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# Five-year survival in 309 patients with colorectal liver metastases treated with radiofrequency ablation

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**Abstract** There is little published long-term survival data for patients with colorectal liver metastases treated with radiofrequency ablation (RFA). We present a multivariate analysis of 5-year survival in 309 patients (198 male, aged 64 (24–92)) treated at 617 sessions. Our standard protocol used internally cooled electrodes introduced percutaneously under combined US and CT guidance/monitoring. The number and size of liver metastases, the presence and location of extrahepatic disease, primary resection, clinical, chemotherapy and follow-up data were recorded. Data analysis was performed using SPSS v.10. On multivariate analysis, significant survival factors were the presence of extrahepatic disease ($p<0.001$) and liver tumour volume ($p=0.001$). For 123 patients with five or less metastases of 5 cm or less maximum diameter and no extrahepatic disease median survival was 46 and 36 months from liver metastasis diagnosis and ablation, respectively; corresponding 3- and 5-year survival rates were 63%, 34% and 49%, 24%. Sixty-nine patients had three or less tumours of below 3.5 cm in diameter and their 5-year survival from ablation was 33%. There were 23/617(3.7%) local complications requiring intervention. Five-year survival of 24–33% post ablation in selected patients is superior to any published chemotherapy data and approaches the results of liver resection.

**Keywords** Radiofrequency ablation · Secondary liver tumours · Colorectal liver metastases · Thermal ablation

## Introduction

Colorectal cancer is the second most common cause of cancer death in developed countries and the third most common malignancy worldwide [1]. Fifty per cent of patients develop liver metastases yet only a minority, 10–15%, can undergo hepatic resection. Five-year survival following liver resection ranges between 31% and 58% in carefully selected patients [2–4]. The remainder may be offered chemotherapy and/or local tumour ablation. Chemotherapy regimens have improved significantly over recent years. In the 1990s 5-fluorouracil regimens were used but did not have a significant impact on survival. The first regimens to produce a significant improvement in survival were reported in 2000 when a median survival of 17.4 months was reported with irinotecan and 19.4 months with oxaliplatin [5, 6]. Sequential irinotecan and oxaliplatin produced a further small increment in survival. Combinations of chemotherapy with the latest antiangiogenic agents achieve median survival of less than 24 months [7, 8]. Radiofrequency ablation (RFA) is an effective technique for the local destruction of tumours. Initial analysis of the European Organisation for Research and Treatment of Cancer (EORTC)-sponsored chemotherapy plus local ablation versus chemotherapy alone in inoperable colorectal metastases (CLOCC) trial reports a significantly ($p<0.05$) improved progression-free survival for patients receiving RFA (Verbal communication, ASCO 2008). Currently RFA is indicated in patients whose tumours cannot be completely resected, most of whom

have multiple tumours with an unfavorable distribution for resection [9]. A common criticism of tumour ablation is the lack of published long-term survival rates. We present 5-year survival rates, in the largest reported series worldwide, of more than 300 patients with colorectal liver metastases treated with percutaneous RFA.

## Materials and methods

### Patient data

All patients gave written, informed consent. Data review was performed under institutional review board waiver. Data management complied with the requirements of the UK Data Protection Act (HIPAA equivalent). The study group comprised all patients with colorectal liver metastases treated with RFA since 1997. There were 309 patients, 111 female, 198 male, mean age 64 years (range 24–92). Data were collected prospectively and analysed at regular intervals.

### Acceptance criteria

All patients were deemed inoperable following multidisciplinary team review, either because the tumour number or distribution would have resulted in inadequate residual liver volume if resected or an inability to achieve margins because of tumour location adjacent to the vena cava and hepatic venous confluence, the presence of extrahepatic disease, or concomitant comorbidity.

Patients were accepted for RFA with five or fewer tumours of 5 cm or less in diameter, or as many as nine tumours but with a maximum diameter of 4 or 4.5 cm, or a solitary tumour of less than 7 cm in diameter. Extrahepatic disease was not a contraindication provided it was stable on treatment. These criteria were drawn from experience with laser ablation [10, 11]. The ablation technology evolved over the study period such that ablation of larger tumours was performed. Some patients progressed between referral for ablation and treatment; therefore, patients with more extensive disease were treated and in some cases the assessment by cross-sectional imaging underestimated the extent of disease found at the time of ablation. Therefore although the aim was to ablate those with limited disease, patients with more extensive disease were treated.

