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ORIGINAL ARTICLE

Hepatectomy after hepatic arterial therapy with either yttrium-90 or drug-eluting bead chemotherapy: is it safe?

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Abstract

Background: The use of hepatic arterial therapy (HAT) with either yttrium-90 or drug-eluting bead therapy for initially unresectable hepatic malignancies has risen significantly. The safety of hepatic resection after hepatic arterial therapy (HAT) is not established.

Objective: The present study evaluates the safety profile for hepatic resection after HAT.

Methods: We identified 840 patients undergoing hepatectomy for primary or metastatic lesions. Forty patients underwent HAT before hepatectomy (pre-HAT). A 1 : 4 case-matched analysis compared three groups: (i) pre-HAT and pre-operative chemotherapy ($n = 40$); (ii) pre-operative chemotherapy ($n = 160$); and (iii) no pre-operative therapy ($n = 640$). Controls were matched for age, resection type, maximal tumour size and magnitude of resection. Morbidity and mortality among groups were compared using a graded complication scale.

Results: There were no differences in post-operative complications, grade of complication or liver-specific complications among the groups. A proportional hazards model for all patients did not demonstrate any association between increased complications and either pre-HAT or pre-operative chemotherapy when compared with patients without pre-operative therapy ($P = 0.7$).

Conclusions: Pre-HAT demonstrated similar morbidity, liver-specific morbidity and intra-operative complications when compared with patients undergoing pre-operative chemotherapy alone or without pre-operative chemotherapy. These results suggest that pre-HAT is safe and should not preclude hepatectomy in carefully selected patients.

Keywords

hepatic arterial therapy, drug-eluting beads, yttrium-90, surgical morbidity, hepatectomy

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Introduction

Primary and metastatic hepatic malignancies are common problems addressed by hepatobiliary surgeons and oncologists. Over 18 000 patients in the United States die from primary liver cancers annually, and over half of the patients dying from aerodigestive cancers will harbour hepatic metastases.[1,2] In properly selected patients, resection of both primary and metastatic hepatic malignancies has been shown to extend survival.[3] Unfortunately, many patients will not be candidates for up-front resection because of unfavourable anatomy, insufficient hepatic functional reserve or aggressive tumour biology.

Recently, the use of hepatic arterial therapy (HAT) has emerged as a useful treatment option for unresectable patients. HAT takes advantage of the preferential hepatic arterial blood supply of hepatic neoplasms to deliver cytotoxic therapies, while minimizing systemic toxicity.[4] Two widely used HAT modalities include

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Yttrium-90 radioembolization and drug-eluting bead (DEB) therapy, which employ hepatic arterial delivery of radioisotopes or chemotherapy, respectively.

After HAT, a subset of initially unresectable patients will show a favourable tumour response, allowing for consideration of hepatic resection. Concerns over increased peri-hepatic inflammation (potentially leading to difficult hepatic mobilization), as well as the potential for hepatic parenchymal impairment (perhaps leading to an increase in hepatic insufficiency after resection) have left many surgeons reluctant to perform hepatectomy in this group of patients. The aim of the present study was to examine the safety of hepatectomy in patients who underwent pre-operative hepatic arterial therapy (pre-HAT).

Materials and methods

Between November 2006 and August 2009, two prospectively collected, institutional review board-approved databases were reviewed. Analysis of a 460-patient, prospective, hepatic arterial therapy registry and a 1642-patient prospective hepato-pancreato-biliary database identified three groups of patients: those who underwent HAT (yttrium-90 or DEB) before hepatectomy (pre-HAT; $n = 40$), those who had pre-operative systemic chemotherapy followed by resection ($n = 160$) and those who underwent hepatectomy without pre-operative treatment ($n = 640$).

All pre-HAT patients were included in the study. Comparison groups were selected using 1 : 4 matching based on patient age, disease distribution (number of lesions and maximal lesion diameter), patient comorbidities (presence of cardiopulmonary disease and hepatic dysfunction) and magnitude of hepatectomy. Major hepatectomy was defined as ≥3 Couinaud segments. Hepatic dysfunction was based upon patient histories, abnormal liver function tests or imaging suggestive of underlying hepatic pathology.

