal liver metastases: an institutional experience of 544 consecutive cases. *J Am Coll Surg.* 2005;201:57–65.
100. Hildebrandt B, Pech M, Nicolaou A, et al. Interventionally implanted port catheter systems for hepatic arterial infusion of chemotherapy in patients with colorectal liver metastases: a phase II – study and historical comparison with the surgical approach. *BMC Cancer.* 2007;24:7:69.
101. Sameshima S, Horikoshi H, Motegi K, et al. Outcomes of hepatic artery infusion therapy for hepatic metastases from colorectal carcinoma after radiological placement of infusion catheters. *Eur J Surg Oncol.* 2007;33:741–745.
102. Seki H, Ozaki T, Shiina M. Side-hole catheter placement for hepatic arterial infusion chemotherapy in patients with liver metastases from colorectal cancer: long-term treatment and survival benefit. *Am J Roentgenol.* 2008;190:111–120.
103. Mathur P, Allen-Mersh TG. Hepatic arterial chemotherapy for colorectal liver metastases. *Hepatogastroenterology.* 2001;48:317–319.
104. Fiorentini G, De Giorgi U, Giovanis P, et al. Intra-arterial hepatic chemotherapy for liver metastases from colorectal cancer: need of guidelines for catheter positioning, port management and anti-coagulant therapy. *Ann Oncol.* 2001;12:1023–1024.
105. Vauthey JN, Marsh W, Cendamo C, et al. Arterial therapy of hepatic colorectal metastases. *Br J Surg.* 1996;83:447–455.
106. Jakob AR, Kuhl M, Jauch KW, et al. Complications using implantable port-systems for regional chemotherapy of liver metastases. *Reg Cancer Treat.* 1996;9:33–36.
107. Oberfield RA, McCaffrey JA, Polio J, et al. Prolonged and continuous percutaneous intra-arterial hepatic infusion chemotherapy in advanced metastatic liver adenocarcinoma from colorectal primary. *Cancer.* 1979;44:414–423.
108. Okuyama K, Thonoson N, Koide Y, et al. Complications and their management in intra-arterial infusion chemotherapy. *Gan To Kagaku Ryoho.* 1992;19:1007–1013.
109. Laffer U, Durig M, Bloch HR, et al. Implantable catheter systems. *Dtsch Med.* 1989;114:655–658.
110. Huk I, Entschaff P, Prager M, et al. Patency rate of implantable devices during long-term intra-arterial chemotherapy. *Angiology.* 1990;41:936–941.
111. Dressing K, Lottner C, Stock W. Duodenal perforation of an intra-arterial port catheter and other complications following port implantation for regional cytostatic infusion of the liver. *Med Klin.* 1991;86:245–250.
112. Henne BD, Marks GH, Marks V, et al. Intra-arterial chemotherapy in the treatment of liver malignancies. *Chirurg.* 1989;114:668–676.
113. Mondini G, De Cian F, Balleto N, et al. Device performances and complications during hepatic arterial chemotherapy. *Reg Cancer Treat.* 1995;8:168–172.
114. Metzger U, Weder W, Rothlin M, et al. Phase II study of intra-arterial fluorouracil and mitomycin-C for liver metastases of colorectal cancer. *Recent Results Cancer Res.* 1991;121:198–204.
115. Liu LX, Zhang WH, Jiang HC, et al. Arterial chemotherapy of 5-fluorouracil and mitomycin C in the treatment of liver metastases of colorectal cancer. *World J Gastroenterol.* 2002;8:663–667.
116. Aldrighetti L, Arru M, Angeli E, et al. Percutaneous vs surgical placement of hepatic artery indwelling catheters for regional chemotherapy. *Hepatogastroenterology.* 2002;49:513–517.
117. Van Nieuwenhove Y, Aerts M, Neyns B, et al. Techniques for the placement of hepatic artery catheters for regional chemotherapy in unresectable liver metastases. *Eur J Surg Oncol.* 2007;33:336–340.
118. Germer CT, Boese LJ, Albrecht D, et al. The totally implantable minimally invasive hepatic artery catheter for intra-arterial chemotherapy of unresectable liver metastases in cases of dysfunction of arterial access devices. *Chirurg.* 1996;67:458–462.