All patients underwent contrast-enhanced CT of the chest, abdomen and pelvis to assess the number and location of metastases. The CT technique varied with changes in CT technology over the study period. In the early part of the study CT data were acquired using a single slice CT system during the portal venous phase by using 2.5-mm collimation and 100–150 ml of IV contrast medium injected by pump at 5 ml/s. With the introduction of 4-row multidetector CT in 2000, the liver was routinely assessed with biphasic CT during the late arterial and portal venous phase and when 64-detector CT became available in 2005, 1-mm collimation became routine. Tumours were measured by maximum linear dimension on hard copy or, subsequently, with electronic calipers on the workstation/PACS. CT/PET was available from 2004 and was used in a few patients where there was doubt about the interpretation of the CT particularly if there was a question as to whether extrahepatic disease was present. The growth of liver lesions with the typical morphology of metastases in patients with a history of colorectal cancer was considered sufficient evidence for metastatic disease without the need for biopsy. Biopsy was performed if there were atypical imaging features, a history of two different primary cancers or a long interval between the primary resection and presentation with liver metastases.

### Radiofrequency ablation technique

The standard treatment protocol was a percutaneous approach with a combination of US and CT guidance and monitoring under general anaesthesia by using internally cooled electrodes powered by a 200-W generator (Covidien, Boulder, CO, USA). Single or triple cluster electrodes were used from 1997–2005. Tumours smaller than 3 cm were treated with single electrodes with a 3-cm active tip and tumours larger than 3 cm were treated with the triple cluster with a 2.5-cm active tip. The single electrode was preferred to the cluster electrode in small lesions as it is more versatile and there is less deformation of the hepatic parenchyma on insertion. Treatment was performed at maximum power and continued until impedance change reduced power deposition to less than 50 W or 6 min or less for the single electrode or 12 min or less for the triple cluster electrode whichever was the shorter. Impedance changes limit useful power deposition and it is more time efficient to resite the electrode and initiate treatment at full power than to leave the electrode in the same position with rapid changes in impedance preventing much power deposition. For all tumours larger than 1 cm in diameter multiple electrode positions were required to achieve overlapping ablations such that the whole tumour and a margin of normal-appearing liver were ablated. Multiple ablations were required as even for a 1-cm-diameter tumour a 3-cm ablation is required and that cannot be achieved with a single electrode placement even with perfect targeting. From 2005 a switching controller, which allowed sequential activation of up to three individual electrodes, became available. In the duty cycle each electrode is powered in turn for 30 s. Switching to the next electrode in sequence occurs in response to a change in impedance or at 30 s whichever is sooner. After 2005, tumours smaller than 2 cm continued to be treated with the single electrode, tumours of 2- to 4-cm diameter were treated with two sequentially activated electrodes and

tumours larger than 4 cm were treated with three electrodes. Dextrose isolation was adopted in 2001. This technique was developed to protect vulnerable structures from thermal injury. Where the tumour lies in close proximity to e.g. colon a space is created between the ablation zone and the bowel by instilling up to 2 l of 5% dextrose via a 19-G spinal needle or 5-Fr pigtail catheter under imaging guidance. Treatment was performed by one or other of the authors, with 12 and 18 years experience in tumour ablation, respectively. Major complications were recorded.

### Follow-up protocol

A CT scan was performed prior to discharge, which served as the baseline for comparison to future studies. Thereafter, patients were followed with CT scans at 3-month intervals. Successful ablation zones become well defined and of homogeneous attenuation and either progressively reduce in size or stabilize over time. New tumour was identified by enlargement of part or all of the ablation zone or by the development of intermediate enhancing soft tissue at the edge of the zone. When new but limited disease developed, further ablation was offered. For those who developed more extensive liver metastases or extrahepatic disease such that further ablation was not possible or not indicated, systemic chemotherapy was given whenever possible.

