The development of electrolysis for local destruction of solid tumours

By:

Guy John MADDERN

Department of Surgery

The Queen Elizabeth Hospital

The University of Adelaide

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Declaration

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text or publication.

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Guy John MADDERN

2nd April 2003

Acknowledgment

The work of this thesis spans almost a decade with considerable assistance from many individuals.

Ashley Dennison helped in the initial idea and experimental protocols and he maintained close collaboration on the project over the 10 years.

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The development of electrolysis for the local destruction of solid tumours
M.D. Thesis
G.J. Maddern

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Abstract

This thesis comprises the collection of publications on the development of electrolysis as a local ablative technique for solid tumours including the liver and pancreas.

This work has been conducted in association with a number of colleagues included as authors on the papers submitted. The research efforts have been under my coordination and direction, with all patient studies exclusively managed by myself. The work presented first establishes the feasibility of electrolytically produced lesions in small and large animal models, and then its effect on tumour cells in a small animal model.

Unfortunately no suitable large animal tumour model exists so dose response calculation was determined in a pig liver that approximates human dimensions and anatomy. Studies were also conducted to better understand the mechanism of the destructive effects of electrolytic treatments. The pH changes not heat production were found to be the primary mechanism of cell death. When applied to patients in both a pilot and limited clinical study for liver tumours, complete destruction of tumour can be achieved without any adverse effects being detected.

The electrolytic destruction has also been applied to pancreatic tissue with similar controllable effects which may offer a palliative option for pancreatic cancer in the future.

Introduction

The papers put forward in this thesis comprise review-type articles of the technology at the time as well as a number of descriptions of the experimental processes taking place relating to electrolytic destruction of tumours. The main sources from which the information in the papers is derived and the extent to which I have made use of the work of others is described for each publication below.

Publication 1

Baxter PS, Wemyss-Holden SA, Dennison AR, Maddern GJ (1998)
Electrochemically-induced hepatic necrosis – The next step forward in patients with unresectable liver tumours?
Australian & New Zealand Journal of Surgery 68: 637–640

This was an experimental study to look at the effects of electrochemically-induced hepatic necrosis. The concept was mine, the work was directly supervised by myself, although the series of experiments were conducted by one of our Research Assistants and MD students.

Publication 2

Robertson GSM, Wemyss-Holden SA, Dennison AR, Hall P de la M, Baxter PS, Maddern GJ (1998)
Experimental study of electrolysis-induced hepatic necrosis
British Journal of Surgery 85: 1212–1216

This was also a study designed by myself and conducted by MD students working within the Department. The original experimental design and the issues associated with its execution were all directly under my supervision,

although again the majority of the work was conducted by higher degree students.

Publication 3

Berry DP, Maddern GJ (2000)
Other in situ ablative techniques for unresectable liver tumours
Asian Journal of Surgery 23(1): 22–31

This is a review of the current state of the literature regarding ablation of unresectable liver tumours and was jointly authored by myself and Mr David Berry.

Publication 4

Wemyss-Holden SA, Robertson GSM, Dennison AR, Vanderzon PS, Hall P, Maddern GJ (2000)
A new treatment for unresectable liver tumours: long-term studies of electrolytic lesions in the pig liver.
Clinical Science 98(5): 561–567

This publication was primarily written by myself and Dr Simon Wemyss-Holden, one of our Registrars working at The Queen Elizabeth Hospital. The work was conceived by our research group and its ongoing supervision and final publication was under my direct control and involvement.

Publication 5

Wemyss-Holden SA, Hall P de la M, Robertson GSM, Dennison AR, Vanderzon PS, Maddern GJ (2000)
The safety of electrolytically-induced hepatic necrosis in a pig model.
Australian and New Zealand Journal of Surgery 70(8): 607–612

This was similarly executed under the same basis as publication 4.

Publication 6

Wemyss-Holden SA, Robertson GSM, Dennison AR, Hall P de la M, Fothergill JC, Maddern GJ (2000)
Electrochemical lesions in the rat liver support its potential for treatment of liver tumors
Journal of Surgical Research 93(1): 55–62

This was conceived by myself and Dr Simon Wemyss-Holden and conducted within the Department under my direct supervision and guidance, although in this particular paper I had little direct hands-on involvement.

Publication 7

Wemyss-Holden SA, Robertson GSM, Dennison AR, P de la M Hall, Maddern GJ (2000)
Electrolytic treatment of colorectal liver tumour deposits in a rat model: A technique with potential for patients with unresectable liver tumours.
Digestive Diseases 18: 50–57

Dr Simon Wemyss-Holden, Mr Gavin Robertson and myself carried out the experiments described in this paper. The conceptual issues were greatly helped by Professor Pauline Hall and Mr Ashley Dennison.

Publication 8

Berry DP, Dennison AR, Ward R, Maddern GJ (2000)
Electrolytic ablation of colorectal liver metastases – 1 year histological patient follow-up
Digestive Surgery 17(5): 518–519

This is a case report which was conducted on a patient of mine. I performed the surgery, conducted the ablation and arranged the followup. The manuscript was prepared by Mr David Berry based on this clinical experience.

Publication 9

Fosh B, Finch JG, Anthony A, Texler M, Maddern GJ (2001)
Electrolytic ablation of the rat pancreas: a feasibility trial
BMC Gastroenterology 1(1): 9

The work associated with this publication was carried out by one of our Research Registrars, Dr Beverley Fosh, under my direct supervision. The conceptual idea behind the work was my own and, indeed, it is at this stage a completely novel and somewhat radical technique designed at managing pancreatic lesions. In this particular study, the technical aspects were worked through by myself and the research group but the experiments were conducted predominantly by Dr Fosh.

Publication 10

Teague BD, Wemyss-Holden SA, Fosh BG, Dennison AR, Maddern GJ (2002)
Electrolysis and other local ablative treatments for non-resectable colorectal liver metastases
Australian & New Zealand Journal of Surgery 72(2): 137–141

This articles encapsulates the current state of knowledge of non-resective techniques available for liver tumours. It was written by myself and the other co-authors as a review article for the *Australian & New Zealand Journal of Surgery*.

Publication 11

Finch JG, Fosh B, Anthony A, Slimani EK, Texler M, Berry DP, Dennison AR, Maddern GJ (2002)
Liver electrolysis: pH can reliably monitor the extent of hepatic ablation in pigs
Clinical Science 102: 389-395

This was a paper put together by the efforts of Dr Guy Finch with input from myself regarding the use of pH changes to monitor the extent of necrosis occurring during electrolytic destruction. The experimental design and the concept behind the work was mainly my own but many of the technical aspects were solved by Dr Finch in discussion with the general research group.

Publication 12

Wemyss-Holden SA, Dennison AR, Finch JG, Hall P, Maddern GJ (2002)
Electrolytic ablation as an adjunct to liver resection: experimental studies of predictability and safety
British Journal of Surgery 89: 579-85

This publication appeared in the British Journal of Surgery and was an important work in that it demonstrated that electrolytic destruction near major vessels did not seem to cause any adverse effects. The experimental design was my own and the work was conducted by both myself and Dr Wemyss-Holden.

Publication 13

Wemyss-Holden SA, Berry DP, Robertson GSM, Dennison AR, Hall P de la M, Maddern GJ (2002)
Electrolytic ablation as an adjunct to liver resection: safety and efficacy in patients
Australian & New Zealand Journal of Surgery 72(8):589-593

This reports the early clinical experience with a number of my patients on whom I performed all of the electrolytic procedures reported and on whom I have maintained on-going followup.

Publication 14

Fosh BG, Finch JG, Lea M, Black C, Wong S, Wemyss-Holden SA, Maddern GJ (2002)
The use of electrolysis as an adjunct to liver resection
British Journal of Surgery 89: 999-1002

This reports further the clinical results of this technique in a number of patients. They are all patients under my care, I performed the surgery on all of them and the followup has also been performed by myself. The data was collated and written up by Dr Fosh.

Publication 15

Wemyss-Holden SA, Court FG, Burrell A, Morrison CP, Morales DR, Teague BD, Rodgers N, Anthony AA, Metcalfe MS, Dennison AR, Maddern GJ (2003)
Palliation of pancreatic cancer using electrolytic ablation
Surgical Endoscopy 17: 207-211
DOI: 10.1007/s00464-002-9109.y

This, again, represented a novel idea using the pancreatic duct as a conduit to deliver the electrolytic dose by the use of an ERCP machine. This paper demonstrates the feasibility of delivering the electrode without the need for an open procedure. The idea was entirely mine, the technical issues were helped greatly by the input of Dr Wemyss-Holden, Dr Fiona Court and Dr Charles Morrison.

Aust. N.Z. J. Surg. (1998) 68, 637–640

ORIGINAL ARTICLE

ELECTROCHEMICALLY INDUCED HEPATIC NECROSIS: THE NEXT STEP FORWARD IN PATIENTS WITH UNRESECTABLE LIVER TUMOURS?

P. S. BAXTER,* S. A. WEMYSS-HOLDEN,* A. R. DENNISON† AND G. J. MADDERN*

**Department of Surgery, University of Adelaide, Queen Elizabeth Hospital, South Australia, Australia and †Department of Surgery, Leicester General Hospital, Leicester, United Kingdom*

Background: The treatment of patients with unresectable liver tumours remains an unsolved clinical problem. Several methods of locoregional treatment have been developed. These methods rely mainly on direct thermal or chemical insults and consequently have their own inherent limitations in clinical usage. The 'ideal' treatment would combine the direct cytotoxic effects of chemical treatments with the relative predictability of thermal insults, without the associated complications. This study aims to investigate whether the direct chemical effect of electrolytic hepatic necrosis is associated with any heating effect, and if so, whether the temperature change is dose-dependent.
Methods: An electrolytic 'dose' sufficient to induce a localized zone of hepatic necrosis was delivered to the livers of rats and pigs via implanted platinum electrodes.
Results: The results showed that there was no significant temperature increase at low current levels (2–4 mA) in the rat liver. In the pig, there was a significant ($P < 0.01$) increase in temperature of 4.2°C during electrolysis, when delivered at between 20 and 50 mA. However, such a small increase in temperature would have been insufficient to cause appreciable thermal necrosis.
Conclusions: This study demonstrates that electrolysis-induced hepatic necrosis is produced without an increase in temperature; clearly cell death results from the direct effects of cytotoxic electrode products and an alteration of intracellular pH. Consequently, it is likely that as a method for ablating liver tumours, electrolysis should be associated with fewer complications than other forms of locoregional treatment.

Key words: electrolysis, liver, thermal, tumour.

INTRODUCTION

The majority of patients who develop hepatic metastases of colorectal origin are incurable. Only 5–10% of these patients are suitable candidates for surgical resection,[1] which is the only treatment that has been shown to improve survival.[2] For the remainder, median survival is 6 months and an effective treatment for these patients is urgently needed.[3]

Several methods of local treatment for unresectable liver tumours have been developed. Many of these techniques, such as interstitial laser therapy,[4] cryotherapy,[5] and microwave hyperthermia,[6] cause tissue necrosis by delivering a direct thermal insult to the tumour. Other methods use the direct cytotoxic effects of certain chemicals such as alcohol,[7] and chemotherapeutic drugs.[8] However, the effects of these are largely unpredictable and uncontrollable. Thermal methods of tumour ablation have certain inherent limitations, and dangers such as fracturing the ice ball with potentially fatal haemorrhage (cryotherapy), carbonization and charring (interstitial laser therapy) would not be encountered if tissue destruction could be produced at ambient temperature. Theoretically, the 'ideal' treatment would combine the relative predictability of the thermal treatments with the direct cytotoxic effects of the chemical methods, without their individual drawbacks.

Electrolysis is a new local treatment for patients with unresectable primary or secondary liver tumours which is currently being developed for use in patients at the Queen Elizabeth Hospital. Early results suggest that this technique incorporates the advantageous properties of chemical and thermal treatments without the associated complications. Localized tissue necrosis is produced by passing a low-voltage direct current (DC) between anode (positive) and cathode (negative) electrodes. When the current is applied *in vivo*, sodium hydroxide and hydrogen are produced at the cathode and hydrochloric acid, oxygen and chlorine gas at the anode.[9–13] This results in a significant pH gradient being established between the electrodes.[14,15] Consequently, the local environment becomes intensely cytotoxic and cell necrosis results. The resulting spherical zone of necrosis is sharply demarcated from the surrounding normal liver and the tissues between the electrodes are unaffected. Results in the rat and pig livers showed that electrolysis is a safe and effective method for creating areas of hepatic necrosis. Histopathology confirmed the presence of necrotic tissue at the electrode sites. Moreover, the induced necrosis was dose-dependent and was produced at a rate of between 2.0 cm^3/100 coulombs (C) (rat) and 2.3 cm^3/100 C (pig). It was proposed that the observed inter-species variation in rates of necrosis resulted from the difference in resistivity of the liver parenchyma between the two species (unpubl. observ.).

Because electrolysis uses electric current, it is reasonable to assume that cell necrosis may in part result from a heating effect. Were this so, it would potentially be associated with the complications of thermal treatments. A review of the literature on the temperature change associated with electrolysis showed variable results. Temperature changes ranging from 0 to 20°C have been reported.[16–18] However, all papers suggest that the thermal effect of electrolysis is negligible.

For electrolysis to be accepted as a new treatment method for

Correspondence: Professor Guy Maddern, Department of Surgery, Queen Elizabeth Hospital, Woodville Road, Woodville, SA 5011, Australia.
Email: <gmaddern@medicine.adelaide.edu.au>

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patients with unresectable liver tumours it must be shown to be superior to those techniques currently available. As such it should be demonstrated that the direct electrochemical insult is delivered without a significant heating effect and the associated potentially life-threatening complications.Using both small and large animal models this study aimed to (i) determine if hepatic necrosis could be produced in the rat liver at low amperage with no associated temperature increase; and (ii) determine if thermally induced necrosis is likely to occur in the clinical setting where higher amperages will be employed using a pig model.

METHODS

The direct current generator was manufactured by the Bioengineering, Transducers and Signal Processing Research Group, University of Leicester, United Kingdom. All experiments on animals were approved by the ethics committees of the University of Adelaide and the Queen Elizabeth Hospital and conform to the statements of Animal Experimentation by the NH&MRC.

Rats

Sixteen SPF female Wistar WAG rats weighing a mean of 199 g (range 192–205 g) were anaesthetized using standard halothane/nitrous oxide/oxygen anaesthesia. Anaesthesia induction was performed using a perspex box with 3.5% halothane, 1 L/min nitrous and 1000 cc/min oxygen. Maintenance of anaesthesia was achieved with an inhalation system using 1.5% halothane, 0.5 L/min nitrous and 300 cc/min oxygen. The liver was exposed and everted through a midline incision. Two platinum electrodes (0.5-mm diameter) were inserted to a depth of 2 mm into one lobe of the rat's liver with a separation of 2 mm. A 0.8-mm-diameter thermocouple (80TK Thermocouple Module FLUKE used with Escort EDM-169S TÜV, Rheinland Group) was inserted into the liver between the electrodes with care taken not to touch the electrodes with the thermocouple. Core temperature was continuously monitored and recorded using a 3-mm-diameter rectal probe (KM250, Kane-May Limited).

Thermocouple and electrodes were placed into the liver and the equipment set up prior to randomization of treatment. The person recording the temperatures was not blinded to the treatment group.

Ambient environmental temperature was also continuously monitored and recorded using a temperature probe (HMP 35, Vaisala Pty Ltd, Helsinki, Finland) connected to an indicator unit (HMI, Vaisala Pty Ltd) placed next to the rat. Liver temperature at the electrode site, ambient environmental temperature immediately surrounding the rat and rectal temperature were all measured and recorded.

From previous work (G. Maddern *et al.* unpubl. data, 1998) it was shown that a current of 4 C produced a 5-mm-diameter lesion in the rat liver. The rate at which the dose could be delivered was altered by increasing or decreasing the current. In order to determine whether increased rate of delivery influenced the temperature, 4 C were delivered at both 2 and 4 mA. All rats were killed at the end of treatment by anaesthetic overdose.

Nine rats received electrolysis: in each rat one lobe of the liver was treated with 4 C at 4 mA, and the other lobe with 4 C at 2 mA. Seven rats were used as controls where every procedure and recording was identical to the treatment rats, but no current was passed between the electrodes. The mean time of each electrolysis treatment was matched with the temperature recording time for the controls (18 min for 4 mA, 32 min for 2 mA) and both lobes of the liver were used.

Pigs

Due to size limitations in the rat liver, pigs were used to deliver the electrolytic dose at higher currents similar to those that are used in the clinical setting to determine if there was significant heating around the electrodes.

Pigs were fasted overnight and sedated with a deep-intramuscular injection of ketamine (20 mg/kg) and xylazine (1.5 mg/kg). Pigs were maintained on gaseous anaesthesia of 1.5% halothane in oxygen via a laryngeal mask airway. Temperature studies were performed on the pigs at doses of between 20 and 50 mA (the range likely to be used in patients) by measuring core temperature, ambient temperature and liver temperature at the electrolysis site every 2 min for a total of 10 min at each setting. Temperature measurements were also continued for 2 min after the end of electrolysis to determine if any rises in temperature continued after the electrolysis had finished. All measuring devices and randomizing methods were the same as those used for the rat studies. The electrodes used were supplied by Johnson & Johnson Medical Pty Ltd, North Ryde, NSW. They were 6 French G with a diameter of 2 mm.

A total of five pigs were used for this analysis. Three pigs were controls with a total of eight 12-minute control studies performed. The remaining two pigs underwent thirteen 12-minute studies (six studies on one and 7 on the other).

A repeated measures analysis of variance was used to analyse the temperature change of the liver around the electrodes over time. Baseline measurements of rectal temperature, liver temperature and ambient temperature were included as covariates, and the rectal and ambient temperatures over time were included as time-varying covariates. An auto-regressive error structure was assumed.

Program 5 V from the BMDP statistical software package was used for this analysis by a consultant statistician.

RESULTS

All animals tolerated the treatment well. No intra-operative complications were observed and no animal died prior to the anaesthetic overdose.

Rats

The change in temperature around the electrodes was significantly different during electrolysis when compared with the control group ($P < 0.01$). Interestingly, a mean temperature increase of 1.5°C was recorded in the control group; no temperature change was observed in the electrolysis group (Table 1). The site of electrolysis in the rat liver (left or right lobe) made no significant difference to the temperature changes.

Pigs

There was also a significant difference in the temperature recordings in the pig liver between the treated and control groups. The baseline liver temperature increased by a mean of 4.2°C over the course of electrolysis and decreased by a mean of 0.7°C in the control group of animals where no current was passed between the electrodes ($P < 0.01$) (Table 2). The mean temperature increase after electrolysis using 20 mA of current

Table 1. Results of the temperature changes in the rat liver (°C) at the site of electrolysis with the estimated mean values and the standard error of the estimate in parenthesis

	Estimated mean liver temperature at the start of electrolysis (°C)	Estimated mean liver temperature at the end of electrolysis (°C)	Temperature change	Significance
Electrolysis group	32.4 (0.22)	32.4 (0.35)	0	NS
Control group	32.4 (0.22)	33.9 (0.35)	1.5°C↑	$P < 0.01$

NS, not significant.

Table 2. Results of the temperature changes in the pig liver (°C) at the site of electrolysis with the estimated mean values and the standard error of the estimate in parenthesis

	Estimated mean liver temperature at the start of electrolysis (°C)	Estimated mean liver temperature at the end of electrolysis (°C)	Temperature change	Significance
Electrolysis group	41.0 (1.31)	45.2 (1.28)	4.2°C↑	$P < 0.01$
Control group	36.3 (1.66)	35.6 (1.63)	0.7°C↓	NS

NS, not significant.

was 2.6°C, 9°C with 30 mA, 8°C with 40 mA, and there was a 2°C mean temperature increase for the 50-mA group. Therefore the magnitude of the current did not significantly affect the temperature change over time. It is difficult to explain why there is a temperature difference at baseline between the control animals and the electrolysis animals. Operative conditions, theatre lights and length of anaesthesia all may contribute to this.

DISCUSSION

This study has shown that with electrolytic doses which have been shown to kill tumours in the rat liver (G. Maddern *et al.* unpubl. data, 1997) the necrosis does not result from hyperthermia. Clearly, the mechanisms involved in tumour ablation are not thermal but are likely to result from the fiercely cytotoxic environment established around the electrodes during treatment. Specifically, sodium hydroxide and hydrogen are produced at the cathode and hydrochloric acid, oxygen and chlorine gas at the anode.[9-13] Chloride ions are attracted to the anode and are largely oxidized to chlorine gas; water is electrolysed releasing both ionic and molecular oxygen. Chlorine is a powerful oxidant which immediately attacks surrounding tissue.[11] As a result of these ionic fluxes, a pH gradient is established between the electrodes with the anode becoming acidic relative to the basic cathode, and a sharply demarcated zone of necrosis results.[15]

In the clinical setting, it is envisaged that relatively large liver tumours will be treated using electrolysis. This will require an electrolytic dose several orders of magnitude greater than that which was typically used in the rat (up to 1000 C). In order to maintain reasonable treatment times, this dose will need to be delivered at a higher current, as was used in the pig phase of this study. The maximum current is likely to be limited by patient compliance.[19] At up to 50 mA there was a statistically but not clinically significant increase in temperature of the local environment during electrolysis; an increase of 4.2°C would be insufficient to induce necrosis. Given at 100 mA temperature increases of only 7°C have been reported.[18]

Several methods of localized tumour necrosis rely upon a thermal insult to cause tissue destruction.[4-6] While excessive heat or cold is undoubtedly effective and relatively predictable, both have been associated with certain complications such as haemorrhage, biliary fistulae and renal impairment,[20] carbonization and charring. Other methods that deliver a direct chemical insult to the tumour such as alcohol injection and locoregional chemotherapy are attractive but largely unpredictable in effect.[7,8] This study has shown that the directly delivered electrochemical insult of electrolysis is not associated with any significant heating effect and is therefore likely to be associated with a lower complication rate than thermal or chemical treatments when treating patients with unresectable liver tumours.

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Experimental study of electrolysis-induced hepatic necrosis

G. S. M. ROBERTSON*, S. A. WEMYSS-HOLDEN, A. R. DENNISON†, P. DE LA M. HALL‡, P. BAXTER and G. J. MADDERN

*University of Adelaide, Department of Surgery, The Queen Elizabeth Hospital, Adelaide, Australia, Departments of Surgery, *Leicester Royal Infirmary and †Leicester General Hospital, Leicester, UK, and ‡Department of Histopathology, Flinders Medical Centre, Adelaide, Australia*

Correspondence to: Professor G. J. Maddern, Department of Surgery, The Queen Elizabeth Hospital, Woodville Road, Woodville South, Adelaide, South Australia 5011, Australia

Background One of the most promising but unexplored methods for treating patients with irresectable liver tumours is electrolysis. This study examined the effect of increasing 'current dose' on the volume of the lesion induced in normal rat liver.

Methods A direct current generator, connected to platinum electrodes implanted in the rat liver, was used to examine the effect of (1) varying current doses from 1 to 5 coulombs and (2) electrode separation (2 or 20 mm), on the volume of liver necrosis.

Results There was a significant correlation ($P < 0{\cdot}001$) between the current dose and the volume of necrosis produced for each electrode separation. Placing the electrodes 2 mm apart resulted in smaller total volumes of necrosis than placing them 20 mm apart when anode lesions were significantly larger than cathode lesions ($P < 0{\cdot}05$). Liver enzymes (aspartate aminotransferase, alanine aminotransferase) were significantly raised 1 day after treatment ($P < 0{\cdot}001$) and predicted the total volume of hepatic necrosis ($P < 0{\cdot}001$).

Conclusion Predictable and reproducible areas of liver necrosis are produced with electrolysis. If these results extrapolate to larger animal models, this technique has potential for patients with irresectable primary and secondary liver tumours.

Primary and secondary liver tumours represent a significant problem worldwide both numerically and socioeconomically. Presently only surgical resection offers the potential for cure with between a quarter and a third of patients surviving 5 years[1,2]. Unfortunately only a relatively small number of patients (less than 10 per cent) are suitable for surgery[3] and the remaining 90–95 per cent have a dismal outlook[4] with a median survival of approximately 6 months[5–7].

A number of different non-resectional approaches have been investigated including percutaneous alcohol injection[8], instillation of specific toxins[9,10], cryotherapy[11], laser thermotherapy[12], both regional and systemic chemotherapy[13], and liver transplantation[14]. These methods have all been shown to be invasive or clinically unreliable and none has conferred a reproducible long-term survival advantage, although several are useful as palliation[4,15,16].

Electrolysis is a simple and extensively investigated electrochemical phenomenon with a negligible thermal effect[17,18]. Potentially it fulfils all of the criteria for safe tissue destruction which would allow its clinical application to liver lesions. The effect is produced by direct current (DC) generated between a pair (or more) of electrodes designated anode and cathode. When current is applied in human plasma, sodium hydroxide and hydrogen are produced at the cathode and hydrochloric acid, oxygen and chlorine gas at the anode[19–23]. This results in a significant pH gradient between the electrodes producing a fiercely cytotoxic local environment and a resulting well defined pattern of cell necrosis[24,25]. The situation is considerably more complex *in vivo*, however, and a direct effect of the DC on ionic transport systems, capillary circulation and movement of immunologically competent cells have all been hypothesized[26].

Animal experiments have been conducted to examine the effects of electrolysis in the mouse[18,21], rat[22,27–29], rabbit[17], and pig[20,30–34]. These studies which started in the mid-1970s were followed by clinical studies in a small number of patients with pulmonary lesions[35–37] and more recently reports from China of the treatment of liver tumours[38,39]. This new treatment modality nevertheless remains in its infancy and considerable evaluation of the basic physiological changes induced and the best method of current delivery are required before its widespread clinical introduction.

This study examined the effect of variations in current dose and electrode separation on the volume of hepatic necrosis and resultant liver enzyme derangement in the normal rat liver.

Materials and methods

A DC generator was designed to deliver a preset current dose (coulombs = current (amperes) × time (seconds)). Automatic voltage adjustment between 1 and 25 V allowed a preset rate of current delivery (variable between 1 and 100 mA) regardless of alterations in hepatic parenchymal resistance during treatment. Anode and cathode electrodes were identical and constructed from fine platinum wire (0·5 mm diameter), which was electrically insulated using a semirigid plastic sleeve. Two millimetres of uninsulated electrode was exposed at the tip producing an effective electrode surface area of 3·34 mm^2.

The use of laboratory animals in this study was approved by local animal ethics committees (University of Adelaide and The Queen Elizabeth Hospital, Adelaide) and conformed with the 'Code of practice for the care and use of animals for scientific purposes' (NHMRC/CSIRO/AAO 1990) and The Prevention of Cruelty to Animals Act 1985.

Fifty Wistar-WAG male rats (210–320 g) obtained from the Animal Resources Centre (Perth, Australia) were divided into

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two groups of 25 according to the separation of the anode and cathode. In group 1, the electrodes were both placed in the same lobe of the liver with the tips separated by 2·0 mm. In group 2, the electrodes were inserted into different lobes of the liver (right and left) 20 mm apart. Under standard halothane/nitrous oxide anaesthesia and aseptic conditions, the liver was exposed through a midline incision and delivered through the wound. Electrodes were inserted into the liver parenchyma to a depth of 5 mm and supported during the electrolysis using a gantry-type frame designed to allow atraumatic electrode movement with respiration.

For each animal the preset combination of coulombs and milliamps was then delivered by the DC generator (1–5 coulombs, delivered at 1–5 mA). In two groups of four control animals, electrodes were implanted as in groups 1 and 2 and connected to the DC generator, but no current was passed between the electrodes. To control for the varying treatment times in groups 1 and 2, the electrodes were left *in situ* for 10, 30, 60 or 90 min. All animals were killed after 48 h.

Blood samples were analysed before operation for levels of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, γ-glutamyltranspeptidase and bilirubin (Technicon AXON analyser, Bayer Health Care, Pymble, Australia). The results were compared with those taken at completion of the electrolysis, 24 h later and at the time of death.

After the experiment the livers were removed and fixed in 10 per cent buffered formalin. After 2 weeks the liver was sectioned into slices 1 mm thick (*Fig. 1a*). The three maximum diameters (D1–3) at right angles to each other of the lesion at each electrode site were then measured, using a micrometer, by two independent observers with no knowledge of the dose used to create the lesion. The mean of the two observers' values for D1–3 were calculated. As these measurements were often slightly different, the volume of each lesion was then calculated using the formula for an ellipsoid rather than a sphere: volume = $4/3\pi(R1 \times R2 \times R3)$, where $R1 = D1/2$ etc.

In most animals there was also a wedge of secondary ischaemic necrosis peripheral to the 'primary' electrolytic lesion at the site of electrode implantation (*Fig. 1b*). This area of secondary necrosis was also measured and its volume was calculated.

Blocks of liver containing the electrolysis-induced lesions were processed, embedded in paraffin, sectioned and stained with haematoxylin and eosin. Coded sections were examined by a hepatopathologist (P.H.).

Results were analysed statistically using the unpaired *t* test and regression analysis (Statworks, version 1.2; Cricket Software, Philadelphia, Pennsylvania, USA).

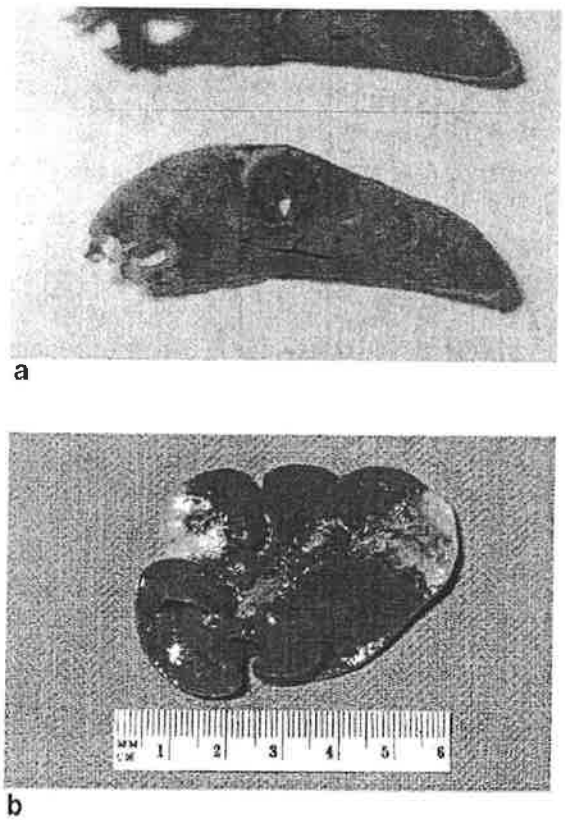

Fig. 1 a Liver section 1 mm thick, taken through the centre of an electrolytic lesion before measurement. This lesion was produced using 5 coulombs. b Yellow wedge infarcts peripheral to the grey, circular 'primary' electrolytic lesions (electrodes separated)

Results

All animals tolerated the treatment well and made a good postoperative recovery. No animal died prematurely. In the control groups the site of electrode placement could barely be discerned macroscopically and there was no evidence of any 'lesion'.

Group 1 (electrode tips 2 mm apart)

There was a significant correlation between the volume of the 'primary' electrolytic lesion and the number of coulombs delivered ($P < 0{\cdot}001$) (*Fig. 2*). The relationship was linear although variability increased with the number of coulombs. The rate at which the treatment was given (1–5 mA) had no significant effect on this relationship.

At autopsy, all 25 animals were found to have not only a 'primary' electrolytic lesion but also a variable amount of 'secondary' ischaemic necrosis peripherally (*Figs 1a* and *1b*). There was no significant correlation between the volume of the 'secondary' lesion and either the number of coulombs delivered or the current flow (milliamperes). There were significant correlations between the total

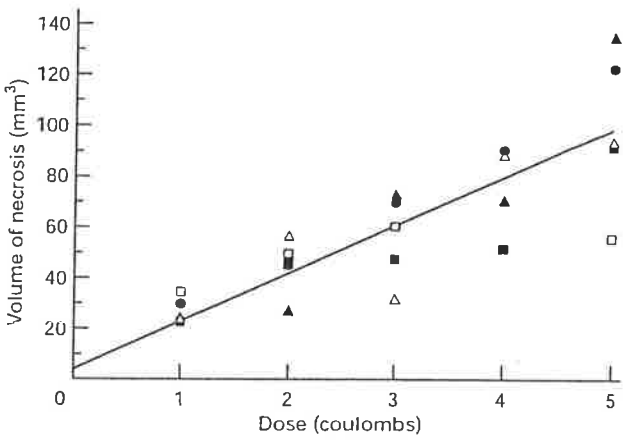

Fig. 2 Correlation between the volume of the 'primary' electrolytic lesion and the number of coulombs delivered with the electrodes placed 2 mm apart ($r^2 = 0{\cdot}804$, $P < 0{\cdot}001$). Current delivery was preset at 1 mA (■), 2 mA (□), 3 mA (△), 4 mA (●) and 5 mA (▲) determining the time over which each dose was delivered

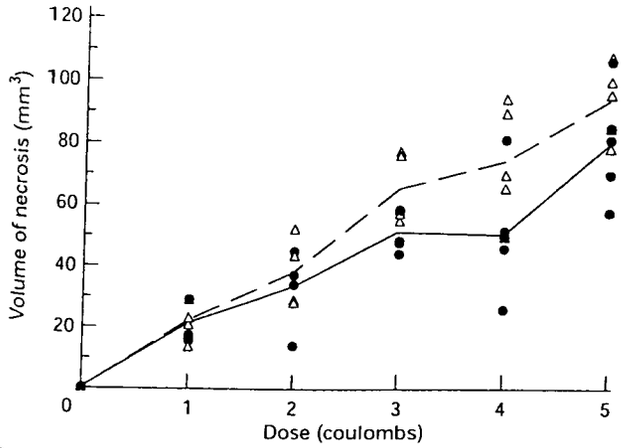

Fig. 3 Correlation between the volume of the 'primary' electrolytic lesion and the number of coulombs delivered with the electrodes placed 20 mm apart. Δ, Values for anode; -----, mean for each dose ($r^2 = 0.875$, $P < 0.001$). ●, Values for cathode; ---, mean ($r^2 = 0.742$, $P < 0.001$)

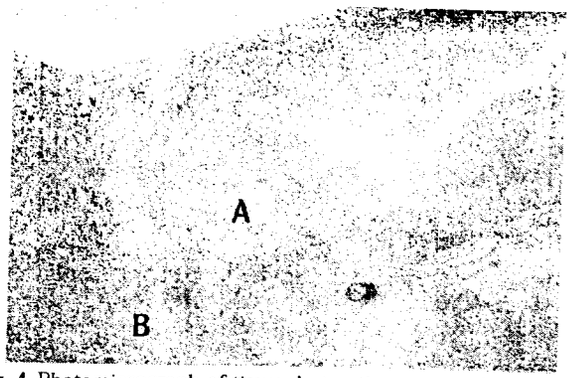

Fig. 4 Photomicrograph of tissue destruction seen at the site of the electrode tip, surrounded by a zone of coagulative necrosis – the 'primary' lesion (A). A peripheral zone of 'secondary' necrosis is located between the 'primary' lesion and the adjacent normal liver (B). Haematoxylin and eosin stain; objective × 4

volume of necrosis produced ('primary' plus 'secondary' lesion) and the 24-h increase in levels of AST ($r^2 = 0.693$, $P < 0.001$) and ALT ($r^2 = 0.720$, $P < 0.001$).

Group 2 (electrode tips 20 mm apart)

There was a significant correlation ($P < 0.001$) between the number of coulombs delivered and the volume of the lesions produced at both the anode and the cathode (*Fig. 3*), although the slope of these lines was different. The line for the anode was always steeper than that of the cathode and at both 3 and 4 coulombs lesions were significantly larger ($P < 0.05$). The rate at which the treatment was given (milliamperes) did not affect this relationship. Twenty of the 25 animals were found to have a wedge-shaped secondary infarct peripheral to the 'primary' lesions in one (seven) or both (13) lobes. There was no significant correlation between the volume of this 'secondary' lesion and either the number of coulombs delivered or the current flow (milliamperes). There were again significant correlations between the total volume of necrosis produced ('primary' plus 'secondary' anode and cathode lesions) and the 24-h increase seen in the liver enzymes AST ($r^2 = 0.587$, $P < 0.001$) and ALT ($r^2 = 0.578$, $P < 0.001$).

Histological examination of the specimens confirmed the results of the macroscopic study with the size of the lesions increasing with the electrolytic 'dose'. In each specimen, an area of tissue destruction was observed at the site of the electrode tips and was clearly discernible from the 'primary' and 'secondary' lesions which were areas of coagulative necrosis (*Fig. 4*). There was evidence of vascular thrombosis in the vessels adjacent to the lesions. The necrotic tissue was sharply demarcated from immediately adjacent normal liver; a mild infiltrate of mononuclear cells and small numbers of proliferating fibroblasts indicated that a healing process had commenced at the junction between the necrotic and normal liver.

None of the livers from the control rats showed a 'primary' or 'secondary' lesion, as described above. However, small localized areas of tissue necrosis were seen microscopically at the site of entry of the electrodes.

Discussion

For any new treatment modality to become established in clinial practice, it must be shown to be safe and efficacious. Previous unpublished work by the authors demonstrated that electrolysis produced areas of hepatic necrosis in the normal rat liver which healed without complications over 6 months, contracting down to a small fibrous scar. There was no long-term alteration in liver function or associated morbidity or mortality rates in any of the 58 rats in this previous study.

If the results of treatment of liver tumours in a clinical situation are to be associated with similar minimal morbidity and mortality rates the dose–response relationship as well as the healing process need to be predictable and reproducible. Dose–response data available to date have been remarkably limited and apparently variable. In studies on the pig lung, approximate rates of necrosis varied between 0·4 and 1·7 cm^3 per 100 coulombs delivered, dependent on electrode type and positioning[20,30]. In human studies in lung tumours this rate varied between 1·5 and 7 cm^3 per 100 coulombs[33,35]. More recently, Chinese workers reported a rate of 1·0 cm^3 per 100 coulombs in treating a variety of tumours[40,41]. In the liver, one study has reported experimental dose–response data[17] and the results suggested that liver necrosis in the rabbit was produced at a rate of 2·4 cm^3 per 100 coulombs compared with the rate of 4·1 cm^3 for lung necrosis. If the relationship between dose in coulombs and response in terms of volume of necrosis in the primary electrolytic lesion remained linear, the present results suggest that a dose of 100 coulombs would create a 2·0-cm^3 lesion with the electrodes together; if they were apart a 2·0-cm^3 lesion would be created at the anode and a 1·4-cm^3 lesion at the cathode. While all of these results appear reassuringly similar, Chinese workers[38,39] have reported a rate of destruction between 200 and 300 times that which the present authors and Samuelsson *et al.*[17,30] observed (485–837 cm^3 per 100 coulombs) in patients with larger hepatocellular carcinomas.

It is clear therefore that while the present data support the observation that the volume of electrolytically-induced liver necrosis is proportional to the current dose in small-volume lesions in normal liver, further studies in a large animal model such as the pig are needed to extrapolate these results and allow their application to the size of liver lesions encountered in the clinical situation. The phenomenon of peripheral ischaemic damage may be unique to the rat liver model used, in which vascular thrombosis created by the relatively large electrolytic lesion results in extensive but variable distal ischaemic necrosis within the relatively small lobe of the rat liver. The flow of blood through such vessels in larger animals would be expected to mitigate such effects.

