

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

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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.¹ 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.²⁻⁴ If untreated, the median survival of patients with hepatic metastases is 6 to 12 months.⁵⁻⁷ Hepatic resection is considered the best chance for long-term survival,⁸⁻¹⁶ but only 10% to 25% of the patients can be resected with curative intention.¹⁷⁻²⁰ In patients submitted to hepatic resection 5-year survival rate is 25% to 40%.²¹⁻²⁶

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.²⁷⁻³³ No randomized studies assessing outcome following hepatic

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

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.^{35–38} An essential requirement for treatment is that all patients with advanced metastatic disease should have a good performance status in order to tolerate chemotherapy.³⁹ 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.^{40–47} 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.^{5,48–52} 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.^{3,42,44,53–54}

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.^{56,57} A recent study demonstrated that preoperative HAI may provide long-term survival comparable to that achieved in patients submitted to liver resection only.⁵⁸

One of the most peculiar events with HAI is the development of frequent complications.^{59–62} 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.⁶³ 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.^{54,64,65} 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 (%)
34 ¹⁰⁶	5-FU	3 (8.8)	3 (8.8)	2 (5.9)	5 (14.7)	2 (5.9)
48 ¹⁰⁷	5-FU FUDR	19 (39.6)	7 (14.6)	21 (43.8)	0 (0)	2 (4.2)
188 ¹⁰⁸	5-FU	21 (11)	0 (0)	50 (26)	10 (5)	10 (5)
29 ¹⁰⁹	5-FU	0 (0)	6 (21)	3 (10)	0 (0)	0 (0)
52 ¹¹⁰	5-FU	9 (17.3)	0 (0)	1 (2)	0 (0)	4 (7.6)
24 ¹¹¹	5-FU	0 (0)	0 (0)	1 (4)	4 (17)	1 (4)
38 ¹¹²	NS ^a	1 (2.6)	4 (10.5)	0 (0)	0 (0)	0 (0)
91 ¹¹³	FUDR CDDP	–	–	6 (6.6)	10 (11)	2 (2.2)
30 ¹¹⁴	5-FU MITO C	8 (26.6)	6 (20)	1 (3.3)	1 (3.3)	2 (6.6)
113 ⁶³	5-FU	29 (26)	–	–	13 (12)	1 (0.8)
31 ⁶⁰	FUDR	–	5 (16.1)	1 (3.2)	1 (3.2)	0 (0)
75 ¹¹⁵	5-FU MITO C	11 (19.8)	–	–	–	1 (1.3)
28 ¹¹⁶	FUDR	1 (3.5)	1 (3.5)	0 (0)	–	–
110 ⁷²	5-FU FUDR	5 (4.5)	28 (25.5)	15 (13.6)	–	2 (1.8)
29 ¹¹⁷	CPT-11 Oxaliplatin 5-FU	1 (3.4)	2 (6.9)	–	1 (3.4)	–
28 ⁴²	Oxaliplatin	–	5 (17.9)	–	2 (7.1)	1 (3.5)

^anot 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 (%)
36 ¹¹⁸	5-FU	0 (0)	8 (22)	2 (5)	10 (28)	0 (0)
33 ¹¹⁹	5-FU	5 (15)	5 (15)	2 (6)	11 (33)	0 (0)
44 ¹²⁰	NS	1 (2.2)	5 (11.3)	4 (9)	0 (0)	2 (4)
31 ¹²¹	5-FU	4 (13)	0 (0)	4 (13)	0 (0)	0 (0)
32 ¹²²	NS ^a	0 (0)	2 (6)	2 (6)	0 (0)	0 (0)
95 ¹²³	FUDR	4 (4)	–	16 (17)	–	1 (1)
52 ⁶³	5-FU	1 (2)	–	–	–	–
4 ¹²⁴	NS	0 (0)	0 (0)	0 (0)	–	–
127 ¹²⁵	5-FU FUDR	30 (24)	10 (8)	46 (36)	0 (0)	4 (3)
28 ¹¹⁶	FUDR	1 (3.5)	1 (3.5)	10 (35.7)	–	–
41 ¹⁰⁰	5-FU MITO C Oxaliplatin	7 (17.9)	6 (15.4)	8 (20.5)	4 (12.8)	3 (7.7)
135 ¹⁰²	5-FU	25 (18.5)	1 (0.7)	11 (8.1)	2 (1.5)	–
42 ¹⁰¹	5-FU	2 (4.7)	–	1 (2.4)	–	–
22 ⁵⁸	5-FU CDDP	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

^anot stated.

Table 3 Complications of fully implantable pump

No. patients (Reference)	Chemotherapy	Catheter/arterial thrombosis (%)	Catheter break up (%)	Infection (%)	Pocket hematoma/seroma (%)	Pump malfunction (%)
50 ¹²⁶	FUDR	0 (0)	1 (2)	1 (2)	–	0 (0)
26 ¹²⁷	FUDR	0 (0)	0 (0)	0 (0)	3 (12)	0 (0)
21 ¹²⁸	FUDR	0 (0)	1 (5)	1 (5)	1 (5)	0 (0)
93 ¹²⁹	FUDR	3 (3)	1 (1)	1 (1)	2 (2)	0 (0)
30 ¹³⁰	FUDR MITO C BCNU	0 (0)	2 (7)	1 (3)	6 (20)	0 (0)
62 ¹³¹	FUDR	0 (0)	0 (0)	0 (0)	–	0 (0)
110 ¹³²	FUDR	0 (0)	0 (0)	0 (0)	–	0 (0)
143 ¹³³	5-FU	16 (11.2)	21 (14.7)	1 (0.7)	19 (13.3)	2 (1.4)
44 ¹¹³	FUDR CDDP	6 (13.6)	0 (0)	2 (4.5)	9 (21)	1 (2.3)
24 ¹³⁴	FUDR	–	–	–	–	–
67 ¹³⁵	FUDR	–	9 (13.4)	1 (1.5)	–	–
33 ¹³⁶	FUDR	5 (15)	–	2 (6)	–	2 (6)
40 ¹³⁷	FUDR	–	–	–	–	–
81 ¹³⁸	FUDR	10 (12)	1 (1.2)	–	12 (15)	–
64 ⁶⁰	FUDR	2 (3.1)	–	3 (4.7)	4 (6.3)	2 (3.1)
70 ⁷²	5-FU FUDR	5 (7.1)	–	4 (5.7)	–	5 (7.1)
544 ⁹⁹	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.^{64,66–73} 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.^{4,18,20,58,74–83} 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.^{84–88} 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^{72,84–87,89,90} and different dosages were proposed.^{91–93} 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.^{68,94–96}

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.^{55,97} The number of these complications can be reduced only if fully implantable pumps are employed.^{60,62,98,99}

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.¹⁰⁰ 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.^{101,102} 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;¹⁰³ therefore the incidence of complications decreases as the experience of the medical team increases and with a careful medical manipulation.^{60,104} 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.¹⁰⁵ 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.^{63,72} 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.

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Disclosures

The authors have no conflicts of interest to disclose.

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