### Chemotherapy

The chemotherapy regimen evolved over the period of the study as new agents became available. In the early and mid 1990s standard chemotherapy regimens included 5-fluorouracil (5FU) and folinic acid. Irinotecan and oxaliplatin were introduced in the late 1990s and in the last 3 years monoclonal antibodies, cetuximab or bevacizumab have been available. The timing of chemotherapy relative to ablation varied. The response to chemotherapy varied with some progressing, others showing stable disease and some, particularly in the latter years of the study, showing a partial response. No patient had a complete response to chemotherapy.

### Analysis

Primary resection, diagnostic, chemotherapy and follow-up data were obtained from primary care physicians and oncologists. Dukes' stage was derived from resection data. In the latter years of the study, TNM staging had been adopted but in the early part of the study Dukes' stage was used; therefore, Dukes' stage has been adopted throughout. Where there were multiple concurrent primaries the Dukes' stage of the more advanced carcinoma was used. The site of the primary was characterized as located in the left colon, right colon or rectum, those with multiple colorectal primaries were excluded from this analysis. Patients who had liver metastases at initial presentation or who developed liver metastases within 6 months of the diagnosis of the primary tumours were classified as having synchronous metastases and those with a more than 6-month interval between the diagnosis of the primary and of the liver metastases as having metachronous metastases. For the year of treatment patients were classified into three groups: 1997–2000, 2001–2004 or 2005–2007. The chemotherapy regimens were grouped depending on whether the regimen included (a) cetuximab or bevacizumab, (b) contained oxaliplatin or irinotecan but not cetuximab or bevacizumab or (c) contained 5FU but not oxaliplatin, irinotecan, cetuximab or bevacizumab. Extrahepatic disease location was grouped into those with pulmonary metastases only and those with other types of extrahepatic disease with or without pulmonary metastases.

### Statistical methods

Kaplan–Meier plots of survival were performed using standard statistical analysis software SPSS v.10. Median, 3- and 5-year survival were calculated. Survival factors were compared using log rank analysis and $p<0.05$ was considered significant. Multivariate analysis was performed using Cox regression; hazard ratios and 95% confidence intervals are provided. The factors selected for multivariate analysis had a $p\leq0.2$ on univariate analysis (Dukes' stage, number and size of liver metastases, the presence of extrahepatic disease, type of chemotherapy and history of liver resection, type of extrahepatic disease). Type of extrahepatic disease was then excluded to avoid multicollinearity or overlap with "presence of extrahepatic disease".

### Patient data

The mean and median number of metastases was 4 and 3 (1–27) and the mean and median diameter of the largest metastasis was 3.7 cm and 3.5 cm (0.9–12); 115/309 (37%) patients had extrahepatic disease. Seventy-nine patients were treated between 1997 and 2000, 142 between 2001 and 2004 and 88 in 2005–2007. The total number of ablation treatment sessions was 617. The mean and median number of ablation treatment sessions was 2 (range 1–8). The location of the primary tumours within the colon or rectum was known in 285 cases; this was left colon in 118 (41%), right colon in 51 (18%), rectum in 95 (33%), multiple 12 (4%) or unspecified colonic in 9 (3%). Dukes' stage data were available in 215 cases, of which 6 were Dukes' stage A (3%), 54 (25%) B and the majority 155/215 (72%) C. The date of diagnosis of liver metastases relative

to the primary was known in 272 cases, of which 186 (68%) were either diagnosed synchronously or within 6 months of the primary and 86 (32%) developed metastases later. The median and mean interval between the diagnosis of liver metastases and ablation was 8 and 10.4 months (range 0–83). Complete chemotherapy data were available in 238 cases, of which 17 (7%) received no chemotherapy, 57 (24%) received 5-fluorouracil-based regimens, 142 (59%) received oxaliplatin or irinotecan, 22 (9%) received cetuximab or bevacizumab. Forty-eight of 309 patients (16%) had had a previous liver resection, 4 had had a previous lung resection.

