Interventional Technologies for Tissue Volume Reduction: A primer

Jennifer Burr, David Hay, Susanne Ludgate

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Produced by: Jennifer Burr 1, David Hay 2, Susanne Ludgate 3

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Organisations:
1. On behalf of the Review Body for Interventional Procedures Programme, the Health Services Research Unit, University of Aberdeen and Health Services Research, University of Sheffield
2. Consultant Surgeon, Glan Clwyd Hospital, Bodelwyddan, Denbigh. LL18 5UJ
3. Medicines and Healthcare Products Regulatory Agency

Correspondence to: Jennifer Burr
Health Services Research Unit
University of Aberdeen
Polwarth Building
Foresterhill
Aberdeen AB25 2ZD
Tel: (01224) 559715
Fax: (01224) 663087; Email: j.m.burr@abdn.ac.uk

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# TABLE OF CONTENTS

1. INTRODUCTION 3

2. THERMAL ABLATION 3
   2.1 Methods of Thermal Ablation 4
      2.1.1 Electrosurgery 4
         2.1.1.1 Diathermy 4
         2.1.1.2 Radiofrequency ablation 4
         2.1.1.3 Coblation 6
         2.1.1.4 Microwave ablation 6
      2.1.2 Ultrasound 6
         2.1.2.1 Direct ultrasound 6
         2.1.2.2 High Intensity Focused Ultrasound 6
      2.1.3 Photocoagulation 7
      2.1.4 Photodynamic therapy 9
   2.2 Efficacy of Thermal Ablation 9
   2.3 Safety of Thermal Ablation 9

3. COLD ABLATION 9
   3.1 Cryoablation 9

4 REFERENCES 10

APPENDIX The tissue / technology Matrix
INTERVENTIONAL TECHNOLOGIES FOR TISSUE VOLUME REDUCTION

1 INTRODUCTION

This review describes the physical properties, indications for use and safety concerns of ablative technologies delivered to organs via an endoscope or interstitially (directly into the tissue) for the treatment of solid tumours (benign and malignant) and tissue hyperplasia. It will not focus on ablative technologies used for surface treatments, e.g. in ophthalmology and dermatology or for the treatment of vascular lesions but will mention the alternative uses of the ablative devices if relevant.

2 THERMAL ABLATION

Irreversible cell injury occurs when cells are heated to 46 °C for 60 minutes. With increasing temperatures the time necessary to induce cell death is shortened and at 60-100 °C cell death is immediate and irreversible. Coagulation necrosis denotes irreversible thermal damage to cells. Temperatures greater than 105 °C result in tissue boiling, vaporisation and carbonisation, which may retard optimal ablation.

Table 1 Temperature and tissue effects

<table>
<thead>
<tr>
<th>Temperature °C</th>
<th>34-44</th>
<th>44-50</th>
<th>50-50</th>
<th>80-100</th>
<th>100-200</th>
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<td>Necrosis</td>
<td>Sloughing</td>
<td>Sloughing</td>
<td>Ulceration</td>
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<td>Mechanism</td>
<td>Vasodilatation and Inflammation</td>
<td>Disruption of cell Metabolism</td>
<td>Collagen denaturation</td>
<td>Desiccation</td>
<td>Vaporization</td>
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<td></td>
<td></td>
<td></td>
<td>hydrocarbons</td>
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</table>

Electromagnetic energy can be used to thermally ablate, in the form of radiowaves (radiofrequency), microwaves and light (laser). The electromagnetic energy can be generated remotely and delivered to the site (visible light from laser via optical fibres) or generated locally using electrodes varying at radiofrequency (RF) or microwave frequency. The production of heat is also the basis for an alternative means of thermal ablation, high-intensity focused ultrasound (HIFU). The success of the thermal ablation depends on the energy source, applicators and tissue characteristics. There are tissue and tumour type variations in response to thermal ablation. Heat deposition is greatest around the electrode/probe with less heat deposited in deeper tissues caused by a rapid fall off of energy density away from the electrode as well as the resistance (impedance) to heat conduction within the tissue.

Many different minimally invasive thermal ablative techniques are described for the treatment of tissue hyperplasia and for benign and malignant tumours either as palliative treatment or to prolong survival. The principle mechanism of tissue destruction is the same and does not depend on the frequency of the electromagnetic energy, i.e. whether radiowaves, microwaves or visible light, however the frequency does determine the extent of the uptake and dissipation in the tissue. The heat generated (Joules) is a product of the power applied (Watts) and duration of application (seconds).
2.1 Methods of Thermal Ablation

2.1.1 Electrosurgery

This broad heading encompasses several different electrical methods used to heat and destroy tissue. Electrosurgery includes surgical diathermy, radiofrequency ablation, coblation and microwave ablation. It does not include electrocautery or the use of electrically heated probes where the electricity does not pass through the body tissues.

