Review

Complications of radiofrequency coagulation of liver tumours

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Background: Radiofrequency coagulation (RFC) is being promoted as a novel technique with a low morbidity rate in the treatment of liver tumours. The purpose of this study was to assess critically the complication rates of RFC in centres with both large and limited initial experience, and to establish causes and possible means of prevention and treatment.

Methods: This is an exhaustive review of the world literature (articles and abstracts) up to 31 December 2001; 82 independent reports of RFC of liver tumours were analysed.

Results: In total, 3670 patients were treated with percutaneous, laparoscopic or open RFC. The mortality rate was 0·5 per cent. Complications occurred in 8·9 per cent: abdominal bleeding in 1·6 per cent, abdominal infection in 1·1 per cent, biliary tract damage in 1·0 per cent, liver failure in 0·8 per cent, pulmonary complications in 0·8 per cent, dispersive pad skin burn in 0·6 per cent, hepatic vascular damage in 0·6 per cent, visceral damage in 0·5 per cent, cardiac complications in 0·4 per cent, myoglobinaemia or myoglobinuria in 0·2 per cent, renal failure in 0·1 per cent, tumour seeding in 0·2 per cent, coagulopathy in 0·2 per cent, and hormonal complications in 0·1 per cent. The complication rate was 7·2, 9·5, 9·9 and 31·8 per cent after a percutaneous, laparoscopic, simple open and combined open approach respectively. The mortality rate was 0·5, 0, 0 and 4·5 per cent respectively.

Conclusion: The morbidity and mortality of RFC, while low, is higher than previously assumed. With adequate knowledge, many complications are preventable.

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Introduction

Radiofrequency coagulation (RFC) is one of several competing interstitial therapies that have recently been developed for the focal treatment of inoperable liver tumours. The purpose of this study was to assess the nature and the rate of complications, including mortality, of RFC of liver tumours from centres with both large and limited initial experience. It was also hoped to establish causation and to comment on prevention and treatment.

Patients and methods

An exhaustive *Current Contents* search was carried out for the period from 1 January 1990 to 31 December 2001 using the keywords '(radiofrequency, radio-frequency or radio frequency) and (liver or hepatic or hepatocellular)' without exclusion of any language. All abstract books from the same period published in *Radiology*, *American Journal of Radiology*, *Journal of Vascular and Interventional Radiology*, *European Radiology* and *Surgical Endoscopy* were searched manually. Furthermore, relevant papers were identified from the reference lists of papers previously obtained through the search. Abstracts from recent international meetings were also analysed. Short reports were not excluded. The authors of one recent large study were contacted for more details concerning their abstract[1].

In cases where the patient population of two or more reports overlapped, only the most detailed report was retained. Reports describing complications without specifying the size of the patient population were excluded from the calculation of global and specific complication rate, but were still included in the discussion of each type of

The Editors have satisfied themselves that all authors have contributed significantly to this publication

complication. Common side-effects of RFC, such as pain, fever and nausea (the post-RFC syndrome, present in 87 per cent of patients[2]), as well as an asymptomatic right pleural effusion[3], were not regarded as complications.

Results

Eighty-two reports[1,4–84] were included in the analysis. In total, 3670 patients were treated with percutaneous, laparoscopic or open RFC. The overall complication rate was 8·9 per cent (*Table 1*). The mortality rate was 0·5 per cent (*Table 2*). The complication rate was similar for the percutaneous (7·2 per cent), laparoscopic (9·5 per cent) and simple open (9·9 per cent) approaches (*Table 3*). However, patients treated by open RFC combined with cryotherapy, hepatic or extrahepatic resection had a much higher morbidity rate (31·8 per cent). The mortality rate was 0·5, 0, 0 and 4·5 per cent respectively.

Bleeding

Clinically significant intraperitoneal bleeding after RFC occurred in 24 instances, one of which was fatal[1]. Bleeding was not limited to treatment of hepatocellular carcinoma (HCC)[19,53,55,62,85], but occurred also in liver metastases[18,73,74]. It originated from an incompletely coagulated subcapsular tumour, from a bleeding electrode track, from a tear in the liver parenchyma[53], from a hepatic rupture due to an intrahepatic haematoma[10] or from delayed rupture of a hepatic artery pseudoaneurysm[86]. Treatment was mainly conservative; one embolization[86] and four surgical interventions[10,18,53,62] were described. Bleeding did not occur in any of 278 patients after cauterization of the electrode track, but occurred in ten (0·9 per cent) of 1154 patients who had no cauterization. It occurred in one (0·3 per cent) of 332 patients after open and laparoscopic procedures, and in 22 (0·8 per cent) of 2898 after percutaneous procedures. No bleeding was noted in 26 patients in whom the track was filled with gelatin sponge[5,43].

Intrahepatic and subcapsular haematoma

A subcapsular haematoma (*Fig. 1*) was most often found after RFC of subcapsular tumours[41,55]. Intrahepatic (*Fig. 1*) and subcapsular haematoma occurred after treatment of both HCC[20,55] and liver metastases[30,41,47,74]. Treatment of this complication was mainly conservative, with therapeutic embolization described in three patients[20,25,41] and surgery in two[10,81].

Hepatic abscess

Thirty-four hepatic abscesses (*Fig. 2*.), two of which were fatal[1,81], have been reported after RFC[1,9,15,22,32,33,46,81,84]. One abscess developed only after 5 months[81,87]. Treatment consisted of percutaneous drainage and intravenous antibiotics[33,81,84,88]. At least eight patients who developed an abscess had an alteration of the biliary system: four had a biliary stent[9,22], three a bilioenteric anastomosis[22,33], and one a bile duct stricture[81].

Peritoneal infection

One fatal case of *Staphylococcus aureus* peritonitis[53] and one fatal case of infected ascites[80] were reported. The former complication was attributed to a disruption of sterile technique.