Reasons for considering the patients inoperable were extrahepatic disease (115/309 (37%)), inadequate liver reserve either because of previous resection or the distribution of liver metastases or inability to achieve surgical margins (162/309 (52%)) and concomitant medical comorbidity (93/309 (30%)). Some patients could not undergo surgical resection for more than one reason.

## Results

### Complications

There was no procedure-related mortality. There were 29 (4.7%) major complications (SIR criteria i.e. requiring intervention or hospital stay beyond 72 h) in a total of 617

**Table 1** Univariate survival analysis

| Variable | From diagnosis of liver metastases | | | | From time of ablation | | | |
|---|---|---|---|---|---|---|---|---|
| | Median (months) | 3-year (%) | 5-year (%) | *p* | Median (months) | 3-year (%) | 5-year (%) | *p* |
| No. and size of liver metastases (*n*=309) | | | | | | | | |
| Five or less of ≤ 5 cm (*n*=192) | 39 | 58 | 26 | 0.000 | 28 | 40 | 18 | 0.000 |
| More than five and/or > 5 cm (*n*=117) | 25 | 29 | 5 | | 14 | 13 | 3 | |
| Extrahepatic disease (*n*=309) | | | | | | | | |
| Yes (*n*=115) | 25 | 30 | 6 | 0.000 | 14 | 10 | 2 | 0.000 |
| No (*n*=194) | 38 | 55 | 24 | | 28 | 39 | 17 | |
| Type of extrahepatic disease (*n*=105) | | | | | | | | |
| Pulmonary metastases (*n*=20) | 32 | 44 | 11 | 0.07 | 26 | 10 | 0 | |
| Other with or without pulmonary metastases (*n*=85) | 22 | 26 | 3 | | 12 | 11 | 0 | 0.016 |
| Dukes' stage (*n*=209) | | | | | | | | |
| B (*n*=54) | 39 | 60 | 28 | 0.05 | 29 | 35 | 24 | 0.13 |
| C (*n*=155) | 33 | 47 | 14 | | 22 | 34 | 8 | |
| Type of chemotherapy (238) | | | | | | | | |
| None (17) | 36 | 51 | 0 | 0.027 | 31 | 29 | 0 | 0.20 |
| 5 FU (57) | 26 | 32 | 6 | | 18 | 19 | 0 | |
| Oxaliplatin and/or irinotecan (142) | 32 | 44 | 17 | | 18 | 27 | 8 | |
| Cetuximab or Avastin (22) | 55 | 87 | 31 | | 38 | 59 | 15 | |
| Prior liver resection (*n*=309) | | | | | | | | |
| Yes (*n*=48) | 55 | 72 | 49 | 0.000 | 37 | 52 | 35 | 0.002 |
| No (*n*=261) | 31 | 39 | 11 | | 21 | 25 | 9 | |
| Year of treatment (*n*=309) | | | | | | | | |
| 1997–2000 (*n*=79) | 40 | 38 | 14 | 0.44 | 22 | 23 | 9 | 0.48 |
| 2001–2004 (*n*=142) | 35 | 50 | 19 | | 24 | 36 | 14 | |
| 2005–2007 (*n*=88) | 34 | 45 | 21 | | 20 | | | |
| Site of primary lesion (*n*=>264) | | | | | | | | |
| Rectum (*n*=95) | 32 | 42 | 19 | 0.76 | 21 | 26 | 14 | 0.76 |
| Left colon (n=118) | 34 | 40 | 17 | | 26 | 31 | 11 | |
| Right colon (*n*=51) | 39 | 53 | 11 | | 21 | 43 | 13 | |
| Timing of liver metastases relative to the primary diagnosis (*n*=272) | | | | | | | | |
| ≤ 6 months (*n*=186) | 33 | 45 | 23 | 0.2 | 22 | 33 | 14 | 0.84 |
| > 6 months (*n*=86) | 31 | 39 | 10 | | 25 | 28 | 13 | |

treatment sessions [12]. These were five systemic complications, one anaesthetic complication and 23 (3.7%) local complications. Of the local complications there was one pneumothorax that required drainage. There were four visceral (two colonic, and two small bowel) thermal injuries which resulted in perforation and required intervention. There were six abscesses all of which responded to antibiotics with or without drainage. Four patients developed jaundice, two secondary to bile duct injury, which were successfully palliated with biliary stents, and two due to inadequate liver reserve in whom the jaundice resolved spontaneously without intervention. There were seven haemorrhagic complications that required transfusion, including one secondary to a pseudoaneurysm. Another patient developed an asymptomatic pseudoaneurysm. Both pseudoaneurysms were treated with percutaneous injection of fibrin tissue glue. Of the haemorrhagic complications two were right-sided haemothoraces which required drainage.

