Segmental and lobar administration of drug-eluting beads delivering irinotecan leads to tumour destruction: a case–control series

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Abstract

Background: Irinotecan-loaded drug-eluting beads represent a novel drug delivery method that allows for the locoregional delivery of irinotecan to colorectal liver metastases (CRLM). The method has shown impressive response rates. However, the pathological response to this treatment has not previously been demonstrated.

Methods: Patients with easily resectable CRLM were treated with drug-eluting beads delivering irinotecan (DEBIRI) 4 weeks prior to resection. Pathological tumour response was graded using a validated system. The intraoperative detection of previously unidentified disease allowed for the assessment of pathological responses directly attributable to bead treatment.

Results: In Patient 1, segmental embolization of the target lesion in segment VIII resulted in 100% necrosis (0% viability). An untreated lesion in segment IV was found to be 30% viable. In Patient 2, subsegmental embolization of the target lesion in segment VI resulted in 60% necrosis and 40% fibrosis (0% viability). An untreated lesion in segment VI remained 60% viable. In Patient 3, lobar embolization of the target lesion in segment II resulted in 0% viability. Two further lesions within the treated hemiliver, both with 0% viability, and one lesion in the untreated hemiliver with 45% viability were discovered at laparotomy.

Conclusions: This series demonstrates the effectiveness of DEBIRI in the treatment of CRLM. High rates of tumour destruction are possible, even with the proximal lobar administration of DEBIRI. Lobar administration appears to be an appropriate method of delivery for integration into future therapeutic regimens.

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Introduction

The majority of patients with colorectal cancer will develop metastases and approximately one quarter are found to have distant metastases at the time of presentation. Surgical resection is the only potentially curative option for these patients and results in reported 5-year survival of around 40%, but is an option for only a minority of patients.1–13 Response to chemotherapy correlates with resection rate14 and it seems logical that patients with unresectable liver-limited disease, regardless of its extent and distribution, should be treated with the most aggressive systemic induction or conversion therapy and that this strategy should represent the primary course of treatment with the purpose of bringing these patients to potentially curative resection. Resectability rates after chemotherapy for initially unresectable disease vary widely, with recently reported regimens achieving conversion rates approaching 60%.14 Attempts to bring unresectable disease to resection are worthwhile and result in overall 5-year survival rates comparable with those in patients found to be resectable at
presentation.\textsuperscript{15} The UK National Institute for Clinical Excellence (NICE) currently recommends the use of regimens based on folinic acid (leucovorin), fluorouracil (5-FU) and oxaliplatin (FOLFOX) with or without cetuximab as first-line therapy in all patients with non-resectable disease, and suggests that irinotecan-based (FOLFIRI) regimens should be used as second-line therapy after the failure of first-line treatment, although the efficacy of FOLFIRI is comparable with that of FOLFOX in the setting of metastatic disease.\textsuperscript{16} Intensive triplet chemotherapy with FOLFOXIRI has been compared with FOLFIRI alone in a Phase III randomized controlled trial.\textsuperscript{17} Response rates were higher after FOLFOXIRI, which resulted in a secondary resection rate of 36\% in patients with liver-limited disease compared with 12\% in those treated with standard FOLFIRI (\( P = 0.017 \)). However, off-target toxicity (mainly manifesting as severe diarrhoea) was high and thus double-agent cytotoxic therapy remains the first-line treatment of choice.

The precise role of true neoadjuvant chemotherapy in the management of resectable disease remains controversial. The European Organization for Research and Treatment of Cancer (EORTC) 40983 Phase III trial assessed perioperative chemotherapy by randomizing patients to perioperative FOLFOX and surgery or to surgery alone and demonstrated a significantly improved 3-year progression-free survival rate in the perioperative chemotherapy arm,\textsuperscript{18} although this did not translate to improved longterm outcome.\textsuperscript{19} Despite these negative long-term findings, the majority of patients with high-risk colorectal liver metastases (CRLM), as indicated by synchronous presentation, bilobar disease, the presence of three or more metastases, metastases measuring >5 cm or high preoperative carcinoembryonic antigen (CEA) levels (>100 ng/ml), continue to continue to receive perioperative chemotherapy irrespective of their initial resectability\textsuperscript{20} on the premise that this will result in the destruction of occult disease, allow a test of biology in patients in whom progression despite chemotherapy signifies poor biology, as well as reduce lesion size and thereby improve resectability.