Biliary tract damage

A biliary stricture was reported in 18 patients[1,10,14,16,22,56,81,84], one of whom died[1]. Seven peripheral strictures[14,16,22] were clinically asymptomatic. Central biliary strictures complicating RFC of hilar tumour[16,56,81,84,89,90] cause cholestasis and require a stent[56,81,84,89]. Strictures may be complicated by an abscess[81], a biliovenous fistula[16], or lead to partial hepatic atrophy[16]. Strictures may become evident as late as 4 months after RFC[56]. There were seven biliomas[1,16,64,70] and six cases of bilioperitoneum[10,22,32]. Three of the bile leaks were attributed to a direct electrode injury of the main bile ducts[10]. Three reports of haemobilia were found[30,53,84], one starting during RFC[91] and another occurring 6 days after the procedure[30]. Other biliary tract damage included a biliocutaneous fistula[5] and a fatal bile leak into the chest[32]. The rate of biliary complications was similar in patients treated by RFC without a Pringle manoeuvre (25 (0·8 per cent) of 3227)[1,5,10,14,22,30,32,53,70,81] and with a Pringle manoeuvre (one (0·6 per cent) of 159)[26,34,37,46,56,59,92,93].

Liver failure

Seven instances of fatal liver failure were reported[1,10,15,22,64,81]. Four were due to central vascular thrombosis[1,22,64] and three to overestimation of liver reserve[1,10,81]. A transient mild deterioration of liver function was noted in 22 patients[10,12,20,27,47,58,59,64,66]. Child–Pugh grade increased by one to three points but returned to the preprocedural value within 2 weeks in most, but not all, patients.

Table 1 Complications of radiofrequency coagulation in 3670 patients

Complication	No. of patients	References
Abdominal bleeding	60 (1·6)	
Intraperitoneal bleeding	24 (0·7)	1, 9, 10, 18, 19, 22, 38, 53, 55, 62, 73, 74
Intrahepatic haematoma	6 (0·2)	10, 20, 25, 30, 39
Subcapsular haematoma	20 (0·5)	5, 9, 20, 22, 32, 41, 47, 55, 74, 81
Abdominal wall bleeding	1 (0·0)	20
Abdominal wall haematoma	6 (0·2)	20, 48, 58
Non-specified haematoma	3 (0·1)	15, 46
Abdominal infection	42 (1·1)	
Hepatic abscess	34 (0·9)	1, 9, 15, 22, 32, 33, 46, 81, 84
Wound infection	4 (0·1)	10, 56, 64
Peritoneal infection	2 (0·1)	53, 80
Unspecified sepsis	2 (0·1)	1
Biliary tract damage	38 (1·0)	
Biliary stricture	18 (0·5)	1, 10, 14, 16, 22, 56, 81, 84
Bilioma	7 (0·2)	1, 16, 64, 70
Bilioperitoneum	6 (0·2)	10, 22, 32
Haemobilia	3 (0·1)	30, 53, 84
Biliovenous fistula	2 (0·1)	16
Biliocutaneous fistula	1 (0·0)	5
Biliopleural fistula	1 (0·0)	32
Liver failure	29 (0·8)	
Fatal liver failure	7 (0·2)	1, 10, 15, 22, 64, 81
Mild liver failure	22 (0·6)	10, 12, 20, 27, 47, 58, 59, 64, 66
Pulmonary	29 (0·8)	
Pneumothorax	10 (0·3)	1, 20, 32, 47, 49, 61
Symptomatic pleural effusion	7 (0·2)	20, 22, 53, 74
Haemothorax	5 (0·1)	1, 9, 45, 53
Pneumonia	5 (0·1)	22, 46, 64
Pulmonary embolus	1 (0·0)	64
Adult respiratory distress syndrome	1 (0·0)	15
Dispersive pad skin burn	21 (0·6)	1, 5, 10, 15, 22, 32, 34, 78
Hepatic vascular damage	22 (0·6)	
Portal vein thrombosis	9 (0·2)	1, 14, 22, 30, 46, 55, 64
Hepatic vein thrombosis	2 (0·1)	16, 32
Hepatic artery damage	9 (0·2)	1, 16, 22, 46, 66
Hepatic infarction, unspecified	2 (0·1)	15, 71
Visceral damage	19 (0·5)	
Cholecystitis	5 (0·1)	27, 53, 57, 66
Diaphragmatic burn	5 (0·1)	1, 25, 32, 54, 81
Colonic burn	2 (0·1)	32, 74
Gastric burn	1 (0·0)	1
Jejunal burn	1 (0·0)	74
Renal burn	2 (0·1)	1, 54
Abdominal wall burn	2 (0·1)	10, 81
Non-specified damage	1 (0·0)	46
Cardiac	15 (0·4)	
Arrhythmia	10 (0·3)	1, 5, 10, 20, 24, 59, 72, 81
Myocardial infarction	2 (0·1)	5, 81
Heart failure	3 (0·1)	10, 56
Myoglobinaemia and myoglobinuria	8 (0·2)	
Myoglobinaemia	3 (0·1)	70
Myoglobinuria	5 (0·1)	10
Renal failure	4 (0·1)	39, 46, 48, 81
Seeding	7 (0·2)	24, 25, 55, 74
Coagulopathy	6 (0·2)	
Thrombocytopenia	5 (0·1)	10, 56
Hypoprothrombinaemia	1 (0·0)	20
Hormonal	4 (0·1)	
Carcinoid crisis	2 (0·1)	33, 81
Hyperglycaemia	1 (0·0)	33
Addisonian crisis	1 (0·0)	33

Table 1 Continued

Complication	No. of patients	References
Miscellaneous	9 (0·2)	
Central hyperthermia	2 (0·1)	20, 48
Brachial plexopathy	2 (0·1)	70
Oesophageal variceal bleeding	1 (0·0)	55
Gastrointestinal bleeding	1 (0·0)	72
Transient ischaemic attack	1 (0·0)	1
Difficult removal of electrode	1 (0·0)	69
Pseudoaneurysm of abdominal wall	1 (0·0)	1
Unspecified, minor	14 (0·4)	53, 74
Total	327 (8·9)	