Further work will also be necessary to apply the observation that the combined volume of necrosis when the electrodes are separated by 20 mm is nearly twice that when the electrodes are together[20,30]. This effect seems likely to be the result of mixing of the electrode products to reform water and sodium chloride when the electrode tips are adjacent, thereby reducing the overall cytotoxic effect[26]. The cathode appears to be less toxic than the anode and the acidic environment around the anode (pH 2) is known to be more toxic than the alkalinity (pH 12) at the cathode[26].

In addition to the placement of electrodes, it is likely that the shape and size of the electrodes will also contribute to the shape and size of the final lesion produced. This is currently under investigation using computer 'current modelling' techniques to allow standardization of various critical aspects of electrode design and placement which will be necessary for safe clinical studies. The observation that the time over which the current dose is delivered does not appear to alter the size of the lesion created similarly requires further validation in view of its importance in determining treatment times.

In conclusion, if, as seems likely from the work of others, the present results can be extrapolated, electrolysis (electrochemical therapy) appears to fulfil many of the criteria required to allow the potentially curative treatment of irresectable liver tumours.

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Other *In situ* Ablative Techniques for Unresectable Liver Tumors

David P. Berry and Guy J. Maddern, University of Adelaide Department of Surgery, The Queen Elizabeth Hospital, Adelaide, Australia.

Without treatment, patients with colorectal liver metastases or hepatocellular cancer have a very poor prognosis. As liver metastases are common and only 20% of patients are suitable for liver resection many non-resectional treatment modalities have been developed and investigated. Percutaneous acetic acid injection, percutaneous hot saline injection, radiofrequency ablation, high-intensity focused ultrasound, interstitial laser photocoagulation, microwave coagulation therapy, and electrolysis are examined in this article. The methods, complications, and limitations of each technique are discussed as well as the results of published experience. Although none of these treatments have been subjected to prospective randomized clinical trials to date, further development of these ablative techniques should be persued to attempt to find a solution to the clinical problem of unresectable liver tumors. (*Asian J. Surgery 2000;23(1):22–31*)

Colorectal carcinoma is common in the Western world with 160,000 patients newly diagnosed each year in the USA alone.[1,2] These patients account for 15% of all cancer-related deaths and the liver represents the most frequent visceral site of metastatic disease with 20–30% of all metastases confined to the liver.[1,2] At the time of diagnosis, approximately 25% of patients have metastatic disease, and up to a further 25% of patients will develop metastases at a later date. At least half of the patients with metastatic disease will ultimately die of their metastatic complications[1,2] and for many patients progressive involvement of the liver will be the major or sole determinant of survival (NIH consensus 1990, Wood 1976, August 1985). Without treatment, patients with colorectal liver metastases have a very poor prognosis with a mean survival of six months.[3–5] The prognosis for untreated hepatocellular cancer is equally poor with a median survival of four to six months from the time of diagnosis.[7]

Surgical resection of colorectal metastases is the only curative treatment option and produces a 40% five-year survival.[1,5,8] However, only 20% of patients[9] are suitable for curative surgical liver resection due to the anatomical distribution of the metastases and/or the presence of extrahepatic disease. Following surgical resection, 20–30% of functioning liver must remain to avoid postoperative liver failure.[10]

As liver metastases are common and only 20% of patients are suitable for liver resection, many non-resectional treatment modalities have been developed and investigated, including percutaneous alcohol injection,[11] cryotherapy,[12] regional and systemic chemotherapy[13] and chemoembolization, immunotherapy,[14] interstitial laser therapy,[15] and liver transplantation.[16] The disadvantage of the methods listed are that they may produce unacceptable side effects, and none have demonstrated a long-term survival advantage.[13,17,18] There is, therefore, a need for a simple, affordable, and effective technique which is safe, predictable, and completely ablates liver tumors.

One possible advantage of focal ablative treatments over surgical resection is that they selectively treat the metastases without destroying large amounts of functioning liver.[19]

The most widely practiced *in situ* technique is percutaneous ethanol injection which has been popularized by the Japanese and Southern Europeans mainly in the treatment of hepatocellular carcinoma. Newer technologies are being developed and as such

Address reprint requests to Professor GJ Maddern, University of Adelaide Department of Surgery, The Queen Elizabeth Hospital, Woodville Road, Adelaide 5011, South Australia, Australia.
e-mail: gmaddern@medicine.adelaide.edu.au
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in situ ablative techniques have received much attention in the recent literature and their role in the management of unresectable liver tumors is reviewed.

Percutaneous Ethanol Injection

Percutaneous Ethanol Injection (PEI) was first advocated for the treatment of hepatocellular cancer (HCC) by Sugiura et al. in 1983.[20] The main reason for the initial interest in local ablative techniques was the poor response of patients with HCC to any form of treatment if they were not suitable for resection. Systemic and regional chemotherapy regimens in hepatocellular cancer[21] are still under investigation, along with possible roles for immunotherapy[22] and gene therapy.[23] There is no convincing data to support any medical treatments and even PEI, which is widely practiced, has not yet been subject to a randomized controlled trial comparing it with symptomatic treatment only in patients with HCC.

PEI is usually performed in several sessions on an outpatient basis but has been performed in a single session under general anesthesia[24] for more extensive tumors. Under local anesthesia, a 22-gauge Chiba needle is introduced percutaneously into a tumor, usually under ultrasonographic (US) control or occasionally by computed tomography (CT) guidance. Absolute (99.5%) or 95% ethanol is slowly injected into the lesion starting at the deepest aspect of the tumor and subsequently withdrawing the needle in small increments to achieve uniform and adequate perfusion of the tumor so as to ensure tissue necrosis within and around the tumor. Ultrasound is regarded as the modality of choice to monitor alcohol injection as the micro bubbles in ethanol create an echogenic blush immediately following infusion.[25]

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 destruction of the tumor cells.[26]

The injected ethanol usually spreads in a 1 to 3 cm radius around the tip of the needle towards the edge of the tumor. Injection of ethanol is stopped when significant leakage outside the lesion can be detected or when diffusion is not clearly visible under US control. Treatment ends when perfusion of the tumor, and therefore complete ablation, is considered total. The number of sessions required to ablate the tumor is approximately twice the lesion diameter in centimeters.[27] After ethanol injection, the needle is left in place for 1–2 minutes to prevent alcohol leakage along the track and 1–2 mL of local anesthesia is injected before removing the needle to minimize the local pain caused by ethanol leakage along the needle track and into the peritoneal cavity. Japanese workers have suggested calculating the total amount of alcohol required according to the formula:

$$V = 4/3\ \pi(r + 0.5)^3$$

where V (in mL) is the volume of ethanol and r (in cm) is the radius of the lesion: 0.5 mL is added to provide a safety margin of normal tissue ablation to ensure complete tumor ablation.[28] The amount of alcohol needed to ablate a lesion is dependant on several factors including tumor consistency, degree of tumor vascularity (hypervascularity washes the ethanol out but predisposes to the effects of chemically induced vascular thromboses), internal septae, areas of tumor necrosis (which would provide a path of preferential alcohol diffusion), and the presence of a tumor capsule (which would contain the alcohol but also protect areas of extracapsular tumor from the ethanol).[29] Until recently, only small volumes (up to 10 mL per lesion per session) were used, however, recent reports suggest that volumes of up to 40 mL can be safely used[30] on an outpatient basis and up to 210 mL under anesthesia.[31]

Limitations/complications of PEI

Common to all percutaneous liver puncture techniques, acceptable clotting studies and platelet count are necessary to minimize the risk of bleeding.

Most patients complain of mild pain during or immediately after the injection of ethanol. The pain is usually in the right upper quadrant but shoulder tip pain is not uncommon.[32] Post-procedural fever is almost universal. Hepatic infarction, intraperitoneal bleeding, pneumothorax, ascites,[32] hemobilia, and cholangitis[31] have all been reported. There are also reports of limited chemical thromboses in portal vein tributaries, which resolve spontaneously.[33] These major complications are rare occurring in up to 3% of patients, and can usually be managed conservatively. Deaths related to PEI have been reported due to massive hepatic necrosis[34] and portal vein thrombosis.[35] Not surprisingly, the complication rate following the more aggressive single

session treatment is higher with a recent report of a 4.6%[31] mortality.

Long-term complications of PEI include a reported case of a bile duct stricture,[36] but perhaps surprisingly needle tract implantation of hepatocellular carcinoma occurred in less than 1% of cases in a recent Japanese study.[37]

Whilst US guidance is optimal during treatment, contrast enhanced CT is the gold-standard non-invasive follow-up imaging modality[38] despite the emergence of MRI and color flow Doppler ultrasound.[39] Before treatment, HCC appears as an area of variable attenuation with some enhancement, whereas, following treatment, a completely ablated lesion should be hypodense without enhancement.

Results of PEI in the treatment of hepatocellular cancer

PEI has become popular for the treatment of HCC because of two important and potentially useful considerations.[40] Ethanol should selectively diffuse through the soft HCC tumor rather than the hard, cirrhotic surrounding liver and PEI does not involve the loss of liver parenchyma in an already compromised liver.

The short-term efficacy of PEI is assessed by histopathological examination of biopsy material after the completion of treatment. In resected and autopsy specimens of HCC, complete tumor necrosis has been observed in up to 80% of cases treated by PEI, however, if residual tumor is present it is usually found in nests around the main lesion, along the edge of the lesion, or within the main tumor mass but isolated by the presence of septae.[41]

The role of PEI in the treatment of HCC has been widely discussed in the literature but this treatment modality has never been subjected to a randomized controlled trial. The largest reports in the literature are summarized.

Shiina et al.[41] reported 98 patients with HCCs up to 6.5 cm in diameter (maximum number of lesions was 3) treated by PEI with a five-year survival of 52%. Tanikawa et al.[42] reported 250 patients with up to 3 HCCs and a five-year survival of 47%. In 1995, Lencioni et al.[33] and Ebara et al.[43] both reported series of 105 and 67 patients respectively. In the Lencioni study, single lesions up to 5 cm or multiple lesions (maximum number of 4) of less than 3 cm in diameter were associated with a five-year survival of 32%. In the Ebara study, single lesions of up to 3 cm or multiple lesions (maximum number of 3) of less than 3 cm in diameter were associated with a five-year survival of 56%.[43] Livraghi et al.[31] from Italy also reported their experience in 1995 with 746 patients with HCC. This is the largest reported series to date and the overall five-year survival rate in 628 of these patients with compensated cirrhosis was 48%. This study demonstrated clear differences in five-year survival between Childs grade A (47%), grade B (29%) and grade C (0%). Livraghi et al.[44] have also recently published their experience with large HCCs. This paper described 24 patients with single encapsulated HCC of 5–8.5 cm, a group of 63 patients with infiltrating HCCs of 5 -10 cm or multiple HCCs, and 21 patients with advanced liver or neoplastic disease. Therapy was performed in a single session with four-year survival rates of 44%, 18%, and 0% for each of the groups.

Results of PEI in the treatment of metastatic liver disease

Colorectal metastatic lesions are far more difficult to destroy by PEI than HCC because the alcohol tends to spread into the soft adjacent liver parenchyma rather than staying within the hard tumor tissue through which it diffuses in an inhomogeneous and irregular fashion.[45] There are few data relating to PEI for metastatic disease, but complete necrosis of the lesions has only been observed in 52–56% of lesions.[46,47] Lesions which responded best in these two small series were small (<2 cm) endocrine metastases and the three-year survival in 40 patients was 39%.[47]

It has recently been suggested that echolaparoscopic-guided alcohol injection of liver metastases[48] be performed as this would allow better tumor localization, but perhaps more importantly, would allow better staging of the disease, in particular, information on the presence or absence of extrahepatic disease.

Percutaneous Acetic Acid Injection

In 1998, Ohnishi[49] published his experience with Percutaneous Acetic Acid Injection (PAAI) for small HCC. To date, this is the only published report of this technique. The pathophysiology of tumor killing is identical to that of PEI as is the method of instillation of 50% acetic acid into the tumors. The proposed advantage

of this technique is that smaller volumes of acetic acid could be injected less often than ethanol because acetic acid has greater necrotizing power than ethanol and will therefore not only destroy tumors but also break down internal septae within the tumor, thereby enhancing its effects.

In Ohnishi's study, 60 patients with 1–4 HCCs smaller than 3 cm were randomized to either PAAI (31 patients) or PEI (29 patients). All tumors were successfully treated but recurrence occurred in 8% of PAAI-treated tumors and 37% of PEI treated tumors. The one- and two-year survival rates were 100%/92% for PAAI and 83%/63% for PEI.[49]

Percutaneous Hot Saline Injection

Honda et al.[50] published their experience with percutaneous hot saline injection therapy for small HCCs in 1994. To date, like the percutaneous acetic acid injection, this is the only published report of this technique. The method of tumor killing is heat destruction causing coagulative necrosis, but the method of fluid instillation is identical to those already described. The proposed advantage of this technique is that whilst the hot saline destroys tumor, as it cools, it becomes physiological saline and should therefore avoid any of the complications associated with ethanol toxicity.

In this study, 20 patients with HCCs smaller than 3 cm received hot saline injections. No local recurrence was seen during the follow-up that ranged from 2 to 36 months. These short follow-ups and small numbers do not allow survival estimations to be made.

Radiofrequency Ablation

Radiofrequency ablation (RFA) is an electrosurgical technique utilizing high frequency alternating current to heat tissues and so cause thermal coagulation. When cells are heated above 45°C, cellular proteins are denatured and cell membranes lose their integrity as their lipid component melts.[51] Radiofrequency ablation is well established as the treatment of choice for many symptomatic cardiac arrythmias because of its ability to create localized necrotic lesions in the cardiac conducting system. During radiofrequency ablation (RFA), a high frequency alternating current (350–500 kHz) flows from the uninsulated tip of an electrode into the tissue. Ionic agitation is produced in the tissue around the electrode tip as the ions attempt to follow the direction of the alternating current and it is this agitation which results in frictional heating in the tissue around the electrode.[52,53] 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.[54–56] A recent report studying RFA *in vivo* in a pig model also suggests that local blood flow is a strong predictor of lesion dimensions.[57]

Theoretically it should be possible to create lesions of 1.6 cm × 8 cm with a single probe[54,55] however, this has not been the case *in vivo* as lesion uniformity breaks down when the length of the exposed probe tip exceeds 3 cm, thereby limiting the actual lesion size to approximately 1.6 cm × 3.6 cm. Modifications of the technique such as multiple probes[58] and saline enhancement[59] have been described to achieve lesions of approximately 4 cm in diameter.

Percutaneous RFA has been described under general and local anesthesia[59,56] along with a laparoscopic approach.[60] Usually, a 15–21 gauge RF probe with 2–3 cm tip exposure is positioned into the lesion. A monopolar RF generator serves as the energy source and a grounding pad is placed on the patient's thigh.[59,56] RF treatment is now often based on intraprocedural temperature monitoring[56] and the probes may be repositioned during treatment to achieve complete tumor ablation in one treatment session.

The largest clinical trials to date[56,59] included only 11 and 17 patients respectively. In the study by Livraghi et al.,[59] 11 patients with 17 metastases and 1 cholangiocarcinoma were ablated. Twelve lesions demonstrated a complete response and six lesions a partial response at six months. In Solbiati's study,[56] 16 patients with 31 metastases were treated. At follow-up of nine to 29 months, there was no growth in 2/3 of the 27 metastases available for imaging. One- and two-year survivals were 100% and 66%, respectively, with lesions less than 3 cm and of colorectal origin responding best to RFA.

RFA is well tolerated and no serious complications have been described in the two largest series to date.[56,59] Minimal right upper quadrant discomfort is common during treatment, as is post-procedural fever. During treatment under ultrasound control, a gradually enlarging elliptical lesion can be seen with ill-defined margins.[56] These appearances persist up to several months after treatment and this heterogeneity precludes the distinction

between the ablated tumor and residual disease.[56] Even with CT or MR follow-up, the appearances of the residual disease or ablated tumor are indistinguishable from one another.

Whilst these two studies represent the largest series yet reported, the patient numbers are small and the length of follow-up is short.

High-Intensity Focused Ultrasound

High-intensity focused ultrasound (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 the diagnostic setting along with a concave ultrasound transducer results in selective, targeted delivery of high energy without, in theory, the possibility of damage to intervening tissues.[61] HIFU exerts its effects primarily by heating — as the sound waves are absorbed by the target organ, the sound energy is converted to heat causing tumor destruction by coagulative necrosis.[61] Another mechanism by which HIFU can exert an effect is in cavitation of the target organ. Cavitation is the mechanism whereby tissue destruction occurs by mechanical shock and free radical formation above a threshold determined by probe frequency, sound wave intensity, and tissue impedance characteristics. Although cavitation causes more rapid tissue destruction, it is less controllable and so the heating characteristics of HIFU have been the most widely used.[61]

HIFU has been performed in animal models using a concave transducer to focus the beam with a frequency range of 1 to 4 MHz, and peak intensity of 100 to 1500 W/cm^2 for 1 to 10 seconds.[62,63] Despite the encouraging early results in animal studies[62,64] of normal liver and tumor,[65] suggesting the potential of this method for liver tumor ablation, human studies have not been encouraging with HIFU either having no effect on the liver tumor or being associated with significant complications such as skin burns and liver laceration.[66] On the basis of these data, the ideal human protocol has yet to be determined and so the results of human studies are still being awaited.

Interstitial Laser Photocoagulation

Interstitial Laser Photocoagulation (ILP) is another method of causing tissue destruction by heating, thereby inducing coagulative necrosis. Its role in the treatment of hepatic tumors has recently been reviewed in detail.[67] ILP was introduced by Bown in 1983 and works by inducing thermal coagulative necrosis of solid tumors by local light delivery using flexible fibres. Recent improvements in fibre design, resulting in better fibre flexibility and thermoresistance in addition to the ability to vary the length of the diffusing tip to coincide with tumor dimensions, should enhance this technique.[68]

ILP uses laser light at low power (typically 3–15 W) with exposure times of 3–20 minutes and it is the conversion of absorbed light energy into heat which is responsible for the necrosis. The absorption of the light may occur directly or after scattering of the light by the treated tissue, which results in greater tissue penetration of more uniform energy distribution.[69] The low absorption and high scatter of the most commonly used Neodymium:yttrium-aluminium-garnet laser (Nd:YAG laser) which has a wavelength of 1064 nm, maximizes tissue penetration and the uniformity of energy distribution.[69] Heat conduction and convection extend the area of necrosis beyond the area of light penetration.[70] The size of the resultant lesion is dependent on fibre position within the tumor and the temperature gradient created by the amount of power and duration of exposure. Absorption of the laser light has several thermal effects and the irreversible thermal damage of coagulation occurs between 55 and 95°C.[71] Increasing both the power (the most important variable) and exposure time during ILP increases the area of necrosis.[72] In addition, the use of multiple synchronous fibres can also increase lesion size[73] to as large as 5 cm.[74]

The first clinical report of ILP treatment was in 1985 by Hashimoto et al.[75] who treated patients with both liver metastases and primary hepatocellular cancer at laparotomy. This study used a YAG laser with a bare tip at low power (5W) and long exposure times, and it proved the feasibility of the technique without major complications. In 1991 Huang[76] reported experience with a diffusing fibre tip to avoid carbonization of the tip. In 1989, Steger[77] introduced the percutaneous technique and several groups have since modified this. ILP is now usually performed percutaneously using a Nd:YAG or diode laser[45] under ultrasound control, although a recent report of MRI-guided ILP[78] appears very encouraging.

Whilst variations in technique exist, the most widely employed method of tumor ablation is to place one or several 19-gauge needles into the deepest aspect of the tumor under ultrasound control. The number of needles required is obviously a function of tumor size. Each

needle is then exchanged for an optical fibre with the tip of the fibre exposed and the fibre coupled to a laser source and the tumor heated. The fibre tips can be repositioned during treatment to allow complete tumor ablation and multiple sessions are often required for lesions of over 3 cm. Energy per metastasis can vary from 1000 to 34,000 J depending on the size of the lesion.[45] Alternatively, when a diffusing fibre tip is used, it can be connected to microthermocouples to monitor the temperature. The fibre is introduced into the centre of the tumor, which is heated until the temperature at the lesion edge reaches either 60°C or 45°C for 15 minutes.[69] Real time non-invasive monitoring is poor, although on-line monitoring with a T1-weighted turbo fast low angle shot (FLASH) MRI has demonstrated a 'dark rim' on the edge of the tumor which is accurate in predicting necrosis in 85% of cases.[79]

There are two large series reported to date. Gillams et al.[80] in 1997 reported their experience of treating 148 metastatic deposits in 55 patients with tumor sizes varying from 1–6 cm and a mean number of 2.2 treatments (range 1–12). This group used multiple bare tip fibres and at six months achieved a CT-assessed 16% complete response, 38% partial response and 46% stable disease/progression. In the series of 282 colorectal metastases in 99 patients measuring up to 5 cm reported by Vogl et al.[78] in 1997, a diffusing tip was used delivering 10 W over a 10–20 minute period for a mean number of eight (range 1–36) treatments. As assessed by MRI and clinical follow-up, the three-year survival was 42%.

Complications are infrequently reported but the published series are small apart from the two recent studies documented above. Pain and fever are common but no major biliary or vascular injuries are reported. Tranberg[81] reported a death following ILP in 1996 after treating a tumor of 8 cm in diameter and this appeared to be due to a systemic inflammatory response to tumor necrosis.

Microwave Coagulation Therapy

Since its introduction in 1979 by Tabuse,[82] Microwave Coagulation Therapy (MCT) has been used at laparotomy,[83] laparoscopically,[84] percutaneously,[85] and thoracoscopically.[86]

MCT is another hyperthermic technique relying on the conversion of energy to heat to destroy the tumors. During treatment with the 2450 MHz microwaves, water molecules polarize with the rapidly alternating electromagnetic field radiation. As the water molecules follow the changing polarity of the field, heat is generated from within the tissue resulting in coagulative necrosis and hemostasis. Tissue coagulation occurs in a spindle-shaped configuration around the monopolar lead (Murakami 1995). Percutaneous MCT (PMCT) is performed under ultrasound control and local anesthetic. The microwave electrode is positioned in the lesion under ultrasound guidance and microwaves are administered at 60 W for 60–120 seconds.[87] For large lesions, a sequential technique with multiple needles[88] has been developed since at 80 W for 60 seconds a lesion of 20 mm diameter is created and so use is made of several overlapping lesions. Real-time ultrasound monitoring demonstrates that the lesion becomes hyperechoic immediately following treatment.[87] Percutaneous lesions appear teardrop-shaped on CT scan whereas intraoperative lesions are round.[89] In 93% of MCT-treated lesions, peripheral enhancement was seen on CT scan immediately following treatment but this later disappeared, suggesting complete necrosis despite this initial appearance.

The efficacy of MCT has been reported in several recent studies although in common with the other ablative techniques, these studies are not randomized controlled trials. In 1994, Seki et al.[90] reported their series of 18 patients with solitary HCCs of less than or equal to 2 cm in diameter. Follow-up was 11–32 months and all but one patient was alive. More recently, Shimada et al.[86] reported their experience in 49 patients with HCC and 29 patients with metastatic disease. They used all forms of microwave applications described in the literature and reported complications in 14% of HCC patients and 21% of patients with metastatic disease. These complications included two biliary fistulae of which one was permanent, a hepatic artery aneurysm which ruptured, and two cases of disseminated intraperitoneal malignancy following treatment. It was noted that complications were significantly higher when lesions of greater than 4 cm were ablated. Seki et al.[91] have further reported their experience with 15 patients with single metastases of less than 3 cm from colorectal cancer. Microwave irradiation of 80 W for 60 seconds was used. Two thirds of the patients were alive at two years and six of the patients were disease free. This equates to 40% of patients from the original good prognostic group who are alive and tumor-free at two years. These rather

disappointing results together with the relatively high complication rate suggest the MCT is not yet ready for widespread clinical use.

Electrolysis

Electrolysis is a novel treatment that uses direct current (DC) to safely produce tissue destruction,[92] with the volume of tissue necrosis produced being proportional to the electrolytic dose.[92,93]

Electrolysis induces tissue necrosis by producing chlorine and hydrogen ions (H^+) at the anode and hydrogen gas and sodium hydroxide at the cathode,[92,94] thereby creating a pH gradient. The electrode products, hydrogen chloride (HCl) and chlorine gas (Cl_2), have been noted to be toxic to tissue.[94] Thermal necrosis plays no role in electrolytic ablation.[92,95,96] There are also many distal field effects which include electrophoretically induced cascade reactions causing intracellular disintegration of neoplastic tissue, the formation of eddy currents, and activation of the immune system. Immune system activation involves the activation of macrophages with the ability to selectively destroy neoplastic cells, and the accumulation of leukocytes in the cathodic field by extravasation through spaces between endothelial cells in the non-contracted venous capillaries.[95,97] Distal field effects also contribute to the necrosis observed[95,97] during electrolysis. The field circulation activates multiple sites of electron transfer in the distal field via endothelial redox proteins (these are oxyreductases which are part of the respiratory enzymes). Reaction products will lead to the destruction of blood and formation of multiple capillary microthromboses. The superimposed electric field over the capillaries also causes strong segmental contractions of the arterial ends by podocytes, to such an extent that blood cells are unable to pass. In addition, there is electro-osmotic transport of water towards the cathodic field. The combination of these distal field effects results in vascular obstruction and a suspended circulation.[95,97] Therefore, during electrolysis, ischemia is induced in the tissue by the superimposed field which contributes to the resultant necrosis.

Much of the preliminary data evaluating liver electrolysis had been obtained from a small animal (rat) model,[98] however, these lesions were small and of limited clinical use. Preliminary data from the pig model[99] using two electrolysis catheters suggest that lesions of up to 7–8 cm can be created but the operative time is of the order of three hours. The data in this study[99] demonstrate a linear relationship between the electrolytic dose and the volume of hepatic necrosis, suggesting electrolysis to be predictable in effect and more importantly, no complications were seen. Electrolysis produced a rate of necrosis of 3.8 cm^3 per 100 coulombs. Dose-response data available in the literature are limited and variable with the majority of data being from small animal models and small volume lesions in the liver. One study on rabbits reported liver necrosis at a rate of 2.4 cm^3 per 100 C and lung necrosis at a rate of 4.1 cm^3 per 100 C.[100] In another study in the rat,[98] liver necrosis was produced at a rate of 2.0 cm^3 per 100 C. In human studies, this rate has varied between 1.5 and 7 cm^3 per 100 C in lung tumors.[101,102]

For any new treatment to be widely adopted it must be proven to increase patient survival or another measureable parameter such as quality of life. A prospective randomized controlled trial with five-year follow-up would be required to produce meaningful results and this is in progress in Australia and the UK. If electrolysis confers a survival advantage in patients, then it has huge potential to impact clinical practice.

From the data available, it is apparent that electrolysis is a reliable, reproducible, and predictable method for the potentially curative treatment of unresectable liver tumors.

Conclusions

All of the aforementioned techniques suffer from the same problem in that none have been subjected to a randomized controlled clinical trial. Many studies have small patient numbers and the length of follow-up is short. Clearly, these shortfalls are partly a function of the availability of the newer technologies but this is not the case for all techniques. The results of prospective randomized trials are needed before any of these technologies will gain widespread clinical acceptance, but in the interim, it is important that these technologies are persued to attempt to find a solution to the huge clinical problem of unresectable liver tumors.

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A new treatment for unresectable liver tumours: long-term studies of electrolytic lesions in the pig liver

Simon A. WEMYSS-HOLDEN, Gavin S. M. ROBERTSON, Ashley R. DENNISON, Paula S. VANDERZON, Pauline de la M. HALL and Guy J. MADDERN
University of Adelaide, Department of Surgery, The Queen Elizabeth Hospital, Woodville Road, Woodville, South Australia, 5011, Australia

ABSTRACT

The majority of liver tumours are inoperable and an alternative treatment to surgical resection is urgently needed. Electrolysis has been investigated in a rat model and the procedure is safe, with accurate and predictable effects. The necrosis produced has also been shown to cause destruction of tumour deposits in the rat liver. A similar evaluation in a large animal model was necessary before clinical trials could commence. Using platinum electrodes connected to a d.c. generator, areas of hepatic necrosis were created in the pig liver. Animals were killed at various time points after treatment to assess the extent of healing. Treatment was uneventful and all animals made a full recovery. No animal died from the treatment or had to be killed prematurely. After 2 days of treatment, healing was minimal but at successive time points there was progressive evidence of healing, such that after 4 months, the original electrolytic lesion was greatly reduced in size and the large area of necrosis seen at the early time points was largely replaced by a fibrous scar with only small islands of necrotic tissue. In a large animal model, electrolysis is a safe method for creating areas of hepatic necrosis. The lesions heal with time and are associated with minimal morbidity. The results support a trial of electrolysis in patients with unresectable liver tumours.

INTRODUCTION

The majority of malignant liver tumours remain inoperable due to their number, distribution or the presence of parenchymal disease. Following apparently curative surgery for colorectal cancer, half the patients will develop hepatic metastases [1]. Under these circumstances liver resection, when appropriate, significantly improves survival with between 25 and 35% of patients being alive at 5 years [2,3]. Unfortunately only 5–10% of patients who present with liver metastases are suitable candidates [4] and in the remainder the outlook is dismal [5–7]. The situation is similar for patients with hepatocellular carcinoma with a resectability rate of less than 20% [8], although when surgery is feasible the 5 year survival rate approaches 50% [9]. Again, however, the survival in untreated patients is extremely poor with a median survival of approximately 4 months and a 3 year survival of less than 15% [10,11].

Clearly a treatment is needed that is applicable to patients who are unsuitable for a surgical approach but which, like surgery, would ideally not only provide symptomatic relief but would be able to improve the outlook due to reduction or eradication of the tumour(s). A number of modalities have been investigated including cryotherapy [12,13], alcohol injection [14], interstitial laser therapy [15] and others. To date none has proved to be safe and minimally invasive, while at the same time

Key words: cancer, electrochemical, electrolysis, liver/hepatic tumours, morbidity.

Abbreviations: C, coulomb (electric charge); ALT, alanine aminotransferase; AST, aspartate aminotransferase; γGT, γ-glutamyltranspeptidase.

Correspondence: Professor G. J. Maddern (e-mail gmaddern@medicine.adelaide.edu.au).

producing a controllable, predictable area of destruction, within which survival of tumour cells is impossible. As a consequence, no presently available treatment has been shown to confer any advantage in terms of disease free interval or survival.

Previous experimental work from this Unit [16,17] demonstrated that electrolysis has considerable potential for treating unresectable liver tumours. In the rat, electrolysis is a safe, effective and controllable treatment. The ellipsoidal zones of coagulative necrosis heal with time and are associated with no long-term morbidity.

Although electrolysis uses electrical current to cause tissue necrosis, its mode of action is new and completely unlike diathermy, laser or cryotherapy where changes are principally due to the thermal effect [17–19]. A small direct electrical current (< 50 mA) is passed between two electrodes which become polarized. A pH gradient is established [20,21] and cytotoxic electrode products are liberated [22–26]. Well defined zones of tissue necrosis are produced around the tip of each electrode.

Nevertheless, progression to the clinical setting requires further evaluation of the method of production of the electrolytic lesion and its evolution in an appropriate large animal model. The aim of this study was to extend the work by a detailed study of the immediate effects and evolution of large electrolytic lesions in the pig, including long term studies.

This study examined the safety, morbidity and rate of healing of electrolytic lesions in the pig liver.

METHODS

The d.c. generator used in this study was manufactured by the Bioengineering, Transducers and Signal Processing Research Group (University of Leicester, U.K.). Once connected to platinum electrodes inserted into the liver parenchyma, it was used to deliver an electrolytic 'dose' of 100 C (coulombs) at 50 mA.

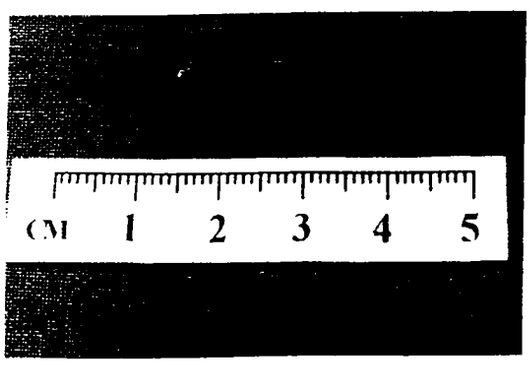

Figure 1 **A 6 French gauge electrode catheter**

Each catheter had three platinum electrodes proximal to the platinum tip electrode (anode). Any one of the three proximal electrodes could be selected and used as the cathode (negative electrode).

Electrode catheters were supplied by Johnson & Johnson Medical Pty Ltd (North Ryde, NSW, Australia). The electrode catheters were 6 French gauge (2 mm diameter). Each catheter had three platinum electrodes proximal to the platinum tip electrode (anode; Figure 1). Any one of the three proximal electrodes could be selected and used as the cathode (negative electrode).

The use of laboratory animals in this study was approved by the local Animal Ethics Committees (University of Adelaide, South Australian Research and Development Institute, Pig and Poultry Production Institute of South Australia and The Queen Elizabeth Hospital, Adelaide), and the study conformed with the Code of Practice for the Care and Use of Animals for Scientific Purposes (National Health and Medical Research Council, Commonwealth Scientific and Industrial Research Organisation, Australian Agricultural Council, 1990) and the South Australian Prevention of Cruelty to Animals Act 1985.

Sixteen female specific-pathogen-free domestic white pigs (28.5 to 32.0 kg) were obtained from the Pig and Poultry Production Institute (Roseworthy Campus, Roseworthy, SA, Australia). The animals were housed in group pens (max. 10 animals per pen) and had access to a single space wet/dry feeder and ad-libitum water. The pens were maintained at 23.0 ± 1.0 °C at ambient humidity. Preoperatively, the animals were fasted for 12 h.

Experimental protocol

In order to establish the rate of healing and morbidity associated with electrolysis, the 16 animals were divided into four groups:

Group 1: four animals were treated with 100 C and killed 2 days after treatment,

Group 2: four animals were treated with 100 C and killed 2 weeks after treatment,

Group 3: four animals were treated with 100 C and killed 2 months after treatment,

Group 4: four animals were treated with 100 C and killed 4 months after treatment.

Operative technique

Animals were sedated with a deep intra-muscular injection of ketamine (20 mg/kg) and xylazine (1.5 mg/kg) and spontaneous breathing general anaesthesia was maintained with 1.5% halothane in 100% oxygen. Each animal was given a perioperative intramuscular injection of antibiotics (teramycin).

To determine the effects of electrode separation on healing and morbidity each animal was anaesthetized once and hepatic lesions were created with electrodes together (12 mm separation, single lesion produced) and apart (200 mm separation, two lesions produced). Each

animal therefore had three discrete electrolytic lesions in total.

The liver was exposed using an upper midline incision. A single electrode catheter was inserted into the dome of the right lobe to a depth of 30 mm. The electrodes were connected to the d.c. generator and a 'dose' of 100 C was delivered to the tissue. The resulting lesion was called the 'composite' lesion, as it consisted of two distinct but overlapping (anode and cathode) lesions.

Two separate electrode catheters were then inserted with the anode peripherally in the right lobe and the cathode in the centre of the left lobe, producing an electrode separation of 200 mm. The tip electrodes of each catheter were connected to the d.c. generator and 100 C was again delivered to the tissue. After treatment the electrodes were disconnected and the catheters were removed. The wound was irrigated with aqueous Betadine, and the abdomen was closed in two layers with 1 polydioxanone and 3/0 monocryl. Each animal was then returned to a single pen.

Blood samples were obtained preoperatively, at 1 day and 1 week postoperatively, and at the time the animal was killed. Serum measurements of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, γ-glutamyltranspeptidase (γGT) and bilirubin were made on each sample (Technicon AXON analyser, Bayer Health Care, Pymble, NSW, Australia). Pre-operative values were compared with those at 1 day and 1 week postoperatively, and at the time the animal was killed.

Once the wounds were healed, the animals were returned to group pens. All animals were killed by lethal injection (lethabarb).

At autopsy, the liver was removed and each of the electrolytic lesions were excised en-bloc and fixed in 10% (v/v) neutral-buffered formalin. Blocks of liver containing the lesions were processed, embedded in paraffin, sectioned and stained by haematoxylin and eosin. Coded sections were examined by a hepatopathologist.

Results of the change in liver enzymes were analysed statistically using the paired Student's *t* test (Statworks, version 1.2, Cricket Software Inc., Philadelphia, PA, U.S.A.)

RESULTS

There were no intraoperative complications associated with the electrolysis. All animals tolerated the treatment well and made a rapid and uneventful postoperative recovery, remaining healthy until they were killed. Postoperative weight gain was within the normal range and no animal died as a result of electrolysis or had to be killed prematurely.

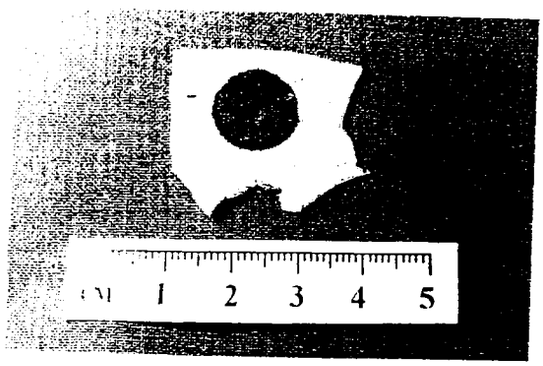

Figure 2 Macroscopic appearance of an electrolytic lesion 2 days after treatment

The spherical zone of necrotic tissue is sharply demarcated from the surrounding normal liver.

Liver enzymes

Liver enzymes (AST, ALT and γGT) were significantly elevated on the first day after treatment ($P < 0.001$, 0.001 and 0.01 respectively). In group 1 (killed 2 days after treatment) the AST was still significantly elevated at the time the animal was killed ($P < 0.05$). In long term studies (groups 2, 3 and 4) liver enzymes had returned to normal one week after treatment and remained so until the animal was killed.

Liver pathology

Group 1 (2 days after electrolysis)

At autopsy fine, fibrinous adhesions were present between the liver and diaphragm in two animals. The abdominal cavity and organs other than the liver were otherwise normal in all four animals. The livers were macroscopically normal apart from small puncture marks at the sites of electrode insertion. There were no liver infarcts. Macroscopic examination of the electrolytic lesions showed discrete, spherical zones of hepatic necrosis, sharply demarcated from the adjacent normal liver (Figure 2). Histological examination of the electrolytic lesions confirmed extensive but well-defined spherical areas of coagulative necrosis surrounding the site of the electrode tips. Small numbers of proliferating fibroblasts, a mild mononuclear cell infiltrate, and bile ductular proliferation were seen at the junction between the electrolytic lesion and the surrounding liver tissue. The immediately adjacent liver showed focal areas of haemorrhage but no other pathology (Figure 3, upper left panel).