Previous work has demonstrated impressive response rates following the delivery of chemotherapy by hepatic arterial pump.\textsuperscript{21} However, the invasiveness of pump insertion and relatively high rates of complications have limited the adoption of this technique.\textsuperscript{22} Drug-eluting beads [marketed as DC Bead\textsuperscript{\textregistered} in Europe (Biocompatibles UK Ltd, Farnham, UK)] are compressible beads produced from polyvinyl alcohol hydrogel that can be loaded with irinotecan. This method offers a theoretical advantage over hepatic arterial infusion because delivery is simplified (embolization and chemotherapy are combined, with no need for a pump) and it offers the potential to add locoregional irinotecan to systemic FOLFOX with the aim of achieving response rates comparable with those seen after FOLFOXIRI whilst minimizing morbidity. In the single-arm, prospective Phase II safety and efficacy PARAGON II study, patients with easily resectable CRLM were given a single neoadjuvant treatment 4 weeks prior to surgery with DC Irinotecan Bead, a next-generation investigational product in which the embolic bead is preloaded with a standardized dose of irinotecan by the manufacturer (Biocompatibles UK Ltd). The primary endpoint was tumour resectability; secondary endpoints included the safety of transarterial chemoembolization (TACE) and post-TACE surgery, radiologic response [using RECIST (response evaluation criteria in solid tumours) and assessment of necrosis] and pathological tumour response.\textsuperscript{23}

In a minority of patients who come to hepatic resection, preoperative imaging fails to detect all disease identifiable at laparotomy.\textsuperscript{24} In the PARAGON II study, three patients were found to have intrahepatic disease that was not identified preoperatively and thus was not treated with drug-eluting beads delivering irinotecan (DEBIRI). The aim of the present study was to investigate findings in those patients in the PARAGON II trial in whom both treated and untreated lesions were identified in order to assess the pathological response directly attributable to treatment with DEBIRI-TACE.

**Materials and methods**

**Recruitment**

The PARAGON II trial (Fig. 1) was approved by regulatory authorities and local ethics committees in the UK, France, Spain and Austria and registered at clinicaltrials.gov (NCT00844233). All patients were fully staged using computed tomography (CT) of the chest, abdomen and pelvis, magnetic resonance imaging (MRI) with liver-specific contrast and positron emission tomography (PET)-CT. All patients recruited had easily resectable CRLM as defined by the specialist hepatopancreatobiliary (HPB)

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{diagram.png}
\caption{CONSORT (consolidated standards of reporting trials) diagram of PARAGON II study. DEBIRI-TACE, drug-eluting beads delivering irinotecan transarterial chemoembolization}
\end{figure}
multidisciplinary team (MDT), with <60% liver tumour replacement. It was the opinion of the MDT that these patients did not require neoadjuvant chemotherapy within the routine standard of care. All patients had undergone complete resection of the primary tumour without gross or microscopic evidence of residual disease (R0), and had not been previously exposed to irinotecan-containing chemotherapy.

**Embolization procedure**

Embolization was performed by an experienced interventional radiologist (EO’G or CK) and started with diagnostic angiography to adequately define hepatic arterial anatomy and ensure no extrahepatic shunting. Particular attention was paid to ensure the catheter tip had passed beyond the cystic artery to avoid chemoembolization of the gallbladder. Treatment consisted of a nominal dose of 2 ml of DC Bead® of 100–300 μm in diameter containing 200 mg of irinotecan (PARAGON Bead®; Biocompatibles UK Ltd), mixed in non-ionic contrast media. Initially, very selective embolization was performed and beads were delivered directly to the subsegment containing the tumour. As experience accumulated, a more proximal catheter placement into the right or left hepatic artery was used. Irinotecan-loaded beads were delivered slowly to near stasis. Patient analgesia was provided using a combination of paracetamol, diclofenac, intra-arterial lidocaine and post-procedural opiate patient-controlled analgesia (PCA).

