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Minimally invasive therapy for the treatment of breast tumours

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Abstract

Minimally invasive therapy has been explored as a potential means of treating breast tumours with minimal disruption to adjacent soft tissues. The purpose of this is to facilitate improved cosmesis and to offer treatment to women who are unfit for surgery. A number of treatment modalities including thermal therapies (intersititial laser photocoagulation, radiofrequency, focused ultrasound and cryotherapy), percutaneous excision and interstitial radiotherapy are being developed. The experience to date of each of these modalities is described and reviewed. Currently there are too few data to indicate the efficacy of these treatments although the preliminary data are encouraging. The need for large-scale studies examining the role of MIT in relationship to the overall management of breast cancer (including chemotherapy, radiotherapy, and the management of the axilla) and outcome is discussed.

Keywords: Breast neoplasms; Therapy

1. Introduction

Breast conserving surgery is well established for the management of breast cancer for patients with localised disease. This usually consists of wide local excision and radiotherapy to the whole breast. In addition, systemic adjuvant chemotherapy is given depending on the nature of the primary tumour. Large studies have shown that this approach to managing breast cancer is safe and does not compromise patient mortality although the incidence of local disease recurrence is slightly higher [1,2]. On this background the use of non-surgical minimally invasive therapies has been explored with the aim of achieving equivalent or greater efficacy but with improved cosmesis and reduced inpatient care.

The introduction of effective breast cancer screening programmes has increased the number of small cancers diagnosed considerably. Screen detected cancers usually have a better prognosis than symptomatic cancers and conventional therapy may be an over-treatment. These tumours may be suitable for alternative or less radical local treatment.

A further consideration in the management of breast cancer is the effect of an ageing population. Many elderly women are affected by breast cancer and they can account for as many as half of all cases [3]. Since a high proportion of these tumours are oestrogen receptor positive, conventional treatment of these women has been oral tamoxifen only. There is evidence that local treatment in addition to tamoxifen is advisable as this reduces breast cancer morbidity and deaths (RR = 0.62, 95%CI 0.41–0.94) and may improve survival [4]. However, many of these women may not be fit enough to stand an operation and less invasive methods of treatment may be appropriate.

The therapeutic modalities investigated are hyperthermia (radiofrequency, interstitial laser therapy and focused ultrasound (FUS)), percutaneous excision, interstitial radiotherapy and hypothermia (cryotherapy).

2. Minimum requirements for therapy

The aim of conventional breast conserving surgery is to remove all local disease and achieve a tumour free margin, ideally of 10 mm or more. Irregular tumour shape and the intrinsic nature of some tumours, such as the ill-defined Indian file margins associated with lobu-

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lar carcinomas, or the extensive intraductal component seen with some invasive ductal tumours, can make complete tumour excision difficult. Minimally invasive alternative therapies must offer at least the benefits of surgery and the minimum requirements are that there is certain total tumour ablation (equivalent to tumour excision) and a proven tumour free margin.

3. Role of imaging

Imaging has a number of roles in the use of minimally invasive therapies to breast tumours:

1. To detect the tumour.
2. To demonstrate the tumour and its full extent.
3. To guide tools and to monitor therapy during treatment.
4. To show the effects of therapy at follow-up.

At the current time, X-ray mammography and ultrasound are the mainstay for imaging diagnosis of breast tumours both for symptomatic disease and for screening. Breast MR has been shown to be more accurate than either of these modalities for showing the extent of disease within the breast and for the detection of multicentric and multifocal disease [4–8]. However there are exceptions to this—the extent of ductal carcinoma in situ (DCIS) [9] and lobular cancers [10] is less reliably shown than with the more common ductal cancers. Furthermore, the specificity of breast MR is relatively low and it may be detecting multifocal/multicentric disease which may not be clinically relevant [11].

Ideally therapy should be monitored during treatment as this could facilitate modification of the procedure at the time of therapy to enable the lesion to be adequately treated. With thermal therapies, MR has the potential to achieve this by using temperature sensitive sequences. The limitations to this have been achieving adequate 3-dimensional maps of treatment zones, scanning in the presence of metallic objects (such as the majority of radiofrequency probes), access to the patient during treatment, artifacts generated by the equipment used for treatment and so on. The challenge is not trivial.

