KEYNOTE LECTURE
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Tumour ablation: current role in the liver, kidney, lung and bone

Alice Gillams
Imaging Department, University College Hospital, 235 Euston Road, London, NW1 2BU, UK

Corresponding address: A. Gillams, Imaging Department, Podium 2, University College Hospital, 235 Euston Road, London, NW1 2BU, UK.
Email: a.gillams@medphys.ucl.ac.uk

Abstract
The last few years have seen a rapid expansion in the use and availability of ablation techniques with hundreds of papers published. Radiofrequency remains the front-runner in terms of cost, ease of set-up, versatility and flexibility but other techniques are catching up. Ablation with cryotherapy and microwave, which were previously only available at open laparotomy due to the large size of the probes, are now readily performed percutaneously, with a predictable reduction in morbidity. Ablation is now accepted as the first line of treatment in patients with limited volume hepatocellular carcinoma who are not candidates for transplantation. There is continuing debate in most other areas but the evidence is increasing for an important role in liver metastases, renal carcinoma, inoperable lung tumours and some bone tumours.

Keywords: Tumour ablation; radiofrequency; microwave; cryotherapy; liver tumours; lung tumours; renal cell carcinoma

Technical developments
The last few years have seen a rapid expansion in the use and availability of ablation techniques with hundreds of papers published. Radiofrequency remains the front-runner in terms of cost, ease of set-up, versatility and flexibility but other techniques are catching up. Ablation with cryotherapy and microwave, which were previously only available at open laparotomy due to the large size of the probes, are now readily performed percutaneously, with a predictable reduction in morbidity. Cryotherapy offers the opportunity to monitor the ice-ball with ultrasound (US), computed tomography (CT) or magnetic resonance imaging (MRI). The edge of the ice-ball represents the 0°C isotherm. Cell death occurs between −20°C and −30°C and this isotherm lies approximately 5 mm inside the ice-ball. More powerful microwave generators have been developed and active research into better impedance matching with specific tissues should result in improved performance. Microwave has several theoretical advantages, it is less vulnerable to the cooling effects of flowing blood in nearby vessels, can be designed to share a spherical geometry with most tumours and has a more predictable dose–response curve. Simultaneous use of multiple energy sources (probes/electrodes) is now available in all the different technologies. Improvements in guidance include the development of real-time co-registration techniques, most commonly CT and US. US contrast is routinely used in the intra-procedural assessment of ablation efficacy in the liver. Collateral injury has been reduced by the widespread adoption of dextrose isolation. Five per cent dextrose is instilled into the area adjacent to the ablation to displace vulnerable structures, usually bowel, away from the ablation zone. A displacement of as little as 1 cm is enough to protect the bowel.

Specific applications
Ablation is now accepted as the first line of treatment in patients with limited volume hepatocellular carcinoma (HCC) who are not candidates for transplantation. There is continuing debate in most other areas but the
Evidence is increasing for an important role in liver metastases, renal carcinoma, inoperable lung tumours and some bone tumours.

**Colorectal liver metastases**

Limited colorectal liver metastases are the most commonly treated metastatic lesion. Surgical resection is the accepted first-line treatment for patients with resectable disease. Five-year survival figures range from 25 to 39\%\cite{10}. Traditionally, most patients (80–90\%) are not candidates for surgical resection due to the extent or distribution of disease, or concurrent medical disability. There are now several chemotherapy regimes that impact survival. Irinotecan was the first agent reported to significantly improve survival to a median 17.4 months and 1-year survival of 69\%. Oxaliplatin and the newer biological agents (Cetuximab and Avastin) also significantly increase survival. The sequential use of multiple chemotherapy regimes, if tolerated, can allow survival <24 months. Neo-adjuvant chemotherapy can be used to down-size inoperable/un-ablatable disease to the point where ablation or resection can be performed.