Before undergoing HAT, all patients underwent triple-phase baseline computed tomography (CT) imaging. All HAT patients were reviewed in a multidisciplinary conference, and determined to be unresectable based on extent of disease, comorbidities and disease histology. Contraindications to HAT included a contraindication to angiographic and selective visceral catheterization; non-patent portal vein; significant extrahepatic disease (>50% of overall tumour burden); greater than 75% of hepatic parenchymal tumour involvement; contraindication to doxorubicin or irinotecan administration, pregnancy; severe liver dysfunction; and severe cardiac comorbidities. Additionally, for patients undergoing yttrium-90 radioembolization therapy, the presence of significant hepatopulmonary shunting (>15%) constituted a contraindication to treatment.

Pre-HAT patients underwent treatment with either yttrium-90 radioembolization using SIR-Spheres (SIRTex Medical Ltd, Sydney, Australia) or DEB therapy using the LC Bead (Biocompatibles UK, Ltd, Surrey, United Kingdom) loaded with either doxorubicin or irinotecan. Methods for HAT delivery have been previously reported.[2,5,6]

After HAT, the response to therapy was assessed using CT imaging and characterized using modified response evaluation criteria in solid tumours (RECIST) criteria.[7] Follow-up CT imaging was performed at 6 weeks to restage and confirm the safety of these novel therapies. CT imaging was then obtained at 3 months post-treatment and thereafter at 3-month intervals to determine treatment response. After each serial scan, the decision on whether a particular patient required additional HAT treatments, resection, observation or cessation of therapy was made at a multidisciplinary conference with active input from surgeons, medical oncologists, radiation oncologists, radiologists and pathologists.

Patients were considered for resection after HAT based on cross-sectional imaging showing a favourable response to HAT, anatomic resectability of residual disease, absence of extrahepatic disease, the patient's functional status and a progression-free interval of at least 9 months for atypical metastatic disease (i.e. non-colorectal and non-neuroendocrine). Hepatic resections were performed by the senior authors (R.C.G.M., C.R.S., K.M.M.) and described based on Couinaud segments.[8]

Endpoints for this analysis were estimated blood loss (EBL), requirement for post-operative transfusion, post-operative complications, grade of complication, liver-specific complications and 90-day mortality. EBL was abstracted from the anaesthesia record. The decision to transfuse packed red blood cells was made by the operating surgeon based on clinical judgment for individual patients. All post-operative complications were monitored for 90 days and graded prospectively according to a previously published standard five-point scale.[9] Briefly, Grade 1 complications required only supportive care or oral medications; Grade 2 complications required intravenous medication or parenteral nutrition; Grade 3 complications required intensive care unit admission or relatively non-invasive procedures (e.g. esophagogastroduodenoscopy, image-guided drainage); Grade 4 complications involved chronic disability or required major reoperation (e.g. organ resection or enteral diversion). Major complications were defined as Grade ≥3. Liver-specific complications were defined as complications directly related to the liver parenchyma (i.e. biliary leakage, ascites or hepatic insufficiency).

Resection specimens were submitted for routine pathologic analysis. The non-tumour bearing liver was routinely assessed for inflammation based on haematoxylin & eosin (H&E) staining.

Statistical analysis was performed with JMP® software, version 7 (SAS Inc., Cary, NC, USA). Groups were compared using analysis of variance. P-values <0.05 were considered statistically significant. Post-hoc analysis was performed using the Tukey's HSD test. A proportional hazards model was used to identify predictors of post-operative complications.

