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Review

The emergent role of focal liver ablation techniques in the treatment of primary and secondary liver tumours

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Abstract

Only 20% of patients with primary or secondary liver tumours are suitable for resection because of extrahepatic disease or the anatomical distribution of their disease. These patients could be treated by ablation of the tumour, thus preserving functioning liver. This study presents a detailed review of established and experimental ablation procedures. The relative merits of each technique will be discussed and clinical data regarding the efficacy of the techniques evaluated. A literature search from 1966 to 2003 was undertaken using Medline, Pubmed and Web of Science databases. Keywords were Hepatocellular carcinoma, liver metastases, percutaneous ethanol injection, cryotherapy, microwave coagulation therapy, radiofrequency ablation, interstitial laser photocoagulation, focused high-intensity ultrasound, hot saline injection, electrolysis and acetic acid injection. Ablative techniques offer a promising therapeutic modality to treat unresectable tumours. Large-scale randomised controlled trials are required before widespread acceptance of these techniques can occur.

Keywords: Liver ablation; Review; Treatment; Hepatocellular carcinoma; Liver metastases

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth commonest malignancy worldwide and although it occurs predominately in Asia and Africa, its incidence in the Western world is increasing [1,2] due to the increased prevalence of Hepatitis C [3]. Colorectal carcinoma is common in the Western World with 160 000 new patients diagnosed each year in the United States of America (USA) alone [4,5]. At the time of diagnosis, approximately 25% of patients with primary colorectal cancer will have metastatic spread to the liver. A further 25% develop metastases at a later date and this progressive involvement of their liver may be the major or sole determinant of survival (NIH consensus, 1990; Wood, 1976; August, 1985).

Surgical resection is the only curative option for colorectal hepatic metastases and it results in a 40% 5-year survival [6] and a 50% 5-year survival for HCC [7]. Unfortunately, only 20% of patients with liver tumours are suitable for surgery because of the anatomical distribution of their tumours or the presence of extrahepatic disease [8]. Following surgical resection, 20–30% of functioning liver must remain to avoid postoperative liver failure [9]. As a result, many non-resectional modalities of treatment have been assessed to provide an alternative to liver resection. These modalities include liver transplantation for small HCCs and cirrhosis [10], systemic and regional chemotherapy [11], chemo-embolisation [12], immunotherapy [13,14] and ablative techniques. Many of these methods suffer from significant disadvantages, such as the shortage of donor livers for transplantation and the often poor response with no increased survival benefits for chemotherapy [15], immunotherapy [16] and chemo-embolisation [17]. This review will concentrate on ablative techniques, both established and experimental, and the possible future such methods hold for the treatment of primary and secondary liver tumours.

2. Percutaneous ethanol injection (PEI)

PEI was first advocated for the treatment of HHC by Suguira and colleagues in 1983 [18] (Table 1). Absolute

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Table 1
Progression and development of focal liver ablation technology

Ablation technique	Preclincial animal models	Pilot trials in humans (1–10 patients)	Series of 10 patients	Series of 10–50 patients	Series of over 50 patients	Randomised controlled trials
Percutaneous ethanol injection and HCC	√	√	√	√	√	
Percutaneous ethanol injection and colorectal liver metastases	√	√		√		
Percutaneous acetic acid injection	√	√		√		√[a]
Hot saline injection	√	√		√		
Radiofrequency ablation	√	√	√	√	√	√[b]
High-intensity focused ultrasound	√	√	√			
Interstial laser photocoagulation	√	√		√	√	
Microwave ablation	√	√	√			√[c]
Electrolysis	√	√				
Cryotherapy	√			√	√	

HCC, hepatocellular carcinoma.
[a] Compared with percutaneous ethanol injection.
[b] Compared with percutaneous microwave therapy.
[c] Compared with radiofrequency ablation and liver resection.

ethanol (99.5 or 95%) is slowly injected into the lesion starting at the deepest aspect of the tumour and subsequently withdrawing the needle in small increments to achieve uniform and adequate perfusion of the tumour. Ultrasound is used to monitor alcohol injections as the micro-bubbles in ethanol create an echogenic blush immediately following the infusion [19]. The therapeutic effect of PEI can be assessed clinically by computerised tomography (CT), which demonstrates a uniform low-density lesion marking the area of liver necrosis [20].

Absolute alcohol diffuses into the cells inducing non-selective protein denaturation and cellular dehydration leading to coagulative necrosis. Subsequent fibrosis and vascular thrombosis may also contribute to the destruction of tumour cells [20]. The amount of alcohol needed to ablate a lesion is dependent on tumour consistency, vascularity, internal septae, areas of tumour necrosis (which provide a path of preferential alcohol diffusion) and the presence of tumour capsule (which contains the alcohol, but also prevents it reaching areas of extracapsular tumour [21]). The number of injections needed for complete ablation of a tumour is approximately twice the lesion diameter in centimetres [22].

2.1. Results of PEI in the treatment of hepatocellular cancer

PEI can induce complete tumour necrosis in patients with HCCs smaller than 3 cm [23,24]. If residual tumour is present, it is usually found in nests around the main lesion, along the edge of the lesion or within the main tumour mass where it is protected from the PEI by the presence of septae [25]. The efficiency of tumour killing by PEI appears to be, at least partly, size-dependent. This and the difficulties in injecting large volumes of ethanol under local anaesthetic have, until recently, limited PEI to small tumours. However, recent reports suggest that larger tumours, over 5 cm can be treated safely using a single injection under general anaesthesia. Volumes of up to 40 ml can be used on an outpatient basis [26,27] and up to 210 ml under general anaesthesia [28].