Between 1993 and 1995 we performed laser thermal ablation and reported a median survival of 27 months\cite{11}. We have previously published our results in 167 patients treated with radiofrequency ablation (RFA)\cite{12}, and recently analysed survival in a cohort of 309 patients with inoperable colorectal liver metastases treated with RFA. The most important factors in survival were the absence of extra-hepatic disease and the total liver tumour volume. For 123 patients with \( \leq 5 \) metastases, \( \leq 5 \) cm with no extra-hepatic disease, median survival was 46 months from diagnosis and 36 months from ablation. Three- and 5-year survival were 63\%, 34\% and 49\%, 24\%, respectively. Sixty-nine patients had 3 tumours or less maximum diameter <3.5 cm and their 5-year survival was better at 40\%. For those patients who only have small solitary tumours <4 cm the survival is even better, >80\% at 3 years\cite{13}. Not only the presence of extra-hepatic disease but the type impacted survival. Patients who had small, CT detected pulmonary metastases as their only manifestation of extra-hepatic disease fared better than those with other sites of extra-hepatic disease. Our figures compare reasonably well with surgical resection data. Other thermal ablation groups have reported very similar survival results\cite{5-7}.

**Patient selection**

Our current recommendation is to accept patients with five metastases or less, each with a maximum diameter not exceeding 5 cm, more numerous tumours, \( \leq 9 \) as long as the largest is <4 cm, and larger tumours <7 cm if they are solitary. Where the distribution of disease is not amenable to surgery, the use of a combination of RFA and resection can be considered. For those with concurrent medical morbidity, RFA is a much less invasive alternative than surgery and has lower complication rates. Other applications for RFA include patients with limited liver disease who have insufficient residual liver to allow resection, usually post hepatectomy patients with new metastases in the residual lobe. RFA, like surgery, is most effective in small tumours. Retrospective comparisons of RFA and repeat hepatic resection show similar survival benefits. At our institution, a retrospective comparison of RFA and surgery in solitary metastases of any size showed a similar survival rate. RFA can be performed either concurrently or sequentially to chemotherapy, and can be repeated if new lesions or recurrence occurs. If the patient develops more extensive disease, such that RFA can no longer be performed, then chemotherapy should be considered.

**Approach: percutaneous, laparoscopic or open?**

RFA can be performed using image guidance and a percutaneous approach, laparoscopic guidance, or at open laparotomy. At open laparotomy, RFA can be combined with liver resection, i.e. resection of one area of the liver and ablation of another. If a patient is undergoing laparotomy for some other surgical procedure then it is reasonable to perform RFA at the same time. With this exception it is difficult to justify the added morbidity, invasiveness and expense of a laparotomy compared to a percutaneous procedure. The laparoscopic approach has been used when the tumour is adherent to structures that would be damaged by thermal ablation, e.g. tumour adherent to stomach, colon or duodenum. Some centres prefer the laparoscopic approach where there is poor tumour visualisation transcutaneously. Initial claims that intra-operative RFA is more efficacious than percutaneous RFA have not been reflected in survival results.

In fact, currently percutaneous RFA enjoys better survival results than intra-operative RFA. This may partly be explained by the ease of repetition of percutaneous RFA compared to intra-operative RFA and also by patient selection. RFA will most commonly be performed in the radiology department, but there is a subgroup of patients who will benefit from open or laparoscopic RFA.

**Neuroendocrine**

The treatment options for these patients are limited. Few patients are eligible for surgery and the alternatives produce symptomatic improvement but have less impact on tumour load. Aggressive cyto-reduction followed by octreotide analogues can be the best way to achieve prolonged symptom control. Radiofrequency can be used to reduce hormone secretion and/or to reduce tumour load. Siperstein et al. initially reported on laparoscopic RFA in 15 patients. Our experience in 17 patients showed benefit in 11, local control of tumour volume in
seven and relief or reduction in hormone-related symp-
toms in four of six with secreting tumours. Control of
tumour load should translate into improved survival
but this is harder to prove. Median survival of 5.5 years
from the diagnosis of liver metastases and 3.9 years from
ablation has been reported in a series of 63 patients with
various neuroendocrine primaries treated with laparo-
scopic RFA[8].