Values in parentheses are percentages

Table 2 Mortality in 3670 patients undergoing radiofrequency coagulation

Cause of death	No. of patients	References
Sepsis	7 (0·2)	
Staphylococcus aureus peritonitis	1	53
Infected ascites	1	80
Biliopleural fistula	1	32
Hepatic abscess with diaphragmatic necrosis	1	81
Hepatic abscess	1	1
S. aureus chest infection	1	46
Unspecified sepsis	1	1
Liver failure	7 (0·2)	
Portal vein thrombosis	3	1, 22, 64
Hepatic infarction	1	15
Extensive resection	1	81
Extensive coagulation	1	10
Advanced liver cirrhosis	1	1
Cardiac complications	4 (0·1)	
Carcinoid crisis	2	33, 81
Cardiac arrest	1	59
Myocardial infarction	1	5
Peritoneal haemorrhage	1 (0·0)	1
Bile duct stricture	1 (0·0)	1
Total	20 (0·5)	

Values in parentheses are percentages

Pulmonary complications

Ten pneumothoraces were noted[1,20,32,47,49,61], mostly after an intercostal percutaneous approach. Seven symptomatic pleural effusions occurred[20,22,53,74]. Five haemothoraces were due to damage of an intercostal vessel by the electrode[1,9,45,53]. On ultrasonography, gas bubbles are frequently seen in the liver veins and in the right atrium, but pulmonary gas emboli have never been reported[68,91]. Five pneumonias[22,46,64] were reported, one of which was fatal[46]. Adult respiratory distress syndrome occurred only once[15].

Dispersive pad skin burns

Twenty-one instances of, mostly, first- and second-degree but also third-degree skin burns near or under the dispersive pad have been noted[1,5,10,15,22,32,34,78] (*Fig. 3*). They occurred using Radiotherapeutics®, (Sunnyvale, California, USA)[5], RITA® (RITA Medical Systems, Mountain View, California, USA)[10,78] and Radionics® (Burlington, Massachusetts, USA)[34,90,94,95] electrodes. In most reported burns, either high power (greater than 50 W) had been used[5,34,94,95], the procedure was long (more than 10 min)[34,94,95] or only one standard dispersive pad (100 cm^2)[34,90] had been placed. Several authors mentioned disappearance[34,94] or decrease[95] of the rate of skin burns after placing more or larger pads.

Portal vein thrombosis

Nine portal vein thromboses were reported[1,14,22,30,46,55,64], three of which proved fatal[1,22,64]. Segmental portal thrombosis may remain asymptomatic[86]. Factors predisposing to portal vein damage are central location of the tumour close to the portal vein[1,64,68], compression of the vein by the tumour[96] and accidental puncture by the electrode. A higher rate of portal vein thrombosis occurred after a Pringle manoeuvre than when no such manoeuvre had been carried out. Of 3227 patients treated with RFC with normal liver blood flow, seven cases of portal vein thrombosis[1,14,22,30,55] were described (0·2 per cent of cases). In 188 patients treated with RFC with a Pringle manoeuvre[26,34,37,46,56,59,64,68,92,93], four cases of portal vein thrombosis[46,64,68] were reported (2·1 per cent of cases). A short (2–3 min) Pringle manoeuvre in the middle of the RFC procedure caused no thrombosis in a series of 92 patients[92], in contrast to four cases (4·2 per cent) in 96 patients when the manoeuvre was sustained throughout the whole RFC procedure[26,34,37,46,56,59,64,68,93].

Table 3 Complication rate of radiofrequency coagulation according to approach

	Percutaneous (n = 2898)	Laparoscopic (n = 168)	Simple open (n = 142)	Combined open* (n = 22)
Intraperitoneal bleeding	22 (0·8)	1 (0·6)	0 (0)	0 (0)
Intrahepatic haematoma	4 (0·1)	0 (0)	0 (0)	0 (0)
Subcapsular haematoma	18 (0·6)	1 (0·6)	0 (0)	0 (0)
Abdominal wall bleeding or haematoma	2 (0·1)	5 (3·0)	1 (0·7)	0 (0)
Abdominal infection	31 (1·1)	0 (0)	0 (0)	1 (4·5)
Biliary tract damage	16 (0·6)	0 (0)	6 (4·2)	1 (4·5)
Liver failure	11 (0·4)	2 (1·2)	3 (2·1)	0 (0)
Pulmonary complications	17 (0·6)	2 (1·2)	0 (0)	1 (4·5)
Pad skin burn	18 (0·6)	0 (0)	0 (0)	0 (0)
Hepatic vascular damage	13 (0·4)	0 (0)	3 (2·1)	1 (4·5)
Visceral damage	14 (0·5)	0 (0)	0 (0)	0 (0)
Cardiac complications	8 (0·3)	1 (0·6)	0 (0)	1 (4·5)
Myoglobinaemia and myoglobinuria	3 (0·1)	1 (0·6)	0 (0)	0 (0)
Renal failure	0 (0)	1 (0·6)	0 (0)	1 (4·5)
Seeding	8 (0·3)	0 (0)	0 (0)	0 (0)
Coagulopathy	0 (0)	0 (0)	0 (0)	1 (4·5)
Hormonal complications	3 (0·1)	0 (0)	0 (0)	0 (0)
Miscellaneous	6 (0·2)	2 (1·2)	1 (0·7)	0 (0)
Unspecified, minor	14 (0·5)	0 (0)	0 (0)	0 (0)
Total	208 (7·2)	16 (9·5)	14 (9·9)	7 (31·8)
Death	14 (0·5)	0 (0)	0 (0)	1 (4·5)

Only series detailing the total number of patients, the approach used, and the number and nature of all complications were included. Patients may have had more than one complication. *Open radiofrequency coagulation combined with cryotherapy, hepatic or extrahepatic resection

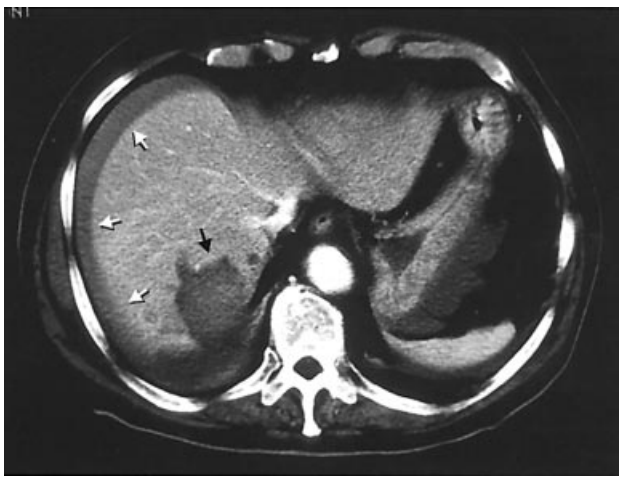

Fig. 1 Subcapsular haematoma (white arrows) and intrahepatic haematoma (black arrow) 24 h after percutaneous radiofrequency coagulation of a subcapsular colorectal metastasis in segment 7

