Liver abscess after radiofrequency ablation of tumors in patients with a biliary tract procedure

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SUMMARY

Aim — The rate of liver abscesses after radiofrequency ablation (RFA) of liver tumors is probably high in patients with a biliary tract drainage procedure connecting the biliary duct system to the upper gastrointestinal tract. And yet, to date this rate, the time of onset of these abscesses, and the prior status of the bile ducts have never been reported in the literature.

Methods — Among 574 patients treated with RFA over 8 years, only 11 patients (with 13 sessions of RFA, 2 patients undergoing two different RFA sessions) presented with an enterobiliary anastomosis or biliary stenting at the time of RFA. This is a retrospective study of patients who were verified prospectively.

Results — Among the 9 patients in whom a biliary tract procedure preceded RFA, 4 developed a liver abscess at the site of RFA, which emerged between 13 and 62 days after RFA. It occurred in spite of different types of short-term antibiotic prophylaxis. Pathogenic bacteria were typical of the digestive flora. Abscesses were cured after percutaneous drainage. No abscess occurred among the 4 patients in whom a biliary tract diversion was performed synchronously with RFA.

Conclusion — When RFA is performed in a patient with a preexisting biliary diversion, the risk of developing a liver abscess is high. Currently, we are unable to recommend any kind of preventive anti-biotherapy. A preexisting biliary diversion is not an absolute contraindication for RFA, but the risk of developing a liver abscess is close to 40-50%. When RFA is performed synchronously with a biliary diversion, the risk of a liver abscess seems to disappear.

Results — Among the 9 patients who were porteurs d’une dérivation bilio-digestive, 4 ont développé un abcès sur le site du traitement, diagnostiqué entre 13 et 62 jours. Ces abcès sont survenus malgré l’utilisation de plusieurs types de courtes antibio-prophylaxies. Les bactéries pathogènes étaient toujours de type digestif. Les abcès ont été traités avec succès par drainage percutané. Aucun abcès n’est survenu chez les 4 patients qui ont eu une dérivation bilio-digestive synchronisée à la RF.

Conclusion — Quand une destruction par RF est réalisée chez un malade porteur au préalable d’une dérivation bilio-digestive, le risque d’abcès hépatique est élevé. Actuellement nous ne pouvons pas recommander un type particulier d’antibio-prophylaxie. Une dérivation biliaire préexistante n’est pas une contre indication absolue à un traitement par RF, mais le risque d’abcès est compris entre 40 et 50 % dans ce cas. Par contre, quand la RF est réalisée au même moment que la dérivation biliaire, le risque d’abcès semble très faible.

Introduction

Radiofrequency ablation (RFA) of liver tumors is widely used to treat unresectable tumors. The risk of developing a post-RFA liver abscess is very low, i.e. less than 0.3% [1-4]. However, when we consider the few cases of post-RFA liver abscesses reported in the literature, and based on our own experience, clearly a high percentage of them occurred in patients having undergone a biliary tract drainage procedure (enterobiliary anastomosis or biliary stenting or sphincterotomy). However, there is no report on the exact risk of developing a liver abscess in this setting, or indicating the timing (metachronous or synchronous) of RFA in relation to the biliary tract drainage procedure, nor the time of onset of such abscesses.

The aim of this study was to analyze the 13 RFA sessions performed in our Institute in 11 high-risk patients because they had previously undergone a biliary drainage procedure.

Methods

Thirteen RFA procedures in 11 patients were retrospectively selected in a prospective data base. The selection criteria were: RFA performed in a liver with retrograde enteric bacterial contamination of the bile ducts, secondary to an enterobiliary anastomosis or a stent (none of our patients had previously undergone a sphincterotomy). They represented 1% (5/383) of the 383 patients treated percutaneously with RFA and 4%
RFA was used because liver tumors were unresectable despite our awareness of the high risk of a secondary liver abscess against which patients systematically received the prophylactic antibiotic therapy detailed in Table I. The origin of the liver tumors and the treatments used are reported in Table I. In two cases, we used an unconventional transcutaneous RFA procedure to treat a solitary liver metastasis from an adenocarcinoma of the pancreas, which appeared two years after pancreatic resection.

RFA was synchronous with the enterobiliary anastomosis in four patients. In addition, two of these 4 patients underwent a second RFA procedure during the second phase of a two-stage hepatectomy, i.e., after the enterobiliary anastomosis (Table II). RFA was performed after the enterobiliary anastomosis or stenting in 9 cases. The mean time between these late RFA procedures and the enterobiliary anastomosis or stent insertion was 27 months (range: 1-132). Finally, 13 RFA sessions (unique or multiple) were performed in 11 patients to treat 41 tumors (Table II). The impact on the main biliary ducts, the type of RFA method used (percutaneous or laparoscopic), the number of RF ablated tumors, and the occurrence of liver abscesses are reported in Table II.