### Survival from the diagnosis of liver metastases

On univariate analysis the size and number of metastases, the presence of extrahepatic disease, type of chemotherapy and a history of liver resection had a significant impact on survival (Table 1). The type of extrahepatic disease (i.e. patients with pulmonary metastases but no other evidence of extrahepatic disease did better) ($p=0.07$) and the Dukes' stage ($p=0.05$) approached significance.

On multivariate analysis the same factors remained significant (Table 2). The presence of extrahepatic disease was the most important factor, hazard ratio 2.7 (95% confidence intervals 1.8–4.1) (Fig. 1). The number and size of liver metastases was the second most important factor. On multivariate analysis those with more than five tumours or a maximum diameter of greater than 5 cm had a hazard ratio of 1.9 (1.3–2.9). Those with no extrahepatic disease and fewer, smaller metastases had the best survival. One hundred and twenty three patients with no more than five tumours of maximum diameter 5 cm or less and no extrahepatic disease had a 5-year survival of 34%. Sixty-nine patients had three tumours or less with a maximum diameter below 3.5 cm and their 5-year survival was better at 40% (Fig. 2). These differences were significant ($p=0.006$).

The timing of the diagnosis of liver metastases relative to the diagnosis of the primary had no impact on survival, nor did the location of the primary. There was a trend towards better results for patients treated in the last few years of the study but this did not reach significance. There was an incremental improvement in survival with the introduction of each new chemotherapy regimen i.e. patients who received oxaliplatin or irinotecan had a better survival than those who received 5FU alone. Those who received cetuximab or bevacizumab had a further improvement in survival. The improvement in survival with the different chemotherapy regimens only achieved significance with the latest agents, cetuximab or bevacizumab.

### Survival from ablation

On univariate analysis liver tumour size and number, the presence of extrahepatic disease, type of extrahepatic disease and prior liver resection were significant (Table 1). On multivariate analysis only liver tumour size and number and extrahepatic disease were significant (Table 2). Those with a history of liver resection had fewer, smaller metastases and therefore prior resection ceased to impact survival once liver tumour load was taken into account. Chemotherapy did not impact survival from the time of ablation. One hundred and twenty three patients with no more than five tumours of maximum diameter 5 cm or less and no extrahepatic disease had a 5-year survival of 24%. Sixty-nine patients had three tumours or less with a maximum diameter of less than 3.5 cm and their 5-year survival was 33%.

## Discussion

The earliest report of survival and thermal ablation described 69 patients treated in the 1990s with bare-tip

**Table 2** Results of multivariate analysis

| Variable | From diagnosis of liver metastases | | From time of ablation | |
|---|---|---|---|---|
| | *p* | Hazard ratio (95% confidence intervals) | *p* | Hazard ratio (95% confidence intervals) |
| No. and size of liver metastases (five or less of ≤ 5 cm vs. more than five or >5 cm) | 0.002 | 1.8 (1.2–2.8) | 0.001 | 1.9 (1.3–2.9) |
| Extrahepatic disease | 0.000 | 2.4 (1.6–3.7) | 0.000 | 2.7 (1.8–4.1) |
| Dukes' stage | 0.17 | 1.4 (0.9–2.1) | 0.37 | 1.2 (0.8–1.9) |
| Type of chemotherapy | 0.037 | 0.7 (0.6–1.0) | 0.53 | 0.9 (0.7–1.2) |
| Prior liver resection | 0.019 | 0.5 (0.3–0.9) | 0.55 | 0.8 (0.5–1.5) |