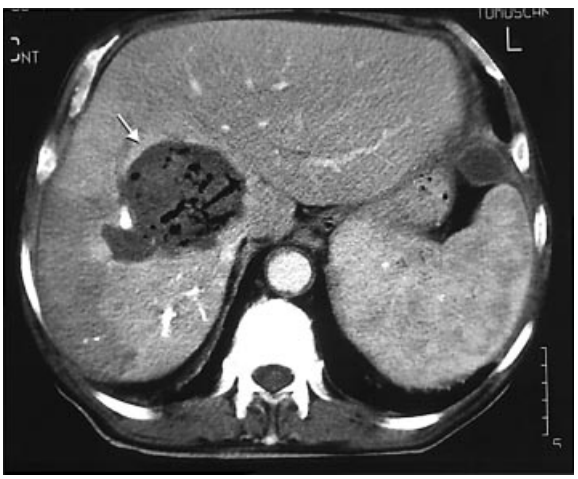

Fig. 2 Hepatic abscess (white arrow) 8 days after percutaneous radiofrequency coagulation of a hepatocellular carcinoma

Hepatic vein thrombosis

Only two instances of hepatic vein thrombosis causing peripheral infarction[32] or collateral vein development[16] have been observed.

Hepatic artery damage

Hepatic artery damage has been reported in nine patients[1,16,22,46,66]. One fatal and one non-fatal hepatic infarction[1] due to simultaneous hepatic artery and portal vein

Fig. 3 Third-degree dispersive pad skin burn after a 2-h radiofrequency coagulation of a 10-cm melanoma metastasis using a 200-W generator with only one 100-cm^2 dispersive pad

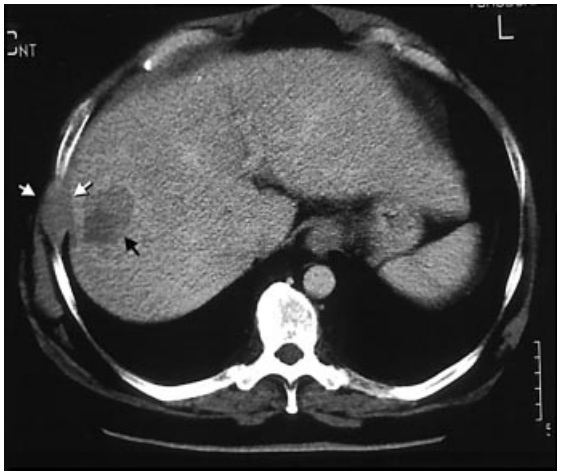

Fig. 4 Parietal wall seeding (white arrows) 1 year after direct percutaneous radiofrequency coagulation of a subcapsular hepatocellular carcinoma (black arrow). The electrode track had not been cauterized

thrombosis occurred after RFC of a central tumour. Three important arterioportal shunts[1,16] and two pseudoaneurysms[16,22] were noted. One intimal dissection of the hepatic artery without clinical sequelae was observed after balloon catheter occlusion[66].

Visceral damage

Visceral damage has occurred exclusively after percutaneous procedures. Five cases of post-RFC cholecystitis have been recognized[27,53,57,66] after coagulation near the gallbladder. All were treated conservatively. Diaphragmatic injury has been described in five of the series of 3670 patients[1,25,32,54,81], and in a further patient in another report[90] after RFC of a subdiaphragmatic tumour. Two burns were fatal as a result of bile leak into the chest[32] or an associated abscess[81]. Two other burns caused pain lasting for 10 days to 3 months[25,54]. Another patient sustained a diaphragmatic paresis[90]. Two colonic burns have been reported, one resulting in perforation[74] and one in fistula[32,95]. One jejunal perforation required operation[74], one gastric burn (*Fig. 4*) was due to RFC of a subcapsular tumour in the left lobe[1], and two renal burns were caused by RFC of a subcapsular tumour in segments 6 and 7[1,54]. Two abdominal wall burns have been reported, one during track coagulation[81] and one without coagulation[10].

Cardiac complications

Ten cases of rhythm disturbances were noted during or shortly after RFC: five vasovagal reactions or bradycardias[1,5,24] (one of which required cardiac massage[24] and another intravenous atropine[5]), one ventricular fibrillation treated by a single electrical discharge[20], two arrhythmias after RFC of carcinoid metastases[72,81], and one fatal cardiac arrest on day 20 after RFC[59]. Three patients with a pacemaker have undergone hepatic RFC[10,97]; malfunction was observed in one pacemaker[10]. Two instances of myocardial infarction were fatal; one was due to a carcinoid crisis[81] and the other was unrelated to the procedure[5].

Renal failure

Four instances of renal failure have been recorded[39,46,48,81]. One involved a *Staphylococcus aureus* chest infection[46], another a fatal carcinoid crisis[81], and a third was possibly caused by myoglobinuria[48].

Electrode track seeding

Seven cases of electrode track seeding (*Fig. 4*)[24,25,55,74,98] occurred in the series of 3670 patients, and a further three[99–101] were reported outside this series. Other unpublished cases have been referred to[102]. They occurred after RFC of HCC[24,55,98] and of colonic[74,99,100], pancreatic[25] and carcinoid[99,100] liver metastases. Seeding occurred after using monopolar[99,100,103,104], RITA[25,101] and Radionics[24, 55,74,98,102] electrodes. In one series of RFC of single HCCs[55], four instances of electrode track seeding after percutaneous RFC of a single HCCs in 32 patients were identified at 4, 6, 7 and 18 months after treatment. All four tumours were subcapsular and two were poorly

differentiated. No cauterization of the electrode track had been used in these patients for fear of burning the abdominal wall.