Although several large-scale series of PEI for HCC have been reported in the literature, there have been no randomised-controlled trials to date comparing PEI with other forms of treatment or no treatment. Table 2 summarises the results of some of these trials. PEI results in good survival rates for HCCs below 5 cm with survival rates for the first year ranging from 85 to 100% [25,29–35]. The survival rate drops to approximately 30% at 5 years following treatment [25,29,36]. Single large HCCs above 5 cm in diameter are associated with a poorer outcome, with only a 72% survival rate after the first year, although a comparable 4-year survival rate of 44%, when compared with smaller tumours [37]. Patient selection has a significant impact on outcome, large HCCs associated with Childs C cirrhosis or portal vein thrombosis have a 4-year survival of 0%. Livraghi and colleagues [28] reported their experience in 1995 with 746 patients and demonstrated clear differences in 5-year survival between Childs grade A (47%), grade B (29%) and grade C (0%). As well as the size of lesion and severity of cirrhosis, other prognostic factors affecting outcome following PEI include pretreatment high alpha feto-protein levels, multiple tumours and the presence of a tumour capsule [25,34,38]. These prognostic indicators would appear to be very much related to both the tumour burden and baseline liver function.

Retrospective studies of PEI versus palliative treatment in HCC show that PEI confers a survival advantage over the latter [39]. Orlando and colleagues [33] found a conferred 3-year survival benefit of 33% versus

Table 2
Table comparing the survival and recurrence rates reported after percutaneous ethanol injection (PEI) for hepatocellular carcinoma

Study and year [Ref.]	Number of patients	Tumour size (cm)	Survival rate (%)							3–5 year recurrence (%)
			1-year	2-year	3-year	4-year	5-year	6-year	7-year	
Ebara and colleagues 1993 [20]	162	⩽3	95.9	–	60.5	–	36.9	–	21.7	63
Livraghi and colleagues 1992 [28]	162	⩽5	90	80	63	–	–	–	–	–
Livraghi and colleagues 1998 [30]	108	5–8.5	72	65	57	44	–	–	–	–
Castells and colleagues 1993 [31]	30	⩽4	83	66	55	34	–	–	–	66
Shiina and colleagues 1993 [25]	146	⩽2	79	64	46	38	38	–	–	60
Isobe and colleagues 1994 [32]	37	⩽5	95	81	70	–	–	–	–	40
Lencioni and colleagues 1995 [36]	82	⩽5	96	87	68	51	32	24	–	40
Orlando and colleagues 1997 [33]	35	⩽4	100	87	71	71	–	–	–	–
Castellono and colleagues 1993 [34]	71	⩽5	89	54	24	–	–	–	–	81
Lin and colleagues 1999 [35]	47	⩽3	85	75	61	39	–	–	–	79

14% in the treated versus non-treated group. Survival benefits of PEI over resection surgery are, however, less clear. Castells and colleagues [31] reported on a cohort of patients where the results of PEI were compared with those of surgical resection. In this series, tumour recurrence was found to be higher in the PEI-treated patients compared with the surgical resection group—66 and 45%, respectively. The results suggested that surgical resection was a better management option for larger tumours, particularly those over 3 cm in diameter. These findings are further supported by a Japanese group. Arii and colleagues [40] reported on a series of over 4000 patients comparing, retrospectively, PEI-treated and surgically resected HCC outcomes. They found that surgery had a superior outcome for solitary tumours over 2 cm. This survival benefit from resection surgery over PEI was consistent, despite the severity of the patient's liver cirrhosis. PEI for the moment seems to be preferable over palliative treatment, but not superior to resection for the management of HCC. Recurrence rates following PEI are variable, ranging from 40 to up to 81% after 5 years (Table 2). These recurrences frequently occur in sites other than the tumour site following PEI, probably reflecting the multifocal pathology of HCC in cirrhotic livers.

2.2. Results of PEI in metastatic liver deposits

Colorectal metastatic lesions are far more difficult to destroy by PEI than primary liver tumours because the alcohol tends to spread into soft adjacent liver parenchyma, rather than staying within the hard tumour tissue [41]. There is little data relating the results of PEI for metastatic tumours. Complete necrosis of tumours has only been observed in 52–56% of lesions [42,43] and progression of disease has occurred in a series of 8 patients undergoing PEI [44]. Lesions which have the greatest response, are small (2 cm) endocrine metastases and a 3-year survival rate of 39% has been reported for these patients [43]. It has recently been suggested that echo-laparoscopic alcohol injection of liver metastases [45] be performed, as this would allow better tumour localisation but, perhaps more importantly, would allow a better staging of the disease. In particular, information on the presence or absence of extrahepatic disease could be obtained.