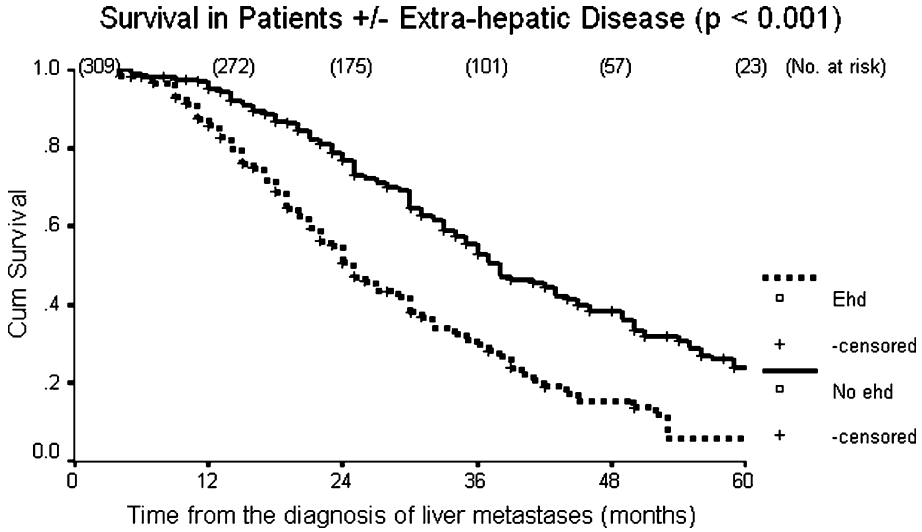


**Fig. 1** Kaplan–Meier survival plot: a comparison of those with or without extrahepatic disease (*Ehd*)

laser interstitial thermal coagulation [8]. Overall median survival was 27 months and for those with less than four tumours of 5 cm or less in diameter the median survival was 33 months. Previous reports of survival following percutaneous RFA of colorectal liver metastases have shown a 3-year survival of 46–68% and 5-year survival of 26–44% [13–15]. Variations in outcome can partly be explained by patient selection. Those with fewer numbers of smaller liver metastases have better results. Solbiati et al. reported an overall median survival of 36 months in 117 patients but for those with metastases below 2.5 cm in diameter the median increased to 42 months [14]. In our cohort those patients with five or less metastases of 5 cm or less in diameter had a 5-year survival of 34% from the diagnosis of liver metastases but for those with no more than three tumours below 3.5 cm in diameter the 5-year survival from the diagnosis of liver metastases increased to 40%. Selection bias dominates the results for surgical resection and other ablative techniques. In order to counter this, it is necessary to stratify the patient population as has been done extensively in the surgical literature. Technical factors also influence outcome. Results of open or laparoscopic RFA have been more variable with reported 3-year survival of 20–57% [16, 17]. The largest cohort published to date included 234 patients treated laparoscopically, 20% of whom had extrahepatic disease, and the overall 5-year survival was 18.4% [18]. In conflict with our findings, and the findings of Machi et al. [19], there was no difference in survival for those with or without extrahepatic disease but the overall survival was not good compared with previous published reports. Historically extrahepatic disease was considered an absolute contraindication to liver resection but more recent papers have revised this whilst still recognizing that the presence of extrahepatic disease does impact survival [20]. We found that both the presence and the type of extrahepatic disease impacted