MR has been widely used to monitor the effects of therapy after treatment for patients where the initial lesion is MR 'visible'. The basis for this is the observation that the majority of viable tumours enhance. Following treatment, tumour that fails to enhance (and that had previously enhanced) has been shown to be non-viable and that this is due to devascularisation of the tumour and cell death [12,13]. No study is of sufficient size to guarantee consistently that an adequate tumour free margin can be ensured.

Unenhanced ultrasound has not been found to be a reliable method for monitoring thermal treatment. Contrast enhanced colour Doppler ultrasound and PET scanning have more recently been reported as useful to confirm tumour death in breast cancer following ILP treatment [14].

4. Radiofrequency ablation

Radiofrequency ablation (RFA) uses radiofrequency alternating current source applied through needles tipped with RF electrodes. Frictional heating is induced via ionic agitation arising from the impedance of the tissue to alternating currents. A major advantage of RFA over ILP is the consistently larger lesions that can be generated with the newer multi-head and cooled-tip RF probes. Lesions in excess of 5 cm can be consistently generated and this is clearly adequate for the treatment of many breast tumours with an adequate margin. RFA can form lesions faster than ILP, but because the deposition of the heat depends upon the electrical characteristics of the tissue, the formation of the lesion may be inhomogeneous especially in regions of tissue boundaries.

Treatment using RF in an MR environment has unique problems. The RF source typically operates at up to 500 kHz, and this will often interfere with the MR acquisition, at all field strengths. Such interference with the MR measurement can be reduced or eliminated with an appropriate choice of electronic filters, or by gating the RF source off during MR signal reception. This latter approach can easily be performed by simple modification of pulse sequence code. The majority of RF probes are metallic and generate significant artifact on the MR images. More recently MR compatible RF probes have been developed for use within a magnet but these are expensive to manufacture.

The main complication that may occur with RF therapy is burning. To complete the electric circuit for the applied AC, grounding pads must be applied to the patient and local skin burns can occur at the site of the pads. As with all thermal therapies, local burns may occur to tissues adjacent to the target lesion-skin and muscle in the case of the breast.

A recent study has reported the use of vacuum assisted tumour resection combined with RFA in a rabbit model with implanted tumours grown to 10 mm before treatment [15]. Tumour excision alone was compared with combined therapy and reduced local tumour recurrence was found in the combined treatment group. In a clinical pilot study from workers in Italy, RFA in 26 patients with biopsy proven T1 and T2 invasive cancers (range 7–30 mm size) were treated with 2-phase RF therapy prior to surgical resection [16]. Complete coagulative necrosis was induced in the large majority of tumours (25/26, 96%) and small volume viable tumour was found in a single patient. A single patient suffered full thickness skin burns. These results are

extremely promising but require further validation, preferably in a randomised controlled study comparing RFA alone with conventional therapy.

5. Interstitial laser photocoagulation therapy

Interstitial laser photocoagulation therapy (ILP) is a technique during which laser light energy is delivered directly to the target organ via optical fibres inserted into tissue. Several types of laser have been evaluated for use in ILP; these include the Nd–YAG laser (1064 and 1320 nm), semiconductor diode laser (805 nm) and the argon ion laser (488 and 514 nm). Of these the 805 nm diode laser has been used extensively for ILP because of its advantages of being portable (the size of a typewriter), operable with standard 'mains' electricity supply and having the wavelength that is effectively absorbed by most biological tissues.

The technique is simple—400 μm optical fibres are inserted into pre-sited needles within the tumour, with the tip of the fibre protruding a few millimetres distal to the needle. It has been shown that pre-charring the tip of the fibre produces a larger and more consistent size to the burn. Typically treatments made with 2–2.5 W per fibre delivered for 500 s (>1000 J per fibre) produced burns of around 10 mm. The size of the burns can be increased with the use of multiple fibres using an optical beam splitter and by using a 'pull back' technique. To do this the fibres are inserted deeply into the lesion, close to the far margin for the initial treatment. The fibres are then gradually withdrawn through the mass and repeat treatments made. However modelling of the treatment zone is less precise than with FUS (although the technique is less susceptible to patient movement).