Group 2 (2 weeks after electrolysis)

Mean weight gain was 7.4 kg (range 6.0 to 9.5 kg). Two animals developed mild superficial wound infections that responded rapidly to antibiotics (penicillin). One animal

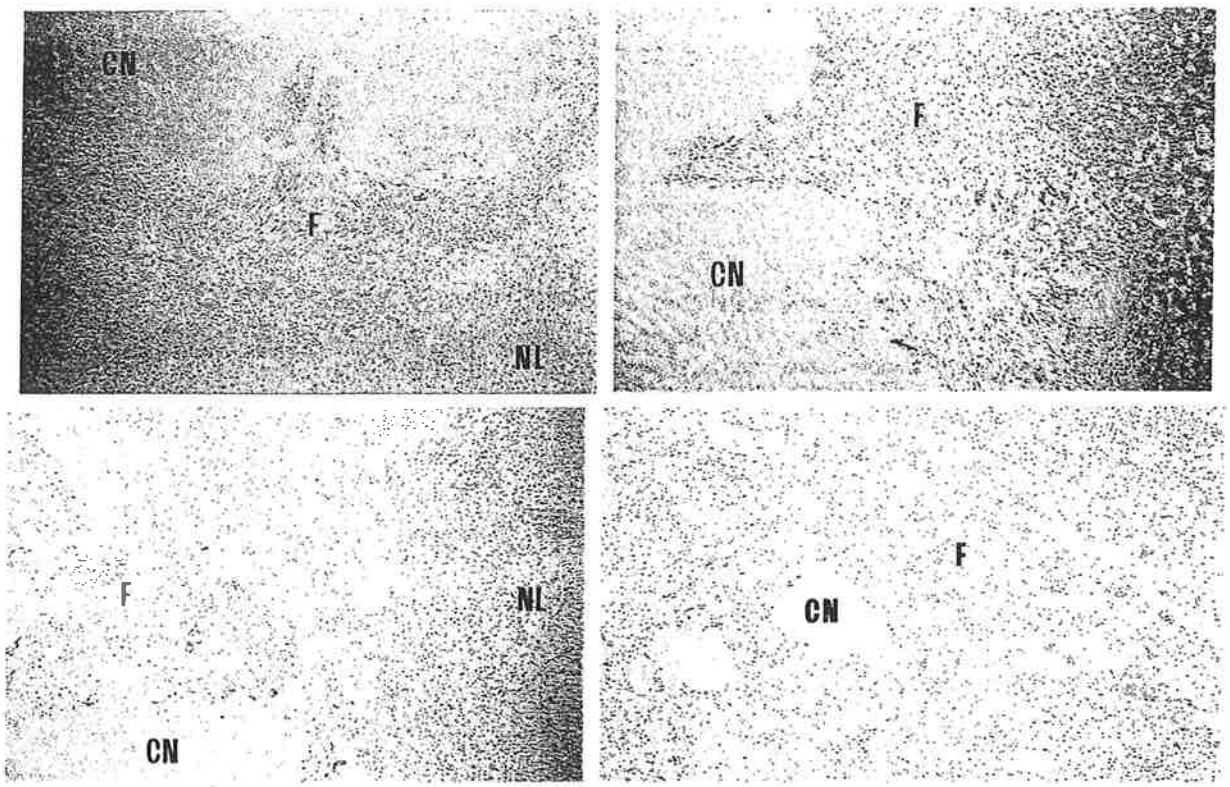

Figure 3 Section of pig liver showing the appearance 2 days (upper left panel), 2 weeks (upper right panel), 2 months (lower left panel) and 4 months (lower right panel) after treatment

(Upper left panel) An extensive but well-defined area of coagulative necrosis (CN) is seen around the site of the electrode tip. A few proliferating fibroblasts (F), a mild mononuclear cell infiltrate and proliferating bile ductules are seen at the junction between the electrolytic lesion and the surrounding liver tissue (NL). The immediately adjacent liver shows areas of focal haemorrhage but no other pathology. (Upper right panel) A large confluent central area of coagulative necrosis (CN) is seen with a peripheral rim of proliferating fibrous tissue (F) and ingrowth of fibroblasts. There is a small amount of focal dystrophic calcification in the lesion. (Lower left panel) There is evidence of advanced healing, with areas of proliferating fibrous tissue (F), intermingled with small islands of residual necrotic tissue (CN); adjacent normal liver (NL). (Lower right panel) There are only small islands of residual necrotic tissue (CN) intermingled with large amounts of mature fibrous tissue (F).

suffered a partial superficial wound dehiscence with abscess formation which was successfully treated with wound toilet and antibiotics. The deep closure remained intact. All animals were healthy at the time of their death. At autopsy, fibrinous adhesions were present in all of the animals between the liver and diaphragm but were easily divided. The livers were otherwise macroscopically normal with no evidence of infarction. The sites of electrode insertion could not be identified. Histological examination showed a large confluent central area of necrosis with a peripheral rim of proliferating fibrous tissue and some proliferating bile ductules, the adjacent liver was otherwise normal. Small amounts of focal dystrophic calcification were occasionally seen in the lesions (Figure 3, upper right panel).

Group 3 (2 months after electrolysis)

Mean weight gain was 43.0 kg (range 36.0 to 48.0 kg). One animal developed a deep wound infection with abscess formation 3 weeks after treatment. The infection responded to wound toilet and antibiotics and the skin healed. However, 5 weeks after treatment it was evident that the deep closure had partially dehisced as the animal developed a wide-necked incisional hernia. The hernia was treated conservatively and was uncomplicated. The animals were healthy at the time of their death. At autopsy, dense adhesions were present between the liver and diaphragm in three of the animals. The abdominal cavity was otherwise normal. The livers were of normal size and macroscopically normal. Histological examination of the electrolytic lesions showed variable degrees of advanced healing, usually with areas of proliferating fibrous tissue, intermingled with small islands of residual necrotic tissue and focal bile ductular proliferation at the junction between the area of necrosis and the adjacent normal liver (Figure 3, lower left panel).

Group 4 (4 months after electrolysis)

Mean weight gain was 80.3 kg (range 73.0 to 88.5 kg). Six weeks after treatment, one animal developed an incisional

hernia secondary to a deep wound infection. The hernia was repaired under general anaesthesia to prevent complications. The animal made an uneventful recovery. All of the animals were healthy at the time of their death. In all four animals dense fibrous adhesions were again evident at autopsy but laparotomy was otherwise normal. Histological examination of the electrolytic lesions showed even more advanced healing, with large amounts of mature fibrous tissue intermingled with small numbers of foreign body giant cells and haemosiderin-laden macrophages (Figure 3, lower right panel).

DISCUSSION

Having previously shown that electrolysis is a safe, predictable and reproducible method for creating discrete areas of hepatic necrosis in a rat model [16], this study was instigated to establish the safety of electrolysis in a large animal model prior to clinical trials. 'Safety' was determined by observing the extent of healing of the induced electrolytic lesions at several time points after treatment, and any treatment related morbidity or mortality.

All of the animals tolerated the treatment well. There were no intraoperative complications associated with the electrolysis and post-operative recovery was universally rapid and uneventful. In this study electrolysis appeared to be associated with minimal initial systemic trauma. In the clinical setting, inadvertent insertion of the catheter into a hepatic vein would be extremely unlikely, due to the use of intraoperative imaging (ultrasound or magnetic resonance imaging) to place the electrode within the tumour. The action of the cytotoxic electrode products would therefore remain localized. However, further studies are currently being performed to establish the systemic effects of the 'worse-case scenario' where the electrodes are placed within the lumen of a hepatic vein and all of the electrode products pass directly into the inferior vena cava. If this extreme situation is well tolerated, it is reasonable to assume that treatment of patients under more controlled conditions would be safe and associated with a minimal level of complications.

Liver enzymes were elevated immediately after treatment but this increase was small and transient. This reflects the initial release of enzymes from 'leaky' injured cells prior to the death of these cells. It also supports our belief that there is no ongoing hepatic ischaemia or necrosis after the initial electrolytic insult in the pig. This finding differs from a previous similar study in the rat [16] where most of the 'primary' electrolytic lesions were associated with a peripheral infarct, an effect which was caused by vascular occlusion resulting from a relatively large 'primary' lesion in a physically small lobe. As the pig liver is much larger, the parenchyma peripheral to the 'primary' lesion is more likely to survive the electrolytic insult because of its collateral supply. The adult human liver is again larger than that of a 30 kg pig and extrapolation of these results would suggest that peripheral infarction in the clinical setting is unlikely although clearly not impossible for large peripherally placed lesions.

Postoperatively, all animals gained weight at a normal rate and remained clinically healthy until they were killed. Five animals developed post-operative wound infections despite antibiotic prophylaxis. All infections responded well to conservative treatment but in one of the two animals that developed incisional hernias it was decided to repair this surgically as it was an animal assigned to the 4 month survival group. The surgery was uneventful but in retrospect it may have been advantageous to keep the animals in individual pens as hygiene in a group pen is difficult although stress levels are reduced when the animals are group housed. Apart from wound problems, no infectious complications were encountered. No animal became clinically septic, developed overt cholangitis or peritonitis.

When patients are treated, secondary infection is a concern in any situation where tissue necrosis is produced but infection in the liver was not a feature of any of the 48 areas of electrolytic necrosis produced in this study. This was probably because the local environment around the electrodes is sterilized during treatment by the cytotoxic electrode products. Platinum salts, leached from the electrodes during treatment may also augment this effect as they are strongly bactericidal even in low concentrations [27,28]. This contributes to the extremely low long-term morbidity associated with electrolysis and suggests that there are unlikely to be any major mid- or long-term complications in the clinical setting.

In each treatment group the composite lesion was larger than either the anode or cathode lesions, but the overall pattern of healing was the same in each of the lesions with progressive replacement of the central area of coagulative necrosis by fibrous tissue. All lesions progressively decreased in size although at 4 months more necrotic tissue remained in the centre of the composite lesions than in the smaller anode and cathode lesions. Healing occurred by proliferation and ingrowth of fibroblasts from the periphery of the lesions. Apart from focal areas of haemorrhage in some of the livers at the early time points, the liver parenchyma immediately adjacent to the lesions was entirely normal. The hepatic trauma associated with electrolysis appears to be short-lived and confined to the initial insult which results at the time of treatment (there was no evidence of ongoing or progressive hepatic necrosis). These findings in normal liver tissue suggest that tumours treated by electrolysis should heal in a similar way. An appropriate electrolytic 'dose' would be selected to not only completely encompass the tumour, but also to cause necrosis of a small rim of surrounding normal liver tissue. It is suggested

that healing of an area of tumour necrosis should differ little from the healing of necrotic normal liver as healing would take place from the periphery of the lesion by the ingrowth of fibroblasts from the surrounding normal parenchyma.

Platinum electrodes were used in this study as they are not obviously corroded by the electrolytic process [25] and may confer a theoretical, albeit unproven, benefit from the liberation of small concentrations of cytotoxic platinum salts [25,27–31]. If any new treatment for unresectable liver tumours is to be used clinically and be widely applicable, it must not only be safe and effective but also relatively inexpensive. In the clinical setting, electrode delivery systems would need to be disposable. It is envisaged that several electrodes would be inserted into single or multiple tumours under local anaesthetic and imaging control (ultrasound, computer-generated tomography or magnetic resonance imaging) and patients could be treated on an out-patient basis (with follow-up imaging). If the electrodes were made of platinum, the expense of such disposable systems may be prohibitive. Preliminary studies suggest that other electrode materials, such as graphite may prove to be equally effective and considerably less expensive.

This study in a large animal model has shown that discrete areas of hepatic necrosis induced by electrolysis are created in a safe way with minimal immediate, mid- or long-term morbidity. The induced lesions heal with time. The results support clinical trials in patients with unresectable liver tumours who are at present incurable.

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SURGICAL RESEARCH

THE SAFETY OF ELECTROLYTICALLY INDUCED HEPATIC NECROSIS IN A PIG MODEL

SIMON A. WEMYSS-HOLDEN, PAULINE DE LA M. HALL, GAVIN S. M. ROBERTSON, ASHLEY R. DENNISON, PAULA S. VANDERZON AND GUY J. MADDERN

University of Adelaide Department of Surgery, Queen Elizabeth Hospital, Woodville, South Australia

Background: Electrolysis fulfils the criteria for an ideal treatment of patients with unresectable liver tumours. Previous studies in the rat and pig have shown that controlled necrosis can be safely produced by inserting platinum electrodes into normal liver parenchyma and liver tumours. As with any new treatment it is mandatory to investigate the 'worst-case scenario' of inadvertent intravascular electrode placement in a large animal model before progressing to clinical trials.

Methods: Under ultrasound control in six pigs, electrodes were inserted into, or immediately adjacent to, an hepatic vein. An electrolytic 'dose' of 100 C was then administered and the evolution of the lesion was monitored using ultrasound. Venous blood was collected before and during the electrolysis to evaluate potential acid/base disturbances and animals were closely monitored during electrolysis and during their recovery until a full autopsy was performed 4–7 days after treatment.

Results: Gas bubbles were seen to enter the hepatic veins or inferior vena cava during treatment in five of the six animals. There were no major complications as a consequence and all animals recovered and remained in a healthy state until they were killed. At autopsy one animal had complete thrombotic occlusion of the left hepatic vein. Otherwise, findings were normal.

Conclusion: In the clinical setting, due to the use of ultrasound to guide electrode placement into the centre of a tumour, the electrodes should rarely juxtapose an hepatic vein. Nevertheless, in this extreme situation, electrolysis is surprisingly safe with only one major vascular occlusion and no morbidity or mortality.

Key words: colorectal liver metastases, electrochemical therapy, electrolysis, intraoperative ultrasound, pig model.

INTRODUCTION

Several methods of treatment for patients with unresectable liver tumours have been reported. These include the use of alcohol[1] or specific toxins,[2,3] various techniques employing thermally induced insults such as cryotherapy[4,5] and interstitial laser therapy,[6] and liver transplantation.[7–9] These treatments are all to varying degrees invasive and at best palliative,[10–12] with unproven long-term benefit. The problem therefore remains that without treatment the prognosis for patients with either colorectal liver metastases[13–15] or hepatocellular carcinoma (HCC)[16] is very poor, with median survivals of the order of 6 and 4 months, respectively.

Liver resection improves long-term survival,[17–19] but is appropriate only in 5% of patients with colorectal liver metastases and in 20% of those with HCC.[20,21]

A treatment is needed for patients with unresectable disease that offers the potential to improve long-term survival. Such a treatment must be safe, predictable in effect, controllable and relatively inexpensive if it is to be widely adopted. Theoretically, however, if any treatment was able to achieve complete tumour ablation, then improvements in outcome similar to those achieved with surgery should be possible. Previous studies in both small and large animal models[22,23] suggest that electrolysis fulfils these criteria. Ellipsoidal zones of hepatic necroses can be created around the tips of implanted electrodes with no damage to the surrounding parenchyma. The lesions are produced in a dose-dependent fashion and heal uneventfully to a small fibrous scar. Unlike diathermy, laser or cryotherapy, electrolysis produces cell necrosis with minimal thermal effect.[24,25] Cell necrosis is caused by a combination of altered intracellular pH[26,27] and the liberation of cytotoxic gases into the local environment.[28–32]

Before any new treatment can be used in the clinical setting, it is essential that it be shown as far as possible to be completely safe. Although previous studies in the rat and pig have shown that randomly placed intrahepatic electrodes are associated with minimal morbidity or mortality, it is important to determine the effects of an 'extreme' electrolytic insult before treating patients (unpubl. obs.).[22,23]

The present study examines the local and systemic effects of the 'worst-case scenario' where electrodes are placed either into or immediately adjacent to an hepatic vein near its entry into the inferior vena cava (IVC) in a large animal (pig) model.

METHODS

The direct current (DC) generator used in the present study was manufactured by the Bioengineering, Transducers and Signal Processing Research Group, University of Leicester, Leicester, UK.

Electrode catheters were supplied by Johnson & Johnson Medical Pty Ltd, North Ryde, New South Wales, Australia. The electrode catheters were 6 Fr and each had four platinum electrodes evenly spaced from the tip (Fig. 1). The tip electrode was used as the anode (positive), and the middle of the three proximal electrodes was used as the cathode (negative).

Correspondence: Professor G. J. Maddern, Department of Surgery, Queen Elizabeth Hospital, Woodville Road, Woodville, SA 5011, Australia.
Email: gmaddern@medicine.adelaide.edu.au

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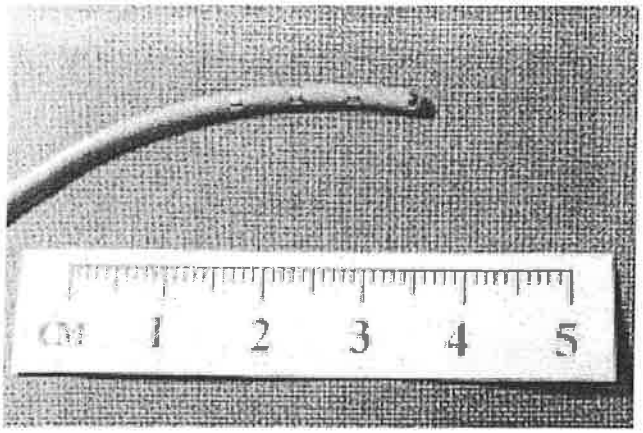

Fig. 1. An electrode catheter. The platinum tip electrode and the middle of the three proximal electrodes were used as the anode and cathode.

The use of laboratory animals in the present study was approved by local animal ethics committees (University of Adelaide, South Australian Research and Development Institute/Pig and Poultry Institute of South Australia and Queen Elizabeth Hospital, Adelaide). The study conformed with the *Code of Practice for the Care and Use of Animals for Scientific Purposes*[33] and the *SA Prevention of Cruelty to Animals Act 1985*.

Six female specific pathogen free (SPF) Domestic White pigs (29.0–33.0 kg) were obtained from the Pig and Poultry Production Institute, Roseworthy Campus, Roseworthy, South Australia, Australia. The animals were housed in individual pens and each had access to a single space wet/dry feeder and *ad libitum* water. Preoperatively the animals were fasted for 12 h. Each animal had a minimum acclimatization period of 7 days.

Experimental protocol

The six animals were divided into two groups of three to investigate the effects of electrode placement either immediately adjacent to or within the lumen of a hepatic vein near its entry into the IVC. Group 1: electrodes inserted adjacent to an hepatic vein (three animals); group 2: electrodes inserted into the lumen of an hepatic vein (three animals).

The animals were sedated with a deep intramuscular injection of ketamine (20 mg/kg) and xylazine (1.5 mg/kg). Spontaneous-breathing general anaesthesia was maintained with 1.5% halothane in 100% oxygen.

In order to evaluate the potential acid–base disturbance caused by the liberation of the ionic and gaseous products of electrolysis, a central venous catheter was inserted into the right internal jugular vein under direct vision. The catheter tip was placed in the right atrium. Venous blood samples were obtained before treatment, at 5-min intervals during treatment, and after cessation of treatment. Blood gas samples were analysed using a Radiometer ABL 625 (Radiometer-Copenhagen, Bronshoj, Denmark). Heart rate, arterial oxygen saturation, end-tidal CO_2 and respiratory rate were monitored continuously during treatment using a Datex OSCAR (Helsinki, Finland).

The liver was exposed through an upper midline incision. In group 1 the electrode catheter was inserted into the liver substance under intraoperative ultrasound control (Aloka SSD-2000, Mure, Mitaka-Shi, Tokyo, Japan; 7.5-MHz probe) such that the anode and cathode were positioned immediately adjacent to an hepatic vein close to its entry into the IVC. In group-2 animals the anatomy of the hepatic veins was mapped using the ultrasound. A peripheral branch of the appropriate vein was surgically exposed and the electrode catheter was inserted under direct vision. The electrode catheter was advanced such that the tip electrode was 2–3 cm from the IVC. In both groups an electrolytic 'dose' of 100 C was then delivered at 50 mA. The entire treatment was monitored and recorded using ultrasound. Specifically, areas of interest included: (i) the local environment around the electrodes; (ii) the presence of gas bubbles in the vein proximal to the catheter; (iii) the presence of bubbles in the IVC; and (iv) the presence of gas bubbles in the heart. After treatment the electrode catheter was removed and haemostasis was secured. The abdomen was closed in two layers using 1 polydioxanone (PDS) and 3/0 monocryl. Each animal was then returned to a clean, dry pen.

Each animal was assessed daily after treatment. All animals were killed 4–7 days after treatment and a full autopsy was performed jointly by the operating surgeon and a pathologist. At autopsy the liver, lungs, heart and brain were removed and examined macroscopically. Representative slices of each organ were fixed in 10% buffered formalin, processed, embedded in paraffin, sectioned and stained by haematoxylin and eosin. Sections were then examined by a hepatopathologist (PH).

RESULTS

All six animals tolerated the treatment well. Intraoperatively no complications were observed as a result of electrolysis. In all cases the heart rate remained stable and no animal suffered from de-saturation. There were no signs of cerebral irritation or respiratory distress. At the completion of treatment all animals recovered and remained healthy until time of death. Two animals in group 2 (intravascular electrodes), however, behaved in a more subdued fashion than normally observed and took more than 24 h to recover fully.

Group 1

In this group the electrodes were inserted adjacent to an hepatic vein (Figs 2–4).

The electrode catheter was successfully placed within 5 mm of a major branch of an hepatic vein in each animal with no bleeding complications. Within seconds of the start of the treatment, bubbles of gas were identified around the electrode catheter within the liver substance. As electrolysis progressed the gas was seen to track around the wall of the vein (Fig. 2) and in two animals intravascular gas could be identified (Fig. 3). During treatment there was progressive, diffuse change in the echogenicity of the liver texture around the electrode catheter. At the end of treatment the generation of gas was seen to stop abruptly, and there was minimal bleeding when the electrode catheter was removed.

Right atrial blood gas results were similar for all animals studied, showing no significant change over the treatment period. Specifically no animal became hypoxaemic or demonstrated a significant alteration in acid–base balance.

At autopsy the hearts, lungs and brains of each animal were macroscopically normal. For each liver there were small (< 2 mm) scars at the site of electrode catheter insertion but there

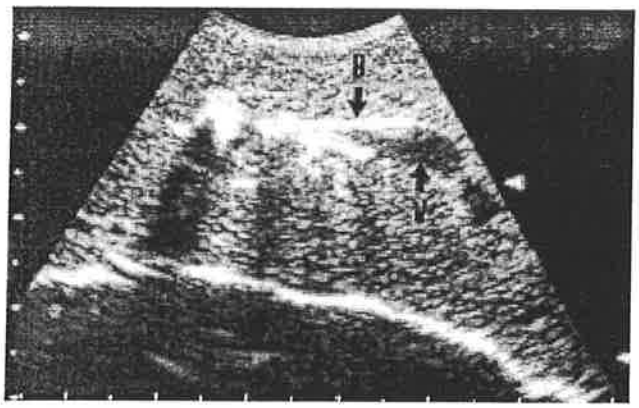

Fig. 2. Gas bubbles (B) tracking around the vein (V) after starting treatment.

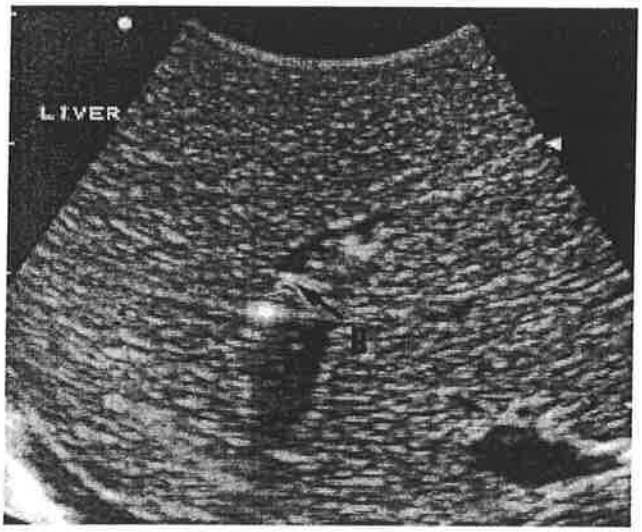

Fig. 3. Gas bubbles (B) in the lumen of the right hepatic vein.

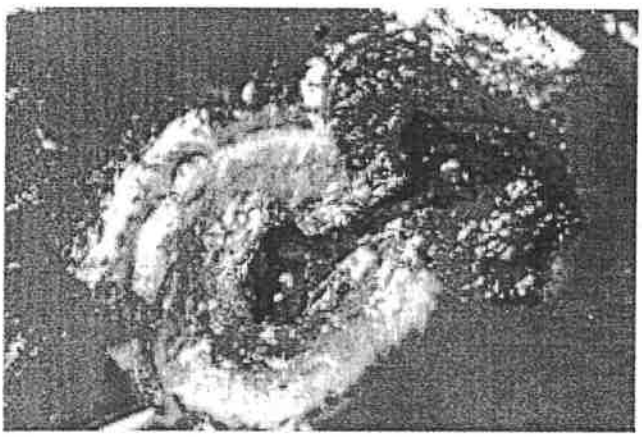

Fig. 4. Macroscopic appearances of the electrolytic lesion and the adjacent normal vein.

were no liver infarcts. On sectioning each liver, electrolytic lesions were identified adjacent to major hepatic veins. The areas of necrosis comprised both anode and cathode lesions that were distinct and abutting, forming an hourglass-shaped single 'composite' lesion (Fig. 4). Histology confirmed that the heart, lungs and brain were normal in each animal. The composite electrolytic lesions consisted of ellipsoidal areas of coagulative necrosis around the electrode sites. The walls of the adjacent veins remained intact and there were no major thrombotic occlusions. The liver parenchyma immediately adjacent to the electrolytic lesions was normal.

Group 2

In this group the electrodes were inserted into the lumen of an hepatic vein (Figs 5–8).

The electrode catheter was successfully inserted into the lumen of the right, middle or left hepatic vein in each animal (Fig. 5) and advanced such that the tip of the electrode catheter was 2–3 cm from the junction of each respective vein with the IVC. Within seconds of commencement of treatment, 'showers' of gas were seen in the lumen of the vein (Fig. 6). During treatment, ultrasound was used to fully 'map' each hepatic vein and in all three animals gas was identified in the IVC (Fig. 7). In one animal, after 70 C had been delivered, no further gas was seen in either the hepatic vein or the IVC. In the same animal there was mild, diffuse change in the echogenicity of the liver texture around the electrode catheter at the end of treatment. A clear 'lesion' could not be identified in the other two animals. At the completion of treatment gas production stopped. When the electrode catheter was removed the vein was ligated at the point of entry to achieve haemostasis.

Right atrial blood gases were identical to the group-1 animals and showed no significant effects during the study period.

At autopsy the hearts, lungs and brains of two of the animals were found to be macroscopically normal. In the third there were three small haemorrhagic lesions on the cusps of the mitral valve and two small areas of focal haemorrhage in each lung. The brain was normal.

In the liver of the animal in whom the presence of intraluminal gas ceased before the end of treatment, the left hepatic vein was completely occluded by thrombus. At the site where the electrode tip was positioned the vein was surrounded by a zone of liver necrosis. Otherwise the liver was normal. The livers of the other two animals were macroscopically normal apart from the peripheral trauma associated with insertion of the electrode catheters.

Histology of the walls of the veins adjacent to the infarcted area was performed and was found to be unchanged.

Histology confirmed the presence of mature thrombus in the lumen of the left hepatic vein (Fig. 8). One animal showed histological evidence of mild bronchopneumonia. Histology of the other organs was normal.

DISCUSSION

Electrolysis has enormous potential for treating patients with unresectable liver tumours. The technique causes dramatic but localized cell necrosis by several mechanisms, including the generation of toxic gaseous products.[28–32] There is, however, a theoretical risk that, if some or all of the gaseous electrode products were to enter the systemic circulation, extrahepatic damage

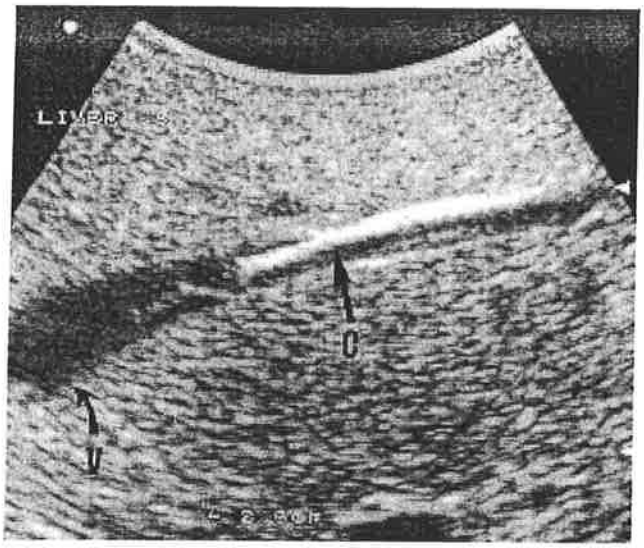

Fig. 5. The electrode catheter (C) is in the lumen of the right hepatic vein (V).

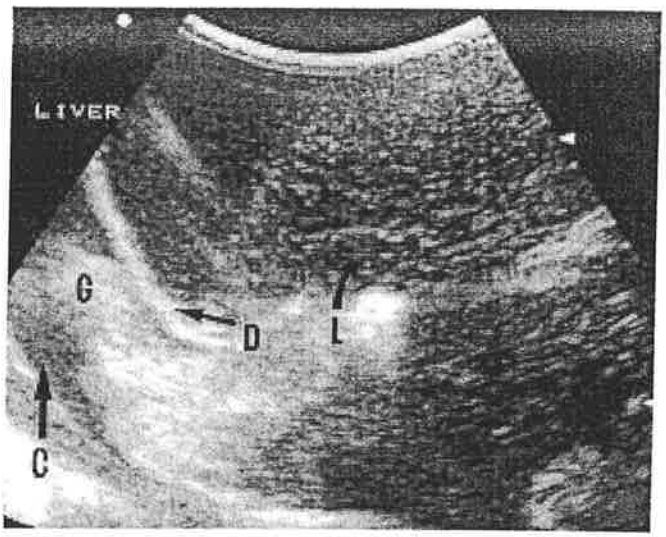

Fig. 7. 'Clouds' of gas bubbles (G) in the inferior vena cava (C) after starting treatment. The liver (L) and diaphragm (D) are also seen.

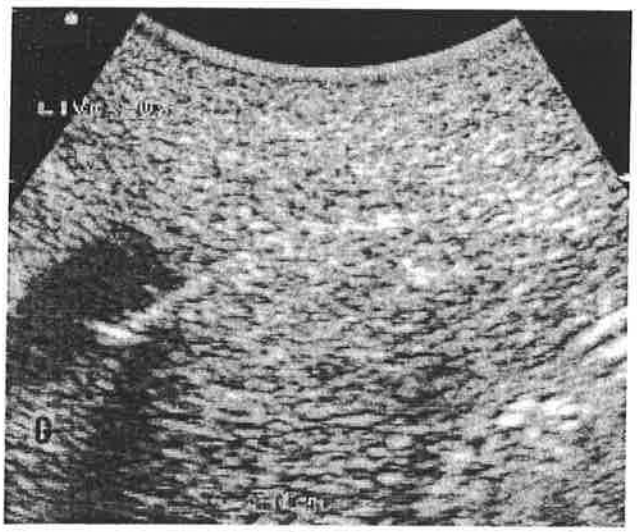

Fig. 6. Within seconds of commencement of treatment, 'showers' of gas (G) were seen in the lumen of the vein.

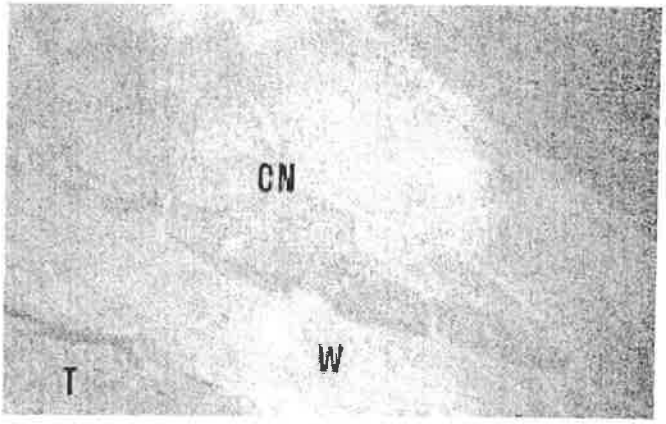

Fig. 8. Longitudinal section of the left hepatic vein showing intraluminal thrombus (T), an intact muscle wall (W) and a zone of coagulative necrosis (CN) in the immediately adjacent normal liver (H&E).

could result. Chinese researchers have recently reported the use of electrolysis to treat patients with a variety of liver tumours.[34,35] Despite the fact that they have attempted to treat tumours up to 21 cm in diameter, there was unfortunately no attempt to formally evaluate the safety of the process either experimentally or clinically. The present study is the first to examine the morbidity associated with the most potentially hazardous clinical situation where electrolysis products are purposefully generated in or adjacent to an hepatic vein. This, together with the production of a local lesion involving the vein, we believe, mimics the worst complication that could be envisaged in the clinical setting. Resultant complications could theoretically include hepatic vein thrombosis, liver infarction, air embolus, pulmonary embolus, chemical pneumonitis, cerebral irritation, major metabolic derangement and secondary haemorrhage. The results show that when the electrode catheter is placed adjacent to an hepatic vein, there is localized hepatic necrosis, with little or no damage to the vein. Despite the fact that gas was seen entering the IVC, no systemic complications were observed and all three animals recovered rapidly and remained healthy until they were killed. The situation where the electrode is selectively placed into the lumen of the vein clearly represents a completely different situation due to the relatively large volumes of gas that have immediate access to the systemic circulation, and the potential for metabolic changes due to electrode products not being used up locally (creating hepatic necrosis).

Consequently we expected the complications associated with this part of the study to be greater, but in two of the three animals no extrahepatic complications were observed either at the time of treatment, in follow up or at autopsy. Time to full recovery was prolonged, probably reflecting the observed intraoperative alteration

in acid–base balance. In one animal in group 2 complete occlusion of the left hepatic vein resulted and this would explain why the intraluminal flow of gas was seen to stop before the end of treatment. Localized gas production continued, however, and this may explain why this was the only animal in this group to have an electrolytic hepatic lesion at autopsy. Despite complete occlusion of the vein by thrombus, which extended to the junction with the IVC, there were no local sequelae, pulmonary emboli or systemic complications 7 days after treatment. The possibility of subsequent embolization cannot be excluded had survival been extended beyond 1 week, but it seems unlikely.

The present study aimed to create an artificial situation that should never occur in the clinical setting because electrodes would be inserted under ultrasound or magnetic resonance imaging control into the centre of a tumour. We did feel, however, that it was important to examine this scenario to obtain further reassurance that lesser electrolytic insults delivered in a controlled, planned way in the clinical setting would be associated with minimal systemic morbidity and no mortality. The present study has also shown that when lesions are created close to major veins the vein remains intact and patent; this has clear implications for centrally placed tumours, which are frequently deemed unresectable for this reason.

Another potential group of complications could result from damage to the biliary system with occlusion or fistula formation. In the present study there was no cholangitis, localized abscess formation, stricture or haematobilia and liver enzymes were normal at time of death. In a separate study in the pig where electrodes were inserted randomly into the liver without ultrasound control, however, it was shown that involvement of bile ducts or bile cannaliculi occurred in approximately 30% of the animals. Again, in the clinical setting inadvertent insertion of the electrodes into a bile duct would not only be difficult but would also be extremely unlikely due to the use of imaging for electrode placement, and because it is envisaged that an electrode catheter delivery system will ultimately be required that should incorporate a suction channel. Even if this were to occur, morbidity would be expected to be minimal.

Our experience to date therefore confirms that electrolysis is a safe treatment that should be associated with minimal local or systemic complications in the clinical setting, and justifies progression to careful clinical trials.

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Electrochemical Lesions in the Rat Liver Support Its Potential for Treatment of Liver Tumors[1]

Simon A. Wemyss-Holden, M.D., FRCS,* Gavin S. M. Robertson, M.D., FRCS,*
Ashley R. Dennison, M.D., FRCS,* Pauline de la M. Hall, MBBS, FRCPA,†
John C. Fothergill,‡ B. Jones,‡ and Guy J. Maddern, Ph.D., M.S., FRACS§,[2]

*Department of Surgery, Leicester General Hospital, Leicester, United Kingdom; †Department of Histopathology, Flinders Medical Centre, Adelaide, South Australia, Australia; ‡Department of Engineering, Leicester University, Leicester, United Kingdom; and §University of Adelaide Department of Surgery, The Queen Elizabeth Hospital, Woodville Road, Woodville, South Australia 5011, Australia

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Background. **An effective therapy is needed for patients with surgically unresectable liver tumors who have very limited life expectancy. One possible treatment is electrochemical tumor necrosis. This study investigated the natural history of electrochemical lesions in the normal rat liver.**

Materials and methods. **A direct current generator, connected to platinum electrodes, was used to create controlled areas of liver necrosis. Animals were sacrificed 2 days, 2 weeks, 2 months, and 6 months after treatment and the macroscopic and histological appearance of the necrotic lesions was followed.**

Results. **No animal died as a result of electrolysis; postoperatively, all gained weight normally. Liver enzymes were significantly ($P < 0.001$) elevated after treatment, but returned to normal after a week. Two days after electrolysis, histology confirmed an ellipsoidal area of coagulative necrosis at the site of the electrode tip and commonly a segment of peripheral necrosis. After 2 weeks there was histological evidence of healing. By 6 months, very little necrotic tissue remained within a small fibrous scar.**

Conclusions. **Electrolysis is a safe method for creating defined areas of liver necrosis that heal well with no associated mortality. This study supports the potential of electrolysis for treating patients with unresectable liver tumors.** © 2000 Academic Press

Key Words: **electrolysis; liver/hepatic tumors.**

INTRODUCTION

Currently, liver resection offers the only hope of significantly improved long-term survival in patients with primary and secondary liver tumors, with 25–35% of patients alive 5 years postresection [1, 2]. Unfortunately, only 5 to 10% of patients have resectable disease [3], and patients with untreated liver metastases from colorectal carcinoma have a poor prognosis [4], with a mean survival of approximately 6 months [5–7] and virtually no 5-year survivors. In this group, a range of locoregional treatments have been investigated [8–19] including liver transplantation [20–22]. These treatments are generally invasive and at best palliative [4, 23, 24].

With the incidence of primary hepatocellular carcinoma approaching 1 million, and with more patients being identified with metastatic liver disease, a widely applicable treatment is needed that would improve long-term survival while ideally being safe, reproducible, minimally invasive, and inexpensive.

Electrolysis is a well-documented electrochemical phenomenon. In mammalian tissue fluid, the main electrode products are known. At the cathode (negative electrode) sodium hydroxide and hydrogen gas are liberated, whereas at the anode (positive electrode), hydrochloric acid, oxygen, and chlorine gas are produced [25–29], assuming electrode "gassing limits" are exceeded [30, 31]. The production of these polarized electrode products creates a pH gradient between the anode and cathode; tissue around the anode becomes acidic relative to the basic environment surrounding the cathode [32, 33]; tissue necrosis at both sites results. There is no thermal effect, with temperature

[1] This work was supported by a grant from the University of Adelaide, Faculty of Medicine.
[2] To whom correspondence should be addressed. Fax: (08) 8222 5028. E-mail: gmaddern@medicine.adelaide.edu.au.

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increases of only 1.5 and 4°C (depending on electrode type) being reported [34, 35].

The first clinical use of electrolysis was reported in 1908 [36]. In the 1970s, the effects of electrolysis in various experimental animals, including the mouse [27, 35], rat [28, 37–39], rabbit [34], pig [26, 40–44], and a small number of patients with lung cancer [45–47], were reported. Areas of necrosis were produced mainly in the lungs, but also in subcutaneously implanted tumors. It was demonstrated that electrolysis created discrete, spherical areas of necrosis around the tips of implanted electrodes in a controlled, safe way. Based on this preliminary work, several Chinese groups have published anecdotal reports of patients in whom malignant tumors including primary liver tumors [48, 49] were treated using electrochemical therapy [50–58]. Although rather variable these studies highlight the potential of electrolysis in treating a range of malignancies.

As part of a scientific evaluation of the use of electrochemical therapy in the treatment of liver tumors, this study examined the morbidity, mortality, and natural history of electrolytically induced necrosis in the normal rat liver and documented its healing over a 6-month period.