Results

Group characteristics are given in Table 1, demonstrating similarity among the three groups based on matching criteria. Table 2

Table 1 Group characteristics

Group	Pre-HAT	Pre-operative chemo	No pre-operative Tx	*P*
Number of patients	40	160	640	
Median age (range)	60 (27–85)	65 (35–82)	66 (25–81)	NS
Median number of lesions (range)	2 (1–5)	2 (1–25)	1 (1–7)	NS
Median maximum lesion diameter, cm (range)	3.5 (1.5–9.5)	4 (1.2–9)	4 (1.5–8)	NS
Cardiopulmonary disease, *n* (%)	18	88 (55%)	192 (30%)	0.07
Underlying liver disease, *n* (%)	8	16 (10%)	32 (5%)	0.06
Major hepatectomy, *n* (%)	18	90 (56%)	28 (44%)	NS

Pre-HAT, pre-operative hepatic arterial therapy; NS, not significant.

Table 2 Disease characteristics of treatment groups

	Pre-HAT *n* = 40	Pre-op erative chemo *n* = 160	No pre-opertaive Tx *n* = 640
Colorectal metastases	16	142 (89%)	120 (19%)
Hepatocellular carcinoma	14	0	132 (20%)
Neuroendocrine	3	2 (1%)	73 (11%)
Cholangiocarcinoma (intrahepatic)	3	3 (2%)	95 (15%)
Sarcoma	0	1 (1%)	22 (3%)
Breast metastases	1	2 (1%)	20 (3%)
Melanoma metastases	0	1 (1%)	14 (2%)
Ovarian metastases	0	0	18 (3%)
Others	3	9 (6%)	146 (23%)

Pre-HAT, pre-operative hepatic arterial therapy; HCC, hepatocellular carcinoma.

Table 3 Previous chemotherapy exposures

	Pre-HAT *n* = 40 pts	Pre-operative chemo *n* = 160 pts
FOLFOX, *n*	7	105
FOLFIRI, *n*	7	31
Sorafenib, *n*	3	0
Gemcitabine, *n*	3	4
Bevacizumab, *n*	7	55
5-FU, *n*	6	32
Other, *n*	18	16

Pre-HAT, pre-operative hepatic arterial therapy.
Note: Many patients had exposure to multiple pre-operative chemotherapy regimens.

Table 4 Hepatic arterial therapy treatment characteristics

	Y-90	DEB	Y-90 + DEB
Number of patients	7	27	6
Number of treatments	18	37	15
Median number of treatments per patient (range)	2 (1–2)	2 (1–6)	3 (2–4)
Histology of non-tumour bearing liver, *n* (%)			
Moderate inflammation, *n*	5	7	6
Minimal inflammation, *n*	0	5	0
Normal, *n*	2	15	0

Y-90, yttrium-90 radioembolization; DEB, drug-eluting bead therapy.

lists the tumour histologies for the three study groups. Differences in the distribution of tumour types across treatment groups reflects the availability (or absence) of effective systemic chemotherapeutic options for the various tumour types. Both the pre-HAT and pre-operative chemotherapy groups had exposure to one or more systemic chemotherapy regimens before hepatic resection, detailed in Table 3.

The 40 pre-HAT patients underwent a total of 92 HAT treatments as listed in Table 4. Six patients [three with cholangiocarcinoma, two with hepatocellular carcinoma (HCC) and one with colorectal metastases] underwent sequential therapy with DEB and yttrium-90 because of a lack of response at initial review, or loss of response at 6–9 months.

The median time to resection after the last HAT treatment was 6.5 months (range 4–13 months), which is a substantially longer time to resection when compared with the pre-op chemotherapy group which was 1 month (range 3 weeks to 3 months), $P < 0.01$.

At the time of hepatic resection, the senior authors did not see any difference in peri-hepatic inflammation or adhesions and the mobilization of all three groups were similar. No increases in difficulty of hepatic parenchymal transaction were noted by any operating surgeon. After hepatic resection, the degree of hepatic inflammation in the non-tumour bearing liver was graded as none (normal), minimal, moderate or severe by pathologists based on H&E sections. On review, pathological examination of the non-tumour bearing liver demonstrated, at most, moderate inflammation in patients who underwent pre-HAT.

