Infectious Complications of Hepatic Cryosurgery

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Hepatic cryosurgery is a novel procedure for patients with metastatic liver disease. To date, no reviews of the infectious complications of this procedure have been published. One hundred and fifty patients underwent 158 hepatic cryosurgical procedures at Allegheny General Hospital (Pittsburgh) from November 1987 through July 1995. Gastrointestinal malignancies accounted for 93% of the underlying diagnoses. The following 12 infections were directly related to the cryosurgical procedure: hepatic abscess (six), intraperitoneal abscess (three), ascending cholangitis (two), and an intrahepatic device (Infusaid; Strato/Infusoid, Norwood, MA) infection (one). Enterococcus was the most commonly isolated organism. Seven of the 12 infections were polymicrobial. The patients who developed infections had longer hospital stays (26 days vs. 13 days) and had more days of fever (6.5 days vs. 2.3 days), than those who did not develop infections. If perioperative manipulation of the biliary tree is avoided, the infection rate in patients who undergo hepatic cryosurgery may be decreased even further. Overall, cryoablation of the liver is not related to an increased risk of infection.

Cryosurgery of the liver is an innovative technique that uses multiple freeze/thaw cycles to ablate hepatocellular carcinoma and other malignancies metastatic to the liver. A significant advantage of cryosurgery over hepatic resection is the ability to destroy multiple lesions without sacrificing large areas of uninvolved liver as well as extended survival for patients with hepatic metastasis [1-6]. To date, the infectious complications of hepatic cryosurgery have not been reviewed, and the fact that infectious complications are rare or absent has not been discussed in detail [4, 7]. We report the infectious complications that occurred in 150 patients who underwent cryosurgery of the liver at Allegheny General Hospital (Pittsburgh).

Patients and Methods

One hundred and fifty-six patients underwent 164 hepatic cryosurgical procedures between November 1987 and July 1995 at Allegheny General Hospital, a 740-bed tertiary care center in Pittsburgh. Medical records were available for 150 of the patients. Eighty patients underwent hepatic cryosurgery twice. Most of the patients were men (63%). The mean age of the patients was 61 years. In most cases (93%), the underlying disease process was a gastrointestinal malignancy, with colon carcinoma accounting for 85% of the malignancies. Other malignancies included sarcoma (4%), carcinoid (4%), uterine or ovarian carcinoma (3%), and renal cell carcinoma (1%).

The procedures were performed by four surgeons who used similar techniques, as previously described [6, 8, 9]. The liver was directly inspected, and intraoperative ultrasound was used to visualize the metastases and their proximity to vascular structures. Ultrasound stereotactic guidance was then used to place the cryoprobe directly into the tumor. One-to-three freeze-thaw cycles were used on each lesion. The frozen tracts were then packed with gelatin foam to control bleeding. On average, each patient had two lesions cryoablated. Infusaid pumps were placed in 10 patients at the time of surgery.

Endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography was performed if biliary tract involvement was suspected. In 1993, this practice was discontinued as a routine procedure for patients with biliary tract involvement. Perioperative antibiotics were prescribed by the surgeons. The patients were observed daily by the surgeons. An infectious disease specialist was consulted for persistent fevers or evidence of infection. All charts were then retrospectively reviewed for infectious complications, antibiotic use, and development of fever. Standard Centers for Disease Control and Prevention (CDC; Atlanta) definitions of infection were applied. Each case was presented to three different infectious disease specialists (D.K.R., T.J.B., and E.B.R.) for documentation of infection.

Data were analyzed with use of EpiInfo version 5 (CDC). Categorical values were compared by Fisher’s exact test or the χ² test. Continuous variables were compared with use of Student’s t-test. All P values were two-tailed. A P value of <.05 was considered statistically significant.