Hormonal complications

Among the 3670 patients treated with RFC, 77 had endocrine liver metastases[7,9,10,18,26,27,32,33,38,39,41,48,50,68,72,79,81], 42 of which were carcinoid metastases[10,18,26,27,33,38,48,68,72,79,81]. In these 42 patients, two (4·8 per cent) fatal carcinoid crises occurred[33,81], both after debulking of extensive disease with RFC with or without cryotherapy. In one of them, the crisis started only after 40 h[33]. One patient with an insulinoma became temporarily hyperglycaemic and one patient with a cortisol-secreting tumour had a transient addisonian crisis[33].

Miscellaneous

Two cases of hyperthermia have been reported after a lengthy (175–420 min) RFC procedure; the core temperature rose to 38·8–40·2°C[20,48]. Difficulty in removing a RITA radiofrequency electrode, because coagulated tissue had become caught between the hooks and the shaft, has been reported twice (Reference 69; F. Meloni, personal communication, 1998).

Approach

The complication rate was similar for the percutaneous (7·2 per cent), laparoscopic (9·5 per cent) and simple open (9·9 per cent) approaches (*Table 3*). Patients treated by open RFC combined with cryotherapy, hepatic or extrahepatic resection had a morbidity rate of 31·8 per cent. The mortality rate was 0·5, 0, 0 and 4·5 per cent respectively. Of two patients treated by a thoracoscopic transdiaphragmatic approach[28,45], one developed pleural bleeding[45].

Discussion

The worldwide reported complication and mortality rates (7·2 and 0·5 per cent respectively) for percutaneous RFC in this cumulative series is higher than the 1·5 and 0·1 per cent rates reported previously in an Italian study[90], indicating that the complication risk of this rapidly spreading technique should not be underestimated. The true complication rate may be even higher than the rate calculated here, as some authors may have ignored minor complications. Furthermore, some late complications, such as bile duct strictures and electrode track seeding, may have been missed because of the short follow-up in many studies. Review of the available data has enabled the formulation of some recommendations on the prevention of complications and identification of risk factors.

Prevention of complications

Intraperitoneal bleeding

Cauterization of the electrode track[17,18,24,44,56,64,81,96,105–109] can be strongly recommended for all patients, to prevent both oozing and significant bleeding. Cauterization is achieved by continuing power during slow withdrawal of the electrode after stopping the cooling for cooled electrodes[64,109] and after retraction of the prongs for expandable electrodes[68]. Oozing from the hepatic electrode track is noted in 30–34 per cent of patients[58,92]. Although oozing is most often limited to less than 7 ml blood[92,109], it has been incriminated as promoting seeding of viable tumour cells[55]. It can be prevented completely by cauterization[109]. Cauterization also effectively prevents post-RFC bleeding: no bleeding occurred in 214 patients having cauterization, compared with ten (1·0 per cent) of 1036 with no cauterization. While some apply cauterization only in cirrhotic liver[7,109], the present authors advise it in all patients as both oozing[109] and bleeding[73,74] have been noted in non-cirrhotic liver.

The recommendation of track cauterization for all patients has two important implications. The first is that general anaesthesia is recommended for all procedures, as coagulation of the most superficial part of the track within 2–3 cm from the hepatic capsule is often painful for patients who are under conscious sedation[55,110]. The second is that a perpendicular percutaneous approach is not advised for RFC of subcapsular tumours, as correct track cauterization using this route will lead to burns of the abdominal wall and skin[55,81].

In the authors' view, cauterization cannot be replaced by visual laparoscopic[58,111] or open[92] control of haemostasis. Coagulation of the point of entry of the electrode alone does not entirely prevent intraperitoneal bleeding, which occurred in one (0·3 per cent) of 332 patients after open and laparoscopic RFC, compared with 22 (0·8 per cent) of 2898 after percutaneous procedures. Furthermore, oozing is stopped rather than prevented, which is less ideal in the prevention of seeding. Experience with filling the electrode track with gelatin sponge[5,43] is too limited to draw meaningful conclusions.

Because of the risk of bleeding, the authors agree with most other workers in the field who recommend a postprocedural monitoring of haemodynamic variables for at least 4-6 h[8,20,50,59,65,78,85,91,105,112–116], only two authors settling for less[73,117].

Intrahepatic haematoma

An intrahepatic haematoma may be caused by accidental transgression of a large blood vessel[109]. Prevention lies in carefully avoiding hepatic vessels on the way to the tumour. Inadvertent injury to blood vessels may be more likely with triple-cooled and expandable electrodes, as it is impossible to visualize all prongs at the same time[118]. Straight electrodes may be advisable for tumours in the vicinity of several blood vessels[118].

Hepatic abscess

Bilioenteric anastomoses are known to increase the risk of septic complications after local treatment of liver tumours[119] as a result of retrograde enteric bacterial contamination of the biliary tract in up to 90 per cent of patients[120]. Germs found in abscesses after RFC, chemoembolization or percutaneous ethanol injection (PEI) in patients with bilioenteric anastomoses included *Escherichia coli*, *Clostridium perfringens*, streptococcus D and enterococcus[88,119]. Since the first description of abscesses after RFC, several groups[88,121,122] have started to give prophylactic antibiotics, although scientific proof of their value is unavailable at this time. A logical choice of antibiotics is amoxycillin plus clavulanic acid, which is active against all these organisms. In high-risk patients (previous biliary tract manipulation), a duration of 48 h has been suggested; otherwise one preprocedural intravenous dose is given[88].

Abscess after RFC is most likely when fever, leucocytosis and abundant intralesional gas are present[116,123]. Although the diagnosis is often obvious, several patients with an indolent course resulting in late diagnosis have been reported (malaise and a subfebrile state as the only symptoms)[124]. Intralesional gas is not synonymous with an abscess; gas bubbles in the coagulated area are seen in 63 per cent of computed tomography scans performed immediately after RFC[116]. At 1-month follow-up, however, gas should no longer be visible[116]. One abscess developed only after 5 months[81,87], suggesting that the devitalized tumour served as a nidus for delayed infection.