2.3. Complications and contra-indications of PEI

Most patients complain of pain during or immediately after the injection of ethanol. The pain is usually felt in the right upper quadrant, but shoulder tip pain is not uncommon [46]. Postprocedural fever is almost universal. Hepatic infarction, intraperitoneal bleeding, pneumothorax, ascites, haemobilia and cholangitis have all been reported following PEI [28,46]. There has been a report of chemical thrombosis in the portal vein, which resolved spontaneously [36]. These major complications are rare, occurring in 0.7–3% of patients [28,47]. Deaths related to PEI have occurred secondary to massive hepatic necrosis [48] and portal vein thrombosis [49]. Perhaps unsurprisingly, the complication rate following the more aggressive single-session treatment is higher with a recent report suggesting a 4.6% procedure-related mortality [28]. Long-term complications of PEI include a reported case of bile duct stricture [50] and needle tract implantation of hepatocellular carcinoma, which has been noted in less than 1% of cases [51].

Common to all percutaneous liver puncture techniques, PEI is contra-indicated in severe thrombocytopenia and clotting dyscrasias. Very large tumours (>8.5 cm in diameter) are also considered a contra-indication to PEI, as is a pre-existing thrombosis in the portal vein and ascites.

3. Percutaneous acetic acid injection (PAAI)

The pathophysiology of tumour killing in PAAI is identical to that of PEI, except that 50% acetic acid is

used in place of ethanol. The proposed advantage of this technique is that because of its greater necrotising power, smaller volumes of acetic acid would need to be injected and less often to achieve the same therapeutic effect. Acetic acid will, therefore, not only destroy tumours more efficiently, but also break down internal septae, thereby enhancing its effects [52].

3.1. Results of PAAI in HCC

Ohnishi and colleagues [53] reported a randomised-controlled trial which compared PAAI with PEI and found a lower recurrence rate (8% for PAAI versus 37% for PEI) and superior 2-year survival rate (92% for PAAI versus 63% for PEI). A smaller study looking at 18 patients [54] showed no recurrences in 17 patients after a 29-month follow-up.

3.2. Complications of PAAI

Despite the limited data on PAAI, several complications have already been reported, including hepatic wedge infarction, fatal hepatic failure [54], liver perforation [55] and severe renal failure [56]. The use of iodinated contrast and CT fluoroscopy could be used to minimise these risks by monitoring acetic acid distribution, so that extratumoral diffusion can be detected and the distribution of acetic acid can be optimised [57]. More data is still needed on the use of PAAI before valid conclusions regarding its safety and efficacy can be drawn.

4. Other percutaneous injection techniques

Two other injection techniques are briefly mentioned here. Percutaneous injection of alkaline solutions has been assessed in animal models against PEI and PAAI. An alkaline solution of dilute sodium hydroxide has been shown to be more effective than ethanol in cell killing, but less effective than acetic acid [58]. Its primary advantage over PAAI is a much better survival rate (100% versus 50%) with no damage to other organs by avoiding the toxic effects of acetic acid on other organs.

Hot saline injection therapy has been proposed as a way of overcoming distal and local toxic effects following injection of cyto-destructive agents. The method of tumour killing is heat destruction causing coagulative necrosis. The method of fluid instillation is identical to those already described, however, because hot saline is used to destroy the tumour; as it cools, it becomes physiological saline and should avoid any of the complications associated with ethanol and acetic acid toxicity. The first human trial of hot saline injection was reported by Honda and colleagues in 1994 [59]. 20 patients with HCCs smaller than 3 cm were injected with hot saline. During a 2–36-month follow-up period, no local recurrences were seen. Yoon and colleagues reported a series of 29 patients with large HCC, mean diameter of 7 cm [60]. Initial regression rates at 3 months following all tumours was 42% with a median survival of 10 months, and no complications. These short follow-ups and small numbers do not allow for accurate survival conclusions to be made. However, hot saline injections may be a feasible alternative for large HCCs.

5. Radiofrequency ablation (RFA)

RFA is an electrosurgical technique utilising high frequency alternating current to heat tissues leading to thermal coagulation. The size and shape of the necrotic RFA lesion has been shown to be dependent on the probe gauge, length of the exposed tip, probe temperature and the duration of treatment [61–63]. A recent report studying RFA *in vivo* in a pig model also suggests that local blood flow is a strong predictor of lesion dimensions by reducing lesion size [64].

Percutaneous RFA has been described under general or local anaesthesia [63,65], along with a laparoscopic approach [66]. Usually, a 15–21 gauge RF probe with a 2–3 cm tip exposure is positioned into the lesion. RF treatment is often based on intra-procedural temperature monitoring to determine the thermal lesion produced. The probes may be repositioned during treatment to achieve complete tumour ablation in one treatment session.

During treatment under ultrasound control, a gradually enlarging elliptical lesion can be seen with ill-defined margins [62]. These appearances persist up to several months after treatment and this heterogeneity precludes the distinction between ablated tumour and residual disease. Even with CT or magnetic resonance (MR) follow-up, the appearances of the residual disease or ablated tumour are indistinguishable from one another; this perhaps represents the biggest disadvantage of RFA.