Results

A total of 19 infections occurred following 158 procedures (12%). Of these infections, 12 (7.6%) were related directly to
the hepatic cryosurgery. The infections related to the cryosurgical procedure included hepatic abscesses (six patients), ascending cholangitis (three), intraabdominal abscesses (two), and Infusaid pump (Strato/Infusaid, Norwood, MA) infection (one) (table 1). Most infections occurred within the first 3 weeks after surgery (range, 10–251 days). Six patients died during hospitalization. For one of the six, infection was secondary to multiorgan failure related to malignancy.

Seven of the infections were polymicrobial. *Enterococcus* species was isolated most frequently from five infections and was the sole isolate obtained in two infections. Enteric gram-negative rods were isolated from four of the infections, including *Enterobacter cloacae, Klebsiella pneumoniae, and Escherichia coli*. Anaerobes were isolated from four of the infections. All the infections were treated with drainage and a variety of antibiotic regimens (table 1). After initial analysis of the infections, manipulation of the bile duct either by cholangiogram or an endoscopic procedure was eliminated as a routine follow-up procedure in patients with biliary tract involvement. There were no infectious complications in the 25 cases in which cryosurgery was performed after this intervention was eliminated (12 of 133 vs. 0 of 25; *P* = NS).

The patients who developed infections tended to be older than the patients who did not develop infections (65 years old vs. 60 years old; *P* = NS), and most of the patients with infections had underlying colon carcinoma. The patients with infections had an average of 6.5 days of fever (range, 0–12 days), whereas the patients who did not develop infections had an average of 2.3 days of fever (range, 0–21 days) (*P* < .001); in addition, the patients with infections had longer hospital stays than the patients who did not develop infections (26 days vs. 13 days, *P* < .001). However, even patients who were not infected had 2 days of fever, most likely secondary to the procedure.

Prophylactic antibiotic use was similar among both groups. Most patients received one of three regimens as perioperative

### Table 1. Features of 12 patients with infections related to hepatic cryosurgery.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (y)/sex</th>
<th>Site or type of primary malignancy</th>
<th>Site or type of infection</th>
<th>Empirical or prophylactic antibiotics</th>
<th>Organism isolated</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65/F</td>
<td>Colon</td>
<td>Hepatic abscess</td>
<td>Cefotetan</td>
<td><em>Staphylococcus epidermidis</em></td>
<td>Drainage alone</td>
</tr>
<tr>
<td>2</td>
<td>65/F</td>
<td>Colon</td>
<td>Hepatic abscess</td>
<td>Cefotetan</td>
<td><em>Enterobacter cloacae</em></td>
<td>Intravenous cefotetan (×7 d)</td>
</tr>
<tr>
<td>3</td>
<td>74/M</td>
<td>Colon</td>
<td>Hepatic abscess</td>
<td>Cefotetan</td>
<td><em>Enterococcus species</em></td>
<td>Intravenous piperaclillin and gentamicin (×7 d); oral amoxicillin</td>
</tr>
<tr>
<td>4</td>
<td>55/M</td>
<td>Colon</td>
<td>Hepatic abscess</td>
<td>Cefotetan, metronidazole</td>
<td><em>E. cloacae</em></td>
<td>Intravenous imipenem (×8 d); oral TMP-SMZ</td>
</tr>
<tr>
<td>5</td>
<td>50/F</td>
<td>Colon</td>
<td>Hepatic abscess</td>
<td>Ampicillin, gentamicin, metronidazole</td>
<td><em>Klebsiella pneumoniae</em></td>
<td>Intravenous ampicillin, gentamicin, and metronidazole (×5 d); oral amoxicillin and doxycycline</td>
</tr>
<tr>
<td>6</td>
<td>67/M</td>
<td>Colon</td>
<td>Hepatic abscess</td>
<td>Cefotetan, metronidazole</td>
<td><em>Clostridium perfringens</em></td>
<td>Intravenous cefotetan (×5 d); oral amoxicillin and doxycycline</td>
</tr>
<tr>
<td>7</td>
<td>63/M</td>
<td>Colon</td>
<td>Bile duct obstruction</td>
<td>Ampicillin, gentamicin, metronidazole</td>
<td>Viridans streptococci</td>
<td>Intravenous ampicillin/ sulbactam (×5 d); oral TMP-SMZ</td>
</tr>
<tr>
<td>8</td>
<td>50/F</td>
<td>Colon</td>
<td>Bile duct obstruction</td>
<td>Ampicillin, gentamicin, metronidazole</td>
<td><em>Propionibacterium species</em></td>
<td>Intravenous cefotetan (×2 d); oral ciprofloxacin</td>
</tr>
<tr>
<td>9</td>
<td>72/F</td>
<td>Colon</td>
<td>Cholangitis</td>
<td>Ampicillin, gentamicin, metronidazole</td>
<td><em>E. cloacae</em></td>
<td>Intravenous ampicillin/ sulbactam (×24 d)</td>
</tr>
<tr>
<td>10</td>
<td>69/F</td>
<td>Leiomyoscarcoma</td>
<td>Intraabdominal abscess</td>
<td>Cefotetan</td>
<td><em>Staphylococcus aureus</em></td>
<td>Intravenous vancomycin (×12 d)</td>
</tr>
<tr>
<td>11</td>
<td>73/M</td>
<td>Colon</td>
<td>Intraabdominal abscess</td>
<td>Ampicillin, gentamicin, metronidazole</td>
<td><em>Viridans streptococci</em></td>
<td>Intravenous ceftazidime and metronidazole (×12 d); oral TMP-SMZ</td>
</tr>
<tr>
<td>12</td>
<td>77/M</td>
<td>Hepatocellular</td>
<td>Infusaid pump</td>
<td>Cefotetan</td>
<td><em>S. aureus</em></td>
<td>Intravenous nafcillin (×8 d)</td>
</tr>
</tbody>
</table>