The indications for RFA followed the usual recommendations: unresectable liver metastases measuring less than 30 mm in diameter, and located more than 1 cm away from a central bile duct. RFA were performed using either the Cool-tip™ RF system (Radionics, Burlington, MA, USA), or the expandable (deployed multiple-array needles) LeVeen Needle Electrode™ (Radiotherapeutics, Mountain View, CA, USA).

Table I. – Details of the treatments. Antibiotic prophylaxis and nature of the abscesses.

<table>
<thead>
<tr>
<th>Case</th>
<th>Primary</th>
<th>Details of the treatments</th>
<th>Antibiotic Prophylaxis</th>
<th>Post-RFA Abscess</th>
<th>Microorganisms in abscess</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Endocrine</td>
<td>CPD + 2 RFA</td>
<td>D0 : Ceftriaxone (2g) + Metronidazole (1 g)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Endocrine</td>
<td>D0 : CPD + in the left liver : 4 wedges + 12 RFA</td>
<td>D0 : Ceftriaxone (2g) + Metronidazole (1g)</td>
<td>No</td>
<td>Enterococcus + E. coli</td>
</tr>
<tr>
<td>3</td>
<td>Pancreas</td>
<td>D15 : Right hepatic arterial embolization</td>
<td>D15 : Piperacillin-tazobactam (4g x 2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Pancreas</td>
<td>D45 : Right portal vein embolization</td>
<td>D45 : Piperacillin-tazobactam (4g x 2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Pancreas</td>
<td>D76: Right hepatectomy + 2 left RFA</td>
<td>D76-80 : Piperacillin-tazobactam (4g x2)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Endocrine</td>
<td>D0 : CPD + in the left liver : 2 wedges + 9 RFA</td>
<td>D0 : Ceftriaxone (2g) + Metronidazole (1g)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Pancreas</td>
<td>D36 : Right portal vein embolization</td>
<td>D36 : Coamoxiclav (1g)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Pancreas</td>
<td>D71: Right hepatectomy + 4 left RFA</td>
<td>D71 : Ceftriaxone (2g) + Metronidazole (1g)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Adenocarcinoma</td>
<td>1994: CPD + 3 distal portocaval anastomosis</td>
<td>D0 : Ceftriaxone (2g) + Metronidazole (1g)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Pancreas</td>
<td>2004: Coeliac lymphadenectomy + Left lobectomy + 1 RFA</td>
<td>D0-D4 : Piperacillin-tazobactam (4g x 2)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Endocrine</td>
<td>1998: CPD</td>
<td>D0 : Ceftriaxone (2g) + Metronidazole (1g)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Pancreas</td>
<td>2002: 2 Percutaneous RFA</td>
<td>D0 : Ceftriaxone (2g) + Metronidazole (1g)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Adenocarcinoma</td>
<td>1999: CPD</td>
<td>D0 : Ceftriaxone (2g) + Metronidazole (1g)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Pancreas</td>
<td>2001: 1 Percutaneous RFA.</td>
<td>D0-D4 : Coamoxiclav (3g) + Amikacin (600mg)</td>
<td>Yes</td>
<td>E. Coli + E. Faecalis</td>
</tr>
<tr>
<td>15</td>
<td>Adenocarcinoma</td>
<td>1998: CPD</td>
<td>D0 : Ceftriaxone (2g) + Metronidazole (1g)</td>
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<td></td>
</tr>
<tr>
<td>16</td>
<td>Pancreas</td>
<td>2000: 1 Percutaneous RFA</td>
<td>D0 : Ceftriaxone (2g) + Metronidazole (1g)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Adenocarcinoma</td>
<td>2000: Right hepatectomy + 6 months: Biliary Stent</td>
<td>D0 : Ceftriaxone (2g) + Metronidazole (1g)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Colon</td>
<td>8 months: Percutaneous RFA</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Adenocarcinoma</td>
<td>1999: Central hepatectomy</td>
<td>D0 : Ceftriaxone (2g) + Metronidazole (1g)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Colon</td>
<td>2001: Biliary Stent</td>
<td>D0 : Ceftriaxone (2g) + Metronidazole (1g)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>2002: 1 Percutaneous RFA</td>
<td>D0-D4 : Piperacillin-tazobactam (4g x 2)</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Cholangiocarcinoma</td>
<td>2001: Left trisectoriectomy + biliary reconstruction + 2 wedges + 1 RFA</td>
<td>D0 : Ceftriaxone (2g) + Metronidazole (1g)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Neurosarcoma</td>
<td>2001: 4 wedges</td>
<td>D0 : Not specified (other hospital)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>2002: 1 wedge + 3 RFA</td>
<td>D0 : Not specified</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>2003: Biliary Stent</td>
<td>D0 : Not specified</td>
<td>No</td>
<td></td>
<td></td>
</tr>
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<td>26</td>
<td>2004: Right hepatectomy + biliary reconstruction + 2 RFA</td>
<td>D0 : Centamycin (80 mg) + Clindamicin (1.2g)</td>
<td>Yes</td>
<td>E. Faecalis</td>
<td></td>
</tr>
</tbody>
</table>