MATERIAL AND METHODS

A direct current generator was constructed by the Bioengineering, Transducers and Signal Processing Research Group at the University of Leicester, England. This was designed to deliver a preset "dose" of coulombs at a constant current, variable between 1 and 100 mA. Positive (anode) and negative (cathode) electrodes, placed in the liver substance of rats, were used to conduct the current. On activation of the generator, the current flow "ramped" up to its preset maximum value (milliamps) over 1 min. Once in a "steady state" the voltage required to maintain a constant current flow was varied by the machine to compensate for any fluctuation in the resistance between the electrodes as treatment progressed. After the preset dose of coulombs was delivered, the current returned to zero over a period of 1 min.

The use of laboratory animals in this study was approved by local animal ethics committees (University of Adelaide and The Queen Elizabeth Hospital, Adelaide), and the study conformed to the Code of Practice for the Care and Use of Animals for Scientific Purposes (NHMRC/CSIRO/AAC 1990) and the SA Prevention of Cruelty to Animals Act 1985. All animals received humane care according to the criteria outlined in the *Guide for the Care and Use of Laboratory Animals* prepared by the National Academy of Sciences and published by the National Institutes of Health (NIH Publication 86-23, revised 1985).

Fifty-eight Wistar-WAG specific pathogen-free male rats (215–345 g), obtained from the Animal Resources Centre, Western Australia, were studied.

The animals were divided into four groups (see below) to evaluate three different electrode placements which produced one or two areas of hepatic necrosis and were compared with a control group. In each rat, under standard halothane/nitrous oxide anaesthesia, the liver was exposed through a midline incision and everted. Electrodes were introduced into the liver substance and supported using a gantry-type frame designed to minimize trauma with respiratory movement. A dose of 5 C at a constant current of 10 mA, known to create a 5-mm-diameter spherical zone of necrosis, was delivered in groups 1–3. In the control group no current was passed. After treatment the abdomen was closed in two layers. Fluids and diet were allowed ad libitum. The animals were weighed preoperatively, on the second postoperative day, and then weekly.

Group 1 (4 animals). The anode consisted of a 0.5-mm-diameter platinum wire inside a semirigid plastic electrical insulating sleeve. Two millimeters of wire was exposed at the tip, giving an effective electrode surface area of 3.34 mm^2. This was implanted to a depth of 5 mm in the major right lobe of the everted rat liver. The cathode consisted of a diathermy patient return electrode (code E7506, Valleylab inc., Surgical Products Division, Boulder, CO) with a surface area of 70 cm^2. This was attached to the back of the rat after shaving to achieve electrical contact.

Group 2 (18 animals). Both electrodes consisted of identical platinum wires as above. The anode was implanted to a depth of 5 mm in the major right lobe of the liver and the cathode to the same depth in the major left lobe, with a separation of 20 mm between the electrode tips during treatment.

Group 3 (18 animals). The two platinum wire electrodes were implanted together (2 mm separation between the tips) in the major right lobe of the liver.

Control rats (18 animals). Each control rat underwent laparotomy and electrode placement. The electrodes were connected to the direct current generator but no "dose" was given. Electrodes remained *in situ* for 10 min to simulate the mean length of active treatment.

Blood samples were obtained preoperatively, immediately postoperatively, and at Day 2, Week 1, and time of death. Measurements of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltranspeptidase (γGT), and bilirubin were made on each sample (Technicon AXON analyser, Bayer Health Care, Pymble, New South Wales, Australia).

Animals in each group (see Table 1) were sacrificed 2 days, 2 weeks, 2 months, and 6 months after treatment to determine the rate of healing of electrolytic lesions. At autopsy, the liver and adjacent organs were examined macroscopically. The size of the lesions was measured and recorded, and the lesions were photographed. The lesions and random slices of liver away from the lesions were fixed in 10% buffered formalin, processed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Coded sections were examined by a hepatopathologist (P.H.).

Results were analyzed using the paired and unpaired Student *t* test.

RESULTS

Within 30 s of starting electrolysis, gas production was observed in the form of bubbles emanating from both the anode and cathode and a discrete zone of discoloration was evident in the liver surrounding the electrodes. These areas increased in size as treatment progressed. Any bleeding following electrode insertion stopped within 60 s of the beginning of treatment, with the formation of a black coagulum. Animals in group 1 developed myoclonic contractions for a 10-s period as the current increased. The remaining 54 animals tolerated electrolysis well. All animals made rapid, uneventful postoperative recoveries and remained healthy until sacrificed. After a small but significant ($P < 0.001$) loss of weight in the early postoperative period, all animals gained weight at a normal rate until sacrificed.

Analysis of the liver enzymes showed that AST and

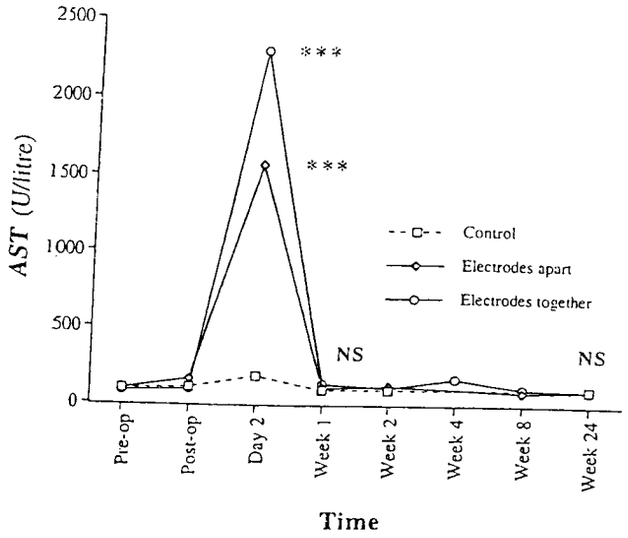


FIG. 1. Change in liver enzyme AST following electrolysis. ***$P < 0.001$. NS, not significant.

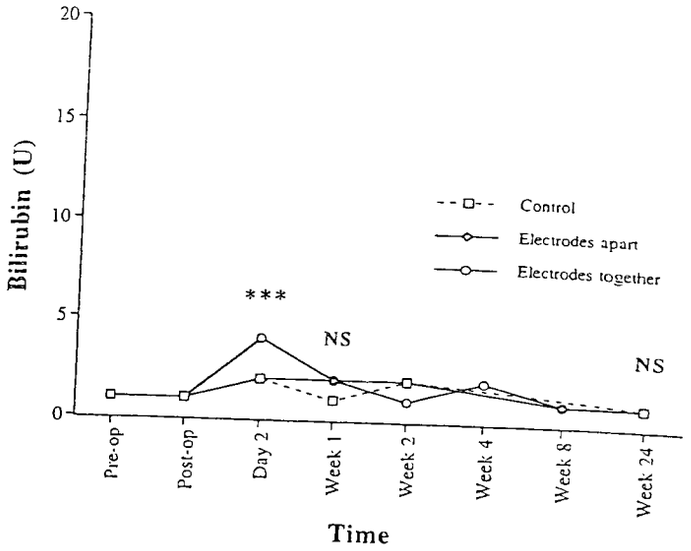


FIG. 3. Change in serum bilirubin concentration following electrolysis. NS, not significant.

ALT were significantly elevated in the treatment groups by Day 2 (Figs. 1 and 2). ($P < 0.001$), but these returned to normal after 1 week and remained normal thereafter. Bilirubin and γGT remained unchanged throughout (Figs. 3 and 4).

Liver Pathology

In group 1, the two animals sacrificed at each of 2 weeks and 2 months showed that a tract of macroscopic and microscopic damage had been created between the anode in the liver and the closest part of the plate cathode on the back with evidence of damage to the diaphragm, lungs, and pancreas. This observation, together with the myoclonic contractions in this group at the start of electrochemical therapy, meant that further evaluation of this electrode configuration was deemed inappropriate.

The results in groups 2 and 3 both macroscopically and microscopically at each time point were very similar and are reported together.

Two days postelectrolysis. Macroscopic examination of the livers demonstrated that the "primary" electrolytic lesions had become hard in texture (anode, cathode, and combined lesions). In 10 of the 12 lesions in group 2 and all 6 of those in group 3 a "secondary" distal wedge-shaped lesion developed in the liver. This "secondary" lesion was yellow in color and firm in texture with appearances consistent with an infarct (Fig. 5); it spread out from the "primary" lesion to the periphery of the lobe. Histological examination of the

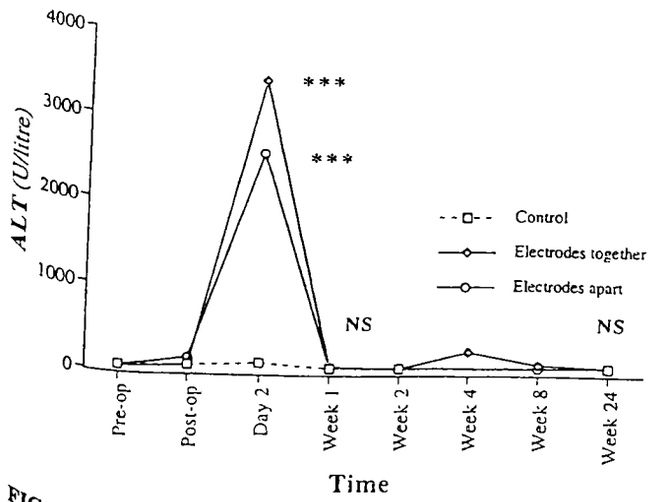


FIG. 2. Change in liver enzyme ALT following electrolysis. ***$P < 0.001$. NS, not significant.

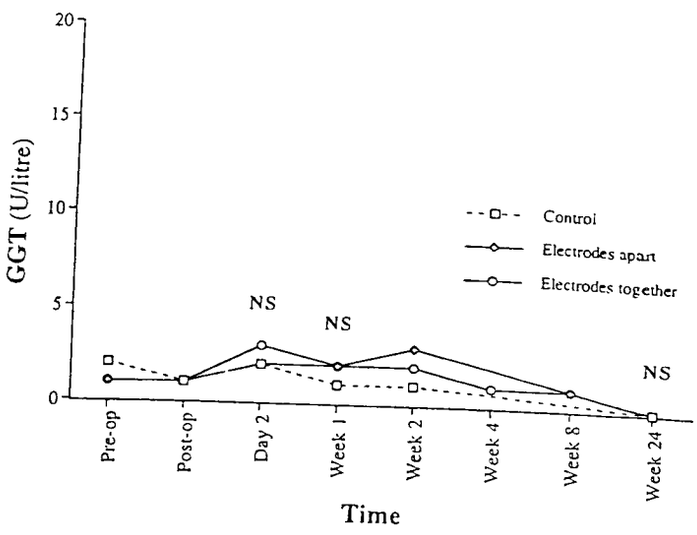
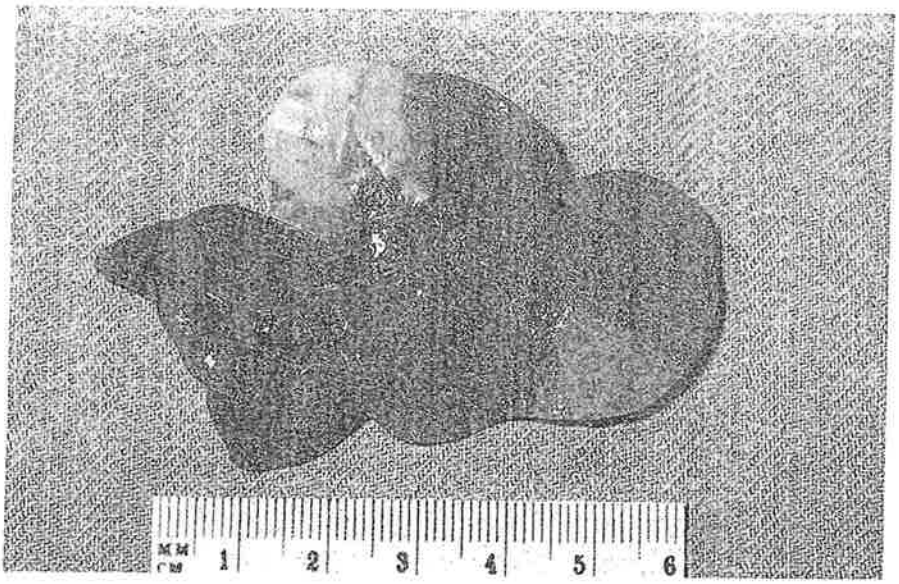


FIG. 4. Change in liver enzyme GGT following electrolysis. NS, not significant.



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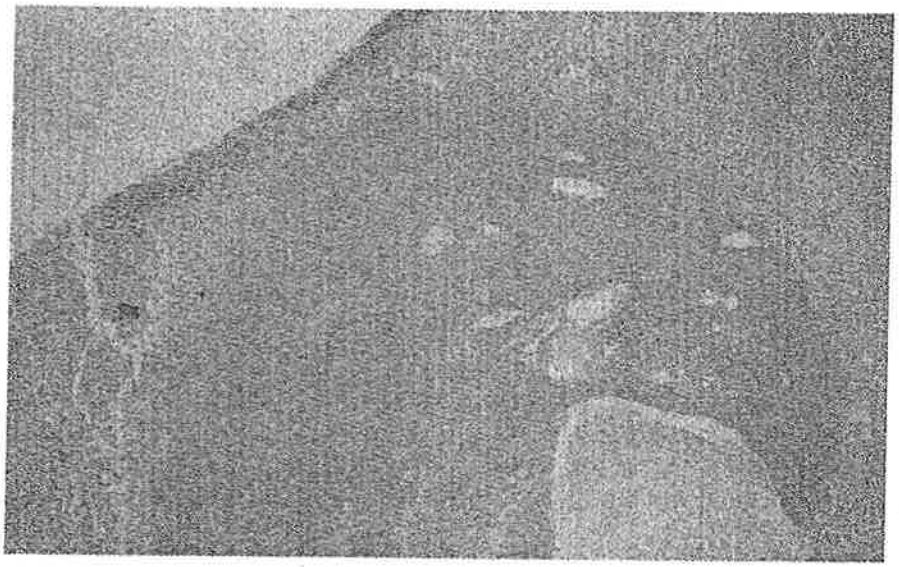

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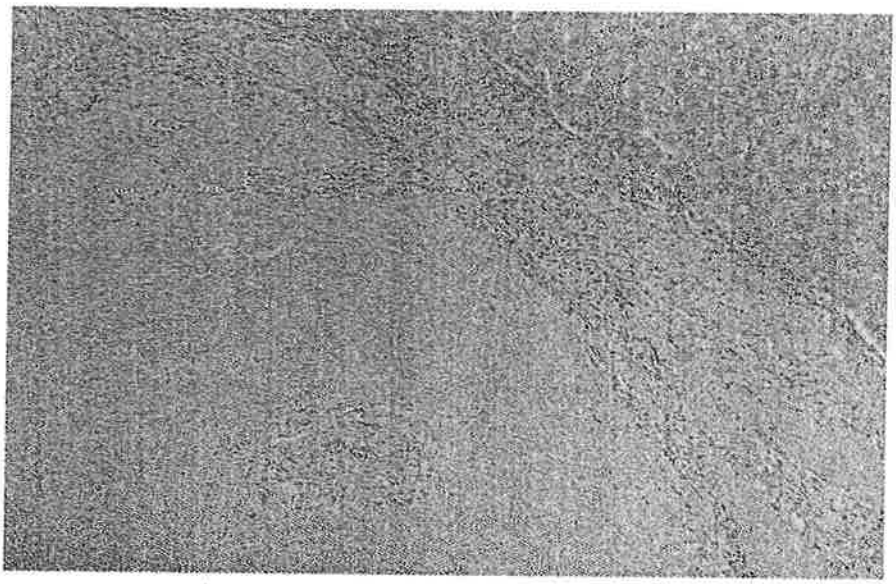

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livers confirmed extensive but well-defined areas of hepatic necrosis as a result of electrolysis (Fig. 6). An area of tissue destruction was observed at the electrode sites and was clearly discernible from the "primary" and "secondary" lesions which were areas of coagulative necrosis, presumably of slightly different ages. The necrotic tissue was sharply demarcated from immediately adjacent normal liver. A variable infiltrate of mononuclear cells and a few proliferating fibroblasts were seen in this junctional zone. Importantly, sections of liver immediately adjacent to the areas of necrosis were normal, as were random sections taken between the two electrode lesions.

Two weeks postelectrolysis. The "primary" electrolytic lesions had become stony hard in texture and black in coloration. Nine of the twelve lesions in group 2 and all of those in group 3 had a peripheral wedge-shaped infarct spreading out from the site of the "primary" lesion. These infarcts were involuting and contracting relative to the surrounding healthy liver. Histological examination showed a rim of proliferating fibroblasts around the entire zone of necrosis (Fig. 7). The fibroblasts were located beneath the capsule of the liver which had remained intact and also at the junction between the necrotic and viable liver tissue. Sections of liver immediately adjacent to the areas of necrosis and between the two lesions were normal.

Two months postelectrolysis. Only small residual black lesions were evident. In all four animals, small, hard, granular, yellow areas of necrosis were observed at and peripheral to the original electrode sites. Histological examination showed small residual areas of necrosis surrounded by fibrous tissue in which hemosiderin-laden macrophages, occasional foreign body giant cells, and focal calcification were observed. The liver elsewhere was normal.

Six months postelectrolysis. Each liver was normal apart from small, hard fibrous scars at the sites of treatment. Histological examination showed only a very small amount of residual necrotic tissue surrounded by mature scar tissue in which focal calcification was apparent.

In the control groups each liver was carefully examined, as it was often impossible to identify the site(s) of electrode insertion. Histological examination of one of the livers 2 days postoperatively showed two small (<1 mm) areas of necrosis at the electrode sites. After 2 weeks, one liver showed a microscopic area of focal congestion, although no lesion was identified. Proliferating fibroblasts were seen on the capsular surface corresponding to the presumed site of electrode insertion. Otherwise the livers were normal. After 2 months a cavity (2 mm) was identified in the center of the lobe where the anode had been inserted in one liver. A small amount of proliferating fibrous tissue and mononuclear cells was identified surrounding the cavity. Otherwise all the livers were normal. After 6 months, all livers were macro- and microscopically normal.

DISCUSSION

This study in the liver confirmed the results of previous studies in other organs [26–28, 34, 35, 37–47] that targeted electrochemical hepatic insults are a safe method of generating areas of discrete, controlled necrosis. These induced zones of necrosis are similar in shape to primary and secondary liver tumors. No such lesions were produced in the control groups where physical trauma was identical but no electrochemical insult occurred. The liver parenchyma between the induced lesions was both macro- and microscopically normal and there was no associated morbidity such as hemorrhage or bile leakage. If primary or secondary liver tumors were being treated, the results suggest that it would be possible and safe to create separate areas of tumor necrosis in different parts of the liver without fear of damaging vital intervening structures.

The lesions created by electrolysis were also shown to heal with time by ingrowth of fibroblasts from the intact capsule and adjacent normal liver. Six months after treatment the site of electrolysis was represented by a small fibrous scar with focal calcification and little residual necrotic tissue. Providing both anode and cathode are placed in the liver the risk of extrahepatic damage appears minimal. No animal died as a result of the treatment.

All animals treated by electrolysis gained weight at a normal rate after the first 2 days. Although liver enzymes (AST and ALT) were initially significantly elevated ($P < 0.001$) in all treated animals, by 1 week they had returned to normal, suggesting a minimal systemic and short-lived local effect.

Superinfection could be a potential clinical problem when creating zones of hepatic necrosis; this was not observed in any animal used in this study. During electrolysis, the local environment surrounding the

FIG. 5. Macroscopic appearance 2 days after electrolysis (electrodes apart): The "primary" lesion is the central, circular dark area. The yellow "secondary" infarct is seen spreading out to the periphery of the lobe.

FIG. 6. Histological appearance 2 days after electrolysis: Area of tissue destruction (bottom right) at the electrode site. Spherical, structureless area of coagulative necrosis surrounding the electrode site—the "primary" lesion (center). Peripheral zone of infarction where the hepatic architecture can still be discerned—the "secondary" lesion (top right, bottom left). Subcapsular hemorrhage (top left).

FIG. 7. Histological appearance 2 weeks after electrolysis: Normal adjacent liver (top right), sharply demarcated from a zone of proliferating fibroblasts which surround and extend focally into an area of coagulative necrosis (bottom left).

electrodes is sterilized by the fiercely cytotoxic local environment and the possible presence of platinum compounds (leached from the electrodes), which even in low concentrations are known to be bactericidal [59, 60]. Subsequently, electrolysis produces considerable hyperemia with consequent increased vascularity in the liver adjacent to the lesion which may also reduce the potential for infection. At the same time, electrolysis is known to preferentially attract white blood cells (negatively charged) to the anode. Infection is therefore unlikely to be as important a complication of this technique as it has been in areas of hepatic necrosis produced for instance by ligation of the hepatic artery.

The results showed that 26 of 36 (72%) lesions created with electrode tips separated (group 2), and 18 of 18 (100%) with electrode tips together (group 3) were associated with infarcts peripheral to the "primary" electrolytic lesion. Histological examination of these specimens confirmed the presence of thrombus in the main vessel supplying the distal lobe. This "electrolytic segmentectomy" has not previously been reported. It is proposed that this phenomenon resulted from creating relatively large electrolytic lesions in lobes that were physically small. However, a similar effect, if reproducible in large animals, would prove valuable in treating patients, since careful placement of electrodes under ultrasonographic control near vascular structures might produce planned, sequential segmentectomies using this thrombogenic effect.

Platinum electrodes performed well in this study. There was no visible erosion of the electrode tips, confirming the finding of other workers [28], although the theory regarding the generation of locally active cytotoxic platinum salts [28, 59–63] remains unproven. The exact relationship between electrode tip sizes and shapes and parameters such as the extent of tissue necrosis and maximal possible rate of current delivery has yet to be established. However, it should be possible to design delivery systems that are close to ideal in terms of the production of predictable lesions that maximize the volume of necrosis for a given dose over a given period. This is presently under investigation using computer "current modeling" techniques.

As a therapeutic modality for the treatment of cancer, electrolysis has been largely overlooked in the Western World. In China, it has been used to treat patients for several years, but the efficacy and safety of the technique have never been fully evaluated in the liver. The remit of this study was to evaluate and develop this "noninvasive" modality for treating liver tumors; nevertheless, it is likely that electrolysis will have wider application in the treatment of other unresectable solid organ tumors and hollow organ malignancies such as esophageal, gastric, and bile duct tumors. While this will obviously require extensive evaluation of the associated morbidity and mortality, basic principles and instrument design are likely to be applicable.

This study has demonstrated that electrolysis is a safe, reliable method of creating localized areas of necrosis in the rat liver. The physical insult of electrolysis appears to be very small and the lesions heal with time without any long-term morbidity. Experience to date suggests this is a safe technique with the potential to be minimally invasive (using ultrasound-guided, percutaneously implanted electrodes) which fulfills almost all of the criteria to allow a treatment to be widely and safely applicable to the treatment of inoperable liver tumors.

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Digestive Diseases

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Electrolytic Treatment of Colorectal Liver Tumour Deposits in a Rat Model: A Technique with Potential for Patients with Unresectable Liver Tumours

Simon A. Wemyss-Holden Gavin S.M. Robertson Pauline de la M. Hall
Ashley R. Dennison Guy J. Maddern

Department of Surgery, University of Adelaide, Queen Elizabeth Hospital, Adelaide, Australia

Key Words
Electrolysis · Colorectal liver metastases · Unresectable liver tumour · Rat model · Electrochemical therapy · 192NRC tumour cell line

Abstract

Background/Aims: Patients with unresectable malignant liver tumours have a poor prognosis. A technique is needed which improves long-term survival. Previous studies in the rat have shown that electrolysis is a safe, predictable and reproducible method for creating areas of necrosis in the normal rat liver. This study examined the effects of electrolysis on colorectal liver 'metastases' in the rat. ***Methods:*** Tumours of colorectal origin were implanted into the livers of Wistar-WAG rats. Two weeks after implantation the tumours were treated with electrolysis. A direct current generator, connected to 2 platinum intrahepatic electrodes was used to examine the effects of various electrode configurations on the extent of tumour necrosis. ***Results:*** Significant ($p < 0.001$) tumour ablation was achieved with all electrode configurations. Tumour necrosis was more complete ($p < 0.05$) with the electrodes positioned on either side of the tumour than with both electrodes placed in the centre of the tumour. Liver enzymes (AST and ALT) were significantly ($p < 0.001$) elevated after treatment, but returned towards normal by 2 days. ***Conclusions:*** This study has shown that colorectal liver 'metastasis' can be ablated by electrolysis in a rat model. Two separate mechanisms of tumour ablation were observed: With the electrodes directly in or adjacent to the tumour, necrosis resulted from the action of cytotoxic electrode products, whereas by positioning the electrodes proximal to the tumour, necrosis was induced by a 'secondary' ischaemic effect. The findings confirm the view that electrolysis has great potential for treating patients with unresectable malignant liver tumours.

Introduction

The treatment of patients with unresectable liver tumours remains a major clinical problem and mean survival remains approximately 6 months [1–3]. Several methods of loco-regional treatment have been described [4–15], but have not been shown to significantly increase long-term survival. These treatments are generally invasive and unpredictable in effect and consequently have a limited role in palliation [16–18]. The need therefore remains for a treatment which improves long-term sur-

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Prof. G.J. Maddern
Department of Surgery, University of Adelaide
Queen Elizabeth Hospital, Woodville Road
Woodville, South Australia 5011 (Australia)
Tel. + 618 8222 6756, Fax + 618 8222 6563, E-Mail gmaddern@medicine.adelaide.edu.au

vival in these patients. To be acceptable, such a treatment must be safe, predictable in effect, minimally invasive, repeatable and relatively inexpensive.

Unlike diathermy, electrolysis (although employing electrical current) causes tissue necrosis without the production of heat [19–21]. A low current (typically < 50 mA at < 25 V) is passed between two electrodes inserted into the liver substance. As a result, sodium hydroxide and hydrogen are liberated at the cathode and chlorine, hydrochloric acid and oxygen are produced at the anode [22–26], assuming 'gassing limits' are exceeded [27, 28]. A pH gradient is established between the electrodes and localised tissue necrosis results around the tips of the electrodes.

Our previous studies [21, 29] have shown that electrolysis is a safe, controllable and predictable method for creating discrete areas of hepatic necrosis in the normal liver of the rat. Electrode separation affects the total volume of hepatic necrosis and in the majority of rats in this study, a wedge of 'secondary' ischaemic necrosis was produced peripheral to the 'primary' electrolytic lesion. This phenomenon results from thrombosis of small branches of the hepatic arteries. An 'electrolytic segmentectomy' resulting from such an arterial occlusion would, if reproducible, have significant implications for tumour ablation. If electrolysis is to be used to treat liver tumours in patients, it must be clearly demonstrated that not only normal liver tissue but also liver tumours can be destroyed using electrochemical therapy.

This study examined the extent of necrosis of colorectal liver tumour deposits resulting from electrolysis in a small animal (rat) model. Various electrode positions and separations were examined in an attempt to define the ideal therapeutic approach.

Methods

The use of laboratory animals in this study was approved by local Animal Ethics Committees (University of Adelaide and Queen Elizabeth Hospital, Adelaide), and the study conformed with the 'Code of Practice for the Care and Use of Animals for Scientific Purposes' (NHMRC/CSIRO/AAC 1990) and the SA Prevention of Cruelty to Animals Act 1985.

The direct current (DC) generator was constructed by the Bioengineering, Transducers and Signal Processing Research Group at the University of Leicester, UK. The generator was designed to deliver a pre-set 'dose' of coulombs (C) at a constant current, variable between 1 and 100 mA.

Tumour cells were obtained from the Department of Surgery, Royal Perth Hospital, Perth, Western Australia. The 192NRC tumour cell line was originally derived from a primary colonic adenocarcinoma in the Wistar-WAG rat [30]. Seventy-three Wistar-WAG SPF male rats (160–240 g) were obtained from the Animal Resources Centre, Perth, Western Australia. Animals were fed and watered ad libitum.

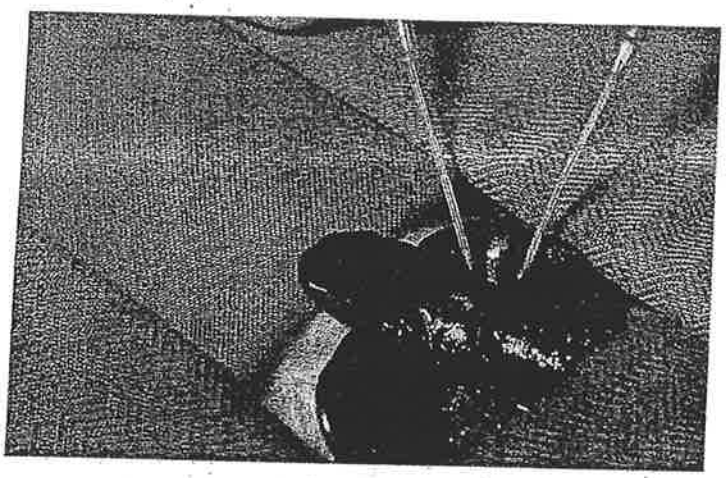
Two rats were used as tumour donors. 1×10^6 tumour cells were suspended in 0.05 ml of DMEM and 10% FCS. The cells were injected into the peritoneal cavity of each animal under standard halothane/nitrous oxide general anaesthesia. The solid tumour was harvested from the peritoneal cavity 2 weeks after inoculation.

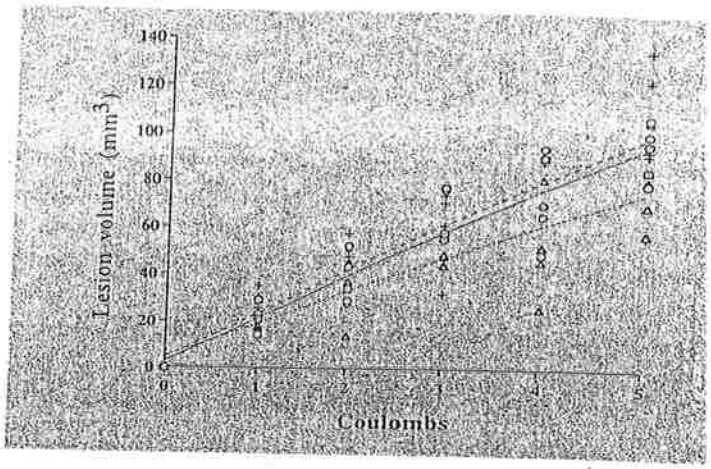
Tumour Growth Rate

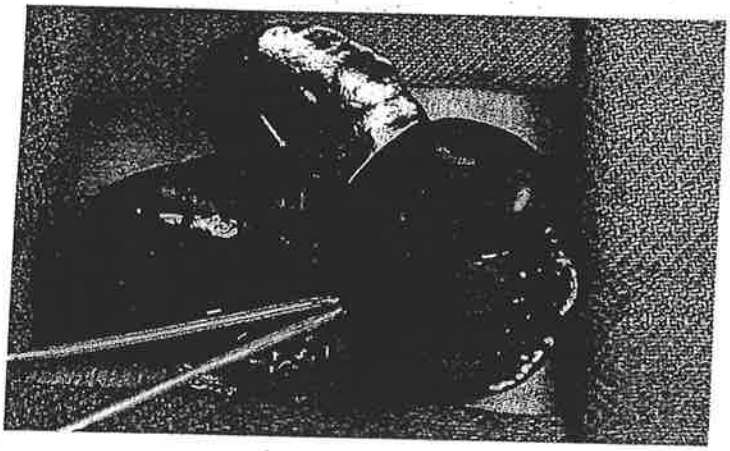
A pilot study was performed to establish the growth rate of the tumour and hence the most appropriate time for treatment after tumour implantation (as judged by the size of the tumour deposits). Under general anaesthesia, 1-mm^3 blocks of solid tumour were harvested from the peritoneal cavity of the tumour donors and kept on ice. In each study animal, a tumour was then implanted into the right and left lobe of the liver. In total, 32 blocks of tumour were implanted into 16 animals under general anaesthesia. This was achieved by exposing and everting the liver through a midline incision. A small 'pocket' was then created in the inferior surface of the major right and left lobes using a 20-gauge plastic cannula (Insyte; Becton Dickinson Vascular Access, Sandy, Utah, USA) to a depth of 5 mm. Direct pressure was applied until haemostasis was achieved. A 1-mm^3 block of tumour was then inserted into each pocket. Further direct pressure was applied until any bleeding again ceased. The entire operative field was irrigated with sterile water and the liver returned to the peritoneal cavity. The abdomen was closed in two layers.

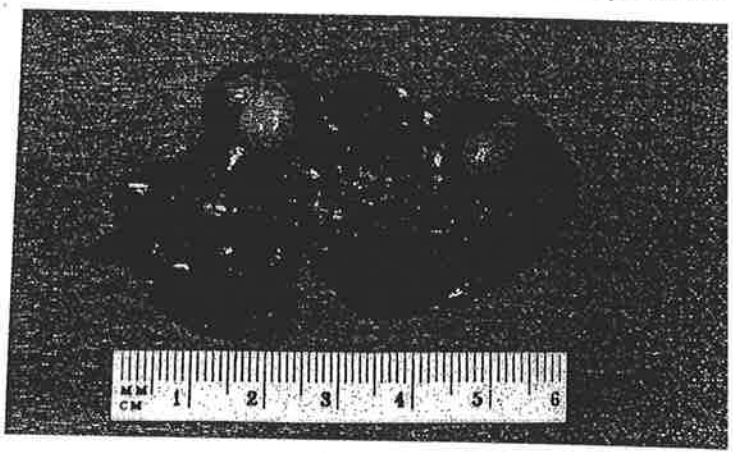
Groups of 4 animals were sacrificed at 1, 2, 3 and 4 weeks after tumour implantation. At autopsy, the size of the metastases were measured macroscopically using a micrometer. A slice of each liver containing the tumour deposit was fixed in 10% buffered formalin, processed, embedded in paraffin, sectioned and stained by haematoxylin and eosin. Coded sections were examined and measured by a hepatopathologist (P.H.).

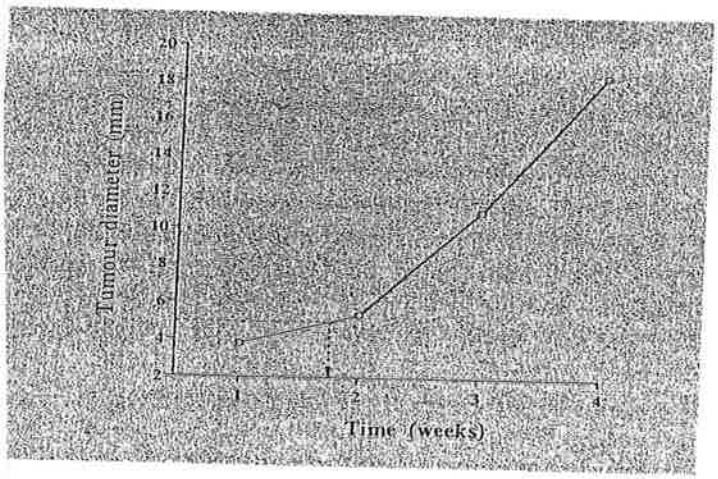
Having established the growth rate of the tumour, two studies were performed to examine: (1) the effect of electrode separation on tumour ablation, and (2) the potential of electrolysis to cause an electrolytic 'segmentectomy' and ablate the metastases.

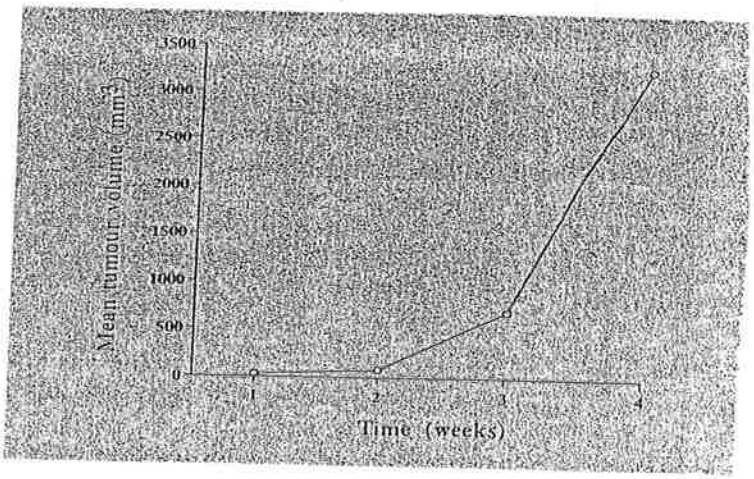










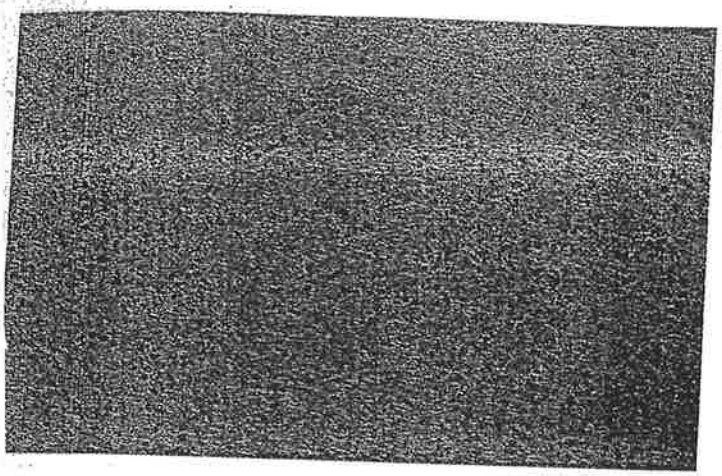


g. 1. Effect of electrode separation. Electrodes being placed on either side of a left lobe tumour. Sufficient current was passed between the ctrodes such that the resulting electrolytic lesion would completely encompass the tumour.

g. 2. Dose/response curves from a previous study for electrodes placed with a tip-to-tip separation of either 2 mm (electrodes together) or mm (anode and cathode). This enabled the appropriate dose to be selected to treat each tumour with each electrode configuration. ..... = Anode lesions; Δ, ····· = cathode lesions, +, ------- = electrodes together.

. 3. Electrolytic segmentectomy. Electrodes placed 5 mm proximal to a left lobe tumour before electrolysis. The aim was to create a peripheral arct (and hence tumour ablation) resulting from vascular occlusion by the 'primary' electrolytic lesion.

. 4. After 2 weeks all 4 animals had macroscopic tumour growth in both lobes of the liver.



ig. 7. Section of liver containing a deposit of anaplastic carcinoma omposed of highly pleomorphic spindle-shaped cells. HE.

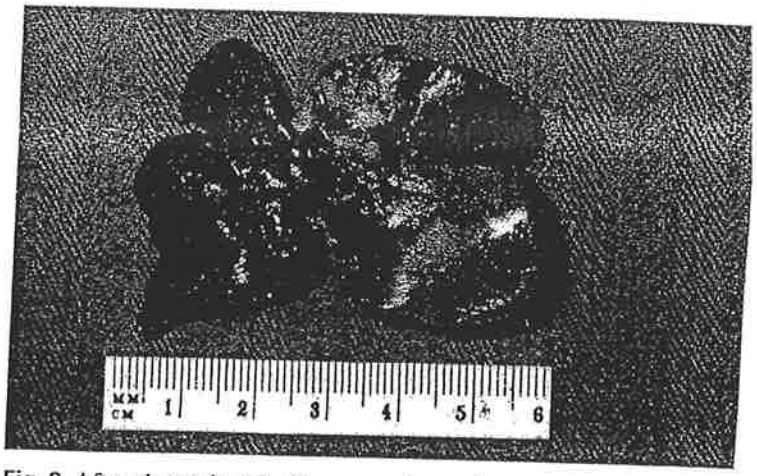


Fig. 8. After electrodes (tips 2 mm apart) were inserted into the centre of the right lobe tumour and treated with electrolysis, the tumour was macroscopically ablated. Note the viable, untreated control tumour in the left lobe.