5.1. Results of RFA in liver tumours

As Table 3 demonstrates, much of the data published on RFA is relatively new with short follow-up times, up to a maximum of 22.6 months [67]. Local recurrence rates following ablation vary greatly from as low as 1.3 to 50% [68–72]. Techniques such as expandable tips, venous occlusion and cooled tips have been used successfully in the management of larger tumours above 4 cm with an 80–95% eradication rate [73–77]. As with PEI, the best results with RFA are observed in tumours with a diameter of less than 3 cm, but RFA appears to

Table 3
Table summarising the success rates for radiofrequency ablation (RFA) in the management of primary and secondary liver tumours

Study and year [Ref.]	Number of patients	Tumour size (cm)	Type of tumour (HCC or METS)	Needle type	Mean follow-up	Local recurrence rate (%)
Rossi and colleagues 1996 [67]	39	⩽3	HCC	Single	22.6 months	5
Curley and colleagues 1999 [72]	48	–	HCC	Expandable	19 months	2.1
Buscarini and colleagues 2001 [66]	88	⩽3.5	HCC	Single and expandable	9.2 months	13
Skjoldbye and colleagues 2002 [71]	37	⩽3	6 HCC 31 METS	Single	16 months	50
Ianittiii and colleagues 2002 [74]	123	Mean 5.2	30 HCC 93 METS	Single	20 months	10
Sitpple and colleagues 2002 [69]	68	⩽3	METS	Single	8 months	11.8
Chan and colleagues 2002 [68]	85	⩽3	57 HCC 28 METS	Single	142 days	5
Bonny and colleagues 2002 [70]	30	⩽3	HCC	Single	10.6 months	1.3
de Braere and colleagues 2002 [73]	10	Mean 4.2	METS	Single plus venous vascular occlusion	9.5 months	1.5
Francica and colleagues 1999 [76]	15	1–4.3	HCC	Cooled tip	15 months	28

METS, metastases.

have a superior eradication rate of the tumours compared with PEI in a series of 44 patients (90% versus 80%, respectively) [78], despite a higher complication rate (12% versus no complications for the PEI group). In comparison to cryotherapy, RFA appears to be safer and more effective at eradicating tumours, with a complication rate of 3.3% versus 40.7% and a recurrence rate of 2.2% versus 13.6% [79]. When RFA was compared with microwave coagulation therapy, there was an equivalent complication and therapeutic effect. However, RFA was found to be superior because tumour ablation could be achieved in fewer sessions [80]. RFA has also been shown to be cost-effective when compared with palliative treatments for both HCC and liver metastases [81].

Factors determining the success of RFA are the size and number of tumours treated [82,83] and the method of RFA delivery. The percutaneous technique is associated with a higher recurrence rate [83,84]. New modifications in RFA may enable larger tumours to be successfully ablated. Using an umbrella-shaped probe and a 200-W generator 100%, destruction of very large colorectal metastases (up to 10 cm) was achieved in a series of 30 patients [85]. Part of the problem in treating large tumours is difficulty in assessing the thermal zone of destruction; new USS techniques can be used to obtain a 'thermal map' of the temperatures produced in tissue, which can be used to control the degree of tissue damage produced [86].

5.2. Complications of RFA

Minimal right upper quadrant discomfort and post-procedural fever is common following RFA therapy. Deterioration in liver function is also common with complete recovery occurring within 1 week [87]. The complication rate of RFA is approximately 5% [88]. Liver abscess followed by occasionally fatal sepsis has been reported following RFA in five studies looking at a total of 215 patients [74,84,89–91]. Other complications from RFA appear to relate to difficulties in limiting the thermal lesion to the target area, such as formation of colonic fistulae or free perforation, (when RFA has been undertaken in tumours next to bowel [85,92]) formation of arterial-portal fistulas [74] and bile duct injury [90]. Finally, sub-capsular haematomas, skin burns, peritoneal dissemination of disease, segmental hepatic infarction and fatal venous thrombosis have also been reported following RFA [70,80,84,91].

6. High-intensity focused ultrasound (HIFU)

HIFU is unique in that it is an extracorporeal, transcutaneous method of tissue ablation. The use of sound waves of much higher amplitude than that used in a diagnostic setting, along with a concave ultrasound transducer, results in selective, targeted delivery of higher energy, without the possibility of damage to intervening tissues [93]. HIFU exerts its effects primarily by heating; the sound waves are absorbed by the target organ and the heat generated leads to coagulative necrosis in the tissues [93]. There is also evidence that HIFU activates aggregation and adhesion of platelets [94] and that its hameostatic action could be useful in reducing bleeding complications following tumour ablation [95].

6.1. Results of HIFU in Humans

HIFU has been performed in animal models and encouraging early results were obtained in animal studies with improved survival rates following HIFU [96,97].

However, data on HIFU in humans is limited. In a series of 30 patients with solid tumours, HIFU therapy

resulted in shrinkage of tumour volume in over 50%, but with a 10% local recurrence rate [98]. Complications recorded included skin burns, liver laceration and peripheral nerve injuries [98,99]. HIFU lesions are very sharply demarcated with a border of only several cell layers between normal and destroyed tissue [100]. This sharp demarcation, coupled with accurate targeting techniques could enable treatment of deep-seated tumours close to structures, which have rendered them inoperable. More trials of HIFU are needed before any conclusions regarding its clinical validity can be drawn.

7. Interstitial laser photocoagulation (ILP)

ILP was introduced by Bown in 1983 and involves local delivery of Laser light via the use of flexible fibres. It is the conversion of the absorbed light energy into heat which is responsible for the necrosis of the liver tumour. The characteristics of the Neodymium: yttrium–aluminium–garnet laser (Nd: YAG), maximises tissue penetration and the uniformity of energy distribution [101]. The size of the resultant lesions can be modified by increasing the power delivered, duration of exposure or using multiple fibres [102–104]. Blood flow along portal vessels acts as a 'heat sink' and it has been found that occluding portal vessels results in larger ablated lesions [105,106].