**Table II. –** Timing of biliary tract drainage procedure and onset of abscess

Four patients developed a liver abscess at the site of RFA after the 13 procedures (31%). The diagnosis was made with the association of fever plus imaging plus drainage results. These liver abscesses were treated successfully with percutaneous drainage, and appropriate antibiotics after bacterial examination and culture of abscess liquid when patients had a temperature.

**Results**

**Prophylactic antibiotics (table I)**

The antibiotics administered evolved over the 8 years of the study. In most cases, it consisted of only one injection of ceftriaxone before pancreaticoduodenectomy and hepatectomy, and metronidazole, just as surgery was about to begin. During the last three years, we used piperacillin/tazobactam alone for 5 days (D0-D4) in three patients.

**Rate of Post-RFA liver abscesses (table II)**

Among the 4 patients who underwent RFA synchronously with the enterobiliary anastomosis, none (0%) developed an abscess.
abscess. In contrast, of 9 patients who underwent RFA following an enterobiliary anastomosis or biliary stent insertion, 4 (44%) developed an abscess.

Abscess development (table II)
After RFA, liver abscesses appeared at day 13, 33, 40 and 62, respectively.

Bacterial examination of abscesses (table II)
In the four cases, germs were typically of a digestive origin, mainly Enterococcus faecalis and Escherichia coli.

Discussion
Currently, the risk of developing a liver abscess after RFA in case of bacterial colonization has not really been estimated. The risk was 44% in this series when biliary drainage procedures existed prior to RFA but 0% when the biliary drainage was performed synchronously with RFA. This was observed in the absence of any systematic and thoughtful policy of prophylactic antibiotics.

The risk of developing a liver abscess is very low when one considers the large series of liver tumors treated with RFA. In their review of 2 320 patients treated with RFA, Livraghi et al. [1] reported only 6 abscesses (0.3%), 2 of which arose in patients with an enterobiliary anastomosis. Mulier et al. [2] reviewed 1931 patients and reported 20 hepatic abscesses (0.1%) and Decadt et al. [3] reviewed 1 902 patients and reported 1 5 hepatic abscesses (0.08%). Finally, in our series [4] that the rate of liver abscesses was the highest: 1.3% among 312 patients, because we were less stringent about indications in case of an associated biliary drainage procedure, and three of them had occurred in patients with an enterobiliary anastomosis.

These current series show that the risk increased when there was an enterobiliary anastomosis, but without reporting the degree of risk. The same pattern has been reported with other types of local tumor destruction, for example, percutaneous ethanol injection and arterial chemoembolization [5, 6]. All these destruction procedures result in necrotic tissue which usually remains aseptic, but which could become secondarily infected in the presence of infected bile ducts.

After a previous biliary drainage procedure, the risk of developing a liver abscess increases considerably, even without RFA. This was underlined by Warren et al. [7] as early as 1968, who reported that among 20 patients presenting a liver abscess, 18 had previously undergone a biliary drainage procedure. Subsequently many series reported the same ascertainment after enterobiliary anastomosis [8, 9], after biliary stents [10, 11] and after sphincterotomy [12-14], but the rate of liver abscesses was below 10% [9-14], far less than the 44% in our present series in which RFA produces a necrotic zone inside the liver.

Chronic bacterial colonization of the biliary tree constantly occurs after biliary-digestive anastomotic procedures [15-17]. Such procedures include enterobiliary anastomosis, biliary stent insertion, and sphincterotomy. Massive bacterial colonization of an hepaticojejunostomy was demonstrated as early as 1 week after bile duct reconstruction [15]. Moreover, in a porcine model, bacterial concentration inside the liver was found to be high 1 week after a Roux-en-Y hepaticojejunostomy, and decreased progressively over 2 months to become two-fold lower [16]. This was associated with chronic inflammation around the portal area on pathological specimens [16]. Most of the infectious pathogens isolated from the liver were also isolated from the hepaticeojenoostomy [16]. Finally, chronic bacterial colonization in a post-RFA zone of necrosis results in the colonization of the necrosis by the bacteria and abscess formation.