Macroscopically, an ILP induced lesion in the breast consists of a central charred cavity surrounded by a broad area of pale tissue and a peripheral haemorrhagic rim beyond which is viable tumour [12]. Microscopically, the pale zone of tissue shows in situ heat fixation characterised by cells which are morphologically normal but have hyperchromatic, smeared nuclei and hypereosinophilic cytoplasm consistent with the presence of coagulated proteins. The extent of in situ fixation is variable, depending on the site of laser fibre in the tumour and its relationship to normal breast tissue and fat. The haemorrhagic rim contains cells which are less damaged whose nuclei are only slightly hyperchromatic and retain their chromatin pattern and nucleoli. These cells become surrounded by proliferating fibroblasts, blood vessels and extravasated red blood cells.

ILP can be performed with virtually any form of image guidance but there are advantages to performing MR guided therapy. 'MR visible-only' lesions can be treated and thermal therapy can be monitored. The technique can be performed in an MR environment using side access or more open breast coil designs and MR compatible needles. Using long optical fibres (up to 4 m) the laser source can stay beyond the 5 Gauss line or even outside the scanning room.

In studies conducted at our institution, MR has been used to monitor therapy during treatment using fast T1-weighted gradient echo sequences. During ILP a region of low signal appears around the optical fibre tip, first appearing at around 36–60 s after the start of treatment and reaching a plateau at its maximum size at about 300 s. The maximum measurement of this region of signal loss corresponds to the extent of thermal damage mapped histopathologically [17]. Delayed follow-up of treatment effect may be made using contrast enhanced MR [12]. The extent of laser damage is seen as areas of non-enhancement and these correspond with areas of necrosis seen histopathologically

The only significant complications occurring with ILP are skin and pectoralis muscle burns. The latter arise from misplaced fibres, mainly because the optical fibres are MR invisible unless specially coated. This could be prevented with real-time monitoring of the thermal effect of the laser on both normal and tumour tissue would be seen during treatment. The skin can be largely protected by irrigation with chilled saline during ILP and by applying ice packs after treatment.

ILP has been piloted as treatment for breast cancer in a number of studies [12,14,18] and it has been shown that small tumours can be completely ablated with negative tumour margins.

ILP has been used successfully for the treatment of benign fibroadenomas [19] and this is now a routine application in some institutions.

6. Focused ultrasound

As ultrasound penetrates soft tissue, when focused, it can cause rapid increases in local temperatures of up to 90 °C and this will cause irreversible cell damage and death [20]. FUS uses an array of ultrasound sources, typically operating at 1.5 MHz, with the energy converging at a point within the body. In this region a significant amount of acoustic energy is converted into heat. The volume of the hyperthermia is very well defined and focal hot spots develop in the target tissue. The transducer is typically coupled to the target organ using de-gassed water in a water bath or sac. The duration of the treatment depends upon the ultrasound parameters, but is usually in the region of tens of minutes. Lesions as small as 1 mm^3 can be created and so high-resolution imaging techniques, such as MRI, are necessary for their accurate detection and monitoring.

This technique has been extensively investigated and developed by F. Jolesz and co-workers [21]. These authors have used MR to monitor therapy and have used an MR compatible system using a focused piezoelectric transducer. The transducer ablates a tissue volume of $\approx 4 \times 4 \times 7$ mm^3 for each 10 s sonication. To produce a lesion of the size necessary to treat a tumour, multiple sonications have to be made with the focused beam moved across and through the lesion. This is achieved by moving the transducer using a computer controlled (MR compatible) positioning device coupled to an optical position feedback system to ensure accurate positioning of the beam [22]. Temperature is monitored using phase difference imaging to show the temperature-dependent proton-resonant frequency shift [23].

In a recent prospective feasibility study of the use of FUS to treat biopsy proven fibroadenomas (mean volume 1.9 cm^3) in 9 women, this group reported partial or nearly total successful treatment of the tumours in 8/11 cases (73%) as assessed by contrast enhanced MR imaging [13]. All patients were treated with local anaesthesia and sedation only. The main problem with this technique is patient motion as very precise lesion targeting is required. Tolerable pain and skin bruising are the main reported adverse effects. Temperature rises in peri-lesional fat cannot be observed using the MR techniques described in this report and consequently the treatment of tumour margins cannot be verified during the procedure. As yet, the technique remains untested in malignant disease.