The first clinical report of ILP treatment was in 1985 by Hashimoto and colleagues [107] who treated patients with both liver metastases and HCC at laparotomy. The study proved the feasibility of the technique without major compilations. In 1989, Steger and colleagues [108] introduced the percutaneous technique and several groups have since modified this. ILP is now usually performed percutaneously under USS control, although a recent report of magnetic resonance imaging (MRI)-guided ILP appears very encouraging [109].

The optical fibre is introduced into the centre of the tumour, which is heated until the temperature at the lesion edge reaches either 60 or 45 °C for 15 min [101]. Real time non-invasive imaging is poor, although on-line monitoring with a T1-weighted turbo-fast low angle shot (FLASH) MRI, demonstrates a 'dark rim' around the edge of the tumour which is accurate in predicting necrosis in 85% of cases [110].

7.1. Results of ILP in liver tumours

Table 4 summarises the results of ILP in humans *in vivo*. Long-term survival data is sparse. Vogl and colleagues [111] in 1997 reported on a series of 99 patients in which a diffusing tip was used to deliver 10 W over a 10–20 min period for a mean number of eight treatments with a 3-year survival of 42%. Shankar and colleagues [112] reported on a series of 19 patients with a mean survival of 16 months following ILP treatment of liver metastases, while Pacella and colleagues reported a 5-year survival of 15% for HCC treatment [113]. The percentage of tumours in which ILP achieves complete destruction varies from as low as 60–98% [113–119]. It would appear, in keeping with other ablative treatments, that ILP is best suited to lesions below 3 cm [113,118, 119]. Monitoring in real time of the lesions produced by ILP has also been reported as problematic [115] and this could be a factor in the wide variation of complete necrosis rates observed with ILP. Comparisons of ILP with other focal ablative treatments are limited. One study by Amin and colleagues [41] compared ILP with PAI and found ILP to be superior in the treatment of colorectal liver metastases. A local recurrence rate of 6% has been reported following ILP in

Table 4
Table showing early results and percentage of tumour necrosis for interstitial laser photocoagulation (ILP)

Group and year [Ref.]	Number of patients	Type of lesions treated	Type of laser used	% of Tumours in which full necrosis achieved	Extent of partial tumour necrosis achieved in remaining tumours
Tranberg and colleagues 1996 [115]	10	5 HCC 7 METS	Nd:YAG	42	50% necrosis in remaining tumours
Amin and colleagues 1993 [116]	22	ALL METS	Nd:YAG	52	87% of remaining tumours achieved over 50% necrosis
Nolsoe and colleagues 1993 [101]	11	ALL METS	Nd:YAG	75	–
Giorgio and colleagues 2000 [117]	104	77 HCC 27 METS	Nd:YAG	82 of HCC 77 of METS	–
Caspani and colleagues 1997 [118]	35	15 HCC 20 METS	Nd:YAG	77.5	–
Pacella and colleagues 2001 [119]	74	HCC	Nd:YAG	97	–
Gillams and colleagues 1997 [114]	55	ALL METS	Nd:YAG	16	38% partial response

Nd:YAG, Neodymium: yttrium–aluminium–garnet laser.

HCC [113]. There is evidence from animal studies that biliary structures may interfere with the therapeutic effect of ILP by acting as a heat sink and they are the focus of local recurrence [120].

7.2. Complications of ILP

Complications are infrequently reported following ILP. Pain and fever are common. Other minor complications are pleural effusion, sub-capsular haematoma, paralytic ileus and one case of gastric haemorrhage [41,117]. Pretreatment liver function is important as ILP can cause severe deterioration in liver function assays and one death has been reported in a patient with Childs C cirrhosis [117]. ILP in larger tumours could be associated with a higher complication rate. At present, no large series of ILP therapy of large liver tumours exists; however, Tranberg and colleagues [115] reported a death from multiple organ failure following ILP of an 8-cm tumour. Animal models have also demonstrated the presence of gas formation in vascular structures during ILP [121]. In a clinical setting, it is theoretically possible that the presence of intracardiac gas in a patient with a patent foramen ovale could lead to a paradoxical embolus. In spite of this, ILP appears to be an extremely well-tolerated procedure.

8. Microwave coagulation therapy

Since its introduction in 1979 by Tabuse [122], Microwave Coagulation Therapy (MCT) has been used at laparotomy [123], laparoscopically [124], percutaneously [125] and thorascopically [126]. MCT is another hyperthermic technique relying on the conversion of energy to heat to destroy tumours. MCT creates a predictable and reproducible area of tissue and it can ablate the tumour capsule and so destroy any surrounding extracapsular invasion. Similar to HIFU, MCT appears to produce a haemostatic effect on surrounding tissues, reducing the risk of haemorrhage postprocedure at least theoretically [123].

Percutaneous MCT (PMCT) is performed under USS control and local anaesthetic. To achieve ablation of large lesions, a sequential technique with multiple needles has been developed [127]. Real-time USS monitoring demonstrates that the lesion becomes hypo-echoic immediately following treatment [128], giving quick and accurate feedback regarding the size of lesion. New microwave tips are currently under development, which can produce much larger lesions (3–6 cm) in diameter without the need for overlapping [129]. These lesions can be produced very rapidly, within 3 min, with a high degree of consistency in interlesion formation. Larger ablated lesions can also be achieved by selectively blocking the blood flow to the liver [130,131].