Peritoneal infection

It is clear that RFC should be performed with a strictly aseptic technique in a custom-designed environment.

Biliary tract damage

Experimental data suggest that the large bile ducts are protected from thermal damage by the cooling effect of the portal vein and the hepatic artery that run along them[124–126]. With intact blood flow, only small bile ducts associated with thrombosed blood vessels with a diameter of less than 3 mm are destroyed[125,126]. Damage to the larger bile ducts (adjacent to blood vessels greater than 3 mm in diameter) has never been observed[124,126]. Main bile duct stenosis has been noted only after RFC during a Pringle manoeuvre[124].

In clinical practice, however, intact blood flow does not decrease the risk of biliary complications. The fact that the number of reported biliary complications is limited is probably related to the warnings of this complication from the early days of RFC[52,111]. Most workers consider tumours closer than 1 cm to the main biliary ducts a contraindication to RFC[3,4,12,20,29,93,107,110]. However, two methods have recently been described to prevent biliary damage while treating central tumours[26,81]. One involved the prophylactic placement of a biliary stent in four patients having RFC of tumours near the major bile ducts; there were no complications[81]. The other involved the (successful) treatment of three central tumours while cooling the biliary ducts with chilled saline[26]. While these methods may decrease biliary damage, they may increase the risk of hepatic abscess formation. Prospective evaluation is needed.

Dispersive pad skin burns

As for electrocautery, the general recommendations for the placement of grounding pads[127–130] must be observed. Specific extra precautions need to be taken for RFC. Using electrocautery, one standard pad is sufficient as the current is limited (700 mA or less) and intermittent. Using RFC, the risk of burns with one pad is much higher, as current can be as high as 2000 mA and is applied continuously for one or more session of 10–20 min[131].

An excellent experimental study[131], using a 200-W generator for 10 min, studied the variables that influenced heating under the pad. On the basis of this study, the use of four (rather than one) 100-cm^2 pads is recommended to increase the dispersive surface. The pads should be placed horizontally to allow a longer leading edge. They should be equidistant from the electrode to prevent excessive heating of the nearest pad. A distance to the electrode of at least 50 cm should be observed as pad temperature rises with shorter distances. In practice, for 200-W generators the pads should be placed horizontally at the anterior and posterior aspect of the mid-thigh, 50 cm from the electrode[131]. This contrasts with earlier recommendations for low-power (50 W) generators[66,107] that advocated pads to be placed on the back. The above study, although extremely useful, does not allow any conclusion on the safety of procedures exceeding 10 min, or of serial procedures with short intervals. It is strongly recommended that manufacturers quickly develop a system of pad temperature monitoring with an automatic audible alarm and current shutdown. Meanwhile, temperature monitoring using thermistors sandwiched between the dispersive plate and the skin is advised[7].

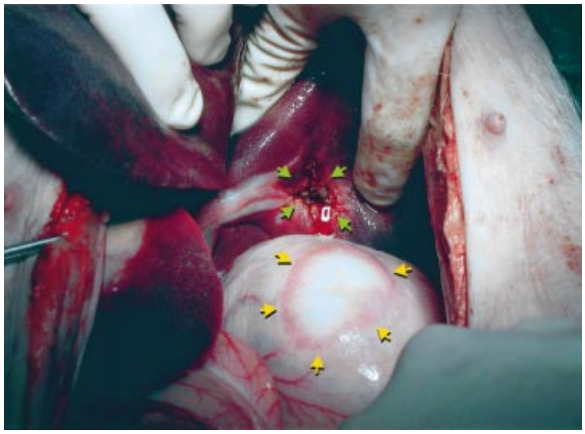

Fig. 5 Full-thickness stomach wall burn (yellow arrows) after a 12-min subcapsular radiofrequency coagulation (green arrows) at the undersurface of the left lobe of a pig liver without retracting the stomach

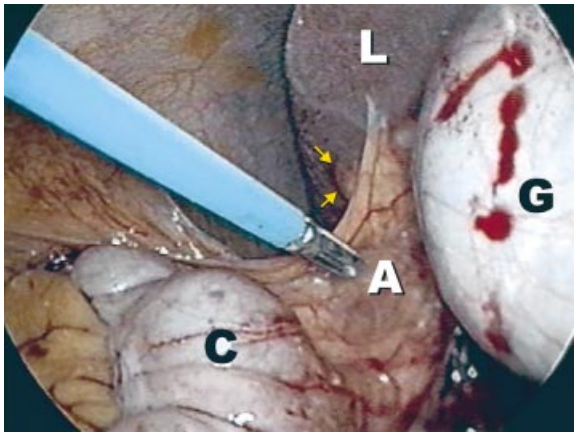

Fig. 6 The laparoscopic approach allows division of an adhesion between the transverse colon and a subcapsular segment 6 colorectal metastasis (yellow arrows) in order to avoid a colonic burn. A, adhesion; C, colon; G, gallbladder; L, liver

Portal vein thrombosis

In experimental studies, a Pringle manoeuvre enhances the risk of hepatic vessel thrombosis. After RFC with normal hepatic flow, vessels up to 3 mm show thrombosis[125,132]; 89 per cent of vessels with a diameter of 3–4 mm and 100 per cent of those with a diameter greater than 4 mm remain patent[125,133–135]. However, in experimental lesions produced with a Pringle manoeuvre, occlusive thrombosis has been observed even in large vessels (greater than 6 mm)[125,126]. The absence of protection of the endothelium by the cooling blood flow during the manoeuvre translates clinically into a higher rate of thrombosis of nearby portal vein branches. The authors refrain from any Pringle manoeuvre in circumstances of portal vein compression by the tumour. The available data also discourage a full manoeuvre for tumours within 1 cm of the main portal vein branches[64,68]. For such tumours a short (2–3 min) manoeuvre is an alternative that has until now never produced portal vein thrombosis[92]. A full Pringle manoeuvre for RFC of tumours at a distance from the main portal branches has, so far, never produced portal vein thrombosis.