**Surgical resection**

Four weeks after embolization, patients underwent repeat CT of the chest, abdomen and pelvis followed by surgical resection (Table 1). All patients underwent open resection performed by an experienced hepatobiliary surgeon. Laparotomy was performed and extrahepatic abdominal disease excluded by full inspection. Intraoperative ultrasound (IOUS) was routinely performed to guide surgical planning. Low-volume anaesthesia was used with the aim of maintaining a central venous pressure of <5 mmHg. Liver parenchyma was transected with the Cavitron ultrasonic surgical aspirator (CUSA®; Valleylab, Inc., Boulder, CO, USA). Intermittent vascular inflow occlusion was used at the discretion of the operating surgeon.

**Pathological examination**

Following resection, surgical specimens were fixed in formalin and macroscopically dissected to produce paraffin-embedded blocks. Tissue was sampled from the centre, mid-part and periphery of the tumour, the tumour and adjacent liver parenchyma, and the tumour and resection margin. After sectioning, specimens were stained with haematoxylin and eosin and reviewed by an experienced hepatobiliary pathologist (MT) and assessed according to the UK Royal College of Pathologists Liver Resection Standard Dataset. Slides from each block were reviewed, and tumour response graded using the method of Rubbia-Brandt et al.25 Briefly, the amount of residual cancer was assessed semi-quantitatively by estimating the proportion of residual cancer cells, necrotic tissue and fibrosis in relation to the total area of cancer.

**Results**

**Patient 1**

A 68-year-old, White man was referred to the regional specialist hepatobiliary MDT and recruited to the PARAGON II study. Angiography at the time of embolization demonstrated a hypovascular lesion in segment VIII, and 1 ml of DC Irinotecan Bead was administered via the segment VIII segmental artery to almost complete stasis. The procedure was well tolerated and the patient was discharged 48 h after embolization. At laparotomy, IOUS demonstrated the previously identified and treated lesion in segment VIII, as well as a second untreated lesion in segment IV. Both were treated with uneventful non-anatomical resection.

The treated lesion in segment VIII had a longest diameter of 25 mm and showed no residual tumour and 100% replacement with necrotic tissue. By contrast, the untreated lesion in segment IV (longest diameter: 25 mm) demonstrated 30% residual tumour, 40% necrosis and 30% fibrosis (Fig. 2).

**Patient 2**

A 40-year-old, White man was referred to the regional specialist hepatobiliary MDT with a suspicious liver lesion. Imaging with MRI and PET-CT demonstrated no other intra- or extrahepatic disease and the patient was recruited to the PARAGON II study. Angiography confirmed a single lesion supplied by the segment VI artery, which was treated by distal embolization with 0.5 ml of DC Irinotecan Bead. The procedure was well tolerated and the patient was discharged 24 h after embolization. At laparotomy IOUS demonstrated the previously identified and treated lesion in...
segment VI, as well as a second previously unidentified lesion in the same segment, both of which were easily resected.

Pathological examination showed the lesion in segment VI seen on CT and targeted with DC Irinotecan Bead had a longest diameter of 15 mm, with no evidence of viable tumour, 60% necrosis and 40% fibrosis (Fig. 3). By contrast, the untreated lesion in segment VI (longest diameter: 14 mm) demonstrated 60% residual tumour, 30% necrosis and 10% fibrosis.

**Patient 3**
A 63-year-old, White man was found to have a suspicious liver lesion on CT and referred to the specialist HPB MDT. Preoperative imaging identified a lesion on the border between segments II and IVa with a longest diameter of 17 mm. The patient underwent embolization and was treated with 1.3 ml of DC Irinotecan Bead delivered in a lobar fashion via the left hepatic artery until partial occlusion of the left subsegmental arteries was achieved. The patient developed post-embolization syndrome (reported in 10% of patients), with transient abdominal pain and nausea, but no change in white cell count or liver function tests (Table 2). The patient made a rapid recovery and was discharged home the following day.

On CT prior to surgery, the target lesion was found to have shrunk to a longest diameter of 10 mm (a 41.2% reduction, indicating a partial response according to RECIST criteria). However, on imaging a second tumour in segment II (within the lobar treatment zone) was clearly identified. Radiological assessment suggested this lesion was 100% necrotic. Retrospective review of the initial staging imaging showed no evidence of this lesion prior to treatment with DEBIRI.