Effect of Electrode Separation

Thirty animals were implanted with 60 tumours (major ght and left lobes, as above). In each rat only one tumour as treated; the untreated tumour acted as the animal's vn control. Two weeks after tumour implantation and ior to laparotomy, the animals were randomly allocated 1 of 2 treatment groups. The tumours were treated h the electrodes either together or apart (fig. 1): group right or left lobe tumour treated, electrodes together, l group 2 = right or left lobe tumour treated, electrodes rt (treatment of the right and left lobe tumour was randomly determined).

n group 1 the electrodes were inserted in the centre he tumour with a tip-to-tip separation of 2 mm. In ıp 2 the electrodes were inserted on either side of the our.

he electrodes (anode and cathode) were identical. consisted of a 0.5-mm diameter platinum wire inside ni-rigid plastic (electrically insulating) sleeve. At the rode tip 2 mm of wire was exposed; this gave an tive electrode surface area of 3.34 mm². Under gen- naesthesia, the electrodes were implanted to a depth mm in or adjacent to the liver tumour.

ıe electrodes were connected to the DC generator ıe dose in coulombs appropriate to the size (volume)

Tumour growth rate. Change in tumour diameter with time nplantation. After 2 weeks the mean tumour diameter was . This was judged to be the most appropriate size/time for nt with electrolysis.

Tumour volume increased exponentially with time after im- on. After 2 weeks the total tumour mass increased rapidly.

of the tumour was delivered at 3 mA. This dose was determined from previous dose/response studies in the normal rat liver (fig. 2) [29] by examining various combinations of coulombs and milliamps and the resulting lesion size in the rat liver. After treatment the electrodes were removed and peritoneal lavage was performed with sterile water. The abdomen was closed in 2 layers.

Electrolytic 'Segmentectomy'

Fifty tumours were implanted into the right and left lobes of 25 animals. Before relaparotomy, two weeks after tumour implantation, treatment of either the right or left lobe tumour was determined randomly. Equal numbers of right and left tumours were treated.

Under general anaesthesia the electrodes (tip-to-tip separation of 2 mm) were inserted to a depth of 5 mm in the liver substance, 5 mm proximal to the tumour (fig. 3). The electrodes were connected to the DC generator and a dose of 4 C was delivered at 3 mA. After treatment, the animals were treated as above.

Blood samples were obtained pre-operatively, on day 1, and at the time of sacrifice. Measurements of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltranspeptidase (γGT) and bilirubin were made on each sample (Technicon AXON analyser, Bayer Health Care, Pymble, NSW, Australia).

In each study, all animals were sacrificed on the 2nd post-operative day and at autopsy the liver was removed and examined macroscopically. The treated and untreated tumours were assessed independently by 2 investigators and described as either: (1) no evidence of tumour abla-

tion, (2) partial tumour ablation, or (3) complete tumour ablation. Each liver was then fixed in formalin and both the treated and untreated tumours examined microscopically as above.

Results were analysed statistically using the paired t test (change in liver enzymes after electrolysis) and the χ^2 test (comparing tumour ablation between treatment and control tumours; Statworks, version 1.2, Cricket Software Inc., Philadelphia, Pa., USA).

Results

All animals treated by electrolysis tolerated the treatment well and made an uneventful postoperative recovery. One animal died on the 1st postoperative day (significant haemorrhage at laparotomy from accidental tear of the right branch of the portal vein). Otherwise, there was no mortality and no animal had to be sacrificed before its predetermined time.

Tumour Growth Rate

At autopsy, 1 week after tumour implantation, 3 of the 4 animals had evidence of tumour growth. Of the 8 tumours implanted, 5 showed evidence of growth. Mean tumour diameter was 3.8 (2.0–4.5) mm. After 2 weeks, all 4 animals had tumour growth in both lobes of the liver (fig. 4); the mean tumour diameter was 5.3 (range 4.25–7.5) mm with no evidence of extrahepatic disease. Three weeks after implantation all 4 animals had extensive bilateral tumour growth. Mean tumour diameter was 10.9 (range 5.0–19.5) mm. There was no evidence of extrahepatic disease in any of the animals. After 4 weeks, 2 of the 4 animals had widely disseminated disease and the liver was largely replaced by tumour; each animal had obvious peritoneal and pleural metastases. The remaining animals had large intrahepatic tumours without evidence of extrahepatic disease. Mean tumour diameter was 18.4 (range 13.0–27.5) mm.

Mean tumour diameter (fig. 5) and volume (fig. 6) were plotted against time after implantation. Figure 5 shows that the optimum time after implantation for treatment was approximately 2 weeks (mean tumour diameter = 5 mm) and figure 6 shows that after 2 weeks the total tumour burden was increasing exponentially with respect to time.

Histopathological Description of the Tumor

Sections of each of the tumour deposits showed the features of an anaplastic carcinoma composed of highly pleomorphic spindle-shaped cells (fig. 7).

Effect of Electrode Separation

Six of the 30 animals were not suitable for electrolysis: 3 had macroscopic evidence of peritoneal seedlings; 2 had no obvious tumour growth, and 1 was used as a tumour donor to maintain the tumour cell line. The remaining 24 animals had good tumour growth in both lobes of the liver, with no evidence of extrahepatic disease and were therefore suitable for treatment (in 2 groups of 12).

Group 1 (Electrodes Together). At laparotomy, mean tumour diameter was 6.0 (range 2.0–11.0) mm for the right and 5.5 (range 3.5–7.5) mm for the left lobe tumours. At autopsy (fig. 8) macroscopic tumour ablation (partial or complete) was significantly ($p < 0.001$) greater in the treated tumours (12/12) than the controls (0/12).

Histology showed that in all cases electrolysis resulted in tissue necrosis, usually in the centre of the tumour deposit, with the peripheral rim of viable tumour. It was estimated that up to 60% of the tumour was destroyed.

Group 2 (Electrodes Apart). At laparotomy, mean tumour diameter was 4.6 (range 1.5–9.5) mm for the right and 4.1 (range 1.0–7.0) mm for the left lobe tumours. At autopsy macroscopic tumour ablation (partial or complete) was significantly ($p < 0.001$) greater in the treated tumours (12/12) than the controls (0/12).

Histology showed that in all cases electrolysis resulted in tumour necrosis, usually in the centre of the tumour deposit, with a peripheral rim of viable tumour. It was estimated that between 30 and 100% (2 rats) of the tumour was destroyed.

Comparison of the extent of tumour ablation (partial or complete) between groups 1 and 2 showed that the extent of tumour ablation was significantly ($p < 0.05$) greater when the electrodes were separated on either side of the tumour than together in the centre.

Electrolytic Segmentectomy

Two of the 25 animals had no evidence of tumour growth at laparotomy and were therefore not suitable for electrolysis. One animal died on the 1st postoperative day (vide supra).

The remaining 22 animals had tumour growth in both lobes of the liver, although in 4 of these the tumour was palpable but not visible. No animal had evidence of extrahepatic disease.

At laparotomy, mean tumour diameter was 6.0 (range 2.0–10.5) mm for right and 5.4 (range 2.0–11.0) mm for left lobe tumours. Macroscopic tumour ablation was significantly ($p < 0.001$) greater in the treated tumours (19/22) than the controls (1/22). The mean volume of the

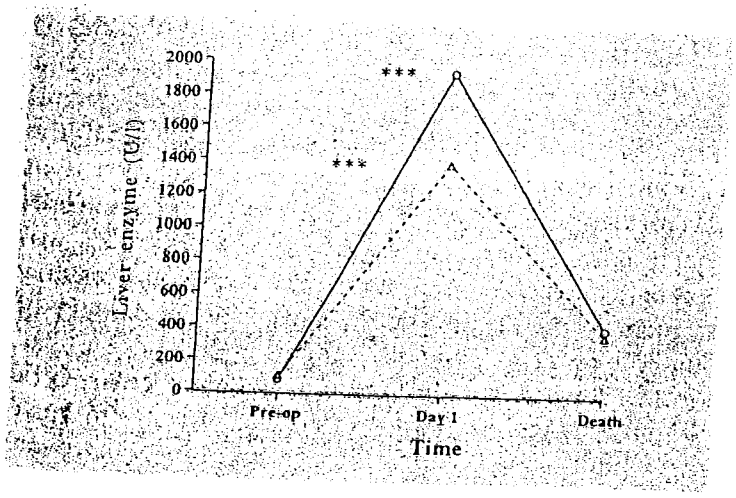


Fig. 9. Change in liver enzymes AST (△) and ALT (○) after treatment by an 'electrolytic segmentectomy' (***$p < 0.001$, $n = 22$).

peripheral infarct was 705 (range 320–1,120) mm^3. Liver enzymes (AST and ALT) were significantly elevated on day 1 post-treatment ($p < 0.001$) but were returning towards normal at time of death (fig. 9). Bilirubin and γGT were not significantly changed. The elevation in liver enzymes after electrolysis correlated with the total volume of liver necrosis (AST, $p < 0.05$; ALT, $p < 0.001$).

Histology showed that in 17 rats 'electrolytic segmentectomy' resulted in destruction of the entire tumour deposit (7/11 left lobe and 10/11 right lobe). The remaining 5 rats had 60–90% tumour destruction.

Sections of each of the untreated tumour deposits showed viable anaplastic carcinoma although some of the deposits contained one or more microscopic foci of tumour necrosis.

Discussion

The purpose of this study was to examine the effects of electrolysis on single colorectal liver metastases in a rat model. The tumour model used was different to that described by Archer and Gray [30]. In their original study, tumour cells were cultured on microspheres and injected into the portal vein. This technique resulted in the growth of multiple, discrete liver tumours. This method was inappropriate in the present study, as solitary metastases were required in each lobe and therefore 1-mm blocks of tumour were implanted directly into the liver substance. This model of colorectal liver metastases proved to be ideal and was predictable and reproducible.

In the tumour growth rate study, 2 weeks after implantation discrete tumours were evident in both lobes of the liver in all 4 animals and of a suitable size for electrolysis, with no evidence of extrahepatic disease. After 2 weeks the tumour growth rate was increasing exponentially, such that at 3 weeks there was evidence of widespread subcapsular spread, and by 4 weeks the tumour load was overwhelming with the liver largely replaced.

Based on this preliminary study, the most appropriate time for treatment by electrolysis (in this animal model) after implantation was clearly 2 weeks as the tumours were large enough to be treated but still small enough to realistically achieve complete ablation. This was subsequently confirmed in the main studies where only 4 of 55 animals implanted with tumours had to be excluded due to a lack of tumour growth and the overall mean tumour diameter at 2 weeks was 5.6 mm with no evidence of extrahepatic disease.

Although other studies have demonstrated the ability of electrolysis to cause tumour necrosis in subcutaneously implanted tumours in the rat [25, 31–33], none have examined the effects on rat liver tumours. In this study it is clear that electrolysis can cause necrosis of implanted colorectal liver tumours in a rat model and that necrosis could probably be induced by 2 separate mechanisms.

Electrodes placed either in or directly adjacent to the tumours cause tumour cell death by the localised production and action of cytotoxic electrode products [34, 35]. However, macroscopic tumour ablation was significantly ($p < 0.05$) greater when the electrodes were placed on either side of the tumour rather than together in the centre of the tumour. This was confirmed histologically. Other workers have reported that the total volume of necrosis is approximately twice as great when electrodes are separated as opposed to closed together [23, 36]. It has been suggested that this effect results from mixing (and potential neutralisation) of the cytotoxic products in the region of the electrodes when their tips are adjacent, thereby reducing the overall effect [36]. This may explain the improved tumour ablation observed in this study when the electrodes were separated on either side of the tumour.

In a previous study in the normal rat liver [29], it was shown that in the majority of cases, the 'primary' electrolytic hepatic lesion was associated with a 'secondary' peripheral infarct resulting from intravascular thrombosis caused by the 'primary' lesion. We believe that it may be possible to induce tumour ablation by producing a planned electrolytic 'segmentectomy'. This study confirmed the efficacy of electrolysis used in this way to

produce tumour ablation by peripheral ischaemia in the rat and while significant tumour destruction resulted, it is likely to have a limited application in large animal models and patients. In the rat this relates to the physical dimensions of the organ to be treated. The cross-sectional diameter of the liver is small (approximately 7 mm) and by creating a 5-mm electrolytic lesion, it is clear that the vascular supply to the peripheral part of the lobe will be compromised. In physically larger livers, even sizeable lesions are very unlikely to compromise the distal blood supply to the same extent and this seems to be supported in our large animal studies, presently in progress.

Platinum electrodes were used in this study because it has been shown that they were not readily eroded by the electrolytic process [25] and can be reused. It has also been suggested that the use of platinum electrodes may increase the toxicity of the local environment by the production of cytotoxic platinum salts [37–41]. This potential benefit, although attractive, remains theoretical and unproven. Other electrode materials such as carbon may be appropriate where disposable electrode systems are necessary for use in the clinical setting and we are presently investigating this material.

Chinese physicians have been using electrolysis to treat patients with a variety of malignancies for several years. Two reports have been published regarding the treatment of primary liver tumours [42, 43]. The results are difficult to interpret but do highlight the potential of electrolysis for the treatment of a wide range of tumours. However, before any new treatment modality can be used to treat patients it should be demonstrated that it is not only safe, controllable, predictable and reproducible but importantly efficacious. Previous work [29] has confirmed the potential of electrolysis for treating patients with unresectable liver tumours by creating areas of liver necrosis in the normal rat liver and this study has shown that electrolysis is also able to cause ablation of colorectal liver metastases. From the results it also appears that the electrodes should ideally be positioned apart such that the resulting electrolytic lesion completely encompasses the tumour, rather than implanting the electrodes together in the centre of the tumour. It will also be necessary to increase the electrolytic dose to ensure a margin of ablation results around the tumour. While in the rat, tumour ablation was also achieved with distal electrolytic 'segmentectomy', we believe that this will prove to have a very limited application in the clinical setting, but nevertheless merits further evaluation.

Electrolysis would seem to fulfill many of the criteria for a suitable method of treatment of unresectable liver tumours. It has the potential to be inexpensive, minimally invasive and repeatable as required within any lesion or patient on an outpatient basis. Ultimately, in patients, it is envisaged that electrodes could be inserted percutaneously under ultrasound or MRI control, and used to produce predictable areas of hepatic necrosis, ablating tumours with very little morbidity. For the treatment of patients with unresectable hepatic malignancy, electrolysis has been largely overlooked in the Western world, and is a technique which is likely to have widespread applications.

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Electrolytic Ablation of Colorectal Liver Metastases: 1-Year Histological Patient Follow-Up

D.P. Berry[a,b], *A.R. Dennison*[a], *R. Ward*[b], *G.J. Maddern*[b]

[a]Department of Surgery, Leicester General Hospital, Leicester, UK, and [b]University Department of Surgery, The Queen Elizabeth Hospital, Adelaide, S.A., Australia

Key Words

Liver · Colorectal metastases · Ablation · Electrolysis

Abstract

Whilst up to 50% of patients with colorectal carcinoma will develop liver metastases, only 20% of those patients will be amenable to potentially curative liver resection. There is therefore great need for other effective therapies, and we report complete ablation of a colorectal liver metastasis using electrolysis, which was histologically confirmed at 1 year. The clinical impact of complete tumour ablation at 1 year means that a proportion of those patients currently deemed inoperable and therefore incurable, may be suitable for curative treatment.

Introduction

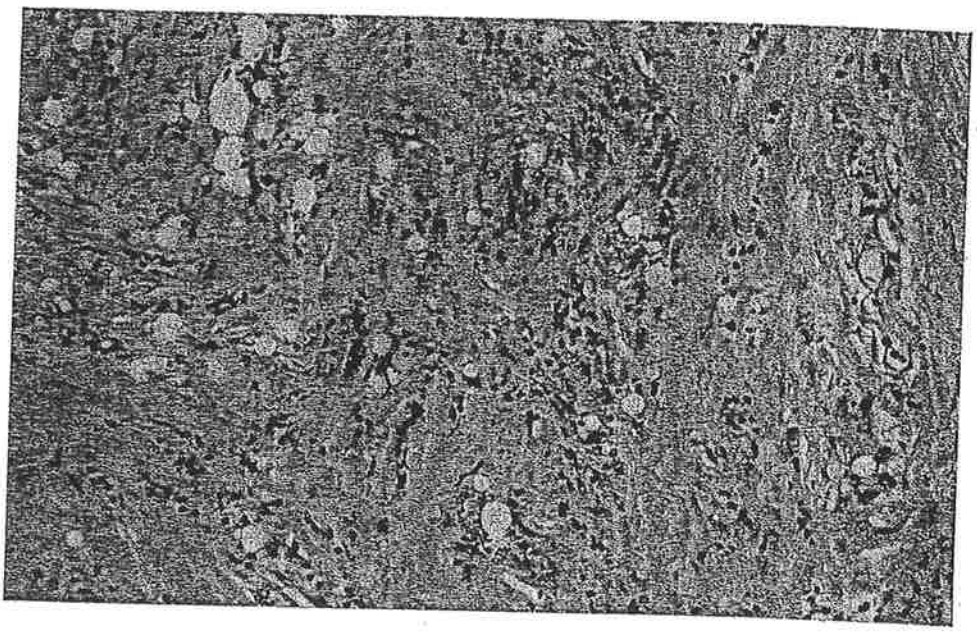
Colorectal carcinoma is common and up to 50% of patients develop liver metastases [1]. Progressive involvement of the liver may be the major or sole determinant of survival and without treatment these patients have a very poor prognosis with a mean survival of 6 months [2].

Surgical resection of colorectal metastases is the only curative treatment option and produces an up to 40% 5-year survival [3]. However, only 20% of patients [4] are suitable for curative surgical liver resection due to the anatomical distribution of the metastases and/or the presence of extrahepatic disease.

An ablative technique is therefore required which is simple, affordable, safe and completely ablates liver tumours. We are investigating the technique of electrolysis and report a case of an electrolytically treated colorectal liver metastasis excised 1 year after treatment without evidence of residual/recurrent tumour.

Case Report

A 58-year-old man presented with a 2-month history of intermittent lower abdominal pain and diarrhoea. Colonoscopy identified two large rectal polyps and two sigmoid polyps. Biopsies of the rectal polyps revealed the presence of a moderately differentiated invasive adenocarcinoma. Pre-operative abdominal CT scan identified 2 metastatic lesions in the left lobe of the liver. Following preoperative radiotherapy he underwent a low anterior resection with covering loop ileostomy and histology confirmed a Duke C adenocarcinoma (1 of 4 lymph nodes involved). He subsequently underwent a left hepatic lobectomy and intraoperative ultrasound revealed a 2-cm nodule in segment V of the liver with appearances consistent with a metastasis. In view of intraoperative instability the right-sided lesion was left in situ. Histology of the left lobe confirmed metastatic tumour. Three months later he underwent closure of his ileostomy and as the lesion in segment V was enlarging (having reached 3 cm in diameter) it was electrolytically ablated. Follow-up CT scan suggested complete tumour ablation. One year later he developed another metastasis in segment VI of the liver in close proximity to, but distinct from the previously ablated region. He underwent a segment V/VI resection which included the metastasis and the previously ablated area. His post-operative course was unremarkable and he was discharged on day 9 without complication. Histology confirmed metastatic adenocarcinoma with clear margins and, importantly, at the site of previous ablation, which was distinct from the metastasis, was



g. 1. Photomicrograph of human liver monstrating carbon pigment deposition, rosis and foreign body giant cell reaction. 12.

an area of heavy scarring with carbon pigment deposition and foreign body giant cell reaction (fig. 1) but no evidence of residual tumour. A follow-up CT scan performed 6 months post-operatively was normal.

Discussion

Several non-resectional treatment modalities have been developed and investigated including percutaneous alcohol injection [5], cryotherapy [6], regional and systemic chemotherapy and chemoembolisation [7], immunotherapy [8], interstitial laser [9] and liver transplantation [10]. None of these modalities has been proven to improve long-term patient survival in a prospective randomised controlled clinical trial. A detailed review of in situ ablative techniques for liver tumours [11] is available but beyond the scope of this report.

Electrolysis is a novel treatment that uses direct current to induce tissue necrosis. Direct current is passed along electrode catheters which have exposed platinum electrodes. The catheters are inserted directly into the tumour under intra-operative ultrasound control and the duration of treatment calculated from a dose-response curve from previous animal experiments [12, 13]. Tissue necrosis is caused by the production of chlorine gas and hydrogen ions at the anode and hydrogen gas and sodium hydroxide at the cathode [14] thereby creating a pH gradient. These electrode products are toxic to tissue but thermal necrosis plays no role in electrolytic ablation [15]. There are also many distal field effects which include electrophoretically induced cascade reactions causing intracellular disintegration of neoplastic tissue, the formation of eddy currents and activation of the immune system. Ischaemia may also play a significant role in the necrosis seen during electrolysis [16].

This is the first reported case of electrolytic liver metastasis ablation in a patient and is especially significant as histological follow-up data are available. The development of electrolysis for patient treatment is in its infancy but in view of the large numbers of patients with liver metastases who are currently unresectable, electrolysis has the potential to have significant impact on the clinical management of such patients.

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Dr. D.P. Berry
Department of Surgery, Leicester General Hospital
Gwendolen Road, Leicester LE5 4PW (UK)
Tel. +44 116 258 8110, Fax +44 116 258 4666

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Evaluation of Splenic Circulation after Spleen-Preserving Distal Pancreatectomy by Dividing the Splenic Artery and Vein

Yoshinobu Sato[a], Satoshi Shimoda[b], Nobuo Takeda[b], Norio Tanaka[b], Katsuyoshi Hatakeyama[a]

[a]First Department of Surgery, Niigata University School of Medicine, and [b]Department of Surgery, Niigata Prefectural Shibata Hospital, Niigata, Japan

Key Words

Spleen-preserving distal pancreatectomy · Splenic circulation · Laser flow meter · Scintigraphy

Abstract

Background/Aim: In the present study, we investigated the acute and late phases of splenic circulation after spleen-preserving distal pancreatectomy (SPDP) involving the division of splenic vessels. ***Methods:*** An acute phase of splenic circulation was evaluated by laser flow meter and the late phase was estimated by ^{99m}Tc-galactosyl human serum albumin spleen scintigraphy. ***Results:*** Splenic blood supply, evaluated by laser flow meter immediately after SPDP, dropped to one half of the prior blood supply. However, blood supply recovered 10 days after SPDP, as estimated by ^{99m}Tc-galactosyl human serum albumin spleen scintigraphy. ***Conclusion:*** There are two variations of SPDP: SPDP without preservation of the splenic artery and vein, and SPDP with preservation of the splenic artery and vein. The disadvantage of the former is the resulting decrease in splenic blood supply. The present findings may help to make up for this disadvantage.

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Electrolytic ablation of the rat pancreas: a feasibility trial

Beverley G Fosh[1], Jonathon Guy Finch[1], Adrian A Anthony[1], Michael Texler[2] and Guy J Maddern*[1]

Address: [1]University of Adelaide, Department Of Surgery, The Queen Elizabeth Hospital, Adelaide, SA, Australia and [2]The Department Of Pathology, The Queen Elizabeth Hospital, Adelaide, SA, Australia

E-mail: Beverley G Fosh - foshy@hotmail.com; Jonathon Guy Finch - guy@guyfinch.fsnet.co.uk; Adrian A Anthony - Adrian.Anthony@nwahs.sa.gov.au; Michael Texler - Michael.Texler@IMVS.sa.gov.au; Guy J Maddern* - guy.maddern@adelaide.edu.au

*Corresponding author

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Abstract

Background: Pancreatic cancer is a biologically aggressive disease with less than 20% of patients suitable for a "curative" surgical resection. This, combined with the poor 5-year survival indicates that effective palliative methods for symptom relief are required. Currently there are no ablative techniques to treat pancreatic cancer in clinical use. Tissue electrolysis is the delivery of a direct current between an anode and cathode to induce localised necrosis. Electrolysis has been shown to be safe and reliable in producing hepatic tissue and tumour ablation in animal models and in a limited number of patients. This study investigates the feasibility of using electrolysis to produce localised pancreatic necrosis in a healthy rat model.

Method: Ten rats were studied in total. Eight rats were treated with variable "doses" of coulombs, and the systemic and local effects were assessed; 2 rats were used as controls.

Results: Seven rats tolerated the procedure well without morbidity or mortality, and one died immediately post procedure. One control rat died on induction of anaesthesia. Serum amylase and glucose were not significantly affected.

Conclusion: Electrolysis in the rat pancreas produced localised necrosis and appears both safe, and reproducible. This novel technique could offer significant advantages for patients with unresectable pancreatic tumours. The next stage of the study is to assess pancreatic electrolysis in a pig model, prior to human pilot studies.

Introduction

Pancreatic cancer is biologically aggressive and the majority of patients present with advanced disease. Radical surgical resection of the pancreas offers the only hope of cure but only 20% of tumours in the head and 3% of tumours elsewhere in the pancreas are suitable for curative resection [1–3]. Many other patients undergo a trial dissection before a palliative surgical procedure is carried out. Locally advanced tumours that involve major blood vessels and metastatic disease are the most common factors that preclude curative resection. Therefore, the mainstay of treatment at present is palliative, directed towards relieving obstructive jaundice, gastric outlet obstruction and pain.

Electrolysis is a simple technique using a direct current passed through a conductive medium between a pair of electrodes, measured in Coulombs (1 Coulomb = 1 ampere × 1 second).Tissue electrolysis produces chemicals at the electrodes [4–6] and the ensuing pH change causes a localised parenchymal necrosis [7]. During the past few years, electrolysis of liver tumours has been extensively investigated at this institution [8–12]. Not only has the process been shown to completely ablate liver tumours in animal models [11] and in humans [13]. It is also safe and predictable in terms of both its inherent tissue destruction and the inability to thrombose or breach large blood vessels in close proximity to the electrolysis [12]. Electrolytic ablation of pancreatic tumours is an entirely novel idea, both for the treatment of pancreatic cancer and for the use of electrolysis. The aim of this study was to assess whether electrolysis of the pancreas gland could be performed in a safe and reproducible manner.

Method

The experiment was approved by the ethics committees of the University of Adelaide and The Queen Elizabeth Hospital. The Direct Current (DC) generator (Bioengineering, Transducers and Signal Processing Research Group, University of Leicester, United Kingdom) was designed to deliver a preset dose of Coulombs, using a continuous current (8 mA) at a variable voltage depending on resistance of the tissue, in accordance with Ohms law (V = IR). The anode and cathode were made from fine platinum wires 0.5 mm in diameter. These were insulated from each other at the proximal end by a semi-rigid plastic sleeve.

Ten SPF female Sprague-Dawley rats were fasted overnight. They were weighed pre-procedure, and anaesthetised using a standard mixture of halothane, nitrous oxide and oxygen. The rats were induced in a perspex box with 3.5% halothane, 1 L/min nitrous oxide and 1 L/min oxygen. Maintenance of anaesthesia was achieved with an inhalation system using 1.5% halothane, 0.5 L/min of nitrous oxide and 0.3 L/min oxygen.

The pancreas was exposed through a midline laparotomy. Swabs were placed around the pancreas to protect the surrounding organs. Two platinum electrodes designated anode and cathode, were inserted into the pancreas at a depth of 2 mm and a separation of 1 mm. A variable dose of Coulombs was delivered, ranging from 0 to 10 Coulombs (Table 1). The control rat underwent the same procedure, but without the delivery of current. Serial blood samples were obtained from the tail vein, preoperatively then at 1, 4, 24 and 48 hours post-operatively and analysed for amylase and glucose. All rats were sacrificed at 72 hours, weighed and the pancreata removed. This tissue was then fixed in 10% buffered formalin for a minimum of 2 weeks to allow for sufficient fixation. The area of pancreas that had been electrolytically treated was then embedded in paraffin, sectioned and stained with haematoxylin and eosin for histological examination. Electrolytic lesions were graded by a histopathologist who was unaware of the Coulombs administered. The lesions were graded according to the scoring system described by Spormann et al [14], to obtain a comparable histological score (Table 2).

Table 1: Dose of Coulombs delivered to rats

Dose Of Coulombs (mA/sec)	Number Of Rats	Deaths
0 (control)	2	1+
2	1	
4	1	
6	2	
8	2	
10	2	1*

+ During anaesthetic induction * Under anaesthetic on completion of electrolysis

Table 2: Histological scoring of pancreatitis

Oedema
1 = Mild
2 = Moderate
3 = Severe
Inflammatory Infiltrate
1 = Mild
2 = Moderate
3 = Severe
Fat Necrosis
3 = Mild
5 = Moderate
7 = Severe
Parenchymal Necrosis
3 = Singular
5 = Sub lobular <1/3
7 = Lobular >1/3
Haemorrhage
3 = Mild
5 = Moderate
7 = Severe

Ref:Spormann Pathol Res Pract 1989 184: 507–13

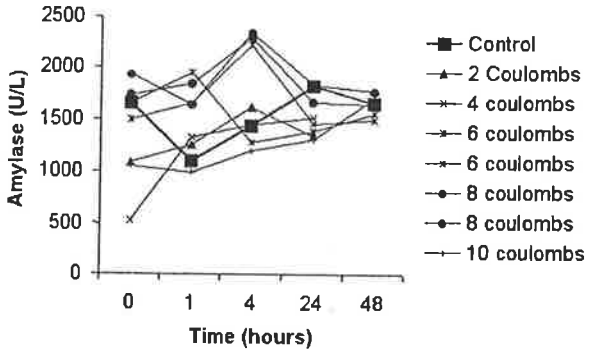

Figure 1
Serum amylase plotted against time (in hours)

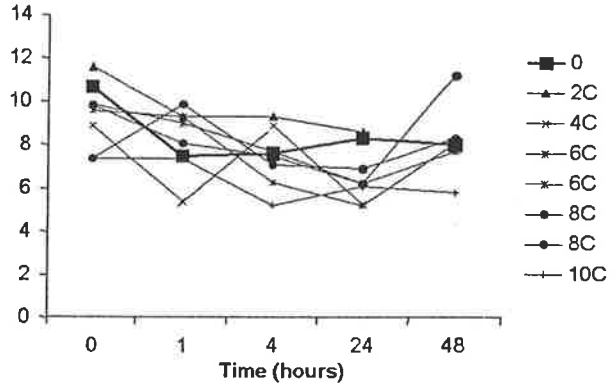

Figure 2
Serum glucose levels plotted against time (in hours)

Results

Median pre-procedure weight of the rats was 250 gm, (range 242–257 gm). There was no weight loss in any of the rats prior to tissue harvesting.

Of the 2 control rats, one animal died on induction of anaesthetic before any procedure had been performed, and the other tolerated the laparotomy and sham procedure without any side effects. In the treatment group, eight rats received between 2 to 10 Coulombs. One rat died immediately post electrolysis whilst under general anaesthetic. Seven rats survived with no morbidity or mortality. All eight animals that survived appeared clinically well, and were all eating and drinking within 2 hours of the procedure. On dissection of the pancreas gland an area of necrosis was evident on all the treated organs.

Blood results

The control group showed no significant change in amylase concentration (Figure 1). The treatment group revealed a transient hyperamylasaemia, peaking at approximately 4 hours which was not dose related and was not statistically significant.

Glucose levels were essentially unchanged in the control and treatment rats over the period of investigation (Figure 2).

Histology

On harvesting, a localised necrotic electrolytic lesion was macroscopically visible in all specimens of the pancreas (Figure 3), with no evidence of bowel perforations, fluid collections or haemorrhage. The necrotic lesion itself was difficult to measure due to the mucinous nature of the rat pancreas gland. The ablated region was surrounded by discoloured pancreatic tissue. There was a small area of inflammation (brown in colour) around the necrotic region, which was graded using the histological score, this was not proportional to the electrolytic dose (Figure 4). The inflammation did not extend through the pancreas.

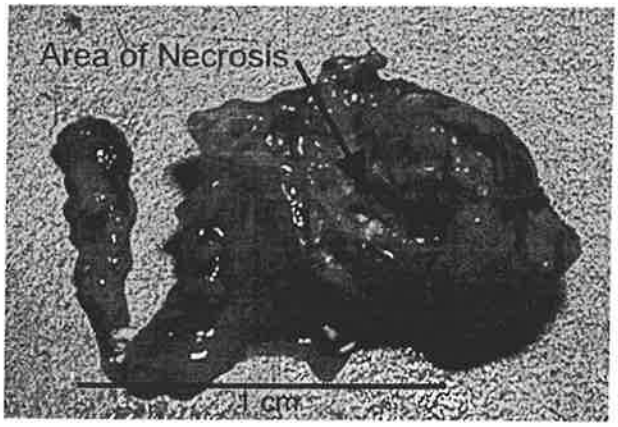

Figure 3
Pancreas after harvest showing electrolytic lesion

Discussion

Pancreatic carcinoma has a poor prognosis, and involvement of major blood vessels and metastatic disease are the most common factors that preclude curative resection [1,15]. Therefore, the mainstay of treatment at present is palliative, and there has been little advancement in new palliative treatments in the last few decades. Symptoms requiring palliation include anorexia, nausea, vomiting, weight loss and epigastric and back pain [15,16]. Nausea and vomiting are due to mechanical and

functional impairment of gastric and duodenal emptying. Pain results from malignant involvement of the splanchnic plexus, or from obstruction to the pancreatic duct. Biliary obstruction may cause jaundice often associated with intractable pruritus. Most symptoms are progressive and reflect locally advanced disease at presentation. A proportion of patients undergo attempted resection but at the time of operation the presence of local and/or distant disease, and invasion of the major vessels, prevents any surgical resection, and palliation is resorted to. Surgical palliation consists of biliary, and or gastric bypass,and an increasing number of patients are undergoing this form of treatment [17]. Palliation is also possible by endoscopic stenting of the obstructed common bile duct [18]. The ideal palliation would include the relief of pain, jaundice and gastro-duodenal obstruction, to improve quality of life measures with minimum morbidity. Local tumour destruction by electrolysis may not affect the overall tumour biology but may ameliorate the mass effect of the tumour, decrease tumour burden and destroy afferent nerves and could be performed at the time of biliary by-pass.

There are several ablative techniques that are currently being investigated and employed mainly for liver tumours. Several of these techniques rely on a direct thermal insult to cause local tissue ablation. These include interstitial laser therapy [19], radiofrequency ablation [20], and cryotherapy [21]. Thermal ablative techniques have limitations, particularly related to cytokine release in "cryoshock phenomenon"[22,23] and charring in the heat methods [24]. Pancreatic cryotherapy has been reported in a single study, but the data reported was inadequate to make any conclusions [25]. A recent report of radiofrequency ablation in the porcine pancreas has shown this to be feasible and safe [26].

Electrolysis has the potential to be adapted for pancreatic tissue ablation. A direct current is passed through a conductive medium between a pair of electrodes. Platinum electrodes appear ideal as they are relatively inert, but also have potential anti-neoplastic properties in the formation of platinum salts [27–29]. Tissue electrolysis produces sodium hydroxide and hydrogen at the cathode (alkaline), and hydrochloric acid and chlorine gas at the anode (acidic) [4–6]. The significant pH changes produced by electrolysis are cytotoxic and cause localised tissue necrosis [7]. Electrolytic ablation does not rely on a thermal effect [8,30].

The hypothesis of this study was that electrolytic destruction of the pancreas would result in a localised pancreatitis. The extent and severity of this was assessed in the experiment using blood and histological analysis.

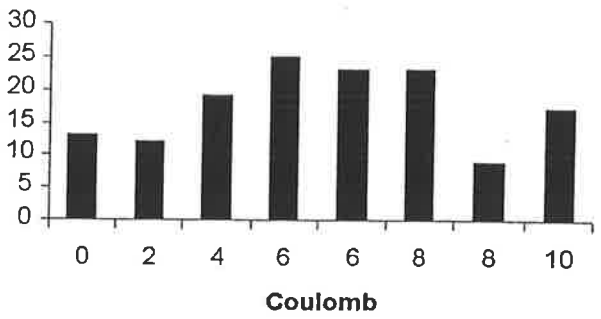

Figure 4
Histological grading graph.

In caerulein-induced pancreatitis in rats serial serum amylase has shown a 2 to 5 fold increase from the control value [31]. The hyperamylasemia with a proportion of the animals in this study (at approximately 4 hours) was not statistically significant in a paired T-test comparing the pre-electrolytic samples, with the 4 hour samples (Sig 2-tailed = 0.72).

Serum glucose would be expected to rise in severe pancreatitis according to Ranson's criteria [32] but this was not demonstrated in this study where it was relatively unchanged throughout all the animals.

The histology of the sections was quantified using a point score originally described by Spormann et al [14]. Electrolysis of the pancreas gland produced a region of necrosis. There was a localised region of pancreatitis around the electrolysis site, but this was not throughout the gland. It shows there is a generalised increase in the cumulative score although this was not dose related and was not significantly different from the control value.

The dismal outcome of pancreatic cancer and the need for low morbidity palliation has prompted the investigation of electrolysis as a possible method of palliation by tumour ablation. This study has demonstrated that electrolysis in the rat pancreas produce localised necrosis that appears both safe and reproducible. This pilot study was performed in only a small number of animals, but all animal deaths were believed to be related to the anaesthesia. All the rats that survived recovered well following electrolysis. The study indicates that localised pancreatic ablation is feasible with electrolysis. There was a localised region of pancreatitis around the site of necrosis, but there were no systemic complications of electrolysis in this model. The next stage is to extensively investigate pancreatic electrolysis in a large animal model, to assess the short and long-term effects, prior to human pilot

studies. In the larger animal model, a larger volume of tissue can be ablated with higher doses of Coulombs. Previous studies have shown that dose of Coulombs delivered is proportional to the volume of necrosis produced [9]. This study investigated the effects of electrolytic ablation in healthy pancreatic tissue, as this would have a greater tendency to become inflamed than that of tumour and thus cause a pancreatitis. A future area of study could investigate the effect of electrolysis in rodent pancreatic tumour model [33–36]. This study was performed on the minium number of animals as a pilot study to show feasibility, but obviously the technique needs to be performed on a greater number of large animal models whose pancreatic anatomy is more similar to that of humans. This novel technique could offer significant advantages for patients with unresectable pancreatic tumours.

Competing interests

None declared.

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REVIEW ARTICLE

ELECTROLYSIS AND OTHER LOCAL ABLATIVE TREATMENTS FOR NON-RESECTABLE COLORECTAL LIVER METASTASES

BENJAMIN D. TEAGUE,* SIMON A. WEMYSS-HOLDEN,* BEVERLEY G. FOSH,* ASHLEY R. DENNISON† AND GUY J. MADDERN*

**Adelaide University Department of Surgery, The Queen Elizabeth Hospital, Adelaide, South Australia, Australia and †Department of Surgery, Leicester General Hospital, Leicester, Leicestershire, United Kingdom*

The present paper is a review of the current ablative treatment options for the treatment of colorectal liver metastases. Cryotherapy, microwave coagulation therapy, radiofrequency ablation and laser-induced thermotherapy are discussed. Electrolysis, a novel non-thermal ablative treatment, is described. Potential benefits of electrolysis include the apparent ability to safely and effectively treat lesions abutting major hepatic structures and the lack of a systemic inflammatory reaction following electrolytic ablation. Further studies in animals and humans are needed to confirm this potential and to further refine the methods of electrolytic treatment of colorectal liver metastases.

Key words: colorectal neoplasms, cryosurgery, electrolysis, laser coagulation, liver neoplasm, radiation, secondary.

Abbreviations: LITT, laser-induced thermotherapy; MCT, microwave coagulation therapy; MRI, magnetic resonance imaging; PET, positron-emission tomography; RFA, radiofrequency ablation.