Electrosurgery can be monopolar or bipolar. Monopolar devices employ a single ‘active’ electrode applied to the target tissue; current is then dispersed to a grounding pad placed on the patient’s skin at a remote location. Bipolar devices have two active electrode applicators, which are usually placed in proximity to achieve contiguous ablation between the two electrodes (e.g. forceps). The current passes only through the tissue in the forceps and not through the patient’s body. For this reason bipolar circuits are generally safer than monopolar circuits.

2.1.1.1 Diathermy

Diathermy is used in almost every surgical operation to cut and coagulate tissue to achieve haemostasis by varying the voltage, current and waveform of RF energy. An RF generator produces RF alternating current at a monopolar electrode tip, or between electrodes for bipolar diathermy, with subsequent heat generation adjacent to the electrode tip or between tips.

In order to get an adequate heating effect the generator has to apply high voltage to drive enough current through the tissues. The voltage used varies between perhaps 100 volts in microsurgical cutting modes up to 5,000 volts in some haemostasis modes. In cutting mode a continuous current with a sinusoidal waveform of around 200 volts is applied to the tissue. In coagulation mode the waveform is pulsed (modulated). This reduces the cutting effect and allows dispersion of heat into the surrounding tissues to enhance a coagulating effect. Because of the effect of modulation the voltage has to be very much higher than that used in cutting mode. Blend mode is a waveform, which uses a lesser degree of modulation to allow for an increased degree of haemostasis during cutting.

The use of radio frequency electrical power allows cutting and coagulation without electrocuting the patient. The disadvantage is that it cannot be completely insulated. This danger is greatly increased by the use of high voltage modes such as coagulation. A current can pass from one instrument to another and cause burning at an unintended site. It can occasionally pass through the intact insulation of an instrument to an organ alongside causing damage, which may not be immediately obvious to the operator. There is a risk of skin burns at the inactive electrode if it becomes detached in any way. Current can escape from the patient to other metal objects such as the operating table or a drip stand. Most problems with diathermy are not due to a failure of the equipment, but due to operator error.

Indications: Diathermy is widely used for tissue dissection and haemostasis in open and laparoscopic surgery.

2.1.1.2 Radiofrequency Ablation (RFA)

RFA is a temperature controlled, and in some cases resistance controlled, form of diathermy. A generator provides an RF radiofrequency alternating voltage on
electrode(s) placed within the tissue. The resulting high frequency alternating current (3.5-5MHz) induces temperature changes in the tissue. The energy, as heat, dissipates rapidly with increasing distance from the electrodes so that the highest temperature is always at the point nearest to the electrodes. The size and shape of the coagulated area is dependent on the probe type, length of exposed tip, and intensity of application, impedance and the duration of treatment. In order for complete and adequate tissue destruction the entire tumour needs to be subjected to cytotoxic temperatures.

Electrodes may be monopolar or bipolar, however, the use of a monopolar probe may not induce adequate coagulation necrosis throughout the target tissue, and therefore multiprobe applicators have been developed. Modifications to the technology such as expandable tips have been developed for treating larger tumours. These multiprobes, also referred to as tines, umbrella electrodes, multi-tined electrodes, multiple hooked electrodes, Christmas-tree electrodes or arrays, allow easy probe placement and create large reproducible volumes of necrosis. A limitation to RF energy deposition is the overheating that surrounds the active electrode. This can lead to local tissue charring, rising impedance and interruption of the RF circuit. In order to limit these effects, internally cooled devices have been developed, with saline solution or water contained around the electrode but not in direct contact with tissue.

Bipolar devices are available. The applied RF current runs from the active electrode to a second grounding electrode. The heat generated by the bipolar probes creates an elliptical volume of necrosis. There has been some development utilising a bipolar array that contains the active and the return electrode on the same probe.

**Indications: malignant tumours**
RFA has been reported for treating both primary cancer (hepatocellular and cholangiocellular) and metastases (liver, pancreas, breast, lung, bone, gastrointestinal, genitourinary and neuroendocrine systems) both to improve survival and for palliation. RFA can be applied percutaneously, laparoscopically or intra-operatively and is indicated for tumours of 3-5 cm in diameter. Factors determining the success of RFA are the electrode tip and the size and number of lesions treated. The main safety concerns are collateral thermal damage to adjacent vital structures. The liver is the common site for RFA treatment, it is a larger organ with a dual blood supply and the risk of damage to adjacent sites is minimal compared to RFA of extra hepatic tumours.