The ease of monitoring lesion size coupled with the rapidity of ablation are MCT's two major advantages over other types of therapy currently being developed.

8.1. Results of MCT in liver tumours

Table 5 summarises the data from some of the major series looking at the therapeutic effect of MCT in humans. Three-year survival rates for MCT appear encouraging ranging from 63% to as high as 92% [132–135]. The local recurrence rate following MCT ablation varies from 0 to 10% [136–138]. MCT appears to be less effective for liver metastases when compared with HCC [134,139]. The efficacy of tumour killing appears to be dependent on tumour size. Ohmoto and colleagues [140] reported the results of percutaneous MCT in 17 tumour nodules and found complete remission in 80% of tumours below 2 cm, with only 71% of tumours above 2 cm showing complete destruction.

Several studies have compared the efficacy of MCT with other focal ablative techniques. Shibata and colleagues [141] randomly assigned 30 patients with colorectal liver metastases to resection or treatment with MCT. All patients included in the study had multiple liver metastases. They found the 3-year survival following MCT or resection to be comparable, 14 and 23%, respectively, and the mean survival times from treatment to be 27 months in the resection group and 24 months in MCT group. This suggests that, at least for multiple liver metastases, MCT is comparable to liver resection. Seki and colleagues [125] compared MCT with PEI in the treatment of HCC. The overall 5-year survival rates for well-differentiated HCCs were no different between the groups, 70% for MCT and 78% for PEI. However, MCT was significantly better in the moderately and poorly differentiated HCCs with a 5-year survival rate of 78% compared with 38% for PEI.

8.2. Complications of MCT

Complication rates of 14% for HCCs and 20% for metastases have been reported following MCT [126]. Pneumothorax following the procedure is a relatively common finding having been reported in three independent series looking at a total of 120 patients [126,142,143]. Other complications include liver and lung abscesses, biliary fistula, portal vein thrombosis, hepatic failure, biloma, haemorrhage, tumour cell dissemination into the peritoneal cavity and along the needle track [126,139,144–148]. The complication rate is related to the size of the tumour treated, rising significantly in tumours over 4 cm [126]. The induction of artificial ascites or hydrothorax has been attempted to reduce the risk of distal heating effects, but this practice has not been adopted widely [149,150]. Although MCT is usually well tolerated, even in cirrhotic patients, it

Table 5
Table showing results of microwave coagulation therapy (MCT) in clinical trials

Group and year [Ref.]	Number of patients treated	HCC or metastatic disease	Method of MCT delivery	Period of follow-up	Local recurrence rate (%)	Survival rate (if applicable) (%)				
						1-year	2-year	3-year	4-year	5-year
Chen and colleagues 2002 [136]	52	–	Percutaneous	12 months	6	–	–	–	–	–
Itamoto and colleagues 2001 [132]	33	HCC	Percutaneous	4 Years	–	94	78	78	62	
Lu and colleagues 2001 [133]	50	HCC	Percutaneous	3 Years	8	96	83	73	–	–
Beppu and colleagues 1998 [134]	94	54 HCC 40 METS	Percutaneous	5 Years	33 HCC 14 METS	–	–	63 HCC 43 METS	–	38 HCC 33 METS
Seki and colleagues 2000 [135]	24	HCC	Laparoscopic	3 Years	14.3	–	–	92	–	–
Sato and colleagues 1996 [137]	19	HCC	12 Laparotomy 5 Laparoscopic 2 Thorascopic	37 months	10	–	–	–	–	–
Seki and colleagues 1999 [138]	15	METS	Percutaneous	37 months	0	–	–	–	–	–
Matsukawa and colleagues 1997 [139]	24	20 HCC 7 METS	Percutaneous	Mean of 18 months		83.1	68.7	–	–	–

may have a negative impact on survival in patients with a very poor hepatic reserve [151]. Finally, disturbing evidence from animal models has emerged which shows that MCT may in fact act to accelerate the growth of small residual tumour in the liver following ablation [152]. This animal model is not supported by any clinical findings, but it does highlight the difficulties in assessing focal ablative treatments, with limited clinical data.

9. Electrolysis

Electrolysis is a novel treatment that uses direct current (DC) to produce tissue destruction [153], with the volume of tissue necrosis produced being proportional to the electrolytic dose [153,154]. Direct currents (80–100 mA) are passed between two electrodes inserted into liver tissue. Electrolysis induces tissue necrosis by producing chlorine and hydrogen ions ($H+$) ions at the anode and hydrogen gas and sodium hydroxide at the cathode [153,155], thereby creating a pH gradient. The electrode products, hydrogen chloride (HCL) and chlorine gas (Cl_2), have been noted to be toxic to tissues [155]. Thermal necrosis plays no role in electrolytic ablation [153,156,157].