INTRODUCTION

Colorectal cancer is a major cause of cancer death in Australia, second only to lung cancer.[1] In Australia each year, approximately 10 000 cases of colorectal cancer are reported and there are 4500 deaths attributed to colorectal cancer.[1] The liver is the most common site of colorectal metastases,[2] with 50% of patients with colorectal cancer developing hepatic metastases within 5 years of initial diagnosis.[1] Without resection, hepatic metastases are invariably fatal with a median survival of approximately 6 months.[3,4]

Surgical resection is the gold standard treatment for hepatic metastases from colorectal cancer; however, only 20–25% of patients with colorectal liver metastases will have surgically resectable disease.[5,6] For surgical resection, 5-years survival rates of 20–51% and median survival times of 30–40 months have been reported.[5,7–11]

Major surgical morbidity, including haemorrhage, bile leak, abscess formation, pulmonary embolism, sepsis and hepatic failure, occurs in 11–37% of patients undergoing surgical resection for colorectal liver metastases.[5,7,12] Perioperative mortality is less than 5%.[5,7,8,11] Advances in surgical resection technique have reduced perioperative mortality and morbidity[2,5] and extended the indications for surgical resection.[6,13,14] Improved diagnostic imaging, such as magnetic resonance imaging (MRI),[15] positron emission tomography (PET) scanning[16,17] and intraoperative ultrasound,[18] has enabled better case selection.

B. Teague MB BS; **S. Wemyss-Holden** FRACS; **B. Fosh** FRCS; **A. Dennison** MBChB; **G. Maddern** FRCS.

Correspondence: Professor G. J. Maddern, Adelaide University Department of Surgery, The Queen Elizabeth Hospital, Woodville Road, Adelaide, SA 5011, Australia.
Email: guy.maddern@adelaide.edu.au

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Colorectal liver metastases may be considered non-resectable for a number of reasons. Metastases may be distributed throughout both lobes of the liver in such a way that resection of the lesions would leave insufficient remaining functional liver tissue. Metastases may lie close to or encompass major vascular or biliary structures, making the resection of these lesions hazardous. Extrahepatic metastatic involvement usually precludes liver resection. Significant patient comorbidity may preclude surgical treatment because of lack of fitness for general anaesthetic and laparotomy.

Approaches to non-resectable patients are varied and many patients will receive only palliative chemotherapy.[6,19] Local ablation modalities aim to preserve residual normal functional tissue by ablating only the metastatic lesions and a margin of normal tissue. A variety of local ablative techniques has been used either in conjunction with surgical resection or as an alternative to resection. These include thermal ablative techniques, including cryotherapy,[20] microwave,[21] radiofrequency[22] or laser.[23] Electrolysis is a non-thermal electrochemical process, which uses low levels of direct current to ablate tumours.[24]

CRYOTHERAPY

Cryotherapy is a thermal ablation technique that uses liquid nitrogen to create an ice-ball of tissue, causing cell death through the effects of dehydration, electrolyte concentration, cell membrane rupture, protein denaturation, thermal shock and vascular stasis.[20] Cryotherapy has been used extensively in the treatment of colorectal liver metastases,[25] both alone and in combination with other therapeutic modalities.[26–32] Percutaneous[33] and laparoscopic[34,35] approaches have been described. Intraoperative ultrasound monitoring distinguishes between frozen and unfrozen liver tissue, allowing monitoring of the size of the ice-ball created and its relation to major hepatic structures.[27]

Significant complications occur in 0–30% of patients undergoing hepatic cryoablation.[27,36–38] These include cryoshock, haemorrhage, subcapsular haematoma, abscess formation, biliary fistula,

pulmonary embolus and pleural effusion.[36] Cryoshock is a syndrome characterized by one or more features of systemic failure, including shock, acute renal failure, acute respiratory distress syndrome, disseminated intravascular coagulation, thrombocytopenia and liver failure.[36] It may be that this syndrome is mediated by cytokines, such as interleukin-6 and tumour necrosis factor-α, which are elevated after hepatic cryoablation in proportion to the volume of liver ablated.[39] Cryoshock occurs in 1% of patients following hepatic cryotherapy and has an associated mortality of 28%.[36] Total perioperative mortality for hepatic cryoablation is approximately 1.5%.[36]

Median survival times of 19–33 months have been reported for patients with colorectal liver metastases treated with cryotherapy.[37,40–43] One retrospective study has compared survival of patients undergoing hepatic resection alone against those undergoing resection combined with edge and/or contralateral lobe cryotherapy.[43] The median follow up was 20 months and median overall survival was 33 months. No difference was found in survival between patients undergoing resection alone and patients undergoing resection combined with cryotherapy.[43]

MICROWAVE COAGULATION THERAPY

Microwave coagulation therapy (MCT) uses a high-frequency electromagnetic wave to generate heat in the target tissue.[44] It has been applied to liver resection,[21] as well as to the ablation of hepatocellular carcinoma[45] and colorectal liver metastases.[44,46] Open[44] and percutaneous MCT[47,48] have been used as has a transdiaphragmatic thoracoscopic approach.[49] Lesion volume is predictable based on the length of treatment and intraoperative ultrasound may be used to monitor the lesions.[44]

Complication rates of 14–20% have been reported for patients undergoing MCT for metastatic liver tumours.[44,50] Reported complications include abscess formation, biliary fistula and haemorrhage. Death as a result of haemorrhage associated with percutaneous MCT has been reported.[50] Microwave coagulation therapy is difficult to perform for lesions close to major hepatic blood vessels or major branches of a bile duct because of the risk of haemorrhage, vessel thrombosis or bile duct fistula.[44] Ultrasound monitoring[44] and transcatheter cooling of the intrahepatic bile duct[50] have been suggested as approaches to minimize the risk of bile duct injury. Incomplete ablation has been reported in large lesions and in those close to vital structures.[47]

Median survival of 24–27 months has been reported for the treatment of colorectal liver metastases with MCT.[44,46] A randomized study comparing MCT and surgical resection in 30 patients with resectable hepatic metastases from colorectal cancer showed no difference in mean survival rates or in perioperative complication rates between the two groups.[44]

RADIOFREQUENCY ABLATION

Radiofrequency ablation (RFA) uses alternating current applied via an electrode to produce ionic agitation in the treated tissue.[51] The resultant frictional heating to above 100°C brings about tissue vaporization, charring and coagulative necrosis.[51] Intraoperative RFA and percutaneous RFA have been described using single or multiple electrodes.[22,51,52] Ultrasound can be used to monitor the progression of ablation; however, the margins may be ill-defined and computed tomography (CT) is a better measure of the real extent of the lesion.[51]

Major complications associated with RFA hepatic ablation occurred in 0–14% of treatments.[52–56] In one study, two perioperative deaths (6%) were reported in a series of 35 patients.[56] Two cases of delayed haemorrhage have been reported in patients undergoing hepatic RFA ablation.[52,55] Neither required surgery; however, one case required transfusion and transarterial embolization.[52] Other reported major complications include vascular injury, haematoma, abscess formation and sepsis.[56] In the case of percutaneous hepatic RFA, mild to severe patient discomfort has been reported.[52,55,56] Incomplete ablation, as assessed on CT or at post-treatment resection, was reported in 0–100% of cases of hepatic RFA.[52–56]

Radiofrequency ablation is relatively new and clinical results are limited. Most of the larger series (16–123 patients) reported to date have combined results for primary and secondary liver tumours.[52–56] Only one study has reported specifically on the long-term results of the treatment of liver metastases with RFA.[55] In this study of 16 patients, nine of whom had colorectal metastases and seven of whom had metastatic disease from other primary sites, complete tumour ablation was reported in eight patients (50%) and disease-free survival was achieved in eight of 12 patients who were followed for 9–26 months.

Laser-induced thermotherapy

Laser-induced thermotherapy transmits neodyium : yttrium aluminium garnet (Nd:YAG) laser through bare quartz fibres to induce hyperthermia in tissues with subsequent coagulative necrosis in the treated tissue.[23,57] Laser-induced thermotherapy can be applied at open operation or percutaneously.[58,59]

Reported complications vary, with one study reporting complications, including pleural effusion, biloma, subcapsular haematoma, pneumothorax and tumour nodule at the needle puncture site, in 31% patients,[60] whereas another study claimed only minor complications, including severe local pain during the procedure, ongoing abdominal and shoulder-tip pain for up to 10 days after treatment, transient fever, asymptomatic subcapsular haematoma and pleural effusion.[58] Incomplete ablation has been reported for a significant number of lesions,[58,61] with complete ablation rates of 69% for lesions ≤ 20 mm in diameter and only 35% for lesions > 20 mm in diameter.[61]

Reports of clinical results are limited. Median survival of 27 months from the diagnosis of liver metastases in 69 patients with inoperable colorectal liver metastases[62] and 16 months from commencement of LITT in 19 patients with recurrent colorectal liver metastases has been reported.[60] In many cases, LITT was combined with surgical resection and/or systemic chemotherapy.

ELECTROLYSIS

Electrolysis is an electrochemical process whereby small direct currents (80–100 mA in the case of liver ablation) are passed through tissue between electrodes inserted into the tissue. As a result, there is decomposition of interstitial fluid and oxidation or reduction of solutes.[63] At the anode, oxygen and hydrogen ions are formed by water decomposition and chlorine is produced by the oxidization of chloride ions.[63] At the cathode, hydrogen gas is formed and hydroxide ions are produced.[63] The changes in tissue pH and the production of cytotoxic products, such as chlorine gas, cause spherical areas of localized tissue necrosis around the respective electrodes.[64] The electrolytic process can cause small changes in tissue temperature, but these are not sufficient in themselves to produce tissue necrosis.[24]

The volume of tissue necrosis is proportional to the dose of electrolysis, measured in Coulombs.[65] The dose is a product of the current (ampere) and the time over which the current is delivered (seconds):

$$1 \text{ Coulomb} = 1 \text{ ampere} \times 1 \text{ second}$$

The volume of tissue necrosis is dependent on the nature of the tissue, the arrangement of the electrodes and on the total electrode surface area.[65] Treatment times are of the order of 3 h,[66] depending on the size of the tumour treated. Shortening the treatment time will require the use of larger currents and/or improved electrode designs.

Electrolysis of normal liver tissue has been studied extensively in a pig model.[24,64,67] Electrolysis was not associated with a systemic inflammatory response or with perioperative mortality.[64] Following electrolysis, liver enzymes are transiently elevated, but rapidly return to normal.[64] Histological examination of lesions shows well-defined spherical areas of coagulative necrosis, sharply demarcated from the surrounding tissue; thrombosis of small blood vessels is seen, but major vessels are unaffected.[64,67] Electrolysis has been safely performed immediately adjacent to hepatic veins.[67] Histology showed localized hepatic necrosis with no damage to the vein wall. In long-term studies of electrolytic lesions, the electrolytic lesions heal with fibrous scar formation and no evidence of biliary fistula or abscess formation.[64]

At present, no established mechanism exists for intraoperative monitoring of the ablated zone. Ultrasound cannot be used to monitor the ablated zone because gas formation at electrodes distorts the ultrasound imaging. Doses of electrolysis are based on the volume of the lesion as assessed on preoperative CT or MRI and at intraoperative ultrasound.

A pilot study was undertaken to determine the safety and effectiveness of electrolysis in the ablation of colorectal liver metastases. Electrolysis was performed in five patients prior to resection of resectable colorectal liver metastases. There was no mortality or morbidity associated with electrolysis and histological examination confirmed complete tumour ablation at the site of electrolysis (B. D. Teague *et al.*, unpubl. data, 1998). A prospective trial of electrolysis in conjunction with surgical resection is in progress at the Queen Elizabeth Hospital in order to study the safety and efficacy of electrolysis in patients with unresectable liver metastases from colorectal cancer.

DISCUSSION

Many options currently exist for local ablation as an adjunct or alternative to hepatic resection in patients with unresectable colorectal liver metastases. No one method is clearly superior to the rest. Cryotherapy and MCT are the methods with the most clinical experience and have demonstrated increased survival rates for unresectable metastases.[25,44] Electrolysis, a non-thermal ablative technique, has good results in animal models, but human data are not yet available.

The assessment of the available methods is made more difficult by the fact that many studies have reported results of hepatic ablation for a mixed group of primary and/or secondary hepatic tumours.[55,56] Some studies[58,61] report on the success of ablation of individual metastases in patients with multiple lesions rather than on patient outcomes. Other studies[32,62] have reported findings from patients treated with a combination of ablative modalities, which confounds any reported survival advantage.

Ablative techniques have the advantage of preserving greater volumes of functional liver than resection; however, histopathological diagnosis and clearance margins cannot be confirmed, meaning that ablation must rely on techniques such as diagnostic imaging and ablation volume prediction in order to determine adequacy of treatment. Treatment of large metastases is difficult with all modalities of ablation[42,44,47,61,66] and, in these cases, a combined approach involving surgical resection and ablation may be the most appropriate.

Concerns exist about over- and under-treatment of metastases adjacent to or encompassing major structures, such as hepatic veins and bile ducts. Thermal treatments risk damage to vessel and bile duct walls, leading to haemorrhage or biliary fistula.[47,50,51] In contrast, thermodilution from blood flow or by artificial cooling of biliary ducts may reduce the effectiveness of thermal ablation in areas adjacent to these structures, with resultant incomplete ablation of tumours.[51] Injury to hepatic veins and bile ducts has not been reported with electrolysis and this does not seem to compromise the extent of ablation.[64,67]

Less-invasive techniques have been developed using laparoscopic or percutaneous approaches for most ablative modalities.[33,46,53,58] The enthusiasm for such treatments[68] must be tempered against the need for adequate assessment of hepatic disease and the risks of uncontrolled haemorrhage.

Only a minority of patients with colorectal liver metastases are suitable for resection. Ablative techniques may extend the scope of treatment with curative intention to include more patients, but similar limitations will apply to ablative treatment. The potential for damage to major hepatic structures is likely to limit the use or effectiveness of thermal ablation in a proportion of patients. Similarly, the risk of significant systemic inflammatory response with the ablation of large tissue volumes, such as the cryoshock response to cryotherapy, may limit the volume of liver able to be ablated in addition to considerations about the volume of residual functional liver.

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Liver electrolysis: pH can reliably monitor the extent of hepatic ablation in pigs

J. Guy FINCH*, Beverley FOSH*, Adrian ANTHONY*, Eric SLIMANI*, Michael TEXLER†, David P. BERRY‡, Ashley R. DENNISON‡ and Guy J. MADDERN*

*University of Adelaide Department of Surgery, Queen Elizabeth Hospital, Woodville, South Australia 5011, Australia, †Department of Pathology, Queen Elizabeth Hospital, Woodville, South Australia 5011, Australia, and ‡Department of Surgery, Leicester General Hospital, Gwendolen Road, Leicester LE2 7LX, U.K.

ABSTRACT

Electrolysis is a method of tissue ablation that creates chemical species and a pH gradient in response to direct current. Initial studies of electrolysis in animal models and humans have shown that it is a safe, predictable and effective process for destroying normal and tumour-bearing liver in a linear, dose-dependent manner. Presently, the amount of current that is applied (in coulombs) has to be calculated using historical data, with inherent inaccuracy. The present study tested whether pH could be used as a real-time monitor in order to predict more accurately the extent of necrosis. A total of 70 electrolytic lesions were created in 14 pigs, with pH monitoring of the lesion edge. The normal range of pH values was 6.5–8.7. A pH of less than 6 (at the anode) or more than 9 (at the cathode) reflected total cellular necrosis. When a pH value was recorded between 6.0 and 6.5 at the anode or between 8.7 and 9.0 at the cathode, the presence of necrosis was variable. In conclusion, during electrolytic ablation, pH measurement can monitor the extent of the induced necrosis.

INTRODUCTION

Patients with untreated colorectal liver metastases have a median survival time of less than 1 year [1–4]. Surgical resection offers the only real hope of cure, with 5-year survival of around 30–40% [1,3–6]. Resection, however, is only possible in about 20% of patients, who have the disease in favourable anatomical locations [1,3,5–7]. In recent years ablative techniques have attracted much interest, as they may allow a less morbid procedure, may palliate or may allow staged resection [3,4,6–9]. Up to 40% of colorectal metastases are confined to the liver [10,11]. In these patients, complete ablation of metastatic deposits may be curative [8,9].

Electrolysis is a form of local ablation that uses direct current to produce tissue destruction. It does not rely on thermal effects at low currents [3,11–15] and has been shown to be safe, predictable and effective in a linear dose-related manner [16–18]. The use of small metallic electrodes makes electrolysis suitable for percutaneous use.

We have successfully ablated liver metastases in patients and have reported complete ablation of such tumours using electrolysis, which was confirmed histologically after 1 year [18]. By placing an electrode catheter into the centre of a colorectal metastasis, electrolysis will result in local cell necrosis around the anode and cathode, and potentially provide a simple and safe ablative technique for patients who may have unresectable disease.

Electrolysis is currently limited by the lack of an effective real-time monitor of the extent of induced necrosis, with a pre-determined ablative dose being calculated on the basis of historical data [3,19]. Development of a real-time monitor would allow confident and accurate tumour destruction during electrolysis without excessive loss of normal tissue.

Electron transfer during electrolysis polarizes the tissue in order to complete the circuit between the implanted

Key words: ablation, colorectal cancer, electrolysis, liver, pigs.

Correspondence: Professor G. J. Maddern (e-mail guy.maddern@adelaide.edu.au).

electrodes [16,19,20]. Numerous chemical reactions occur as a result, and differential hydrogen ion concentrations form at the electrodes according to the following equations [15,21,22]:

$$\text{Anode: } 2H_2O \rightarrow O_2 + 4H^+ + 4e^-$$

$$\text{Cathode: } 2H_2O + 2e^- \rightarrow H_2 + 2OH^-$$

Consequently, the anode becomes acidic and the cathode alkaline. This differential pH was investigated as a possible real-time monitor of the extent of hepatic necrosis induced by electrolysis. The aim was to compare absolute pH values created by electrolysis with the histological appearance of normal pig liver.

METHODS

Local Animal Ethics Committees (University of Adelaide, SARDI/PISA and The Queen Elizabeth Hospital, Adelaide) approved the use of laboratory animals in this study. The study conformed to the Code of Practice for the Care and Use of Animals for Scientific Purposes (NHMRC/CSIRO/AAC 1990) and the SA Prevention of Cruelty to Animals Act 1985.

Direct current was applied to normal pig liver, and the pH of the parenchyma 8 mm from the electrodes was recorded until a pre-determined pH was reached. The position of the pH probe was marked and compared with the appearance of the liver on histology.

A total of 14 domestic white pigs (of approx. 30 kg body weight) were used. After ketamine/xylazine sedation (20 mg/kg and 1.5 mg/kg respectively), the pigs were anaesthetized with 1.5% halothane via a laryngeal mask airway [23]. All animals underwent a midline laparotomy, with intra-operative monitoring by a pulse oximeter attached to the tail.

A 6 French platinum electrode catheter, comprising four platinum electrodes evenly spaced from the tip, was used (Cordis Webster; Johnson and Johnson Medical Pty. Ltd, North Ryde, NSW 2113, Australia). The electrode under study (anode or cathode) was situated in the middle of the three proximal electrodes. The catheter was placed in the liver so that this electrode was just under the liver capsule. The electrode at the tip of the catheter not under study was therefore 11 mm deep from the liver surface. The electrodes were connected to a purpose-built direct-current generator (Bioengineering, Transducers and Signal Processing Research Group, University of Leicester, U.K.) that was designed to deliver a constant current (80 mA) to a pre-determined 'dose' (in coulombs) by automatically varying the voltage (1 C = 1 A × 1 s).

At a distance of 8 mm and directly facing the electrode, an antimony monocrystal pH probe with external reference (Zinetics 24ME Multi-use pH catheter; Medtronic, Salt Lake City, UT, U.S.A.) was inserted with the sensor at a depth of 1 mm. The pH probe was calibrated against proprietary solutions of pH 1 and pH 7 (Medtronic) for acidic readings, and against a phosphate solution of pH 9.2 for alkaline readings. The probe was kept moist in the peritoneal cavity between readings. A pH recorder (Digitrapper MKIII; Synetics Medical, Stockholm, Sweden) was used to read the pH prior to electrolysis and then after every increment of 10 C until the pH began to change or the electrolytic lesion was visible on the surface of the liver and close to the pH recording site, at which point readings were recorded at 5 C increments. The direct current was disconnected for each pH reading to avoid interference of the current with the electropotential of the pH probe, and equally to prevent the metallic pH probe entering the electrical field and possibly acting as an electrode (Figure 1).

Several (between three and six) electrolytic lesions were made in each liver. When the pH had reached a predetermined reading, the current was stopped entirely and

Figure 1 Evolution of a visible necrotic lesion around an electrode

The pH probe (white) is located 8 mm from the electrode (blue). The edge of the necrotic area appears to have reached the probe.

Table 1 Number of lesions created for each predetermined pH value

The maximum alkaline reading with this pH recorder was 10.4. When it became apparent that a relatively small pH change equated with necrosis, only pH values close to the normal range were studied.

Anode (acidic)		Cathode (alkali)	
pH required	Number of lesions	pH required	Number of lesions
6.5	10	8.5	5
6.0	6	9	5
5.5	3	9.5	6
5.0	4	10	1
4.5	2	10.4	2
4.0	2		
3.5	1		
3.0	2		

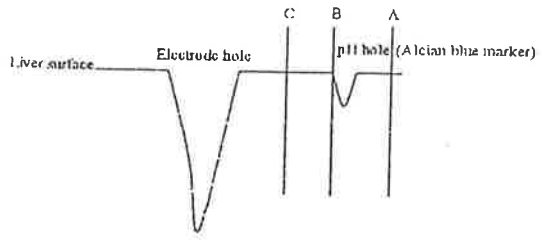

Figure 2 Histological grading of the extent of electrolytic lesion

Grade A, necrosis past pH/Alcian Blue hole; grade B, necrosis up to but not beyond the pH hole; grade C, necrosis short of the pH hole; grade D, no necrosis; grade 0, no Alcian Blue seen. The liver was sectioned perpendicular to the liver through the plane of both pH and electrode holes.

the hole left by the pH probe was marked with Alcian Blue dye (Table 1). Lesions were created to reach pH values at increments of 0.5 pH units between 6.5 and 3.0 at the anode and between 8.5 and 10.4 at the cathode. As the experiment progressed, the pH under study was narrowed to values close to the normal range.

Electrodes were removed and the pigs were given analgesia (buprenorphine 0.1 mg/kg) before closing the abdomen in two layers (one polydioxanone and 3/0 monocryl) and waking the pig. The livers were harvested 3–4 days later, when preliminary studies have shown that electrolytic lesions attain maximum dimensions. The lesions were then separated and fixed in 10% buffered formalin for up to 1 week, before being sectioned in the plane of the electrode and pH holes, perpendicular to the surface of the liver. After embedding in paraffin, the samples were stained with routine haematoxylin and eosin. All specimens were analysed histologically by a pathologist, who was blinded to the experimental method, and graded A–D, defined as follows: A, necrosis past the pH probe; B, necrosis up to but not beyond the pH hole; C, necrosis short of the pH hole; D, no necrosis seen (Figure 2 and Figure 3a–3c).

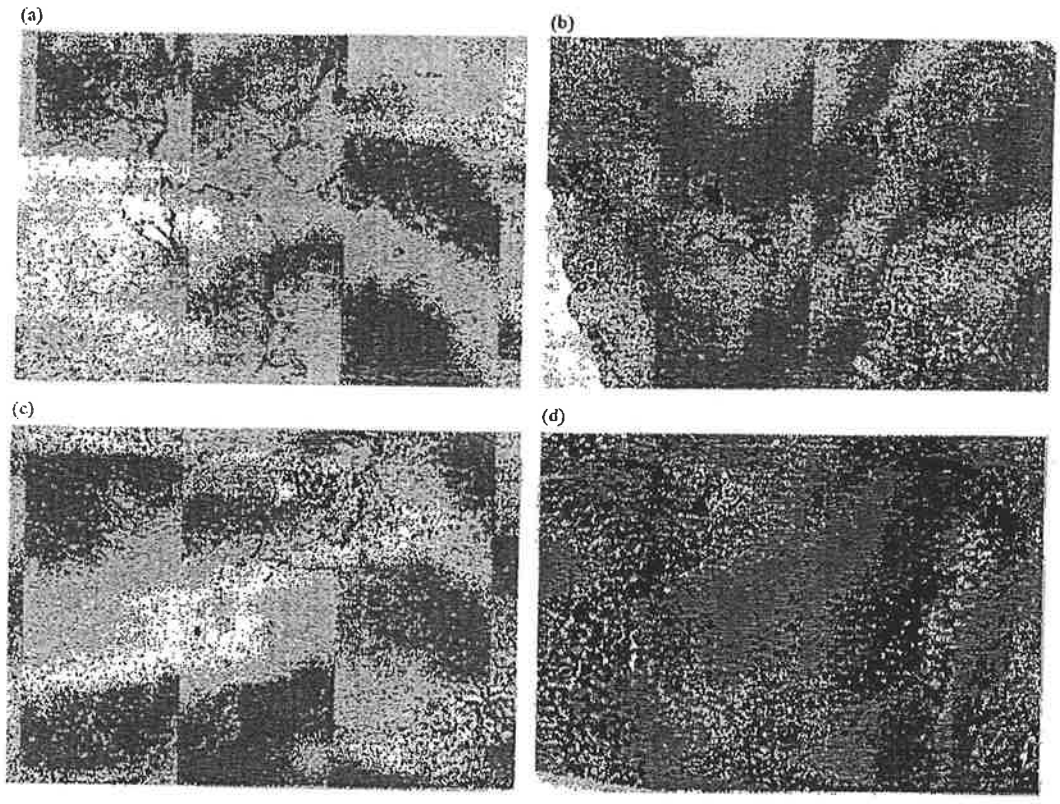

Figure 3 Histological grading of created lesions

(a) Example of grade A histology. Alcian Blue is seen in the pH hole, surrounded by necrotic tissue. The necrosis has extended past the pH probe hole, and this is therefore a grade A lesion. (b) Example of grade B histology. This lesion was graded B, as the necrotic tissue is up to but not beyond the Alcian Blue. (c) Example of grade C histology. The Alcian Blue is in a thin area of necrosis, but has viable liver lobules either side of it. There is therefore a discontinuous lesion between the electrolytic necrosis and the pH probe, and this equates with a grade C lesion. (d) Histology of the edge of an anodic lesion. A rim of neutrophils is visible, then an area of congestion surrounds the eosinophilic necrotic zone on the right. To the extreme left of the picture is normal hepatic parenchyma. Original magnification: (a) × 4, (b)–(d) × 10.

Four control animals were subjected the same procedure except that no current was delivered. Electrodes were left *in situ* for 20 min, with pH read every 2 min (corresponding to the delivery of 10 C).

Significant methodological problems were encountered, and 17 lesions were excluded prior to analysis. Four lesions were not harvested due to technical problems with the method (incorrect pH calibration in two lesions, pH meter failure and failure to stop the experiment at the pre-determined pH). In eight lesions no Alcian Blue was seen with histology, in three the pH probe lost contact and required re-calibration, and in one the pH probe hole bled after repeat trauma and the probe was moved. One specimen was lost.

In a further five lesions electrolysis was stopped early because of protracted anaesthesia (in two lesions) or erosion of the electrode catheter and loss of the circuit (three lesions). These lesions were analysed and are discussed.

RESULTS

In total, 14 pigs were used and 70 lesions were created (40 at the anode, 25 at the cathode and five controls). One pig died of hyperthermia, as an idiosyncratic reaction to anaesthesia, before a lesion was made. All other animals survived and had uncomplicated recoveries. Following exclusion of 17 lesions from the analysis due to methodological problems (see above), there were 30 anode, 19 cathode and four control lesions available for analysis.

The range of pH readings obtained prior to electrolysis was 6.5–8.7 (mean 7.36; median 7.4), and this was taken as the 'normal' range.

Histology

A central cavity, corresponding to the position of the electrode, was surrounded by variable amounts of 'cellular debris'. This, in turn, was surrounded by necrosis, characterized by featureless, eosinophilic hepatocytes lacking glycogen vacuoles. There was invariably a sharp demarcation between this necrotic tissue and an actively proliferating surrounding zone, with fibroblast and biliary proliferation and a mixed picture of white-cell infiltration. Predominantly neutrophils were found, but often macrophages and giant cells were already present. Beyond this, a 'congested' zone occurred in some specimens (Figure 3d). On several sections there was a subcapsular rim of necrosis tapering away from the main lesion. This rim was only a few cells thick in all except one section (see 'Anode' section and Discussion), where it contained the Alcian Blue dye and contributed to the only false-positive result. In addition, the control lesions showed a very small rim of necrosis around the electrode and pH probe, presumably from the local trauma.

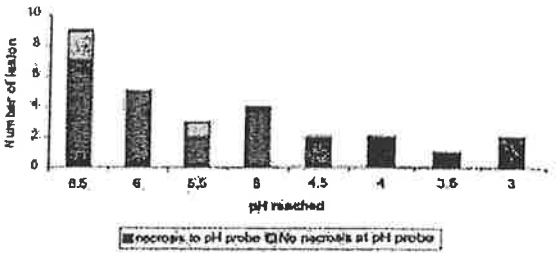

Figure 4 Histology of anode lesions

All lesions with pH values below 6 juxtaposed necrosis around the anode. One false positive at pH 5.5 is discussed in the text.

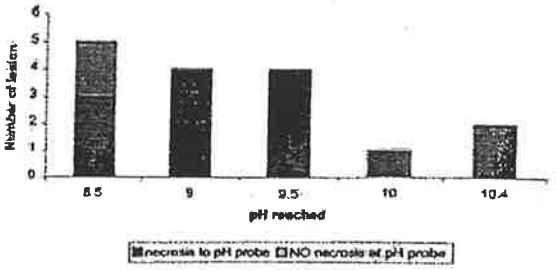

Figure 5 Histology of cathode lesions

At the cathode, all probe holes with pH values of 9 or over juxtaposed necrosis.

Anode

All lesions reaching a pH of 6 or less were necrotic at the pH probe or beyond (grade A or B) on histology (Figure 4). Two lesions were stopped without the desired pH reading, as the pigs showed some instability from a long anaesthetic. Both of these lesions revealed necrosis up to the pH probe hole and were consequently falsely negative. A further lesion that registered a pH change to 5.5 was falsely positive, as the pH probe was in a rim of necrotic subcapsular liver with no deeper necrosis corresponding to the electrode lesion. Between pH 6 and 6.5, two of nine lesions failed to show necrosis to the probe (grade C) and were not explained by the Alcian Blue being in a subcapsular necrotic rim.

Cathode

All lesions reaching a pH of 9 or greater were necrotic at or beyond the pH probe (grade A or B) (Figure 5). Of the five lesions registering between pH 8.5 and 9, three were necrotic at or beyond the probe (grade A or B) and two showed necrosis, but this was short of the pH probe (grade C) (Figure 3c). Three lesions were discontinued without reaching their desired pH because of erosion of the electrode. They had not reached their target pH of 9

or more, but all passed pH 8.5 at some stage. None of these lesions were necrotic to the pH probe (grade C).

Controls

Five control pigs had electrodes inserted but no current passed. There was no evidence of necrosis in one (grade D). Three other animals showed a small rim of necrosis consistent with trauma from insertion of the instruments, but no necrosis resembling that of the specimens that had undergone electrolysis. The fifth specimen was lost before histological section.

DISCUSSION

Electrolysis is emerging as a safe, predictable and effective method of ablating colorectal liver metastases [3,17,18,24]. While there is a linear relationship between the number of coulombs delivered and the volume of necrosis induced, this relationship is prone to some inherent inaccuracies. That there must be a range of volume of necrosis per coulomb is predictable given the number of possible electrical conductors and resistors that are within the liver. For instance, the walls of blood vessels are good insulators of plasma, which in turn is a good conductor of electricity which can alter the extent of necrosis [25]. For these reasons, it is necessary to develop a real-time monitor of the effects of hepatic electrolysis, so that tumours can be ablated with greater predictability and without excessive loss of normal parenchyma. In the presence of neoplastic tissue, with disorganized tubular structures and sclerotic connective tissue, rates of necrosis are likely to be more difficult to predict. Given that the removal of a margin of normal tissue around a tumour is thought desirable [4,26,27], the use of pH readings in normal parenchyma, as in the present study, may have clinical application.

The cellular cause of necrosis is unknown. It is probably due to a combination of cytotoxic chemical production, pH changes and membrane disruption, although ischaemia and other host factors may also play a role [13–22,24,28–31].

Protons diffuse for a greater distance than the other chemical products of electrolysis and may well be responsible for the peripheral limit of destruction [19,21]. Measurement of pH is therefore rational as a means of real-time monitoring of electrolysis to determine the leading edge of the products of electrolysis. As cell death may not be solely pH-dependent, it is necessary to determine the pH that corresponds to cell death. The two false-negative cases in this series indicate that cell death may occur without deviation from the 'normal' pH change.

The assessment of anodic lesions was more reliable than that of cathodic lesions, as the pH probe is specifically designed to measure acidic pH. Anodic lesions characteristically desiccate, becoming well demarcated [21,28]. Conversely, cathodic lesions attract water and swell [21,28]. This may dilute and buffer the alkaline products and distort the margin of necrosis. The alkaline calibration solution used in the present study had pH of 9.2, and pH values more alkaline than this may have been inaccurate. However, as all specimens with a pH greater than 9 were necrotic, more refined accuracy is probably superfluous. The possibility of altering electrode configurations for electrolysis (e.g. central cathode surrounded by anodes) is under investigation [32] as a method of delivering electrolysis, and may allow standardization of the pH cut-off.

The 'normal' range of pH readings during the present study was surprisingly wide, at 6.5–8.7. The range of naturally occurring interstitial pH values is 6.4–7.55 [33,34]. The electrochemical reactions underlying the measurement of pH with antimony electrodes are largely unknown, but antimony corrosion is thought to generate a readable potential [35,36]. The phosphate buffer used for alkaline calibration also corrodes the crystal [35]. In addition, antimony monocrystals are known to be oxygen sensitive [35–37]. Aging (i.e. corrosion of the probe) and local fluctuations in oxygen tension may therefore contribute to the wide range of 'normal' values observed. Repeated insertion of pH probes has also been noted to add to inaccuracy [38]. On the single occasion that the pH probe hole began to bleed after repeated insertions, the pH was noted to increase, and it is assumed that variable capillary blood flow also affects interstitial pH until such time as the area becomes ischaemic from the advancing lesion. Given the wide 'normal' range, it is not surprising that pH values between 6.0 and 6.5 at the anode and between 8.5 and 9.0 at the cathode were inconsistently associated with cell necrosis.

The two false-negative outcomes (normal pH values associated with necrotic tissue) may have been the result of persistent circulation at the periphery of the lesion. Our observations suggest that large-calibre vessels (cut-off unknown) appear to be protected from the effects of electrolysis by the flow of blood, whereas smaller vessels will thrombose and contribute to the ablative process [15,24,28,30,31]. In the present experiment, it was noted that as the edge of the lesion approached the pH probe, the pH would fluctuate before returning to the normal range. This occurred for 5–10 C until a persistent change indicated necrosis. This observation is consistent with homoeostatic buffering at the periphery of the lesion by blood flow prior to necrosis.

The false-positive result (acidic pH value associated with viable tissue) was caused by the pH probe recording in a thin rim of subcapsular necrosis, discontinuous with the main electrode lesion (Figure 3d). Frequently, the cytotoxic effervescent fluid from the anode (chlorine, hydrochloric acid and hypochlorous acid) is seen tracking

along the liver capsule with gravity, and there is invariably a small amount of capsular necrosis tapering away from the lesion proper.

A pH probe has methodological limitations associated with its use, and it is not an ideal clinical tool. Nonetheless, the present study has demonstrated that tissue reaching pH values of below 6 at the anode or above 9 at the cathode reflects cell death with a high degree of specificity (95% for the anode and 100% at the cathode). The use of pH as a real-time monitor of electrolysis is thus rational and feasible.

Magnetic resonance spectroscopy measures cellular pH with a high degree of accuracy by extracorporeal continuous monitoring [39–42], and would provide a less crude method of pH monitoring during electrolysis. This technique would avoid major inaccuracies associated with our method, as it is atraumatic and is not dependent on local oxygen tensions, local blood flow or crystal corrosion. In addition, magnetic resonance spectroscopy would be compatible with the percutaneous use of electrolysis.

Normal human tissue has a physiological range of extracellular pH of 6.4–7.55 [33,34], whereas tumours tend to be more acidic [42,43]. If a rim of normal tissue is ablated as part of the process of electrolysis, the pH of the normal tissue will be the parameter determining the extent of necrosis. Physiological pH levels are unlikely to differ significantly between pigs and humans, but corroboration will be required before recommendations pertinent to electrolysis in humans can be made. The findings from the present study cannot be extrapolated to procedures using the Pringle manoeuvre, as conditions of global hepatic acidosis appear to protect against cell death to a degree [44,45].

In conclusion, the present study establishes that changes in pH can reliably predict cell death from electrolysis in normal pig liver. The pH values may vary with the equipment and method used, and further study with highly sensitive pH-measuring equipment (e.g. magnetic resonance spectroscopy) is necessary before absolute values equating with cell death can be recommended. Corroboration with pH changes during electrolysis in normal and tumorous human tissue is also necessary in order to develop pH as a monitor in the clinical situation. These studies are under way.

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Original article

Electrolytic ablation as an adjunct to liver resection: experimental studies of predictability and safety

S. A. Wemyss-Holden, A. R. Dennison, G. J. Finch, P. de la M. Hall and G. J. Maddern

University of Adelaide Department of Surgery, The Queen Elizabeth Hospital, Adelaide, South Australia 5011, Australia
Correspondence to: Professor G. J. Maddern (e-mail: guy.maddern@adelaide.edu.au)

Background: Combined liver resection and local ablation may offer the only chance of cure to patients with liver metastases who are presently deemed unresectable because of a single awkwardly placed metastasis. By definition, such a metastasis is often close to a major vein. An ablative technique is needed that is both predictable and safe in such a circumstance.

Methods: Electrolytic liver lesions were created in 21 pigs using platinum electrodes, connected to a direct current generator. Both electrolytic 'dose' and electrode separation were varied to produce different sized lesions. The 'dose' was correlated with the volume of necrosis and any vascular damage was determined histologically.

Results: There was a significant ($P < 0.001$) correlation between the electrolytic 'dose' and the volume of liver necrosis. For a given 'dose' the volume of necrosis was less when the electrodes were together, rather than separated. Liver enzymes were only transiently deranged. There were no significant vascular injuries.

Conclusion: Predictable and reproducible necrosis is produced by electrolysis in the pig liver. The treatment appears to cause little or no damage to immediately adjacent liver or major vascular structures and, when combined with resection, may offer the chance of a cure to many patients who are currently unresectable.

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Introduction

Surgical resection remains the only potentially curative treatment for patients with colorectal liver metastases. Without treatment the prognosis is poor[1], with a median survival of 6 months[2,3]. Only approximately 20 per cent of such patients are suitable for liver resection for a variety of reasons[4]. Patients are often deemed unresectable because of one or two metastases that are awkwardly placed close to a major vein. If such a lesion could be treated with local ablation, the patient may then become resectable and potentially curable.