Non-colorectal, non-neuroendocrine including breast

Isolated liver metastases are an uncommon occurrence in
breast cancer. Breast cancer patients with liver meta-
stases are a heterogeneous population and the tumour
biology is unpredictable. Some surgeons will perform
hepatic resection for limited liver metastases, others
are more reluctant. Nevertheless, a 22% 5-year survival
post-resection has been reported. Radiofrequency has
also been used in small cohorts of patients. Livraghi
reported on 24 patients of whom 10 were free of disease
at a mean follow-up of 10 months[5]. A more common
clinical scenario is liver metastasis in the presence of
extra-hepatic disease. Current chemotherapeutic regimes
are less effective in controlling liver disease than extra-
hepatic disease. We achieved a 30-month survival of
41.6% in 19 patients, 11 of whom had extra-hepatic dis-
ease. Sofocleous performed ablation in 12 patients, 10 of
whom had extra-hepatic disease and achieved a median
progression free survival of 13 months. The largest group
treated to date included 232 patients, 72 (31%) of whom
had bone metastases, who underwent laser ablation in
conjunction with chemotherapy[9]. The mean survival
was 4.8 years for patients with no extra-hepatic disease
and 4.3 years for those with bone metastases; this differ-
ence was not significant. There is limited experience of
RF in other non-colorectal, non-neuroendocrine metasta-
ses, but good surgical results have been reported when
there has been an interval of more than 2 years between
the primary and the development of detectable metastatic
disease. Therefore, RF could be considered in these patients
if they are not candidates for surgery.

Hepatocellular carcinoma

Unlike liver metastases, local ablative therapy is well
established in HCC. Historically, ablation was performed
using pure ethanol. Trials of percutaneous ethanol
injection (PEI) and liver resection suggest a comparable
survival. In one trial, Childs Pugh Class A patients had a
3-year survival of 71% following PEI compared to 79%
following surgery, and Childs Pugh Class B patients had
a 3-year survival of 41% and 40%, respectively. Several
randomised, prospective comparisons of PEI and RFA
in patients with small tumours have shown that RFA is
superior to PEI as it has lower local recurrence rates, less
operator variability, longer disease-free survival and a
better overall increase in survival. There are still some
indications for PEI (e.g. in patients with exophytic
tumours) and PEI is very cost competitive. Microwave
therapy has been shown to be effective in small HCC.
Encapsulated HCC is generally easier to destroy than
metastases as the heat is contained and amplified
within the lesion. Several centres use laser effectively
in the treatment of HCC and, to date, there has been
no comparison of laser and RF in HCC. Current recom-
endations for RF in HCC are Childs Pugh Class A or B
cirrhosis and no more than three lesions, no larger than
3 cm or a single tumour <5 cm in diameter. Long-term
results for patients treated with RFA from several groups
in Europe and Asia confirm the efficacy of RFA. Three-
year survival rates for Childs A patients treated with
RFA vary between 71 and 87%. These data compare
well with 3-year survival rates of 76–86% for resection.
Five-year survival for RFA is 48–64%, which is not
dissimilar to that after resection 44–59%[10–12].

Screening programmes for the detection of early HCC
in patients with hepatitis C or B are not widespread
and, therefore, many patients present with large tumours.
Although the survival advantage of transarterial che-
moembolisation (TACE) remains controversial, the com-
bination of selective TACE and thermal ablation has
been explored with some success in this cohort.

Tumours of the kidney

Nephron-sparing surgery presents a challenge to the
surgeon. Yet, there is increasing evidence that even mod-
erate degrees of renal failure can significantly impact sur-
vival following cardiovascular events. This will increase
the focus of all physicians on the need to preserve renal
function wherever and whenever possible. Local ablative
techniques are the optimal nephron sparing treatment
for small renal tumours. One study found that 95.2%
of patients had a glomerular filtration rate (GFR)
>60 ml/min per 1.73 m 2 at 3 years post RFA compared
with 70.7% post partial nephrectomy and only 39.9% post
radical nephrectomy[13]. Therefore patients with a soli-
tary kidney and others with borderline renal function will
increasingly be treated with ablation. Both tumour size
and location are important predictors of outcome post
ablation. Renal tumours up to 3.5 cm in diameter can be
destroyed in situ by laser, RF or cryotherapy with virtu-
ally no damage to the surrounding normal renal tissue.
Some authors advocate cryotherapy for larger renal
tumours <5 cm in diameter. Exophytic tumours are
more readily ablated than central tumours. Multiple
renal tumours are not rare and can be difficult to resect
without complications but complications are rare after
ablation, particularly if a percutaneous approach is
used. Haemorrhage is the most common, bowel injury
can be prevented by dextrose isolation but it remains
necessary to maintain a distance of >1cm from the pro-
ximal ureter as ablation can result in ureteral stricturing.
Several series have now been published including one retrospective comparison with partial nephrectomy which showed comparable oncologic efficacy albeit with a shorter mean follow-up in the radiofrequency group (30 months versus 47 months)\cite{14}. An apparently promising meta-analysis was heavily skewed away from recent innovations by the inclusion of early technology, failure to analyse by tumour size and location and the stipulation that success after a single procedure was the main endpoint\cite{15}. Percutaneous ablative techniques are relatively easy to repeat compared with either surgery or laparoscopic cryotherapy. The question as to whether cryotherapy or radiofrequency is better is yet to be resolved and would be better addressed with mature technology and in a specific tumour cohort e.g. <3.5 cm non-central tumours.