**NOTE.** TMP-SMZ = trimethoprim-sulfamethoxazole.
antibiotics: cefotetan alone (49 patients, 33%), cefotetan and metronidazole (44 patients, 20.9%), or ampicillin, gentamicin, and metronidazole (42 patients, 20.8%). The total duration of empirical antibiotics therapy was similar among the two groups (5.5 days for the patients with infections compared with 4.5 days for the patients who did not develop infections; \( P = \text{NS} \)).

Seven infections that were not directly associated with the cryosurgical procedure occurred in five patients. These infections included *Clostridium difficile* colitis, an enterococcal wound infection, a urinary tract infection, *Serratia marcescens* bacteremia (noted at autopsy in the patient who died of multiorgan failure related to his malignancy), *Stenotrophomonas maltophilia* bacteremia, and a *Staphylococcus aureus* line infection and subsequent endocarditis.

### Conclusions

Hepatic cryosurgery is a relatively new procedure for cancer patients with liver metastases. Since previous reports have not discussed the infectious complications of hepatic cryosurgery, we report the infections related to this procedure.

Hepatic abscess and cholangitis were the most common infections related to hepatic cryosurgery, and *Enterococcus* was the most commonly isolated organism. In more than one-half of the cases, the infections were polymicrobial; Enterobacteriaceae, anaerobes, and skin flora were isolated along with *Enterococcus* species. Most of the infections responded well to antibiotic therapy and drainage, with only one death secondary to multiorgan failure.

The patients who developed infections were older, had longer hospital stays, and had more days of fever. Infection was not associated with the type of malignancy, the number of liver lesions ablated, the duration of empirical antibiotic therapy, or the type of antibiotics used.

Initially, manipulation of the biliary tree was performed if biliary tract involvement was present or to assess the effects of cryoaablation on the biliary tract. This practice changed after it was realized that cryosurgery did not compromise the biliary system and that patients who had biliary tree manipulation seemed to have a higher incidence of infection. Once the manipulation of the bile ducts was eliminated, no procedure-related infections occurred.

In conclusion, hepatic cryosurgery has a relatively low infection rate. The most common procedure-related infection is hepatic abscess. If manipulation of the bile ducts can be avoided, the infection rates are similar to those of other intraabdominal operations. By decreasing the infection rate, the length of stay in the hospital can be decreased, ultimately lowering the cost of the procedure.

### References