*Figure 2* Preoperative imaging in Patient 1 showing a small 25-mm colorectal liver metastasis in segment VIII on (a) computed tomography (CT), (b) contrast-enhanced magnetic resonance imaging and (c) positron-emission tomography-CT. No other disease was identified on preoperative imaging.

*Figure 3* Histopathology in Patient 2 showing (a) targeted and (b) non-targeted colorectal liver metastasis. The treated lesion shows an absence of viable tumour, with complete replacement with necrotic tissue. In (a), the irinotecan beads are clearly visible within the vasculature. By contrast, the untreated lesion (b) shows islands of viable cells with minimal necrosis and fibrosis. (Haematoxylin and eosin stain; original magnification ×20)
During surgery, IOUS detected two further lesions. One, in segment III, had been treated by lobar infusion. The second intraoperatively detected lesion was in segment VII and had not been treated by DC Irinotecan Bead.

Postoperative examination of all four resected tumours showed varying degrees of response. All three lesions in the left hemiliver, which had been treated with DC Irinotecan Bead, demonstrated the absence of viable tumour and 100% replacement with fibrotic or necrotic tissue; these included the original target lesion in segments II and IVa, the second lesion in segment II that had been inadvertently treated and was identified after treatment with DC Irinotecan Bead but before resection, and the lesion in segment III that had been intraoperatively identified and inadvertently treated. By contrast, the lesion in segment VII, which was outwith the zone covered by DC Irinotecan Bead treatment, demonstrated 45% residual tumour, 50% necrosis and 5% fibrosis.

**Discussion**

Findings in these three patients offer further evidence of the effectiveness of DEBIRI for the treatment of hepatic metastases of colorectal cancer. The DC Bead loaded with irinotecan is CE (Conformité Européenne)-marked in Europe for the treatment of metastatic colorectal cancer. LC Bead® does not yet have market approval in the USA for use in combination with irinotecan, but is used in US Food and Drug Administration-approved investigational clinical trials and has shown impressive results in both chemo-naive and heavily pretreated unresectable patients.26,27 An international registry reported response rates of 66% at 6 months and 75% at 12 months in 55 patients who had failed first- and second-line systemic therapy for metastatic colorectal cancer and were treated with DC Bead® with irinotecan. In a further prospective study of 75 patients with liver-only metastatic colorectal cancer randomized to FOLFI RI or irinotecan beads, patients treated with beads showed a statistically significant improvement in median survival over those treated with chemotherapy (22 months versus 15 months; \( P = 0.03 \)).28 However, the safety of this treatment in a true neoadjuvant setting and the degree of pathological response directly attributable to DEBIRI has not previously been demonstrated. Pathological tumour response was chosen as a surrogate marker for potential longterm benefit as it has been clearly demonstrated that patients who exhibit a good pathological response to chemotherapy have better overall survival. Blazer et al.29 found that patients treated with preoperative chemotherapy who demonstrated fewer viable tumour cells on post-resection examination had much better longterm outcomes. Only 9% of patients were found to have no viable tumour, whereas 33% had tumours with viability of >50%. Five-year survival was 75% in those with complete tumour destruction and 33% in patients with tumours with viability of >50% (\( P = 0.007 \)).29

Metastatic colorectal cancer often presents with a multi-focal liver-dominant pattern. In this setting, targeted embolization is not feasible, but lobar administration may be an option. At the beginning of the PARAGON II study, selective embolization was performed to deliver maximum treatment to target lesions. However, as experience of the procedure accumulated, a more proximal lobar delivery was used. The present report includes a patient with undetected disease that was not directly targeted by DEBIRI, but was located in a treated hemiliver. This patient was also found to have a further undetected lesion in an untreated lobe. This allowed for further comparison among three lesions which were, respectively, directly targeted with DEBIRI, treated with DEBIRI using lobar infusion, and non-treated.