7. Cryotherapy

Cryosurgery involves the use of a needle that is continuously cooled by liquid nitrogen and which is insulated along the length of its shaft except at the tip. The tip of the needle acts as a heat sink for the tissue and so acts as a point source for cooling and an ice-ball forms at the needle tip. Thermal conduction increases the volume of cooled tissue. There is a well-defined boundary between normal and treated tissues. There are limited reports of the experimental use in breast tumours in animals [24,25], and even fewer cases of treatment in patients with breast cancer [25]. A major problem with cryotherapy is the time taken to form and then thaw the iceball.

8. Interstitial radiotherapy

The use of localised intraoperative radiotherapy to the tumour bed following surgical excision using a miniature electron beam has been reported [26]. The same device can be coupled with the Mammotome vacuum-assisted biopsy device to treat tumour percutaneously and this technique has been piloted at our institution with the apparatus mounted on a prone biopsy table [27]. The PRS400 (PeC) is an electron-beam driven soft X-ray source that provides a point source of low energy X-rays at the tip of a 3.2 mm diameter tube. During this procedure an initial biopsy using the Mammotome needle is taken [28] and this verifies the needle tip position within the tumour and creates a tract. The radiotherapy device is then mounted on a modified arm and positioned along the Mammotome tract. With a 50 kV machine, the typical dose is about 130 Gy at the centre and 20 Gy at the surface of the tumour, delivered in about 12 min. As the radiotherapy device is positioned with the tip lying within the centre of the tumour, the maximum dose is delivered centrally. Consequently the region of maximum tissue anoxia, and thus the most likely site of treatment failure, receives the highest dose whilst normal surrounding tissues receive the least.

In our institution we have piloted this technique in three patients aged 73, 78, and 85 years who had unrelated medical conditions that precluded surgery-partial pseudobulbar palsy in the first and cardiac dysfunction in the other two. The diagnosis of cancer was established cytologically in each patient and the tumour sizes varied from 2.5 to 3.0 mm. In each case the procedure was performed using local anaesthesia alone and was reasonably well tolerated. Contrast enhanced MR scans at 6 days showed no central enhancement of the masses and only a thin rim of residual enhancement was seen. The latter disappeared on follow-up scans made over the next 6 months. Core biopsies taken at 1 week and 1 month after treatment confirmed treatment effect with evidence of apoptosis, occluding blood vessels and progressive fibrosis. Tamoxifen was given as additional therapy immediately after treatment in one case and 1 month later in the remaining patients. All masses were impalpable by 3 months and the patients were disease free at 13, 18 and 12 months following treatment. Two patients (1st and 3rd) succumbed to their co-morbid conditions. This illustrates that the increased likelihood of death in the elderly from non-cancer related causes should be taken into consideration when planning invasive therapy.

The real potential of this technique is for women with screen detected cancers in whom the combination of larger volume vacuum biopsy with percutaneous radiation could achieve localisation, excision and radiotherapy in a single out-patient visit.

9. Discussion

Almost without exception, large-scale studies with each of these treatments are not reported and conse-

quently they must be considered experimental and unproven in terms of outcome. Although many of these treatments have been shown to be technically feasible there are many problems that remain before they can be considered for conventional treatment. Validation of margin status is important and this needs to be tackled in further studies. Modelling of the treatment volume remains imprecise with all these therapies with the probable exception of the radiotherapy device and FUS.

Nevertheless, the less aggressive and possible out-patient treatment that these novel treatments offer is attractive to both the patient and the health care system. Screening mammography detects more in situ disease than is clinically relevant and, when this is extensive, it can prompt mastectomy. This has lead to the paradox that the screened population has 30% more mastectomies than the symptomatic patients [29]. It has also been established that the extent of local treatment does not effect survival [30]. With these observations it may be possible to obtain ethical approval for randomised studies comparing these novel therapies with standard treatment and thus establish the scientific basis for the tailored use of these less radical therapies to patients with single invasive cancers.

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