It is surprising to note that no post-RFA abscess occurred when the biliary tract procedure was synchronous with RFA, although it has been documented that the biliary tree is rapidly and massively colonized with pathogens [16]. This colonization probably occurs much later or the colonization process is not chronic enough to be considered risky, or the usual short-term
preoperative antibiotic prophylaxis is sufficient to cover the high-risk period. On the other hand, even when antibiotic prophylaxis is prolonged for 5 days, it does not appear to be efficient in preventing post-RFA abscesses if the patient has previously undergone biliary drainage. In addition, we must emphasize that the post-RFA abscesses appeared between 10 and 62 days after RFA. We can therefore postulate that short-term antibiotic prophylaxis is not sufficient to prevent abscesses in case of a preexisting biliary procedure but at the same time we know that prolonged and blind antibiotic prophylaxis is more dangerous than useful.

In fact, at present, we do not know when and why a post-RFA liver abscess occurs on necrosis colonized by the pathogens from the bile ducts. The following questions remain unanswered: Is there a particular high-risk period? What is its timing and duration? Is there an impact of the concentration of the pathogens inside the bile ducts? Are pathogens particularly aggressive? Is there a selection of resistant pathogens after antibiotic prophylaxis? Is there a particular pathologic pattern of chronically colonized bile ducts? Do pathogens have a predilection for the chronic inflammation of the biliary system? Is there a particular pathological pattern of destruction of the bile ducts after RFA? Considering this last question, it was depicted on imaging that bile duct lesions in an animal model were far more extensive than just the area destroyed by RFA [18].

The microorganisms cultured from our 4 patients were enterobacteriaceae (namely Escherichia Coli, Proteus vulgaris), enterococci and/or anaerobes. No pathogens with a well-recognized tendency to form abscesses, i.e. Klebsiella sp. or Streptococcus intermedius, were isolated. Thus, the pathogens do not appear to be particularly aggressive.

The role of antibiotic prophylaxis is difficult to assess in our series. In fact, its modalities were unknown in 1 patient, and were atypical (clindamycin + gentamicin) in another patient due to severe allergy. In 1 patient, microorganisms subsequently isolated in the abscess were completely sensitive to the prophylactic antibiotics (piperacillin/tazobactam) employed. In the last patient, who received coamoxiclav and amikacin, culture of the abscess grew E. coli and wild E. faecalis which were resistant to coamoxiclav.

Attempts to prevent liver abscesses with prophylactic antibiotics have been extensively reported in the literature but have not met with much success in preventing their occurrence in patients undergoing intra-arterial chemoembolization and percutaneous ablation therapy. A good example is the study by Shibata et al. [5] who reported their results of 358 patients with a percutaneous ethanol injection, microwave coagulation or RFA between 1995 and 2002. Initially, the patients did not receive prophylactic antibiotics, but when they observed that liver abscesses were occurring frequently (1.5%), they systematically administered 1g of cefazolin or cefmetazole every 12 hours, after July 2000, from the day before ablation until the patient was discharged from hospital. They did not however, observe a lower rate of liver abscesses in the group treated with prophylactic antibiotics. A microbiological analysis of bile in stented patients was systematically performed [19-22]. The frequency of polymicrobial infection ranged from 50 to 90%. The most frequent organisms were Escherichia Coli and Enterococci, followed by Klebsiella and Streptococcus viridans. Then, the following were also observed, but to a lesser extent: Morganella morganii, Staphylococcus epidermidis, Bacteroides fragilis, and a fungal infection with Candida albicans [19-22]. Antibiotic prophylaxis encompassing this large spectrum of pathogens is difficult to devise. Recently, two short reports were published on empirical antibiotic therapy with a single agent (piperacillin/tazobactam) to prevent liver abscesses in such patients [23, 24]; it should be effective in 80% of cases. Indeed, this single-agent therapy exhibited a broad spectrum of activity, and had demonstrated its effectiveness as a single empirical agent in high-risk, febrile neutropenic patients with cancer [25]. Recently we used piperacillin/tazobactam in three patients (with RFA being performed later than the biliary drainage procedure) for 5 days and observed one abscess which was diagnosed at day 33. We could conclude that this empirical prophylactic therapy is not efficient, but the number of patients is very low.

Based on our study, when RFA is performed synchronously with an enterobiliary anastomosis, there is no reason to modify the usual preoperative antibiotic therapy for digestive surgery (ceftriaxone plus metronidazole) because we did not observe any abscesses.

In conclusion, if a biliary drainage procedure is performed prior to RFA, the risk of developing a post-RFA liver abscess is very high, and the abscess can arise much later (up to 2 months after RFA). No empirical antibiotic prophylaxis can be proposed as an effective preventive measure. A high risk of infection can be expected in the weeks following the procedure, and liver US or CT scans should be performed regularly so that the abscess can be diagnosed and treated early. If the biliary procedure is performed simultaneously with RFA, the risk of a post-RFA abscess is zero.

REFERENCES