**Indications: benign tumours**
RFA ablation is reported in the treatment of osteoid osteomas, uterine fibroids, and prostatic hypertrophy. Needles are inserted directly into the lesion/tissue percutaneously or endoscopically depending on the site.

**Indications: other**
RFA is reported for the treatment of chronic lumbosacral radicular pain by ablation of the dorsal root ganglia, and for allergic rhinitis, nasal obstruction, and snoring and sleep apnoea by inferior turbinate reduction. Additionally RFA is used for the control of cardiac arrhythmias.
2.1.3 Coblation

This technique employs a bipolar probe to generate an RF electric current applied to a conductive medium (usually saline), causing a highly focused plasma field to form around the energized electrodes to dissect and coagulate tissue. The plasma field dissects tissue, while a co-existing low power current coagulates vessels. Larger vessels are coagulated using the coagulation only pedal. Coblation operates at lower temperatures than diathermy with the potential advantage over diathermy of reduced damage to surrounding tissue with reduced postoperative pain and earlier healing.

**Indications:** Coblation is used in tonsillectomy, for inferior turbinate reduction and soft palate treatments to alleviate chronic nasal congestion and snoring, and nucleoplasty for decompression of herniated vertebral disc.

2.1.4 Microwave ablation [synonymous terms: microwave coagulation therapy (MCT)]

With microwave ablation alternating ultra high frequency (2450MHz) waves emitted from a probe induce rotation of water molecules to heat tissue. If irradiation time for microwave ablation exceeds 120 seconds or 60W output the temperature of the shaft electrode rises and can cause skin burns. Microwave ablation therapy creates a predictable and reproducible area of tissue ablation, it can ablate tumour capsule and so destroy any surrounding area of extra capsular invasion. It appears to produce a haemostatic effect on surrounding tissues, theoretically reducing the risk of haemorrhage post procedurally. MCT has the advantage over other thermal ablative techniques in that ablation is rapid and the area of ablation is immediately hypo-echoic on real time ultrasound monitoring and therefore completeness of ablation can be easily monitored. In general microwave ablation therapy is indicated for tumours of 2-3 cm in diameter.

**Indications:** Microwave ablation is used in the treatment of primary and secondary tumours of the liver, uterine fibroids, prostatic tumours, prostatic hypertrophy and for the control of cardiac arrhythmias.

2.1.2 Ultrasound

2.1.2.1 Direct Ultrasound

Direct ultrasound ablation denotes the placement of a probe containing multiple small piezoelectric transducers to deposit sound energy to heat tissue. Such probes can be placed laparoscopically or percutaneously.

2.1.2.2 High Intensity Focused Ultrasound (HIFU) [Also known as ultrasound ablation, focused ultrasound surgery and pyrotherapy].

HIFU relies on the same principles as conventional ultrasound. If the ultrasound beam carries sufficient energy and is brought into a tight focus, the energy within the focal volume can cause a local rise in temperature of sufficient magnitude leading to
coagulative necrosis in the target tissue\textsuperscript{6}. Sound waves, at higher amplitude than used in the diagnostic setting, delivered via an ultrasound transducer mounted in a water reservoir are focused into a high energy beam resulting in the selective thermal ablation of the target tissue without damage to adjacent tissues.

HIFU is a non-invasive technique. The main categories of device in current clinical use are extracorporeal, and transrectal or transurethral for prostatic treatments. The extent of tissue ablation is monitored either by real time ultrasound or MRI.

When HIFU is used for tumour ablation, currently its optimal effect is for the treatment of small tumours 0.4-1cm in diameter. Technological improvements may allow the treatment of larger tumours in the future. HIFU may activate platelet aggregation and adhesion and this haemostatic effect may prevent bleeding complications following tumour ablation\textsuperscript{7}.

\textit{Indications:} HIFU has been reported for the treatment of uterine fibroids, breast fibroadenomas and for localised malignant tumours of the liver, kidney, breast, prostate, lung, kidney, bladder and bone.

\subsection*{2.1.3 Photocoagulation}

\textit{Definition}

Laser (Light Amplification by Stimulated Emission of Radiation) light is coherent, collimated and monochromatic. The type of laser reflects the components of the solid, liquid or gas that constitutes its active medium and determines the wavelength of the radiation produced. Laser light can be described according to whether the beam is continuous, pulsed, or quality switched (Q switched). The mechanism of laser surgery can be to ablate, incise, vaporize, resect and dissect and this depends upon the laser’s wavelength, power and type of emission (continuous or pulsed). The wide choice of laser parameters and modes of delivery permit a close control of the desired effects.