Hepatic vein thrombosis, Budd–Chiari syndrome and inferior vena cava thrombosis

Hepatic vein thrombosis has been reported only twice[16,32]. Until now, no Budd–Chiari syndrome or inferior vena cava thrombosis has occurred after RFC, although both have been described after interstitial laser coagulation[14,136]. RFC of tumours in the fork between the inferior vena cava and one or more hepatic veins is probably safe, unless the veins are compressed by the tumour.

Hepatic artery damage

A small arterioportal shunt[14,116,137] is found in 25 per cent of patients when carefully looked for at computed tomography immediately after RFC[116]. It is seen as a wedge-like high-attenuation lesion during the hepatic arterial phase. Eighty per cent of arterioportal shunts have disappeared at the 1-month follow-up; the remaining 20 per cent are no longer visible at 4-month follow-up[116]. The majority of arterioportal shunts heal spontaneously and need only simple follow-up. Only one massive shunt[116] and one shunt associated with a growing pseudoaneurysm[16] have been reported so far; such shunts should be embolized. Embolization of all pseudoaneurysms[138] seems advisable, as they may experience delayed rupture with haemoperitoneum[86].

Visceral damage

A tumour closer than 1 cm to the gallbladder is a contraindication for a percutaneous procedure[12,29,110,139]. For tumours near the gallbladder, a laparoscopic or open approach allows cholecystectomy to avoid thermal cholecystitis or gallbladder perforation[96,107]. In contrast to other workers who remove the gallbladder before RFC[107], the authors prefer to remove it after RFC to prevent spillage of tumour cells that are still viable[96].

Burns of adjacent viscera have been predicted by a pig liver model, in which full-thickness burns of the stomach, small bowel and colon have been observed when the edge of the thermal lesion was less than 1 cm from the surface of the liver[125,134,140] (*Fig. 5*). In the light of this an open or laparoscopic approach has been advocated for subcapsular tumours within 2 cm of adjacent viscera[20,58,107,125,141]. This

way, these organs can be protected by separating them from the liver surface (*Fig. 6*). In the absence of adhesions between the viscus and the liver, peritoneal saline instillation creating artificial ascites is being studied as an alternative[142].

Cardiac complications

The reports of rhythm disturbances stress the importance of continuous monitoring of vital signs and the presence of an anaesthetist during and for 1 h after the procedure, even if performed percutaneously[3,20,34,143,144]. Significant problems have been reported in patients undergoing RFC in a radiology suite without adequate anaesthesia[20]. Defibrillation devices should always be immediately available.

Hypotension

In experimental conditions, the combination of a pneumoperitoneum and clamping of the liver hilum may cause hypotension due to decreased venous return[145]. So far, this has not been reported in the clinical situation, but published experience with a Pringle manoeuvre during laparoscopic RFC is limited to four cases[21,37].

Acute renal failure

Only one case of acute renal failure, which may have been caused by myoglobinaemia, has been reported after RFC that lasted for 7 h[48]. However, the frequency of myoglobinaemia or myoglobinuria after RFC is probably underestimated. When looked for routinely, myoglobinaemia was found in three of ten patients being treated for large or multiple tumours[70]. Similarly, myoglobinuria has been reported in none of 25[146], and in five (6·6 per cent) of 76 patients[10], and was associated with RFC of very large (up to 15 cm) tumours[10]. In the near future, renal failure after RFC may become more frequent due to increasing coagulation diameter. More data are needed about the real prevalence and risk of myoglobinaemia. Until then, it is recommended that myoglobinaemia and myoglobinuria are measured routinely in situations of extensive coagulation to allow prompt recognition and preventive therapy (mannitol diuresis and alkalinization of the urine)[48]. Furthermore, a staged procedure should be considered for extensive disease[48].

Electrode track seeding

The risk of electrode track seeding has been the subject of recent debate[24,55,98,102,147–150] since one group noted this complication in 12·5 per cent of patients[55]. Most other workers report lower rates of seeding, from 0·2 per cent[90], 0·6 per cent[149], to 2·8 per cent[24]. The reasons for these differences are not clear. It may be that the real incidence of seeding is underestimated in many series with a short follow-up, as it may be recognized as late as 18 months after the procedure[55].

Several mechanisms may contribute to seeding. Viable tumour cells may adhere to a biopsy needle or to the electrode during its retraction. Tumour cells may also be carried into the track with a little bleeding. Furthermore, cells may be forced into the track by sudden intratumoral hyperpressure that is frequently encountered during RFC, audible as a popping sound. Finally, cells may be driven in when saline is injected into the tumour during or before RFC[151]. Incriminated risk factors for seeding are preprocedural biopsies[152,153], poor differentiation of the tumour[55], no cauterization of the electrode track[55], and a perpendicular approach to subcapsular tumours[55]. Some authors perform a preprocedural percutaneous[20,37,65,66,85,113,143,146], laparoscopic[7,111,121,154], or open[56] fine-needle or core biopsy of the liver tumour. However, a 5 and 25 per cent risk of tumour seeding have been reported for HCC and colorectal liver metastases respectively[152,153]. It therefore appears that biopsy proof of the nature of the tumour before RFC should be avoided when the clinical picture (history, imaging and tumour markers) is sufficiently diagnostic[3,85]. Poor differentiation of the tumour is a known risk factor for seeding after fine-needle aspiration biopsy and PEI[155], and is also associated with a higher risk of seeding after RFC[55].

Oozing after retraction of the electrode, which occurs in 30 per cent of cases[92], may promote seeding of viable tumour cells[55] and can be prevented completely by cauterization[109]. One group[55] systematically cauterized the electrode track, except for subcapsular tumours for fear of abdominal wall burns; all four cases of seeding occurred in patients with subcapsular tumours. Although unproven, the authors feel strongly that cauterization should be performed not only at the end of each RFC procedure, but also before every repositioning of the electrode. The seeding risk seems to be greater for subcapsular tumours, especially when a direct, perpendicular approach is used[148]. Once Glisson's capsule is breached, the tumour can bleed and cells can leak out immediately[102,156]. Furthermore, correct cauterization in this approach would lead to burns of the abdominal wall and skin[55,81]. An indirect oblique approach, through a sufficient layer of non-tumoral tissue, first aiming at the hilar pole of the tumour, is advised[148]. In this way the tumour is devascularized before it is coagulated, Glisson's capsule is coagulated only at the end, and cauterization of the intrahepatic track can be performed safely[24]. No seeding occurred in a series of 63 patients in which direct puncture

of subcapsular tumours was avoided[148]. While some groups at this time consider a subcapsular location to be a contraindication to RFC, especially for patients awaiting transplantation[55,102,147], the present authors feel rather that a direct approach to these tumours is contraindicated. For subcapsular tumours, laparoscopy and laparotomy may often be the approach of choice, as they offer a greater degree of freedom for the indirect introduction of the electrode.