Patient 1 underwent segmental embolization. At laparotomy, two distinct lesions were resected, including one from within the treated segment and one from an untreated segment. The difference in viable tumour (0% versus 30%) was stark and suggests that the lack of viable tumour seen within the post-treatment specimen is directly attributable to DEBIRI treatment. An indirect effect of DC Irinotecan Bead on the untreated segment cannot be completely ruled out as the patient received 100 mg of irinotecan with the beads. However, pharmacokinetic modelling has suggested that systemic exposure after treatment with DEBIRI is low and thus this seems unlikely.27 A similar pattern was observed in Patient 2, in whom targeted delivery of irinotecan led to complete tumour destruction, whereas the non-targeted lesion retained a large proportion of viable tumour (0% versus 60%). Although the non-targeted lesion was located in the treated segment, embolization was very distal and the second lesion was not detected on angiography and thus is unlikely to have been sited within the treatment zone. In Patients 1 and 2, the treated and untreated lesions were of comparable size. This also means it is unlikely that the varying degrees of viable tumour were attributable to anatomical variation, such as

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**Table 2 Results of peri-procedural blood tests in Patients 1–3**

<table>
<thead>
<tr>
<th></th>
<th>Pre-DEBIRI-TACE</th>
<th>Post-DEBIRI-TACE</th>
<th>Pre-resection</th>
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<tbody>
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<td>7.8</td>
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<td>ALT, U/la</td>
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<td>22</td>
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<tr>
<td>ALP, U/l</td>
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<tr>
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<tr>
<td>ALP, U/l</td>
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</table>

*Routine laboratory profile changed from AST to ALT prior to this patients treatment.*

DEBIRI-TACE, drug-eluting beads delivering irinotecan transarterial chemoembolization; WCC, white cell count; AST, aspartate aminotransferase; ALT, alanine aminotransferase.
when the blood supply to a larger lesion is inadequate to maintain tumour viability.

In Patient 3, the radiological appearance of a lesion after embolization suggests an inherent change in the structure of that lesion. Post-resection analysis demonstrated that this lesion had 75% necrosis and 25% fibrosis. Therefore, it seems likely that the initial effect of the delivery of DC Irinotecan Bead in this lesion was mediated predominantly by occlusion of the blood supply to the tumour rather than the effect of the irinotecan because chemotherapy-associated change seems to be represented by fibrotic involution rather than necrosis. Interestingly, all the lesions within the treated lobe showed 0% viable tumour. By contrast, the untreated lesion in segment VII demonstrated a large amount of viable tumour (45%) and a very low amount of fibrosis (5%), as would be expected in a chemo-naïve lesion.

The large amount of viable tumour observed in lesions supplied by arterial flow proximal to the point of bead release and the absence of tumour in previously unidentified lesions targeted by lobar embolization support the oncologic rationale for very proximal ‘whole-lobe’ embolization. These results suggest that undetected micrometastatic lesions within a lobar embolization zone can be treated as effectively as lesions that are identified preoperatively and more selectively embolized. This finding is important for the design of future trials. Over 60% of patients who undergo liver surgery with curative intent will experience recurrence within 2 years of resection as a result of preoperatively undetected micrometastatic disease. Lobar treatment with DC Irinotecan Bead may be sufficient to destroy these micrometastases and thereby reduce postoperative recurrence.

The impressive pathological response rates reported in this series, in which multiple treated lesions showed no viable tumour cells, may raise questions about the utility of surgery in this setting. If disease can be adequately treated by chemotherapy, is it necessary to resect? Currently, surgery remains the reference standard treatment, even after a complete radiological response has been achieved. Lesions that are not identified in preoperative imaging are often detected at laparotomy by IOUS and these lesions can be surgically resected at the time of detection, resulting in low rates of local disease recurrence. A complete pathological response also remains a pathological diagnosis and 80% of lesions that show a complete radiological response are found to contain viable tumour. Thus it is likely that even in lesions that show a complete radiological response, a number of viable tumour cells remain. Advances in imaging, including the use of PET-CT, have failed to accurately identify patients who have achieved a complete pathological response and this diagnosis therefore continues to rely on microscopic examination.

**Conclusions**

This patient series demonstrates the effectiveness of the investigational product DC Irinotecan Bead in the treatment of CRLM. High rates of tumour destruction are possible, even with the proximal lobar delivery of irinotecan-loaded beads. Lobar administration appears to be an appropriate method of delivery if this treatment is to be integrated into future therapeutic regimens with the aim of reducing occult micrometastatic disease.

**Acknowledgement**

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**Conflicts of interest**

None declared.

**References**