\textit{Common Medical Lasers}

- **CO\textsubscript{2} Laser:** CO\textsubscript{2} lasers have a penetration depth of 0.1-0.2 mm. The wavelength emitted (10,600 nm) is heavily absorbed in all tissue and so is widely used for tissue incision and excision. It allows for precise cutting, and leaves only a narrow region of thermally damaged tissue. It is used widely in surgery and minimally invasive surgery, for example in tonsillectomy surgery, for cervical dysplasia, endoscopic removal of small laryngeal tumours, and ablation of inferior turbinates. It cannot be transmitted by optical fibres, which limits its use to surface treatments and endoscopic delivery.

- **YAG Lasers:** YAG lasers use Yttrium-Aluminium-Garnet crystals as the lasing medium. YAG Lasers can be Neodymium (Nd) Erbium (Eb) or Holmium (Ho).
  - **Nd YAG Laser:** Nd YAG Laser emits a near infrared radiation at 1064nm or 1320 nm and has a penetration depth of 3-4 mm. It may be delivered in long pulse or continuous wave to cut tissue or, because of its deep penetration, can be used to coagulate and vaporise tissue. It can be transmitted by optical fibres.
- **KTP laser**: When Nd YAG laser light at 1064nm is passed through a potassium-titanyl-phosphate (KTP) crystal, the wavelength is halved to 532nm, the emitted green light in continuous wave mode can incise and vaporise tissue.

- **Er YAG laser**: Emits a mid-infrared beam at 2940nm and has a shorter tissue penetration depth than that of the CO\textsubscript{2} laser. Its principal use is for the cosmetic laser resurfacing of wrinkles.

- **Ho: Yag Laser**: Emits at a mid infrared beam at 2070nm. It can vaporise, incise and ablate tissue. It can be transmitted by optical fibres and has many applications in orthopaedics for arthroscopy and tissue removal, urology for lithotripsy, ENT for endoscopic sinus surgery, spinal surgery for disc decompression, and for prostatic hyperplasia.

- **Diode lasers**: Diode lasers have an operating wavelength of between 600-1600nm and are absorbed relatively independent of tissue type. The diode laser compares favorably with several of the other thermal lasers; its tissue-cutting effect is comparable to that of the CO\textsubscript{2} laser, its coagulation effect is comparable to that of the argon laser, and it results in a slightly higher degree of absorption by tissue than does the Nd:YAG laser. Like the Nd: YAG lasers, it can be transmitted by optical fibres and therefore can be used for interstitial treatment of solid tumours.

- **Argon Laser**: A continuous wave gas laser that emits blue green light at 488nm and 514nm with a penetration depth of 1-1.5mm. It is strongly absorbed by melanin and haemoglobin and can be used for coagulation processes in all vascular tissue. It can be delivered by a fibre optic cable to a hand piece, slit lamp or operating microscope. It is commonly used in ophthalmology to treat retinal lesions, and in dermatology.

- **Ultraviolet laser**: Also known as an excimer laser, with an operating wavelength between 180 to 350nm. It causes disintegration of individual cells and hence removal and reduction of tissue. To prevent excessive secondary heating within the plume of ablation products, excimer lasers are generally operated in a pulsed mode separated by periods of 50 to 100 milliseconds to allow the ablation plume to dissipate. If the period between pulses becomes too short, excessive heating within the plume causes an increase in collateral tissue damage as well as a decrease in the rate of ablation.

**Laser Procedures**

Lasers can be used for surface ablations for example to the cornea and skin. This review will not describe the extensive use of lasers for surface treatments.

**Interstitial laser photocoagulation (ILP):** **Synonyms:** interstitial laser therapy (ILT), interstitial laser photocoagulation (ILP), laser-induced interstitial thermal therapy (LITT)

ILP is a process where laser light can be delivered into lesions in solid organs, endoscopically or percutaneously under image guidance via the insertion of a thin optical fibre into the centre of the lesion. Laser light is emitted from the fibre tip and the exposed cells then undergo thermal necrosis. The laser systems used for ILP are Nd YAG and diode lasers.