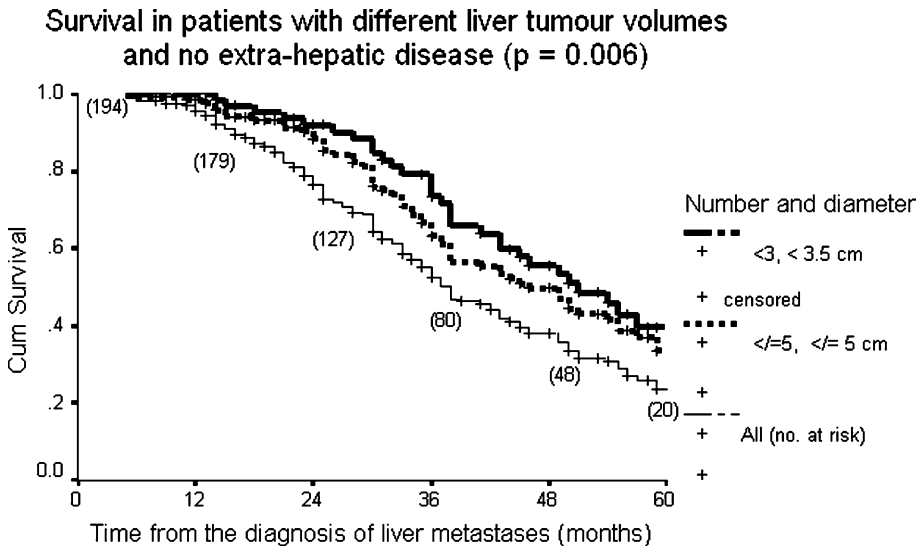


**Fig. 2** Kaplan–Meier survival plot comparing different liver tumour loads in patients without extrahepatic disease. There are three groups: all those with no extrahepatic disease ($n$=194), those with five or fewer tumours of 5 cm or less in diameter ($n$=123) and a third group of those with three or fewer tumours with a maximum diameter of less than 3.5 cm ($n$=69)

outcome. Patients with lung metastases as the only site of extrahepatic disease fared better than those with other types of extrahepatic disease.

The significance of Dukes' stage, the location of the primary tumours and the interval between the primary resection and the presentation of liver metastases have variously been reported as both significant and not significant in the liver resection literature [21–23]. Patients with Dukes' stage B had a better survival and this was nearly significant ($p=0.05$) on univariate analysis but not on multivariate analysis. The timing of the detection of liver metastases relative to the primary lesion did not impact survival. Historically, late presentation was associated with slow growth and a better outcome. Now improved imaging techniques and regular surveillance programmes allow earlier detection of smaller metastases. The location of the primary cancer can impact prognosis: right-sided and rectal carcinomas tend to present later and to carry a worse prognosis, but in this cohort the proportion of left-sided cancers which were Dukes' stage C was greater than for the rectal and right-sided cancers. There was a trend towards better results over the 10-year study period but this did not reach significance.

We have reported survival both from the time of diagnosis of liver metastases. Without this, there is a dichotomy between the oncological literature which uses time from diagnosis and the surgical literature which uses survival from time of resection. Randomised controlled trials have proven difficult to organize as patients in clinical practice will often receive all available treatments with overlap between the different groups. Patients who do remain within one group or another often have very different characteristics. Crossover between one treatment arm and the other is also very common. For instance RFA may be used in conjunction with chemotherapy to treat recurrence after resection. In our cohort there was an incremental improvement in survival from the diagnosis of liver metastases with successive chemotherapy regimens but only the most recent innovation with biological agents (cetuximab and bevacizumab) produced a significant improvement and there was no significant impact on survival from the time of ablation. The interaction between chemotherapy and ablation is an area that needs further study. Animal experiments have shown significant synergistic effects with RFA and doxorubicin and paclitaxel [24]. Anecdotally the best results have been seen in patients who have undergone ablation of all visible tumour immediately followed by chemotherapy.

A history of liver resection showed better survival both from diagnosis, as would be expected, and from ablation. Post liver resection patients had significantly lower tumour load than nonresection patients. Once tumour load was taken into consideration on multivariate analysis, a history of resection ceased to be significant.

The complication profile and rate are in line with previous reports. Since 2001 we have used dextrose isolation to prevent collateral injury to adjacent structures and have had no further incidences of visceral injury. Limitations of this study include the heterogeneous population and the evolution of imaging, ablation technology and chemotherapy over a 10-year study period. There has been continual technical change in both surgical practice and RFA. New chemotherapy regimens are introduced into clinical practice almost on an annual basis.

In conclusion, this is the first multivariate analysis in a large group of patients to show that the dominant factors influencing survival post RFA are the liver tumour volume and the absence of extrahepatic disease. Our 5-year survival of 24–33% post ablation in selected patients is superior to any published chemotherapy data and approaches the results of liver resection.

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