Several methods of local ablation have been reported, including radiofrequency ablation[5,6], cryotherapy[7], interstitial laser therapy[8], microwave hyperthermia[9] and direct injection of toxic agents such as alcohol[10], acetic acid[11] and hot saline[12]. The majority of these methods use extremes of temperature to cause tumour necrosis. However, all thermal methods of ablation are limited in their use close to major intrahepatic veins because of a combination of the 'heat-sink' effect[13,14] and direct damage to the vein. In the 'heat-sink' phenomenon, the thermal insult is reduced close to major vascular structures owing to the effect of local blood flow. As a result, if a tumour is adjacent to a major vein, a cuff of viable tumour may be left untreated around the vessel[15]. Conversely, the thermal insult may actually cause a direct 'burn' to the vessel. Indeed with cryotherapy, cracks may form in the ice-ball during freezing. As thawing begins, any involved hepatic veins may then bleed, causing potentially fatal haemorrhage[16,17]. Cryotherapy is also associated with the 'cryoshock' phenomenon in which patients develop a systemic inflammatory response to the products of cell necrosis. Patients have died as a direct result of this phenomenon[18,19]. Additionally it has been shown that radiofrequency ablation may achieve incomplete tumour necrosis within the treated area[20,21].

Clearly, if a locally ablative treatment is to be used as an adjunct to surgical resection, it is crucial that it is: (1) predictable in effect; (2) safe and effective close to major veins; and (3) achieves complete necrosis of the treated tumour.

Electrolytic ablation was first described by Nordenstrom[22,23] for the treatment of lung tumours.

However it was not until recently that this method was applied to the local ablation of liver tumours[24]. Rather than relying on a rapid 'burn', electrolysis causes cell death by a more subtle, yet equally effective, chemical action. Platinum electrodes are inserted into the tumour and a small direct electrical current is passed between them, thereby polarizing the electrodes. As a result, negatively charged ions are attracted to the anode and positively charged ions to the cathode, resulting in a change in intracellular pH of the tissues surrounding the electrode tips. Additionally, cytotoxic gases (such as chlorine) are liberated into the tumours and necrosis results from a combination of these two effects; importantly, there is no heating effect[25].

Previous studies[24,26] have shown that electrolysis is a safe, predictable, reproducible and controlled method for producing spherical areas of hepatic necrosis in the rat. Colorectal liver metastases were also ablated using this technique in a rat model[27]. Importantly, more recently it has been shown that electrolytic treatment caused little or no damage to hepatic veins when the electrode catheters were placed either directly adjacent to or within the lumen of the vein[28]. In this study of six pigs, only one animal developed thrombosis of the hepatic vein and there was no evidence of endothelial damage in any of the animals, even though the necrotic lesion directly abutted the vein wall.

Because of this lack of vascular damage, electrolysis would appear to be ideally suited to the treatment of perivascular liver metastases. However, before treating patients it is essential that the extent of the necrosis can be predicted accurately by the electrolytic 'dose' given using data generated from a large animal model with a liver of similar physical size to that of the human. This study examined the effects of varying both the electrolytic 'dose' and electrode separation on the volume of the resultant electrolytic lesion(s) in normal pig liver and any associated vascular damage.

Materials and methods

Twenty-one female Domestic White pigs (24–33 kg) were used. All animals were anaesthetized in the same way; the pigs were sedated with a deep intramuscular injection of ketamine 20 mg/kg and xylazine 1·5 mg/kg. Anaesthesia was maintained using a laryngeal mask airway with 1·5 per cent halothane in 100 per cent oxygen. The oxygen saturation, pulse rate and end-tidal carbon dioxide were monitored throughout the procedure. Each animal underwent electrolysis with electrodes 'together' (12 mm separation) and 'separated' (200 mm separation).

During the early part of the study, intraoperative ultrasonography was used in an attempt to monitor the evolution of the electrolytic lesions. However, this was abandoned as the production of gaseous electrode products produced a 'snowstorm' effect, making images uninterpretable.

Electrodes together (12 mm)

The liver was exposed through an upper midline incision. A single 6-Fr (2 mm) electrode catheter (Johnson & Johnson Medical, North Ryde, New South Wales, Australia) (*Fig. 1*) was inserted centrally into the dome of the left lobe to a depth of 30 mm, such that the electrodes were in close proximity to the left hepatic vein. The tip electrode (anode) and the middle of the three proximal electrodes (cathode) were connected to the direct current (DC) generator (Bioengineering, Transducers and Signal Processing Research Group, University of Leicester, Leicester, UK), giving an electrode separation of 12 mm. The unused electrodes were electrically isolated. The electrolytic 'dose' (25–300 coulombs (C), delivered at 30–80 mA) was then given. Depending on the 'dose' delivered, treatment time varied from 8 to 100 min. At the end of treatment, the electrode catheter was removed. The resulting 'composite' lesion consisted of two distinct but overlapping anode and cathode lesions.

Electrodes separated (200 mm separation)

Using the same animal, two separate electrode catheters were inserted adjacent to major veins; the anode was inserted centrally in the right lobe and the cathode was inserted centrally in the left lobe, giving an electrode separation of 200 mm. The tip electrodes of each catheter were connected to the DC generator and the same electrolytic 'dose' was delivered. After treatment the electrodes were removed.

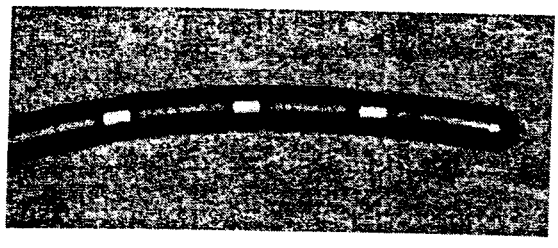

Fig. 1 A 6-Fr (2 mm) platinum electrode catheter. The tip electrodes of two catheters were used when the electrodes were separated. The tip and middle electrodes of a single catheter were used when the electrodes were placed together

Analysis

All animals were killed 72 h after treatment by lethal injection.

Blood samples were obtained before operation, 24 h after treatment and at the time of death. Serum measurements of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), γ-glutamyltranspeptidase (γGT) and bilirubin were made on each sample (Technicon Axon analyser; Bayer Health Care, Pymble, New South Wales, Australia). At autopsy, the liver was removed, and the electrolytic lesions were excised *en bloc* and fixed in 10 per cent formalin.

After 2 weeks' fixation, each electrolytic lesion was cut into 1-mm sections in its entirety (*Fig. 2*). Sections were then measured blindly by two separate investigators. For each lesion, the three maximum diameters at right angles to each other were measured and recorded. The mean of the observer's measurements for the three diameters was calculated. The volume of each lesion was then calculated.

Each electrolytic lesion was processed, embedded in paraffin, sectioned and stained using haematoxylin and eosin. Coded sections were examined by a hepatopathologist to determine both the extent of necrosis and any associated vascular or biliary damage.

Results were analysed statistically using the paired *t* test and regression analysis.

Results

No animal died as a result of electrolysis or had to be killed prematurely. Treatment was uneventful and all animals made a rapid and full postoperative recovery.

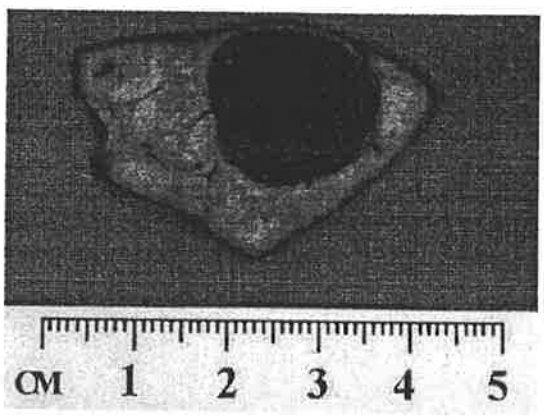

Fig. 2 Section (1 mm) of an electrolytic lesion created at the anode using 200 C

Electrodes together (12 mm separation)

The volume of necrosis increased with the electrolytic 'dose'. There was a significant correlation between the volume of the electrolytic lesion and the 'dose' delivered (r^2 = 0·64, P < 0·001) (*Fig. 3*). The relationship was linear, although with doses greater than 75 C, the variability in the volume of the lesion increased. The rate at which the treatment was given (milliamperes) had no significant effect on this relationship. At the maximal 'dose' of 300 C, lesions of 2·05 cm in diameter were created.

Electrodes separated (200 mm separation)

Anode lesions

There was a significant correlation between the volume of the electrolytic lesion and the 'dose' delivered (r^2 = 0·91, P < 0·001) (*Fig. 4*). The rate at which the treatment was given again had no significant effect on this relationship.

Cathode lesions

As with the anode lesions there was a significant (r^2 = 0·73, P < 0·001) correlation between the volume of the electrolytic lesion and the 'dose' delivered (*Fig. 4*). The rate at which the treatment was given had no significant effect on this relationship. At the maximal 'dose' of 300 C lesions of 2·75 cm were created.

Comparison of electrode arrangements

Fig. 5 shows the mean volume of necrosis per coulomb delivered with the electrodes together or separated. For a

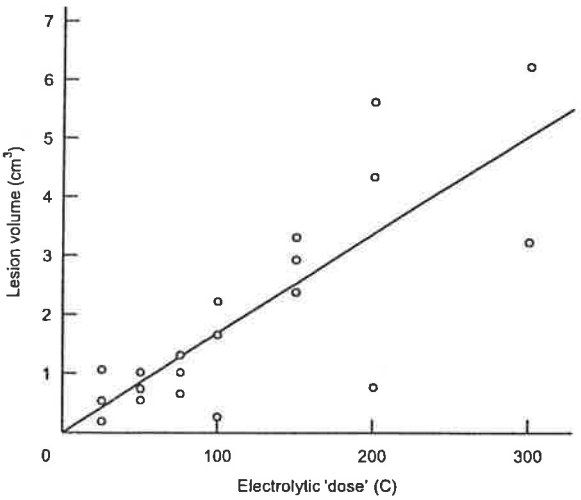

Fig. 3 Correlation between the volume of the composite lesion and the electrolytic 'dose' delivered (r^2 = 0·636, P < 0·001)

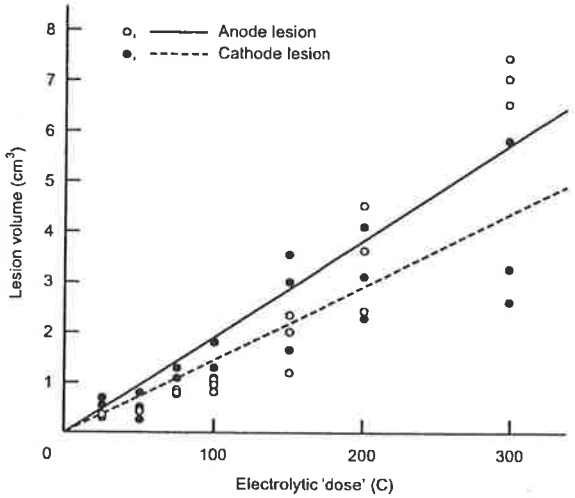

Fig. 4 Correlation between the volume of necrosis and the electrolytic 'dose' delivered for both anode (r^2 = 0·91, P < 0·001) and cathode (r^2 = 0·73, P < 0·001)

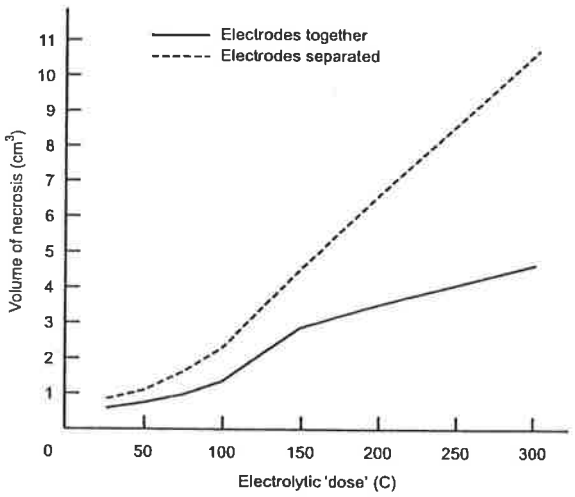

Fig. 5 Mean volume of necrosis with the electrodes together or separated

given 'dose', the volume of necrosis produced was greater when the electrodes were separated; this disparity increased with higher doses.

Liver enzymes

Levels of liver enzymes (AST, ALT and γGT) were significantly raised 1 day after treatment (P < 0·001 for AST) (*Fig. 6*). The initial increase in AST was significantly correlated with both the volume of the anode lesions (r^2 = 0·54, P < 0·001) and the total volume of liver necrosis (r^2 = 0·38, P < 0·01). Similarly, the initial increase in ALT was significantly correlated with both the volume of the anode lesions (r^2 = 0·45, P < 0·001) and the total volume of liver necrosis (r^2 = 0·26, P < 0·05). There was no correlation between either the cathode or composite (electrodes together) lesions and the increase in liver enzyme levels. At the time of death the liver enzymes had returned to normal apart from the AST level which remained significantly raised (P < 0·05).

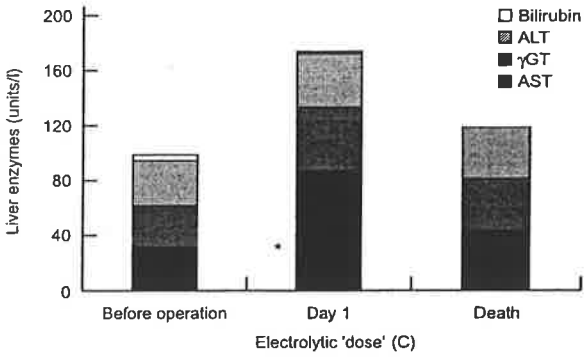

Fig. 6 Change in liver enzyme levels after electrolysis. ALT, alanine aminotransferase; γGT, γ-glutamyltranspeptidase; AST, aspartate aminotransferase. *P < 0·001 (AST; before operation to day 1; paired t test)

Histopathology

Histological examination confirmed the macroscopic observation that the size of the electrolytic lesion increased with the dose delivered. Each lesion consisted of a central zone of coagulative necrosis around the site of the electrode tip. No viable tissue was seen within the electrolytic lesions. The necrotic tissue was sharply demarcated from the surrounding liver tissue, which was histologically normal (*Fig. 7*).

Small blood vessels (less than 1 mm) were thrombosed in a narrow rim (0·5–1·0 mm) of normal liver surrounding each lesion. Only one major vein was thrombosed. In all other specimens, veins directly adjacent to electrolytic lesions were undamaged (*Fig. 8*) and there were no major bile duct injuries.

Discussion

Previous studies in both small and large animal models[26,29] have demonstrated that electrolytic lesions in the liver heal

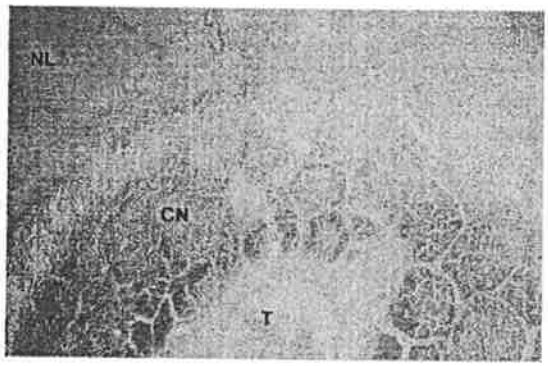

Fig. 7 Histological appearances. There is a circular area of tissue destruction at the site of the electrode tip (T) surrounded by a circular zone of coagulative necrosis (CN), with sharply demarcated normal liver at the periphery (NL). (Haematoxylin and eosin stain, original magnification × 4)

Fig. 8 Undamaged, patent hepatic vein, directly adjacent to an electrolytic (cathode) lesion

with time without complications. Six months after treatment little necrotic tissue remained at the site of the original lesion, which was replaced by a small fibrous scar. It was also shown that colorectal liver metastases as well as normal liver tissue could be destroyed completely by this technique[27].

If the treatment is to be consistently associated with minimal morbidity and mortality rates, however, it must be demonstrated that the effect of treatment is both predictable and reproducible. To date the dose–response data in the literature regarding electrolysis are limited and variable. However, one study has reported experimental dose–response data in rabbit liver[30]; liver necrosis was produced at a rate of 2·4 cm^3 per 100 C compared with a rate of 4·1 cm^3 for lung necrosis in the same study. In a recent study[24] it was demonstrated that electrolytic necrosis in rat liver was produced at a rate of approximately 2·0 cm^3 per 100 C when the electrodes were placed together and 3·4 cm^3 per 100 C when the electrodes were separated. In anecdotal reports of patients with large hepatocellular carcinomas treated with electrolysis, Chinese workers have reported completely different rates of destruction with two orders of magnitude difference in response (between 485 and 837 cm^3 per 100 C)[31,32]. Before treating patients, however, it is essential that reliable dose–response data are generated using a large animal model with a liver of similar physical size to that of the human.

The present results show that the volume of necrosis produced by a given electrolytic 'dose' is both predictable and reproducible in pig liver. However, the effect is greater, and the final lesion larger, when the electrodes are separated by a distance of 200 mm rather than with minimal separation. This finding is consistent with other experimental studies[33,34]. It is likely that this discrepancy results from a combination of factors. One such factor may be that when the electrodes are very close the cytotoxic gases generated from each electrode mix, effectively cancelling out their respective effects[34].

In this study, a maximum 'dose' of 300 C was used. With the electrodes separated, this produced two lesions with a combined volume of nearly 11 cm^3, or individual diameters of 2·2 cm. In clinical practice metastases are often larger than this. However, there is no reason to suggest that electrolytic 'doses' far in excess of 300 C could not be used safely. Indeed, as a part of a pilot study in patients, 1500 C has been given to a patient with a hepatoma, without adverse effects.

Histological examination of all the specimens in this study demonstrated three important beneficial effects of electrolytic ablation that may be of relevance when treating perivascular metastases. First, no viable tissue remained in the area treated by electrolysis in any of the lesions that were created. There was 100 per cent necrosis of the cells that were contained within the macroscopically apparent electrolytic lesion. Additionally, there was a very sharp 'transition zone' between the area of total necrosis and normal surrounding liver. This finding is in contrast to the results of radiofrequency ablation where recurrence has been reported within the treated area, presumably resulting from incomplete ablation at the time of treatment[20,21].

Second, although there was an hepatic vein occlusion in one specimen, there was no histological evidence of major vascular or biliary damage in any of the remaining specimens, despite the close proximity of many lesions to hepatic veins. If local ablation is intended for use in this situation, these results support the view that electrolysis may be more

efficacious than treatments such as cryotherapy and radiofrequency ablation.

Third, although there was virtually no damage to large veins as a result of electrolysis, each lesion was surrounded by a narrow rim of normal liver in which the small sinusoids were thrombosed. It is proposed that these small, occluded vessels may form a 'cocoon' around the necrotic lesion. This vascular isolation may in turn prevent the rapid efflux of necrotic debris into the systemic circulation and hence avoid the systemic inflammatory reaction that is known to occur with cryotherapy[18,19]. This theory requires further evaluation but is supported by the lack of a systemic response in experimental studies to date[26,28,29].

Levels of liver enzymes were significantly raised after treatment and the magnitude of the increase correlated with the total volume of liver necrosis. However, while the increase in liver enzymes was statistically significant, there were no clinical sequelae and no animal developed hepatic failure or became jaundiced after treatment. Indeed, 72 h after treatment the enzyme levels had either returned to or were returning to normal. The local trauma associated with electrolysis appears to be minimal and transient.

Platinum electrodes were used in this study because it has been shown that they are durable and not readily eroded by the electrolytic process[21]. Furthermore, it has been suggested that the use of platinum electrodes may increase the toxicity of the local environment by the production of cytotoxic platinum salts[35–38]. This remains theoretical and unproven, and requires further evaluation. The potential toxicity of platinum salts and other products of electrolysis entering the systemic circulation has been investigated[28]. No systemic toxic effects were observed either during or after treatment.

This study has confirmed that electrolysis fulfils many of the criteria for an ablative technique which may be used as an adjunct to surgery to make the 'unresectable' patient 'resectable' by treating one or two awkwardly placed metastases. In this study electrolytic ablation produced predictable areas of necrosis with no significant complications, close to major vascular structures. Additional theoretical advantages, such as the lack of a systemic inflammatory reaction and the local production of cytotoxic platinum salts, require further evaluation.

Presently, electrolytic ablation is performed at laparotomy. However, there is no reason why the treatment could not be performed percutaneously in the future, as delivery systems are currently available which would accept the 6-Fr catheters used in this study. Based on the encouraging results of this study, preliminary clinical trials have started and several patients who would otherwise have been deemed inoperable have been treated successfully.

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SURGICAL TECHNIQUE

ELECTROLYTIC ABLATION AS AN ADJUNCT TO LIVER RESECTION: SAFETY AND EFFICACY IN PATIENTS

SIMON A. WEMYSS-HOLDEN,* DAVID P. BERRY,† GAVIN S. M. ROBERTSON,‡ ASHLEY R. DENNISON,† PAULINE DE LA M HALL§ AND GUY J. MADDERN*

*University of Adelaide Department of Surgery, The Queen Elizabeth Hospital, Adelaide, Australia, †Department of Surgery, Leicester General Hospital, ‡Department of Surgery, Leicester Royal Infirmary, Leicester, United Kingdom, §Department of Histopathology, Flinders Medical Centre, Adelaide, Australia

Background: Electrolytic ablation is a relatively new method for the local destruction of colorectal liver metastases. Experimental work in animal models has shown this method to be safe and efficacious. However, before proceeding to clinical trials it was necessary to confirm these findings in a pilot study of five patients.

Methods: Five patients with colorectal liver metastases were studied prospectively. Each patient underwent a potentially curative liver resection. One of the metastases to be removed was treated using electrolysis before resection. Each patient was monitored closely during and after electrolysis to determine any morbidity associated with the treatment. Once resected, the metastases were examined histologically for completeness of ablation.

Results: All patients tolerated the electrolysis well; there were no deaths or complications related to the treatment. Histological examination of the resected metastases which had been treated electrolytically showed complete tissue destruction with no viable malignant cells remaining at the site of treatment.

Discussion: This pilot study of electrolytic ablation of liver metastases in five patients showed the treatment to be well tolerated and safe. Additionally, it demonstrated total destruction of the malignant tissue at the site of electrolysis.
Based on these encouraging results, clinical trials can now begin.

Key words: ablation, electrolysis, liver, metastases.
Abbreviations: ALT, alanine aminotransferase; RFA, radiofrequency ablation; ECG, electrocardiogram.

INTRODUCTION

The prognosis for patients with untreated colorectal liver metastases is poor with a median survival of 6 months.[1–4] Liver resection is the only treatment currently available which significantly prolongs survival.[5,6] Unfortunately, only approximately 10% of these patients are candidates for surgery[7] because of a variety of factors including the anatomical distribution of the metastases, proximity to major vascular structures, bilobar disease and dissemination. For those patients with unresectable disease, palliative chemotherapy is the only treatment option.

A group of patients exists, however, who are deemed unresectable by virtue of one or two awkwardly placed metastases, situated either in the proposed hepatic remnant or close to a large vein. Localized wedge resection of these tumours is not always technically feasible, particularly if they are deep within the hepatic parenchyma. If such lesions could be treated by local ablation, then many patients currently deemed unresectable may achieve increased long-term survival from combined resection and local ablation.

S. A. **Wemyss-Holden** MD, FRCS; **D. P. Berry** MD, FRCS; **G. S. M. Robertson** MD, FRCS; **A. R. Dennison** MD, FRCS; **P. de la M Hall** MB BS, FRCPA; **G. J. Maddern** PhD, FRACS.

Correspondence: Professor G. J. Maddern, University of Adelaide Department of Surgery, The Queen Elizabeth Hospital, Woodville Road, Woodville, South Australia 5011, Australia.
Email: guy.maddern@adelaide.edu.au

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Many methods of local ablation are currently available including radiofrequency ablation,[8,9] cryotherapy,[10] alcohol injection,[11] microwave hyperthermia[12] and laser interstitial therapy,[13] amongst others. The majority of these methods use extremes of temperature (either heat or cold) to destroy the tumours. However, this thermal insult may actually cause a direct 'burn' to major vascular structures adjacent to the tumour. Indeed with cryotherapy, cracks may form in the 'ice-ball' during freezing. As thawing begins, any involved hepatic veins may then bleed, causing potentially fatal haemorrhage.[14,15] Cryotherapy is also associated with the 'cryoshock' phenomenon where patients develop a systemic inflammatory response to the products of cell necrosis. Patients have died as a direct result of this phenomenon.[16,17]

Additionally it has been shown that radiofrequency ablation may achieve incomplete tumour necrosis within the treated area.[18,19]

Electrolytic ablation was first described by Nordenstrom[20,21] for the treatment of lung tumours. However, it was not until recently that this method was applied to the local ablation of liver tumours.[22] Rather than relying on a rapid 'burn', electrolysis causes cell death by a more subtle, yet equally effective chemical action. Platinum electrodes are inserted into the tumour and a small direct electrical current is passed between them, thereby polarizing the electrode tips. As a result, negatively charged ions are attracted to the anode and positively charged ions to the cathode resulting in a change in intracellular pH of the tissues surrounding the electrode tips. Additionally, cytotoxic gases (such as chlorine) are liberated into the tumours[23] and necrosis results from a combination of these two effects; importantly, there is no heating effect.[24]

This new treatment has been extensively evaluated over the past 5 years in Adelaide using both small and large animal models. Electrolysis creates well circumscribed, spherical areas of necrosis with a sharp transition from necrotic to normal tissue.[25,26] There is a thin (1 mm) surrounding zone of acute inflammatory tissue.[26] This effect has been shown to be equally effective in destroying normal hepatic parenchyma and liver metastases.[27] Importantly, because of its relatively subtle action there is no damage or thrombosis to major vascular or biliary structures intimately associated with the electrolytic 'lesion'.[26] Electrolytic lesions heal with time, forming a mature fibrous scar; septic complications of the induced necrosis have not been observed.[25,26] The treatment is controllable and the volume of induced necrosis is accurately predicted by the electrolytic 'dose' (Coulombs) given.[22]

Using this new treatment, in combination with surgical resection, it may be possible to offer increased long-term survival to patients who would otherwise be deemed inoperable.

Before using electrolysis as a therapeutic tool in patients, it is essential to demonstrate that the treatment is safe and capable of achieving complete tumour ablation.

In this pilot study, the safety and efficacy of electrolytic ablation of colorectal liver metastases was investigated by ablating metastases in patients undergoing potentially curative resections. The intention of this study was not to achieve complete destruction of individual metastases, rather to demonstrate complete tumour ablation around the implanted electrodes while monitoring the patients in the peri- and postoperative periods for any electrolysis-related morbidity or mortality.

METHODS

Five consecutive patients (4 men, 1 woman; mean age: 63 years) with colorectal liver metastases were studied prospectively. Each patient had a preoperative computed tomography scan to define the extent of the disease (Fig. 1) and subsequently underwent a potentially curative liver resection (three right hepatectomy, one left hepatectomy, one right wedge resection). One of the metastases to be resected was treated using electrolysis before resection in each patient.

At laparotomy, prior to resection, a platinum tipped electrode catheter (Johnson and Johnson, North Ryde, NSW, Australia; Fig. 2) was inserted into one of the liver metastases to be resected under ultrasound control (Aloka SSD-2000, Mure, Mitaka-Shi, Tokyo, Japan; 7.5 MHz probe). The catheter was then connected to a direct current generator (ECU 100, Söring GmbH, Justus-von-Liebig-Ring 10, D-25451 Quickborn, Germany; Fig. 3) and an electrolytic 'dose' of 100 C was delivered to the tumour at 60 mA (mean treatment time: 35 min). After electrolytic treatment, the electrode catheter was removed and the liver resection completed as planned.

Each patient was monitored closely during the procedure. Heart rate, rhythm, blood pressure, O_2 saturation and end-tidal CO_2 concentration were monitored throughout the procedure. Additionally, the electrocardiogram (ECG) was monitored closely for evidence of electrical disturbance. Arterial blood

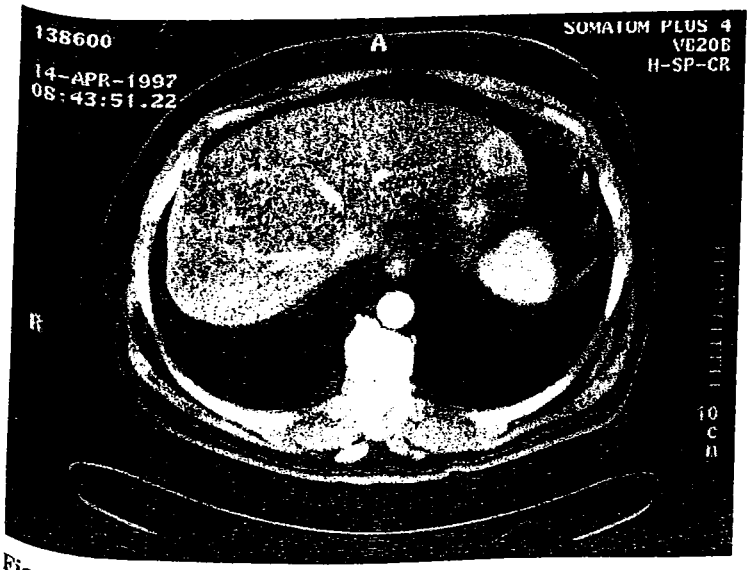


Fig. 1. Computed tomography scan showing a metastasis in segment III.

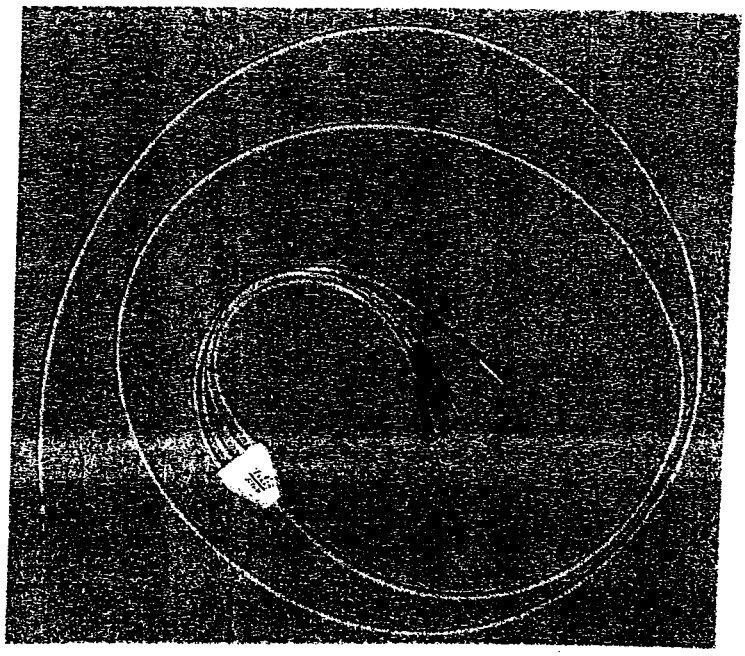


Fig. 2. 6 French (2 mm) platinum-tipped electrode catheter. The tip and middle electrodes of a single catheter were connected to the DC generator.

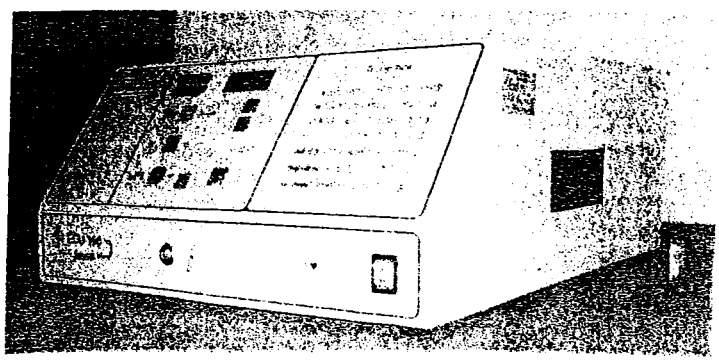


Fig. 3. Direct current generator (Söring GmBh).

gases were measured every 5 min during treatment. Additionally, blood samples were taken from the main hepatic vein draining the lobe being treated electrolytically during the procedure. Blood samples from this vein were analysed to determine whether any gaseous by-products of electrolysis entered the systemic circulation during treatment.

Liver enzymes were measured preoperatively and daily for 1 week after treatment or until they had returned to normal.

After resection each metastasis treated by electrolysis was examined both macro- and microscopically (using standard H&E staining methods) to determine the extent of tumour necrosis.

RESULTS

General

All patients tolerated the treatment well; there were no deaths and the 30 day mortality was 0%. During electrolytic treatment there was no evidence of systemic upset in any of the patients, with no clinically significant changes in any of the monitored parameters (heart rate, rhythm, ECG, blood pressure, O_2 saturation and end tidal CO_2) during treatment. No patient became acidotic during electrolysis. There was no evidence that any of the gaseous products of electrolysis entered the systemic circulation as determined by the pH of the blood draining the electrolytically treated lobe.

Liver enzymes

Four of the five patients developed transient derangement of liver enzymes after resection and electrolytic treatment (three right hepatectomy, one left hepatectomy).

In the patient who underwent wedge resection and electrolysis, the liver enzymes were unchanged, apart from a very slight increase in alanine aminotransferase (ALT).

In all patients the liver enzymes returned to normal within 1 week of resection/electrolytic ablation.

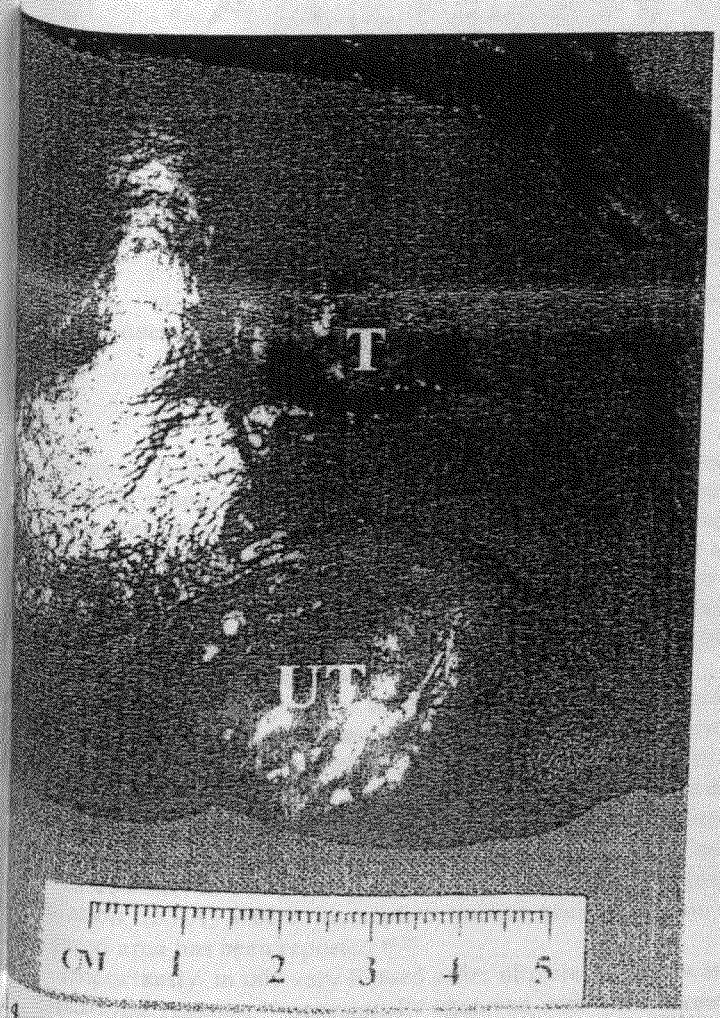
Macroscopic appearances

After resection of the electrolytically treated tumour, each specimen was examined macroscopically for evidence of tumour ablation.

All of the specimens showed the same appearances at the site of electrolytic treatment. On the surface of the resected specimen, there was a brown/black, circular zone, surrounding the site of electrode insertion (Fig. 4). Each specimen was subsequently sectioned in a plane at 90 degrees to the liver surface. This confirmed that the apparent zone of necrosis observed on the surface of the liver was centred about the tip of the electrode catheter (Fig. 5). The surrounding normal liver (and untreated metastases) were unaffected by the electrolysis.

Histological appearances

The appearances were similar in all of the resected specimens. At the site of electrolytic treatment, there was histological evidence of complete tumour necrosis, with no viable malignant cells remaining within the treated zone. There was a sharp demarcation between the treated (non-viable) and untreated (viable) tumour (Fig. 6). The surrounding hepatic parenchyma was normal apart from mild 'surgical hepatitis' and there was no histological evidence of any major biliary or vascular damage.



4. Resected specimen showing electrolytically treated (T) and ated (UT) metastases.

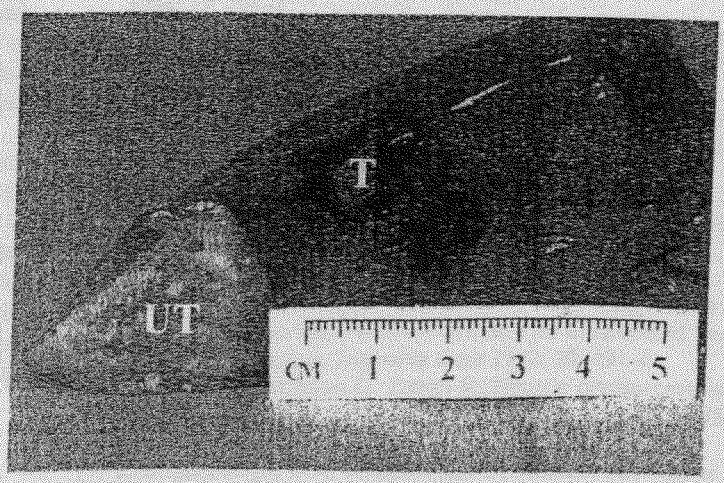


Fig. 5. Resected specimen after sectioning, showing electrolytically treated (T) and untreated (UT) metastases.

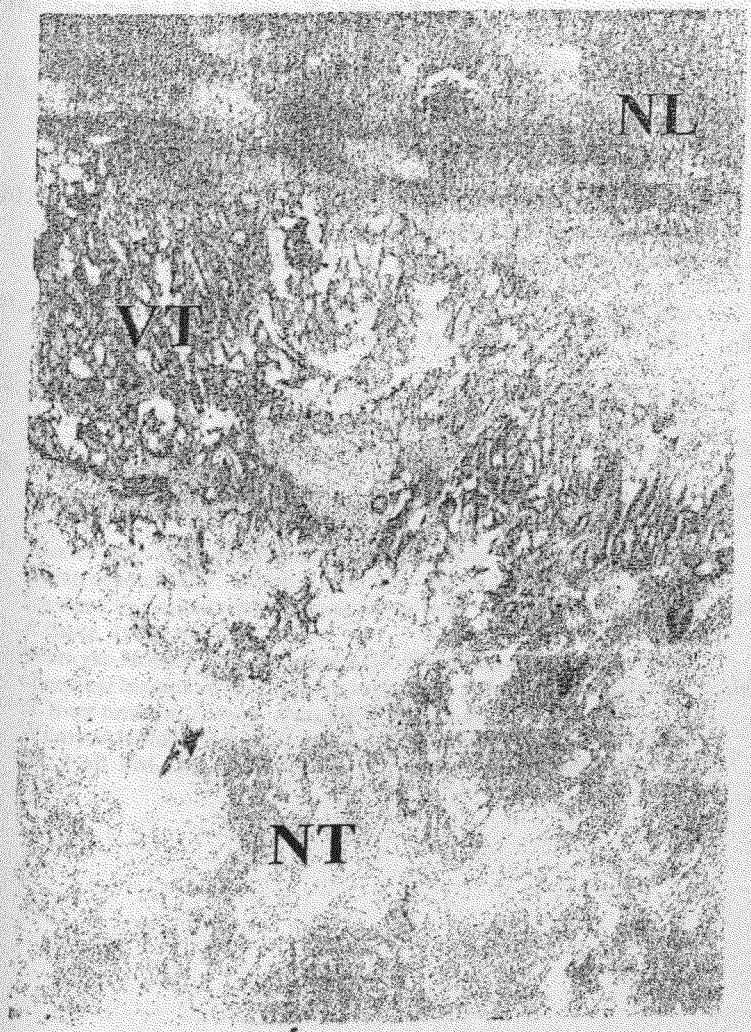


Fig. 6. Histological appearances of ablated metastasis. Viable tumour (VT), necrotic tumour (NT), normal liver (NL).