**Indications:** Localised malignant tumours of the liver, breast, and prostate and for the treatment of uterine fibroids and benign prostatic hyperplasia.
2.1.4 Photodynamic therapy (PDT)
In PDT a photosensitive drug, most commonly a porphyrin derivative, is administered systemically which is then absorbed by the lesion. When irradiated with the appropriate wavelength of laser light, a photodynamic reaction occurs with local generation of an active form of molecular oxygen, singlet oxygen, which selectively destroys the lesion. The optimal drug-light time interval is the time at which there is maximum difference between the photosensitizer retention in the lesion and the surrounding normal tissue. Dye lasers are the usual devices used in PDT to activate the photosensitive drug and the light is guided to the tissue by fibres and endoscopy. PDT is described for the treatment of new vessels under the macula in age related macular degeneration, to treat superficial skin malignancies and mucosal lesions accessible via the endoscope, for example bladder, oesophageal, bronchial and head and neck cancers. More recently with the development of special catheter systems, optical fibres and new photosensitiser that are selectively absorbed by cancerous tissue, PDT has become a feasible option for the interstitial treatment of solid tumours, especially for liver tumours. PDT is reported as having a low rate of side effects, is painless and acceptable to patients.

2.2 Efficacy of Thermal Ablation (RFA, Microwave, HIFU and laser)
Modifications to the electrode/probe tips can increase the area of lesion that it is possible to treat. All thermal effects are influenced negatively by blood flow as it can potentially remove heat before complete tumour ablation is achieved (the heat sink effect). The heat sink effect protects blood vessels and prevents bleeding of large vessels, it is also a reason for incomplete ablation.

2.3 Safety of Thermal Ablation (RFA, Microwave, HIFU and laser)
Unintentional burns to adjacent tissue are a potentially serious side effect of thermal ablation. Transient pain, post ablation syndrome (fever and malaise) for 2-7 days post treatment, skin burns, intraperitoneal bleeding (liver tumours), infection (hepatic abscess) and needle track seeding have been reported for percutaneous treatments of malignant tumours. Minor skin burns and transient sciatic nerve root pain have been reported with HIFU treatment.

3 COLD ABLATION

3.1 Cryoablation
Cryoablation is the use of low temperatures to achieve tissue destruction. The freezing of tissue to approximately -40 to -80°C and subsequent rapid thawing leads to disruption of cell membranes and induces cell death. In the neck, chest, abdomen or pelvis cryoablation is generally performed at open surgery using a closed cryoprobe placed on or inside the tumour, and argon gas or liquid nitrogen is used to achieve cooling.

Cryoablation can also be applied using minimally invasive techniques, percutaneously, laparoscopically or by slender cryoprobes inserted through small skin incisions, under image guidance.
**Indications:** Cryotherapy is used for the treatment of benign skin lesions, breast fibro adenomas, localised breast cancer, renal tumours, hepatic tumours (primary and secondary), prostate cancer, bone tumours, and for the control of cardiac arrhythmias in association with open heart surgery.

**Potential adverse events:** Damage to adjacent tissues, fever, pain and haemorrhage are the commonly cited potential adverse events.

**References**


APPENDIX - The tissue / technology Matrix

Underpinning the original work on this review of ablative technologies was an extensive literature search, and an exhaustive screening of identified titles and abstracts, to determine the volume of literature available and to which body tissues and technologies of ablation the published material related.

Searches (using appropriate terms to cover all synonyms for ablation coupled with relevant expressions for technology and body site) were run across the primary medical databases (Medline, Embase, Cinahl, DARE etc) during late 2003 and early 2004. The output from the searches was used to populate a Reference Manager database which in turn allowed for ease of handling the search output and eventual ordering of papers.

The Reference Manager database was built up to 2,622 papers. The title and abstract data (not all titles had corresponding abstract data) for each reference were then screened and where the reference appeared to be relevant the full paper was then ordered. By this process more than 600 papers were ordered and these in turn had to be read in detail in order to check for relevance. Eventually 579 papers were deemed relevant. A process of cross referencing was now undertaken (of technology against body site) to arrive at the tissue/technology matrix appended below.

The category headings used in the matrix were arrived at after perusal of the initial search results (which indicated which technologies were being used and where). Further refinement and modification of the subject headings continued as more results accrued and the full papers were scrutinised. Some papers referred to more than one technology or body site, often because these were comparative studies of one kind or another. Such papers were classified into one ‘box’ in the matrix, the placing being determined by the primary technology/body site as given in the paper.
<table>
<thead>
<tr>
<th>Technology</th>
<th>RF</th>
<th>Laser</th>
<th>Microwave</th>
<th>Ultrasound (HIFU)</th>
<th>Radiation</th>
<th>Cryo</th>
<th>Resection</th>
<th>Chemo</th>
<th>Endometrial Ablation</th>
<th>DC shock</th>
<th>Hormonal</th>
<th>Minimally invasive technology</th>
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