119. Wacker F, Boese LJ, Wagner A, et al. Minimally invasive catheter implantation for regional chemotherapy of the liver: a new percutaneous trans-subclavian approach. *Cardiovasc Intervent Radiol.* 1997;20:128–132.

120. Strecker E, Boos I, Ostheim DW, et al. Percutaneous implantable catheter-port system: preliminary technical results. *Radiology*. 1997;205:574–577.
121. Oi H, Kishimoto H, Matsushita M, et al. Percutaneous implantation of hepatic artery infusion reservoir by sonographically guided left subclavian artery puncture. *Am J Roentgenol*. 1996;166:821–822.
122. Herrmann KA, Waggershauer T, Sittek H, et al. Liver intra-arterial chemotherapy: use of the femoral artery for percutaneous implantation of catheter-port systems. *Radiology*. 2000;215:294–299.
123. Zanon C, Grosso M, Clara R, et al. Combined regional and systemic chemotherapy by a mini-invasive approach for the treatment of colorectal liver metastases. *Am J Clin Oncol*. 2001;24:354–359.
124. Morandi C, Colopi S, Arai Y, et al. Percutaneous positioning of port catheter in the hepatic artery for chemotherapy of metastases using the Arai technique. *Radiol Med*. 1998;95:357–361.
125. Clouse ME, Ahmed R, Ryan RB, et al. Complications of long term transbrachial hepatic arterial infusion chemotherapy. *Am J Roentgenol*. 1977;129:799–803.
126. Cohen AM, Kaufman SD, Wood WC, et al. Regional hepatic chemotherapy using an implantable drug infusion pump. *Am J Surg*. 1983;145:529–533.
127. Johnson LP, Wasserman PB, Rivkin SE. FUDR hepatic arterial infusions via an implantable pump for treatment of hepatic tumors. *Proc Am Clin Oncol*. 1983;1:337–344.
128. Weiss GR, Garnick MB, Osteen RT, et al. Long-term hepatic arterial infusion of 5-fluorodeoxyuridine for liver metastases using an implantable infusion pump. *J Clin Oncol*. 1983;1:337–344.
129. Niederhuber JE, Ensminger W, Gyves J, et al. Regional chemotherapy of colorectal cancer metastatic to the liver. *Cancer*. 1984;53:1336–1343.
130. Schwartz S, Jones LS, McCune CS. Assessment of treatment of intrahepatic malignancies using chemotherapy via an implantable pump. *Ann Surg*. 1985;201:560–567.
131. Shepard KV, Levin B, Karl RC, et al. Therapy for metastatic colorectal cancer with hepatic artery infusion chemotherapy using a subcutaneous implanted pump. *J Clin Oncol*. 1985;3:161–169.
132. Balch CM, Urist MM. Intra-arterial chemotherapy for colorectal liver metastases and hepatomas using a totally implantable drug infusion pump. *Recent Results Cancer Res*. 1986;100:234–247.
133. Curley SA, Chase JL, Roh MS, et al. Technical considerations and complications associated with the placement of implantable hepatic arterial infusion devices. *Surgery*. 1993;114:928–935.
134. Chang AE, Schneider PD, Sugarbaker PH, et al. A prospective randomized trial of regional versus systemic continuous 5-fluorodeoxyuridine chemotherapy in the treatment of colorectal liver metastases. *Ann Surg*. 1987;206:685–693.
135. Hohn DC, Stagg RJ, Friedman MA, et al. A randomized trial of continuous intravenous versus hepatic intra-arterial floxuridine in patients with colorectal cancer metastatic to the liver: the Northern California Oncology Group trial. *J Clin Oncol*. 1989;7:1646–1654.
136. Martin JK Jr, O'Connell MJ, Wieand HS, et al. Intra-arterial floxuridine vs systemic fluorouracil for hepatic metastases from colorectal cancer. A randomized trial. *Arch Surg*. 1990;125:1022–1027.
137. Wagman LD, Kemeny MM, Leong L, et al. A prospective, randomized evaluation of the treatment of colorectal cancer metastatic to the liver. *J Clin Oncol*. 1990;8:1885–1893.
138. Rougier P, Laplanche A, Huguier M, et al. Hepatic arterial infusion of floxuridine in patients with liver metastases from colorectal carcinoma: long-term results of a prospective randomized trial. *J Clin Oncol*. 1992;10:1112–1118.