Much of the preliminary data evaluating electrolysis has been obtained from small rodent and porcine models. Electrolysis produces a dose-dependent and predictable response [158]. Its safety when used adjacent to vascular structures appears promising. Electrolysis next to the hepatic vein resulted in some intravascular gas, but no damage to the vessel itself [158]. The size of the lesion produced by electrolysis can be varied by increasing the 'dose' of current administered and also by placing the electrodes a greater distance apart [159]. Data from porcine models has shown that lesions of up 8 cm in diameter can be produced by a combination of multiple electrodes and hepatic inflow occlusion, via the Pringle manoeuvre [160]. Real-time monitoring of pH changes during electrolysis has been shown to accurately predict the degree of liver damage produced during electrolysis [161]. Currently, the biggest disadvantage to electrolysis is the length of time required to obtain liver destruction with a three-hour ablation time needed to produce an 8-cm lesion.

9.1. Results of electrolysis in patients

Few clinical trials of electrolysis in human subjects are reported in the literature and no long-term follow-up or large series exist. An isolated case of 1 patient, who had no histological evidence of recurrence 12 months following electrolytic ablation of a liver metastases, was reported by Berry and colleagues in 2000 [162]. A further series of 5 patients exists from 2002 [163], which

demonstrated that electrolysis was well-tolerated and that following treatment the lesion had been completely ablated. A series of 9 patients with a mean follow-up of 9 months, showed that 7 patients had no evidence of local recurrence on CT follow-up and median survival post-electrolysis was 17 (9–24 months) [164]. A multicentre, prospective, randomised controlled trial of liver resection versus liver resection with electrolytic ablation is currently in progress in Australia and the UK, and until the results of this trial are known, the value of electrolysis in a clinical setting remains to be seen.

10. Cryotherapy

Cryotherapy involves rapid freezing of tissue to subzero temperatures which results in ice formation in the extracellular space and cellular damage by dehydration and destruction of normal cellular structures [165]. A probe, cooled with liquid nitrogen or argon is inserted into the tumour mass under USS control. The ice ball produced is monitored using USS, where it can be seen as a growing hyperechoic lesion [166]. A margin of 1 cm is normally frozen beyond the tumour edge to ensure complete ablation. Cryotherapy is normally undertaken at laparotomy although percutaneous and laparoscopic methods have also been described [167,168]. Iceballs of 4.9×2.2×2.2 cm can normally be produced with one cryoprobe [169]. However, with the use of multiple probes, these ablated lesions can be increased to 6.0×4.9×5.6 cm [169].

10.1. Cryotherapy and liver tumours

Table 6 summarises the data from the largest series of cryotherapy in humans to date. The median survival time following cryotherapy for liver tumours is a mean of 30.7 months (range 22–42 months) [170–176]. Few studies report the long-term survival rates. However, 5-year survival rates appear reasonably consistent at around 20–30% following [174,176,177]. Cryotherapy appears less effective for carcinoid metastases with only a 60% survival [177,178] rate following the first year of treatment compared with a 70–80% survival for primary HCCs and colorectal liver metastases [174,175,177]. Local recurrence rates following cryosurgery vary from 16 to 24% [173–175,179], although the mean period of follow-up between reports varies from group to group.

Cryotherapy has been used in conjunction with liver resection, to ensure adequate resection margins and to reduce the tumour load, rendering liver resection possible. This combination of treatment has been found to achieve similar 5-year survival rates, when compared with tumours that were suitable for resection without cryotherapy (37% versus 36%, respectively) [180]. This finding is supported by other studies which have found equivalent survival rates between patients undergoing primary liver resection and those with tumours rendered operable by the combination of cryotherapy and resection [181–183].

Tumour size appears to influence the efficacy of cryotherapy. Seifert and colleagues [184], found that tumours with a diameter of over 3 cm were associated with a shorter disease-free interval at the cryosite, and Zhou and colleagues [177] found that HCCs under 5 cm had a better 5-year survival (55.4% versus 39.8%).

10.2. Complications of cryotherapy

The overall complication rate following cryotherapy has been reported at 27% [173], with a postprocedure mortality of 2–4% [176,185]. Haemorrhage is common following cryotherapy, usually because of cracking of

Table 6
Table showing the results of cryotherapy in clinical trials

Group and year [Ref.]	Number of patients	HCC or METS	Method of delivery	Median survival (months)	Local recurrence (%)	Long-term survival			
						1-year	2-year	3-year	5-year
Sheen and colleagues 2002 [170]	57	METS	Laparotomy	22	–	–	–	–	–
Shimonov and colleagues 2002 [171]	18	8 HCC 10 METS	Laparoscopy	32	–	–	–	–	–
Chung and colleagues 2001 [172]	14	METS	Laparotomy	42	–	–	–	–	–
Seifert and colleagues 2000 [173]	49	METS	Laparotomy	29	16	–	–	–	–
Shaprio and colleagues 1998 [178]	5	Carcinoid METS	Laparotomy	–	–	60	40	20	–
Zhou and colleagues 1998 [177]	245	HCC	Laparotomy	–	–	78.4	–	54.1	39.8%
Weaver and colleagues 1998 [185]	136	HCC	Laparotomy	30	35	85[a]	60[a]	40[a]	20[a]
Hewitt and colleagues 1998 [185]	20	METS	Laparotomy	32	35	88	60	–	–
Seifert and colleagues 2002 [184]	71	6 HCC 65 METS	Laparotomy	28	–	–	–	38	30
Junginer and colleagues 1998 [179]	29	METS	Laparotomy	–	24	–	–	–	–

[a] Figures taken from survival graph.