**Lung tumours**

This is predicted to be the single largest growth area in ablation over the next few years. Laser, radiofrequency, cryotherapy and microwave have all been used. Currently the most widely used technique is radiofrequency. Good results can be achieved in small, peripheral tumours. Both inoperable primary and limited numbers of metastatic tumours have been treated. Computed tomography fluoroscopy facilitates electrode placement as small, scirrhouss lung lesions can be difficult to penetrate with a large calibre needle. The complication profile is well described. Pneumothorax occurs in about 40%, a similar incidence to that seen with trucut biopsy, but only a small percentage (10–15%) require drainage. The likelihood of a pneumothorax increases with the length of aerated lung that is traversed by the electrode and is more common when treating multiple tumours\cite{16}. The second most common complication is pleural effusion. Other complications include infection, haemorrhage and bronchopleural fistulae.

During treatment a penumbra of ground glass opacification develops around the tumour representing the ablation zone and a surrounding inflammatory reaction. Histological studies have shown that the zone of cell death lies 2–4 mm inside the outer margin of the ground glass shadowing. Over time the ablation zone becomes increasingly dense and then reduces in size. At 12 months, up to 33% of successfully treated small lesions will have shrunk to a linear scar. Recurrence is identified by enlargement of the ablation zone, or a change in the shape of the zone indicating enlargement in one area or the development of focal nodular enhancement. Tumours <3.0 cm can usually be ablated at a single session, larger tumours, 3.0–5.0 cm, may require more than one ablation or other additional therapy. Multivariate analysis has shown size to be the dominant feature determining complete ablation, but contact with >3 mm blood vessels or bronchi also increases the chance of recurrence\cite{17}. Current indications include patients with small volume, but inoperable metastases and early primary lung cancer in medically inoperable patients. Early clinical studies report 3- and 5-year survival of between 46 and 57% in patients with colorectal metastases\cite{18,19}. Combinations of radiotherapy and RFA have been used to good effect in primary lung cancer in inoperable patients\cite{20}.

**Bone tumours**

One of the first accepted indications for ablation was the minimally invasive treatment of benign osteoid osteomas. Malignant primary bone tumours will be treated by chemotherapy, radiotherapy and surgery. However, if aggressive therapy is delivered at an early stage, recurrence can be very difficult to treat. Treatment by RFA may be curative, but is more likely to form part of a palliative treatment regimen. CT or MR are the usual guidance methods. Radiofrequency ablation and cryoablation have been advocated in the symptomatic palliation of bone metastases following radiotherapy. Initial results suggest that ablation can produce significant reductions in pain levels and analgesic requirements. Only limited numbers of metastases can be treated\cite{21}. It is important to select patients with a clearly defined and understood dominant site of bone pain. Some authors promote the combination of ablation and cementoplasty, others argue that cementoplasty alone would be adequate. A trial to establish the relative merits of the two techniques has been suggested.

**Conclusion**

The last few years have seen a sharp increase in our understanding of ablation, maturation of the technology, an improvement in the safety profile, ablation efficacy and monitoring techniques and the publication of results in larger patient cohorts. Ablation will soon be sufficiently established to allow trials comparing ablation with conventional therapies in specific patient groups.

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