DISCUSSION

Surgical resection currently offers the only chance of increased long-term survival in patients with colorectal liver metastases.[5,6] However, there is a group of patients who are deemed unresectable by virtue of one or more metastases which are either awkwardly placed (close to a major vein) or deep within the parenchyma of the proposed hepatic remnant. These patients may be offered potentially curative treatment if surgery is combined with a locally ablative technique.

Although electrolysis has been extensively evaluated in animal models,[22,25–27] its safety and efficacy have never been investigated in humans. The results of this pilot study confirm the findings of animal studies and a previous case report[28] that electrolysis appears to be safe and capable of achieving complete tumour ablation at the site of electrolytic treatment. This finding is in contrast to other forms of ablation, such as radiofrequency ablation (RFA) where incomplete tumour necrosis within the treated area has been reported.[19,29]

Importantly, in this very limited series of patients there was no SIRS-type reaction,[30] occasionally observed with other forms of local ablation.[31–33] It is proposed that this lack of systemic response seen with electrolysis results from the peri-lesional microvascular thrombosis associated with the treatment.[25] This in turn prevents the rapid efflux of immunologically active cellular debris (cytokines) into the systemic circulation, thereby preventing the initiation of the inflammatory cascade. Experimental work has shown that even if the electrode catheters were inadvertently placed directly into a hepatic vein, the resulting systemic upset was minimal, and all animals made uneventful recoveries.[34] Additionally, there was little or no damage to the vein wall.

Because of its controlled, subtle action, and the absence of vascular or biliary injury with no associated SIRS reaction, it is proposed that electrolysis may have certain advantages when compared to other forms of local ablation.

Based on the encouraging results of this pilot study, it is proposed that the therapeutic efficacy of electrolytic ablation should be determined in a prospective trial.

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Original article

Use of electrolysis as an adjunct to liver resection

B. G. Fosh, J. G. Finch, M. Lea*, C. Black, S. Wong, S. Wemyss-Holden and G. J. Maddern

University of Adelaide Department of Surgery and *Department of Radiology, The Queen Elizabeth Hospital, Woodville Road, Woodville 5011, Adelaide, South Australia, Australia

Correspondence to: Professor G. J. Maddern (e-mail: guy.maddern@adelaide.edu.au)

Background: Patients with hepatic metastases are potentially curable if all the diseased tissue can be resected. Unfortunately, only 10–20 per cent of patients are suitable for curative resection. Electrolysis is a novel non-thermal method of tissue ablation. When used in conjunction with surgery it may increase the number of resectable liver tumours with curative treatment.

Methods: All patients had been deemed inoperable using currently accepted criteria. Nine patients with hepatic deposits from colorectal carcinoma underwent combined surgical resection and electrolytic ablation of metastases.

Results: The treatment was associated with minimal morbidity. Within the electrolytically treated area seven patients had no radiological evidence of recurrence at a median follow-up of 9 (range 6–43) months; local recurrence was detected in two patients. Six of the nine patients had metastases elsewhere in the liver with four having extrahepatic metastases. Three patients remain tumour free. Three patients died. The median survival was 17 (range 9–24) months from the time of treatment.

Discussion: Electrolysis with resection may confer a disease-free and overall survival benefit. The small size of this initial study precludes statistical analysis, but preliminary results are encouraging.

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Introduction

Colorectal carcinoma is the third most common malignancy and the most common source of liver metastases, with the liver being the earliest and often the only site of metastatic disease[1]. These patients are potentially curable if all diseased tissue can be removed[2,3], but have a poor prognosis (measured in months) if this is not feasible[4]. The size, number or position of the metastatic lesions allows only 10–20 per cent of patients to be eligible for a formal resection[5].

Several ablative techniques have been investigated as alternatives to surgical resection for the treatment of colorectal metastases[4,6]. Electrolysis is a novel non-thermal method of tissue ablation[7]. A direct current is passed through a conductive medium between a pair of electrodes (cathode and anode). The electrolytic 'dose' is measured in coulombs (amperes × seconds). Tissue electrolysis produces sodium hydroxide and hydrogen at the cathode, and hydrochloric acid and chlorine gas at the anode[8,9]. The significant pH changes produced by electrolysis are cytotoxic and cause localized parenchymal necrosis with a negligible thermal effect[7–9].

Over the past few years electrolysis of liver tumours has been investigated extensively at this institution[7,10–13]. Not only has the process been shown to ablate liver tumours completely in experimental models[12,14], but it is also safe in terms of both its inherent tissue destruction and the inability to thrombose or damage large blood vessels in close proximity to the electrolytic lesion[13]. A pilot study was performed in five patients before tissue resection to determine whether this method could be used safely. No adverse effects resulted from the treatment (D. Berry, S. Wemyss-Holden, G. J. Madden, A. Dennison, unpublished results). Nine patients were then subjected to a formal liver resection, with electrolytic ablation of metastases that would have deemed the cancer irresectable using currently accepted criteria.

Patients and methods

The records of nine patients with a histologically confirmed diagnosis of secondary liver metastases from colorectal carcinoma between the dates of April 1997 to May 2000 were reviewed. The median age was 57 (range 44–66) years.

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

Conventional surgical treatment was not possible because of the multiplicity of tumours, proximity to major vessels or distribution of metastases, or a combination of these factors. Patients were excluded from the study if they were ineligible for laparotomy, or had extrahepatic disease or multifocal liver metastases such that resection and ablation would compromise liver function. All patients included in the study had previously undergone resection of a primary colorectal tumour. Four patients had previously undergone hepatic resection and presented with irresectable hepatic recurrence over a period of 37 months (August 1997 to September 2000). One patient had undergone previous hepatic resection and was receiving electrolysis alone for a single irresectable metastatic deposit.

The patients underwent formal resection of hepatic metastases, followed by electrolytic ablation of metastases that could not be resected surgically. Ethics committee approval was obtained before any of the patients was treated. Before electrolysis, all patients were fully informed about the experimental nature of the study.

Two 6-Fr electrolysis catheters (Cordis Webster, Johnson and Johnson Medical, North Ryde, New South Wales, Australia) were inserted into the tumour, 9–24 mm apart, depending on the size of the tumour. Electrode positioning was confirmed ultrasonographically. The catheters were attached to a direct current generator (Medizintechnic, Soring, Quickborn, Germany), and a predetermined 'dose' was delivered at a constant current, calculated for the desired volume of necrosis. Tumour dimensions and position were determined using previous computed tomography (CT) scans and confirmed by intraoperative ultrasonography. The volume of each lesion was calculated using the formula $V = 4/3\pi(r_1 \times r_2 \times r_3)$. A 5-mm margin of normal parenchyma surrounding the tumour was also ablated. Previous experimental studies had shown a linear dose–response of 3·5 cm^3 per 100 coulombs (C)[10]. Tumour radius ranged from 5 to 30 mm. The 'dose' varied from 200 to 1000 C according to the calculated volume. The length of time taken for electrolysis ranged from 42 to 210 min. Platinum was chosen as the electrode material because of its inert nature, and theoretical antineoplastic properties[15].

White cell count and liver function tests were carried out before and after treatment. Carcinoembryonic antigen (CEA) levels were monitored after operation to assist in determining any tumour recurrence.

CT scans were reviewed retrospectively by a radiologist, who was blinded to treatment details for each patient. The radiologist interpreted and compared CT findings before electrolysis with those obtained at 1 week, 3, 6 and 9 months, and annually after electrolysis to determine the effectiveness of treatment. The electrolytic lesion was evaluated for size, shape and location following electrolysis as well as for evidence of recurrence. Successful treatment was associated with no tumour recurrence within the electrolytically treated lesion, while failure of electrolytic treatment was associated with recurrence within the treated area. Recurrence elsewhere was considered to be due to the natural course of the metastatic disease and not a failure of treatment.

Results

Of the nine patients treated, six are still alive. The procedures were performed with a median hospital stay of 9 days. Median follow-up was 9 (range 6–43) months. In two patients who had electrolysis of lesions lying adjacent to the inferior vena cava, there was no damage to the vascular structure.

Seven of the nine patients with hepatic metastases from colorectal carcinoma showed no evidence of radiological recurrence within the electrolytically treated lesion in the follow-up period. In each of these patients, electrolytic treatment was deemed successful. Recurrence within the electrolytically treated area occurred in two patients.

Six of the nine patients experienced hepatic recurrence of tumour outside the electrolytically treated area, which was not related to the previously treated area. There was no evidence of recurrence around the position of the electrodes due to seeding in any patient. Four patients had extrahepatic disease that was histologically confirmed to resemble adenocarcinoma, consistent with metastasis from the primary colorectal carcinoma.

CEA levels were increased after operation in four of the seven patients who had tumour recurrence. One patient, who experienced shrinkage of the treated tumour and no recurrence, had reduced CEA levels after operation. Liver enzyme levels and white cell counts were raised in the early postoperative period, but returned to normal within 3 months of treatment. No major complications occurred either during or after treatment.

All patients received chemotherapy before or after treatment.

Discussion

In recent years there has been an increasing interest in the use of ablative techniques for treating previously irresectable disease[4,16–19]. These techniques have the advantage of preserving more liver parenchyma, and are associated with fewer complications than resection[4]. The use of ablation as an adjunct to surgical resection is not yet established.

Electrolytic ablation of liver tumours has previously been described in China[20,21], with promising results. It is a non-

thermal technique, and therefore not limited by the 'heat sink' effect of nearby vessels[7]. It is also safe in terms of its inherent tissue destruction and inability to thrombose or breach large blood vessels in close proximity to the site of electrolysis[13]. Electrolysis is also predictable, with the volume of the lesion created being proportional to the electrolytic 'dose' (in coulombs) administered[10]. Currently, a limitation of the technique is that it is time consuming, with an increase in tumour size necessitating an exponential increase in treatment time. At present it is limited to lesions of less than 5 cm in diameter and requires a laparotomy. However, further development of appropriate electrode delivery systems may result in the treatment being administered percutaneously.

CT has been used in this study for follow-up evaluation as it has been proven to be sensitive in characterizing hepatic lesions[22]. A small margin of normal tissue at the periphery of the tumour is ablated to prevent residual viable tumour cells persisting at the margin and leading to recurrence. An initial increase in size of created lesions in the first week after operation is expected on the CT scan as this represents ablation of a margin of normal tissue (*Figs 1* and *2*). A decline in lesion size after the first week reflects successful treatment, while an increase in size suggests failure[23]. Conservative electrolytic treatment in the early stages of the trial may have resulted in undertreatment of tumours, allowing residual viable tumour cells to persist within the lesions, causing recurrence. With greater experience more accurate 'doses' of current were delivered, based on tumour geometry.

Necrosis in the electrolytically treated area appears hypodense on CT. Fibrosis within the treated area of some patients is evidence of shrinkage of the electrolytically treated area from a fluid-filled necrotic zone to a smaller fibrosed area (*Fig. 3*). Areas of fibrosis appear enhanced on contrast CT. Magnetic resonance imaging may be useful in evaluating these patients and a study to investigate this has been initiated.

The increase in liver enzyme levels after electrolysis was transient and short-lived. In most patients enzyme levels had returned to normal within 3 months of treatment.

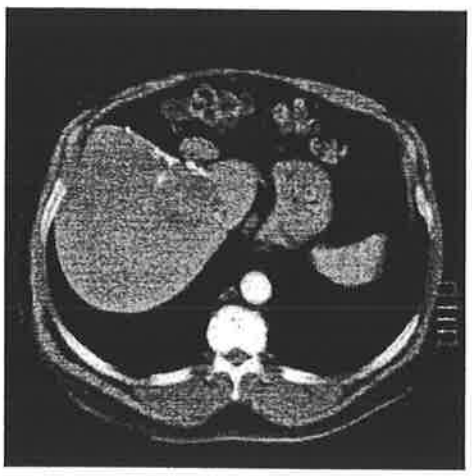

Fig. 1 Computed tomogram of a lesion before treatment

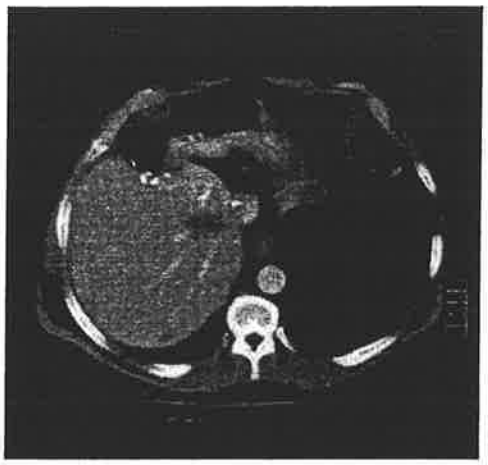

Fig. 2 Computed tomogram of the electrolytically treated lesion in the same patient 1 week after operation, showing ablation of a margin of surrounding normal tissue

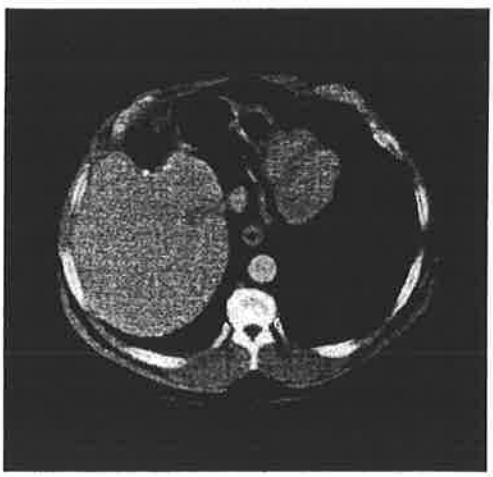

Fig. 3 Computed tomogram of the electrolytically treated lesion in the same patient 3 months after electrolysis, showing fibrosis and shrinkage of the treated area

In patients with colorectal hepatic metastases CEA is a serum tumour marker that can be useful in detecting tumour recurrence. CEA is not associated specifically with colorectal carcinoma but may be raised in up to 70 per cent of patients affected[22]. Four patients had a significantly increased CEA level after electrolysis, consistent with the tumour recurrence noted. One patient in whom treatment was effective had a reduced CEA level following electrolysis.

There was no detectable additional morbidity associated with the electrolytic treatment when used as an adjunct to surgical resection. The lack of major complications associated with electrolysis suggests that it is safe as a method of local ablation.

The median survival from the time of the procedure was 17 (range 9–24) months. This result should be interpreted in the context of the natural history of untreated colorectal liver metastases, for which untreated median survival is of the order of 3–6 months[6,24,25]. The increased survival time in this group of patients receiving electrolysis with resection may have an overall survival benefit. The small size of this initial study precludes statistical analysis of the results. The use of electrolysis in the ablation of liver tumours requires further long-term studies and evaluation; however, preliminary results are encouraging.

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SURGICAL ENDOSCOPY
and Other Interventional Techniques

Palliation of pancreatic cancer using electrolytic ablation

S. A. Wemyss-Holden,[1] F. G. Court,[1] C. P. Morrison,[1] B. D. Teague,[1] A. Burrell,[1] D. R. Morales,[1] N. Rodgers,[2] A. A. Anthony,[1] M. S. Metcalfe,[1] A. R. Dennison,[3] G. J. Maddern[1]

[1] Department of Surgery University of Adelaide, The Queen Elizabeth Hospital, Woodville Road, Adelaide SA 5011, Australia
[2] Department of Pathology, The Queen Elizabeth Hospital, Woodville Road, Adelaide SA 5011, Australia
[3] Department of Surgery, Leicester General Hospital, Gwendolen Road, Leicester, United Kingdom

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Abstract
Background: Inoperable pancreatic cancer has a dismal prognosis. Palliation involves either stenting or surgical bypass. Stenting does not relieve gastric outlet obstruction, and surgical bypass is a major procedure. A minimally invasive procedure is needed that relieves both gastric outlet and biliary obstruction, with the potential for relieving pain.
Methods: In an experimental model, pancreatic electrolysis was investigated. The pancreatic duct was cannulated via a transduodenal approach with an electrode catheter. In 6 animals an electrolytic "lesion" was created using a direct current generator. 6 animals were controls. The local and systemic effects of electrolysis were assessed using histological and biochemical parameters.
Results: The pancreatic duct was cannulated in all animals and treatment was uneventful. Electrolytic lesions comprised a central area of necrosis with a sharp demarcation between necrotic and viable pancreas. All animals developed transient hyperamylasemia after electrolysis. There was no significant difference between treatment and controls. Importantly, no animal had clinical, biochemical, or histological evidence of pancreatitis.
Conclusions: This experimental study suggested that electrolytic palliation of inoperable pancreatic cancer via the gastrointestinal tract is potentially safe. In patients, this treatment could be performed during endoscopic retrograde cholangiopancreatography and may have therapeutic advantages when compared to stenting or biliary bypass.

Pancreatic cancer is the fifth most common cause of cancer death in the United States, with an incidence of approximately 10 per 10,000 population [14]. The prognosis is dismal. Median untreated survival from the time of diagnosis is between 4 and 7 months, and the overall 5-year survival is between 1 and 3% [29]. Radical surgery offers the only chance of cure [15, 20], but is possible in only 15% of patients [16, 21]. Additionally, of those who undergo potentially curative surgery, the median survival is 10–18 months [4, 5, 30], and only approximately 10% survive to 5 years [7, 12]. Therefore, for the majority of patients, palliation is the only therapeutic option.

Effective palliation should aim to relieve the distressing symptoms of locally advancing disease, namely jaundice (often with its intolerable pruritis), gastric outlet obstruction, and pain. Managing these patients is a therapeutic conundrum. The treatment options currently available are limited and are at the extremes of a spectrum of intervention. Therapeutic endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic stenting of the malignant stricture is the least invasive technique available [10]. This procedure has the advantage of rapidly relieving the symptoms of obstructive jaundice without the need for a prolonged hospital admission in a patient with a very limited survival. However, the symptoms of gastric outlet obstruction and pain remain unpalliated, and readmission rates for stent occlusion and cholangitis are high [2].

Conversely, surgical bypass achieves extremely effective palliation of the symptoms of both biliary and gastric outlet obstruction, and recurrent jaundice or cholangitis occurs in less than 10% of patients [24]. However, surgical bypass is associated with a higher 30-day mortality than stent insertion [11, 24], and patients often experience prolonged hospital admission. Much controversy exists regarding how these patients should be managed. The implication is that neither is ideal.

After the recent introduction of new chemotherapeutic agents including gemcitabine, it was hoped that survival would improve [3, 19]. This may have led clinicians to consider the more permanent palliation associated with biliary bypass worthwhile. Unfortunately, following early optimism [3], results have been disap-

Correspondence to: G. J. Maddern

pointing, although large multicenter trials continue [23]. The benefit of adjuvant and neoadjuvant chemotherapy remains unresolved.

The need clearly exists for a palliative treatment that combines the highly effective palliation of surgical bypass with the minimally invasive nature of an endoscopic procedure. Potentially, this could be achieved by "debulking" the tumor using an ablative technique, thereby relieving the locally compressive effects of the tumor. Locally ablative techniques, including radiofrequency ablation [13], cryotherapy [22], and recently, electrolysis [6], have been used in an experimental setting. However, with each technique the approach to the pancreas was transperitoneal, with the potential attendant risk of pancreatic fistulae, bleeding, and enteric perforation. If a locally ablative technique is to become accepted as a palliative option, it must be associated with the minimal morbidity of an endoscopic procedure. It is therefore proposed that ablation should be performed via the pancreatic duct, such that the necrotic products of tumor ablation can drain into the gastrointestinal (GI) tract rather than into the peritoneal cavity. However, it is accepted that cannulation of the biliary tree at ERCP is associated with a significant risk of acute pancreatitis and death [9].

Using the pancreas of a large animal model, this study aimed to determine (1) the feasibility of performing pancreatic electrolytic ablation using an electrode catheter introduced into the pancreatic duct via the duodenum, (2) the nature of pancreatic necrosis caused by electrolytic ablation, and (3) whether pancreatic electrolysis caused acute pancreatitis or other significant local or systemic effects.

Materials and methods

Specific pathogen-free (SPF) female domestic white pigs were used for the study. Mean weight was 31 kg.

All pigs were anesthetized in the same way. Sedation was achieved with an intramuscular injection of ketamine (20 mg/kg) and xylazine (1.5 mg/kg). Each animal was cleaned with a solution of chlorhexidine and taken into the operating theater. A laryngeal mask airway was inserted and anesthesia maintained with 1.5% halothane in oxygen. Oxygen saturation and heart rate were monitored continuously throughout the procedure.

In a preliminary pilot study, three animals were used to determine the pancreatic anatomy, feasibility, and technical requirements for pancreatic duct cannulation and ablation. A pancreatogram was obtained by injecting the pancreatic duct (PD) with contrast medium (Fig. 1). This study showed that the proximal 6 cm of the PD ran parallel and in close approximation to the second part of the duodenum (Fig. 1, P) before turning approximately 90°. Therefore, it was evident that the pancreas should be mobilized from the medial wall of the duodenum before cannulation with the electrode catheter to avoid duodenal perforations. Additionally, it was shown that the electrode catheter should be inserted to a minimum depth of 80 mm, such that the tip of the catheter would be in the main "splenic" lobe of the gland.

Following the pilot study, the main study was performed using 12 SPF pigs. A tunneled catheter was inserted into the right femoral vein for postoperative blood sampling. A midline laparotomy was performed, and a 5-cm longitudinal duodenotomy was performed 20 cm distal to the pylorus. The ampulla was identified and a 6-Fr (2-mm) electrode catheter (Fig. 2; Part No 1086-547-S, Cordis Webster, Baldwin Park, CA, USA) was inserted into the PD of the splenic lobe to a depth of 80 mm and secured with a suture (Fig. 3). Each catheter had four electrodes, which were 4 mm long. Each electrode was separated by 3 mm. Electrolytic treatment was given using the tip and middle electrodes. The "unused" electrodes were electrically isolated.

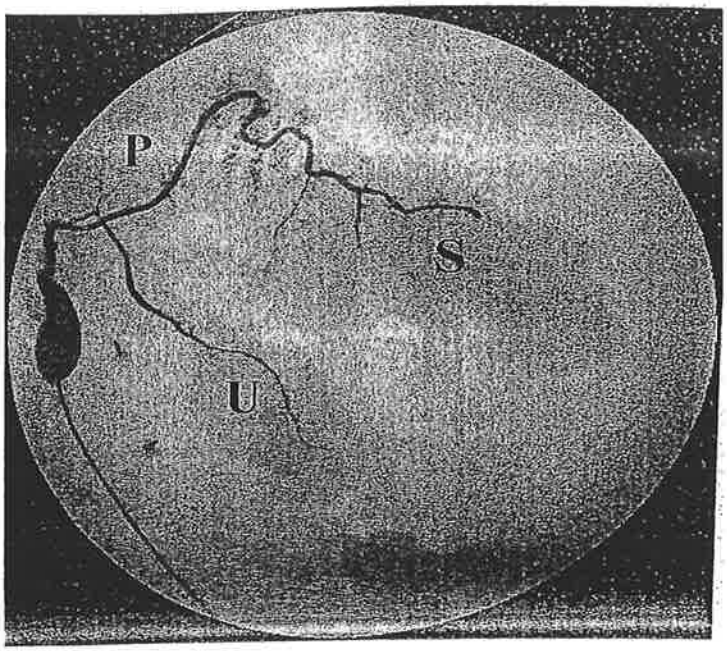

Fig. 1. Pancreatogram showing the unique anatomy of the porcine pancreas. S, splenic lobe; U, uncinate; P, Paraduodenal segment.

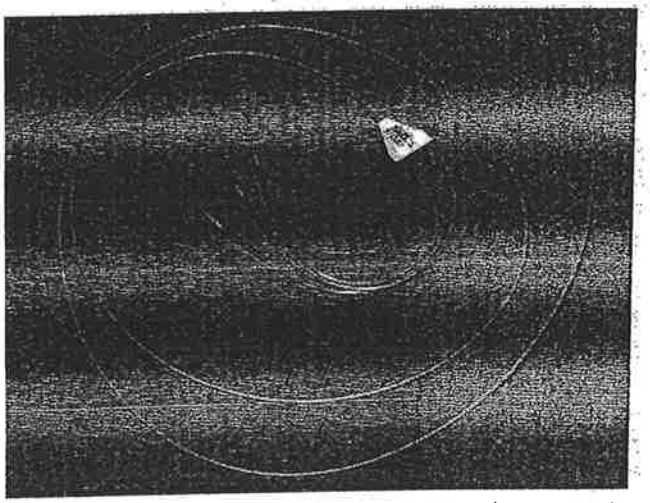

Fig. 2. A 6-Fr (2-mm) electrode catheter. The distal and third electrodes were connected to the DC generator. The "unused" electrodes were electrically isolated.

Each animal was then randomized to either the treatment or control arm of the trial. In the treatment group (n = 6), the electrode catheter was connected to a direct current (DC) generator (ECU 100, Söring, Quickborn, Germany), and an electrolytic "dose" of 50 C was delivered to the gland at 50 mA. Median treatment time was 23 min. (range, 19–25 min). In the control group (n = 6), the electrode catheter was connected to the DC generator, but no current was delivered.

At the end of treatment, the electrode catheter was removed from the PD and the duodenotomy was closed. An intramuscular injection of buprenorphine (0.01 mg/kg) was given before the animal was woken.

Blood samples were taken using the femoral catheter immediately before and after electrolysis and at 1, 4, 24, 48, and 72 h postoperatively for the measurement of serum amylase, glucose, C-reactive protein (CRP), calcium, urea, and electrolytes.

After 72 h, the animals were euthanized. A postmortem examination was performed. In particular, the pancreas was examined to

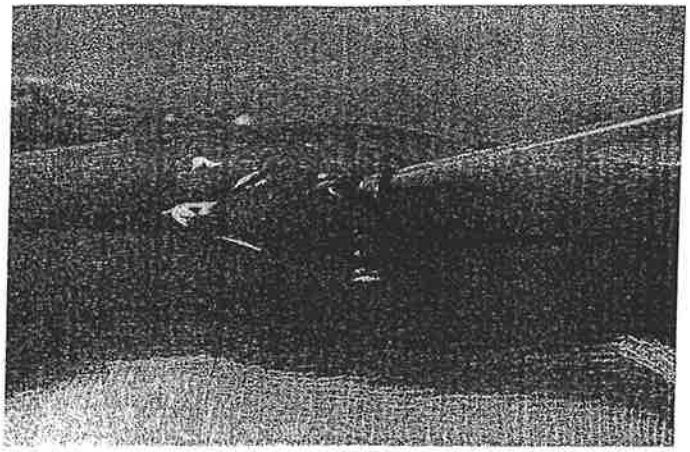

Fig. 3. Cannulation of the pancreatic duct using a 6-Fr (2-mm) electrode catheter. The catheter was inserted to a depth of 80 mm and secured with a suture.

determine the extent of the induced necrosis, the patency of the PD, the presence of any peripancreatic fluid collections, and any involvement of adjacent organs. The pancreas was examined histologically to determine the extent of the electrolytic necrosis and whether there was any associated pancreatitis in the surrounding parenchyma. Results were analyzed statistically using the unpaired *t*-test.

Results

All animals tolerated the electrolytic treatment well. One animal died during surgery from an anesthetic-related complication. This animal was a control and was replaced. Recovery was variable. The majority of the animals (n = 8) were eating, drinking, passing urine, and defecating normally 48 h after the procedure. However, four animals experienced a more prolonged return to normal activities. This prolonged recovery was equal in both the treatment (n = 2) and control (n = 2) groups and was unrelated to the increase in serum amylase or other biochemical parameters. No animal was euthanized prematurely.

Macroscopic appearances

Control group

One of the pancreata was slightly edematous. Otherwise, the glands of the control animals were of normal macroscopic appearance. Specifically, there was no saponification, fluid collections, or pancreatic fistulae. The pancreatic duct was patent in all specimens. There was no damage to adjacent organs.

Treatment group

In all the pancreata, there was evidence of an electrolytic "lesion" in the splenic lobe of the pancreas with a mean diameter of 1.45 cm (range, 1.2–1.85 cm). This lesion was spherical in nature and clearly demarcated from the adjacent normal pancreas. In four of the six glands, the electrolytic lesion had breached the pancreatic capsule, and there were associated small fluid collections. However, the proximal and distal pancreatic duct remained patent in all specimens, and there was no damage to adjacent organs. One of the glands was mildly erythematous, but there was no other evidence of acute pancreatitis in any of the pancreata.

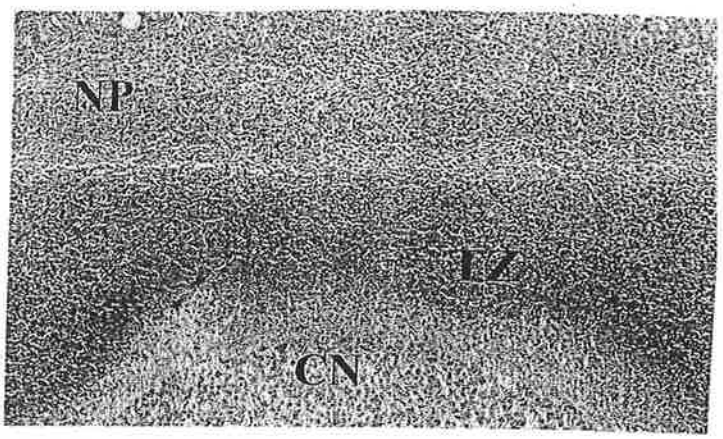

Fig. 4. Typical histological appearances (pancreatic ablation). C, coagulative necrosis; NP, normal pancreas; TZ, transition zone.

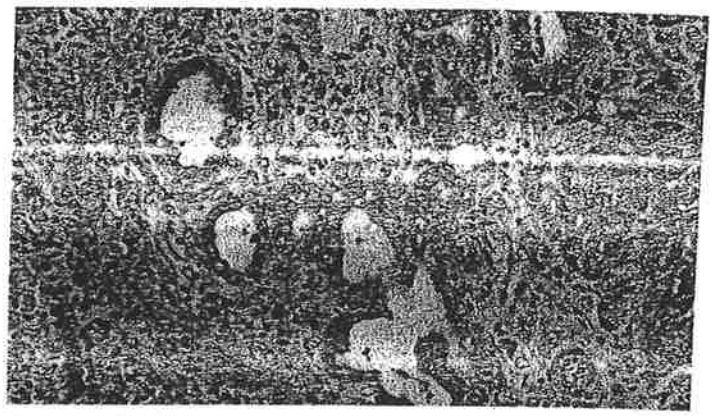

Fig. 5. Typical histological appearances adjacent to the PD (control).

Histological appearances

Treatment group

All of the electrolytic lesions were of similar appearance (Fig. 4). There was a central zone of coagulative necrosis in which there was no residual viable tissue. There was a transition zone surrounding this area of coagulative necrosis. This area was less than 1 mm wide and was infiltrated by neutrophils and lymphocytes. Cell viability in this area was variable.

Outside this transition zone, the pancreatic parenchyma was normal, apart from mild interlobar inflammation that radiated out a variable distance from the lesion. Bubbles of gas were also seen in these fibrous septa. There were no abscesses.

Control group

There was no evidence of parenchymal necrosis or inflammation in any of the control specimens (Fig. 5). However, in one pancreas there was a necrotic area surrounding the pancreatic duct (2.5-mm diameter) with associated local inflammatory changes.

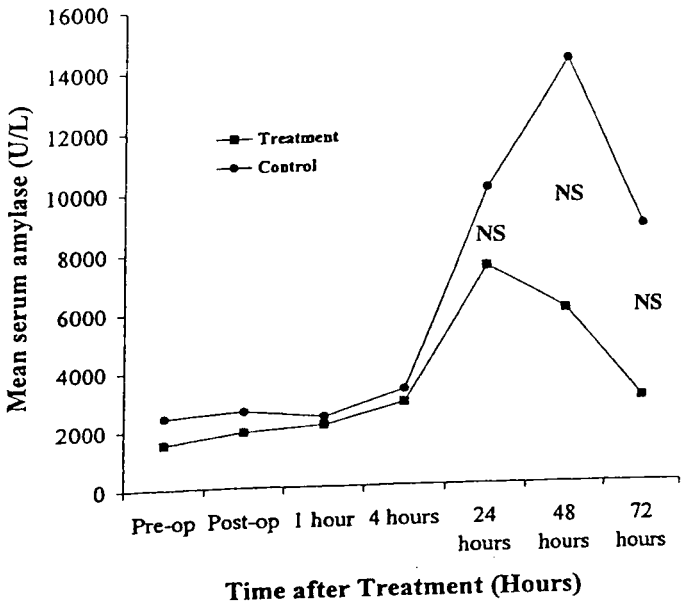

Fig. 6. Mean change in serum amylase after electrolysis. NS, not significant.

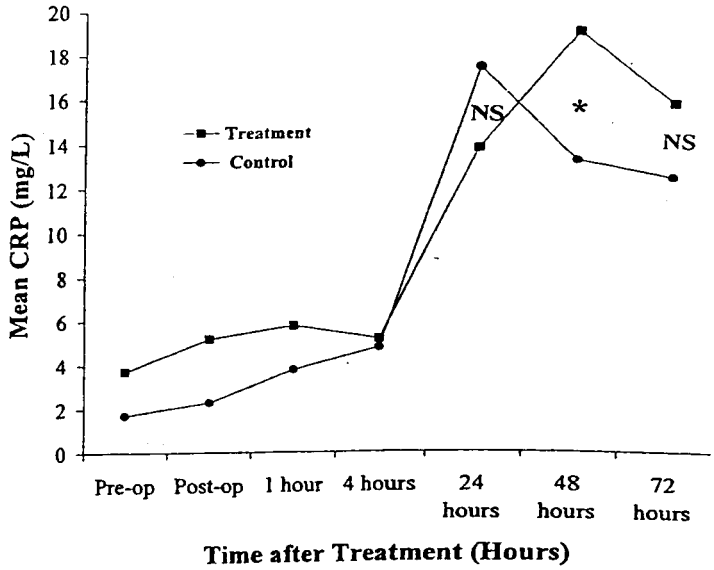

Fig. 7. Mean change in CRP after electrolysis. NS, not significant, $^{*}p < 0.05$.

Biochemistry

Amylase

All of the control and treated animals developed postoperative hyperamylasemia (Fig. 6). The mean serum amylase reached a peak concentration after 48 h in the control group and after 24 h in the treatment group. However, in both groups the serum amylase was returning toward normal at 72 h. There was no significant difference between the two groups with regard to the elevation in serum amylase after operation.

C-reactive protein

The CRP was elevated in all the animals after operation (Fig. 7). The mean serum CRP reached a peak concentration after 24 h in the control group and after 48 h in the treatment group. The mean serum CRP was significantly ($p < 0.05$) higher after 48 h in the treatment group. However, in both groups the serum CRP was returning toward normal at 72 h.

Glucose, calcium, urea, and electrolytes

There was no significant change in serum levels of glucose, calcium, urea, and electrolytes after operation in either group.

Discussion

The optimal management of patients with inoperable pancreatic cancer remains controversial. Despite their relative merits, the current therapeutic options of either endoscopic stenting or surgical bypass are suboptimal. Debulking the tumor from within the gland using the novel technique of electrolytic ablation is an attractive option. This method potentially offers the excellent palliation associated with surgical bypass without the need for a major surgical procedure or the stent-related complications of ERCP [2].

Electrolytic ablation has been extensively investigated for use in patients with unresectable liver tumors [18, 26–28]. Unlike other forms of local ablation, electrolysis is a nonthermal technique [1] that causes cell death by a more subtle chemical action. Platinum electrodes are polarized using a small direct electrical current. As a result, the intracellular pH changes and cytotoxic gases are released into the local environment, causing cell necrosis.

It has been shown that electrolytic ablation can be safely used in close proximity to large intrahepatic veins, with the vein wall remaining intact [25]. Conversely, thermal methods of ablation may cause a direct burn to large vessels. Indeed, cryotherapy has been shown to damage large veins due to cracking of the "ice-ball" during the freezing phase of the process [8, 17]. It is proposed that the ability of electrolysis to treat tumors directly adjacent to large veins may confer a benefit when compared to other forms of ablation for debulking tumors of the pancreas. This is of relevance because of tumors of the pancreas are usually situated in the head of the gland, intimately associated with the portal vein. Damage to the portal vein would be rapidly fatal.

The electrolytic "dose" chosen for this study was based on dose–response data from work in the liver [26]. However, in four of the six animals treated with electrolysis, the pancreatic capsule was breached by the lesion, which was larger than predicted. It is likely that this is due to relatively high concentrations of electrically active ions in the pancreatic parenchyma compared to the liver. Consequently, in future studies a lower dose should be used to avoid fistula formation. In the clinical setting, breaching of the pancreatic capsule would be far less likely because the electrode catheter would be inserted into the center of a bulky tumor rather than into a normal gland.

If electrolytic ablation is to become accepted as a palliative treatment, it is important that complications are minimal. In this study, the pancreatic duct both proximal and distal to the electrolytic lesion remained patent after treatment. This is vital, because cellular debris can drain effectively into the GI tract, thereby preventing fistula formation. It is proposed that a stent could also be inserted at the time of treatment to facilitate drainage.

Although all the animals developed transient hyperamylasemia after operation, none developed clinically, biochemically, or histologically significant pancreatitis, and all were well at the time of sacrifice. Interestingly, although not statistically significant, the three animals with the highest peak amylase level were all controls. This is likely a result of the fact that these animals were the first three to be operated on due to the randomization process. This was early in the operator's learning curve, and the time taken to cannulate the duct was prolonged in these animals.

The serum CRP was elevated in all animals after operation. This finding is consistent with the trauma associated with laparotomy. However, there was a significantly higher mean serum concentration in the treated animals 48 h after operation. It is proposed that this resulted from the additional effect of electrolytic necrosis. This effect was transient.

This experimental study confirms previous findings that pancreatic ablation using electrolysis is technically feasible and potentially safe for debulking inoperable pancreatic tumors. Importantly, there was no evidence of pancreatitis after treatment. This is the first study in which pancreatic ablation was achieved by accessing the pancreas from the GI tract. This not only has implications for minimizing complications, such as fistula formation, but also the treatment could potentially be given during ERCP, thereby avoiding a prolonged hospital stay.

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Conclusion

The contribution of this body of work to the science and practice of surgery is significant. At this stage, we are the foremost group in the world conducting this research, looking at its application in both hepatic and pancreatic organs. We have also commenced more recently the use of this technology in renal cell tumours. This work has been presented at a number of scientific meetings, both local, national and international, and has led to the commencement of collaborations now with not only the UK but also a group in Stockholm and a further group in Bordeaux. The potential place of this approach is well illustrated in a number of the review articles which are included in the body of this thesis.

Unfortunately the studies detailed have raised more questions than they answer. However they do demonstrate electrolytic tumour destruction is safe reproducible and able to destroy tumour in both animals and patients.

Satisfactory imaging of the process remains to be developed with magnetic resonance scanning likely to be the most promising. Better electrode systems and percutaneous technique remains to be developed. The role of electrolytic treatments in pancreatic and renal tumour remains to be proven. However this, as other ablative techniques, may offer a paradigm shift in our approach to "surgical" management of solid organ tumours replacing the need to surgically excise with adequate ablation. The attendant morbidity associated with major surgical procedures may be avoided in the future for many patients with suitable tumours.