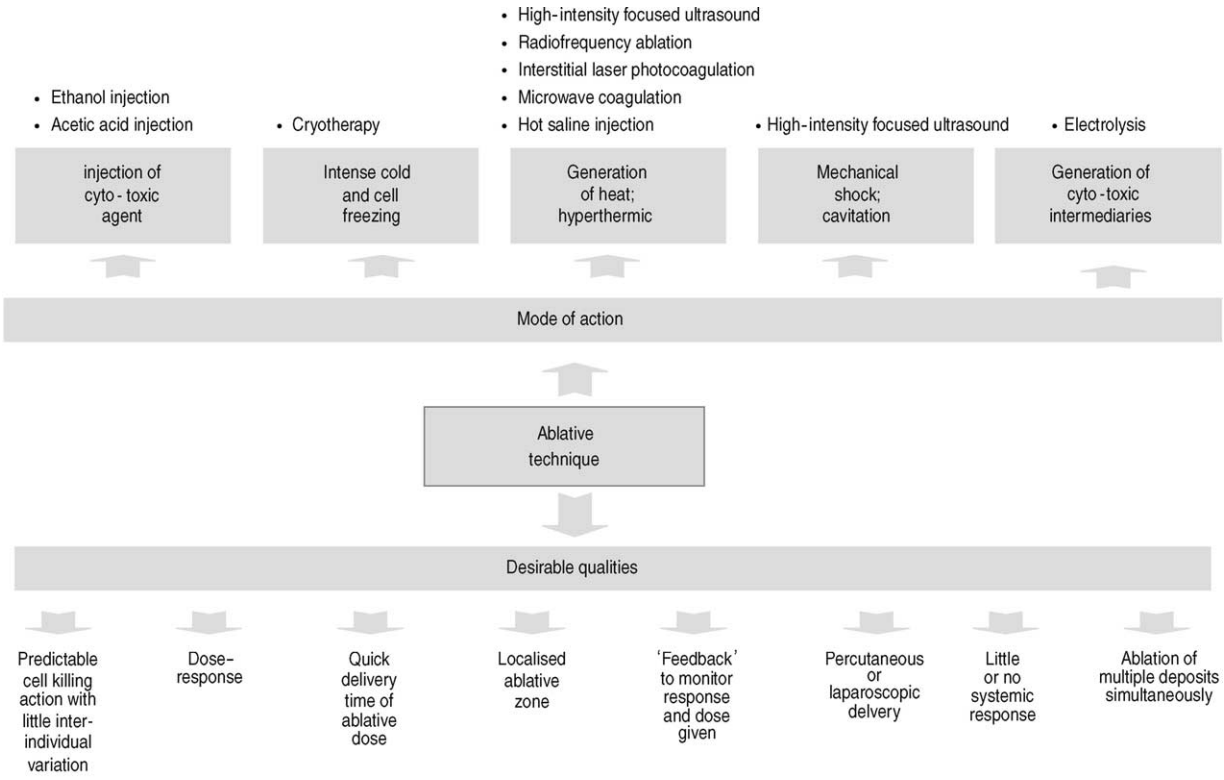

Fig. 1. Figure summarising the action of focal liver ablation techniques and their desirable clinical properties.

the liver parenchyma during the freeze–thaw cycles, and is a frequent complication following cryotherapy [172,186,187]. This bleeding is exacerbated by the transient thrombocytopenia and coagulopathy following cryotherapy [188]. Other complications reported are small bowel obstruction, pleural effusions, liver abscess, bile leaks, biliary fistulas and bilomas [172,187,189].

The condition of cryoshock has also been observed following tumour ablation. This appears to be a systemic inflammatory response that complicates 1% of all cryotherapy procedures, with a mortality rate of 18.2% [190]. Cryoshock appears to be mediated via the release of the pro-inflammatory cytokines; interleukin-6 and tumour necrosis factor [191] and there is evidence from animal models that its severity may be related to the size of the tumour lesion treated [170]. This same mechanism may be responsible for the deterioration in renal function noted in some patients following cryotherapy, which also appears to relate to the size of the tumour treated [192].

11. Conclusions

Fig. 1 summarises the properties and actions of the ablative techniques reviewed. There are limited data to evaluate fully the place of ablative techniques in the clinical setting. Many positive early reports suggest that ablative therapies could be a key component in the future treatment of unresectable liver metastases. However, large randomised control trials are needed comparing ablative therapy with the other therapeutic modalities available. Tandan and colleagues [193] commented in a recent review that "cryosurgery studies were methodologically-poor" and that this (and the small numbers treated) made valid conclusions regarding their results difficult. Many other ablative studies suffer from this same criticism. A study comparing two groups of patients, resectable and unresectable, who differ only in the anatomical placement of their lesions, is required for each of the ablative methods discussed here to obtain significant data. Alternatively, treating patients with unresectable disease purely on the basis of distribution within the liver and demonstrating a survival advantage at 2 years over chemotherapy might be a reasonable endpoint. As hepatobiliary surgery continues to develop and with liver resections for patients with large tumour burdens becoming more common, the distinction between what constitutes an operable or inoperable tumour is becomingly increasingly blurred. In many centres, tumours which would have initially been considered for ablation are now being assessed for resection surgery without the help of ablation.

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