Table 5 describes the peri-operative characteristics and complication rates for the study groups. The most common major (grade

Table 5 Peri-operative outcomes after hepatic resection

	Pre-HAT $n = 40$	Pre-operative chemo $n = 160$	No pre-operative Tx $n = 640$	*P*
EBL, median (range), mL	550 (100–850)	400 (125–900)	375 (50–1500)	0.3
Post-operative transfusion requirement, *n* (%)	10	77 (48%)	192 (30%)	0.04
90-day complication, any grade	13	56 (35%)	147 (23%)	0.7
90-day complications, grade ≥3	6	22 (14%)	76 (12%)	0.08
90-day liver-specific complications	2	12 (8%)	44 (7%)	0.2
90-day mortality	0	6 (4%)	32 (5%)	0.7

Pre-HAT, pre-operative hepatic arterial therapy; EBL, estimated blood loss.

≥3) complications in the pre-HAT group were liver dysfunction and ileus. This was similar to the distribution of complications in the two comparison groups. The most common liver-specific complication was liver dysfunction. No specific complication occurred more often in the pre-HAT group vs. the comparison groups.

A proportional hazards model for all patients did not demonstrate any association between increased complications and either pre-HAT or pre-operative chemotherapy when compared with patients without pre-operative therapy ($P = 0.7$).

Discussion

Pre-HAT showed similar morbidity, liver-specific morbidity and mortality when compared with either patients undergoing pre-operative chemotherapy or those without pre-operative chemotherapy. These results demonstrate that pre-HAT is safe and should not preclude hepatectomy in well-selected patients.

The lack of operative difficulty in the pre-HAT groups may, in part, be because of the long interval between HAT therapy and resection. When comparing the pre-HAT and the pre-operative chemotherapy groups, the median time to resection after the last HAT treatment was substantially longer compared with the median time since last chemotherapy (6.5 vs. 1 month, $P < 0.01$). Accordingly, the possibility of greater peri-hepatic inflammation in the pre-HAT group at earlier resection intervals cannot be excluded.

On comparison between groups, no statistically significant difference was found among the three groups with regard to EBL, complication rate (any complication), occurrence of major complications, frequency of liver specific complications or 90-day mortality. An increased need for post-operative transfusions was noted in the pre-operative chemotherapy group ($P = 0.04$). We attribute the increased transfusion rate in this group of patients to the propensity for bone marrow suppression associated with systemic chemotherapy administration.

The similarity between groups in terms of liver-specific complications after resection is somewhat intuitive, given the ability of HAT to deliver locally effective doses with minimal systemic or regional toxicity. The finding of minimal to no inflammation in the non-tumour-bearing liver specimens provides further support for this concept. As highlighted in our group's previous report finding no difference in post-resection morbidity or mortality after neoadjuvant chemotherapy,[10] the duration and timing of pre-operative therapies are likely related to post-operative outcomes. Similarly, longer observation times after HAT may allow for assessment of tumour biology and facilitate a safer hepatectomy.

Successful downstaging of hepatocellular carcinoma with yttrium-90 HAT has been described previously.[11,12] Our group has reported on the safety of hepatic resection after yttrium-90 radioembolization for colorectal liver metastases.[2] These data expand upon prior analyses to further demonstrate the safety of hepatic resection after HAT with either yttrium-90 or drug-eluting beads in multiple disease histologies. There are limitations to this analysis, related to its retrospective nature, selection bias and the relatively small sample size in the pre-HAT group. However, to our knowledge, this comprises the largest analysis of patients undergoing HAT followed by resection reported to date.

Judicious selection of candidates for hepatic resection after HAT is critical to ensure patient safety and to maximize the potential for oncological benefit in this challenging patient population. This requires careful consideration of tumour biology (response to treatment, disease histology and progression-free interval), patient comorbidities and functional status, tumour distribution, hepatic anatomy and estimation of hepatic reserve. While this study has demonstrated a favourable safety profile in this cohort of patients undergoing pre-operative hepatic arterial therapy, further study is warranted to quantify the survival benefit associated with this novel approach.

Conflicts of interest

Robert C.G. Martin is a consultant for Biocompatibles. Partial research support was received from an unrestricted education grant from Biocompatibles.

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