Haematogenous seeding

There is concern that RFC may increase the release of neoplastic cells into the circulation during the treatment, as has been observed after transarterial embolization[157]. In a recent study of 32 patients, tumour cells in peripheral blood were present in 34 per cent of patients just before RFC and in 44 per cent of patients 1 h after RFC[55]. No definite conclusion can be drawn because of small numbers. Furthermore, increased release of tumour cells in the bloodstream does not necessarily translate into increased haematogenous metastases.

Coagulopathy

A slight decrease in platelet count on the first day after RFC is common[3,154]. However, significant thrombopenia is rare after RFC, probably because there is no reperfusion, as in cryotherapy[146]. Platelet count less than 60 000 μl has been reported once after extensive RFC during 248 min[56]. The international normalized ratio usually shows little fluctuation in the postoperative period[154].

Hormonal complications

A carcinoid crisis is an extremely dangerous complication after RFC of a carcinoid tumour due to haemodynamic instability and cardiac rhythm disturbances. Patients should be monitored in the intensive care unit for at least 48 h after such a procedure and receive a prophylactic octreotide infusion[48,158]. Both recorded fatalities occurred after extensive procedures[33,81]; whether a staged approach for extensive disease is safer is not presently known.

Risk factors for complications

Complications after RFC for HCC are more common in Child–Pugh class C (27·6 per cent) than in class A (8·0 per cent) or class B (6·5 per cent)[20]. RFC of subcapsular tumours carries a higher risk of intraperitoneal bleeding, subcapsular haematoma, seeding and visceral damage; RFC of central tumours predisposes to biliary tract and central vessel damage. Thermal damage to neighbouring organs is found exclusively in the percutaneous approach. The same is true for seeding, probably because of the impossibility of coagulating the electrode track for superficial tumours using the percutaneous approach[55]. The laparoscopic approach has a complication pattern similar to that of the percutaneous approach, while avoiding seeding and visceral damage. Complication and mortality rates of open RFC combined with resection were not significantly different from those of hepatic resection alone for colorectal metastases (19 and 2 per cent respectively)[159]. Extensive procedures for large or multiple tumours carry a higher risk of liver failure, dispersive pad skin burn, myoglobinaemia or myoglobinuria, thrombocytopenia and central hyperthermia. Staged treatment should be considered for these patients.

Comparison with other interstitial techniques

Percutaneous ethanol injection

Several trials have compared PEI and RFC in the treatment of small (3 cm or less) hepatocellular cancers. In a prospective non-randomized trial, no complications occurred after PEI in 44 patients, whereas five complications occurred after RFC in 42 patients[91]. In a prospective randomized trial, no complications were observed after PEI in 50 patients or after RFC in 52[51]. In a comparative study that assessed seeding alone, seeding was observed after PEI in none of 100 patients, and in three of 28 patients after RFC[98]. This difference was attributed to the larger diameter (15–18 G) of radiofrequency electrodes compared with PEI needles, which increases bleeding during the procedure and so, in turn, seeding[55].

Cryotherapy

In a retrospective study comparing cryotherapy (n = 130) and RFC (n = 14), the complication rates were 17 and 0 per cent, thrombocytopenia rates 90 *versus* 0 per cent, and mean blood loss was 800 *versus* 40 ml respectively[106]. In a prospective non-randomized trial comparing intraoperative cryotherapy (n = 54) and RFC (n = 92), the complication rates were 41 and 3 per cent, and the mortality rates 2 and 0 per cent[146]. Brisk intraoperative haemorrhage from the cryoprobe track that required packing was encountered in almost 80 per cent of those undergoing cryotherapy; there was no instance of such haemorrhage after RFC. Intrahepatic abscess developed in 19 per cent after cryotherapy; no abscess developed after RFC. Renal failure occurred in 4 per cent after cryotherapy and in 0 per cent after RFC[146].

In contrast to cryotherapy, there is no reperfusion through injured blood vessels after RFC because vessels of up to 3 mm in diameter are coagulated along with the tumour[125,132]. There is therefore neither consumption of platelets nor activation of coagulation to cause a coagulopathy[146,160]. RFC probes are smaller than cryoprobes and

their tracks can be coagulated during electrode withdrawal such that track bleeding is much less frequent[146]. Cracking of the parenchyma during thawing of the iceball, resulting in severe haemorrhage[160], is not relevant to RFC. Furthermore, the instantaneous coagulation of proteins and the absence of reperfusion in RFC result in a diminished release of toxic factors[161]. This explains why renal failure due to myoglobinuria occurred in only one (0·03 per cent) of 3670 patients after RFC, compared with 1·4 per cent after cryotherapy[162].

Laser

Complications after percutaneous interstitial laser therapy are similar to those after percutaneous RFC. In 676 patients, pleural effusion requiring drainage occurred in 2·2 per cent, subcapsular haematoma in 7·7 per cent, hepatic abscess in 0·9 per cent, peritoneal bleeding in 0·4 per cent, wound infection in 0·6 per cent, and bile duct injury in 0·3 per cent[163]. The mortality rate was 0·4 per cent. In a retrospective study comparing laser therapy (n = 36) and RFC (n = 38) for the percutaneous treatment of HCCs of up to 6 cm in diameter, no major complications were observed in either group[164].

Microwave

In a prospective randomized study comparing microwave (n = 36) and RFC (n = 36), the respective complication rates were 11 and 3 per cent[71].

Conclusion

The morbidity and mortality rates associated with RFC, while low, are higher than previously assumed. With adequate knowledge, many complications are preventable. It is conceivable that the complication rate may rise in the future when larger tumour volumes are coagulated by more powerful electrodes.

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