The Evolving Role of Radiofrequency Ablation Therapy of Breast Lesions

B. SOUKUP1, S. BISMOHUN1, S. REEFY2 and K. MOKBEL1,2


Abstract. Background: The potential for radiofrequency ablation (RFA) therapy is an area of increasing interest in the context of breast conserving therapy for breast cancer. This non surgical technique potentially provides a non invasive, cosmetically pleasing result that is preferable to surgeon and patient. Materials and Methods: A literature review was carried out facilitated by PubMed and Medline databases. Cross referencing of the obtained articles was used to identify other relevant studies. A total of 17 studies were reviewed. Results: RFA is emerging as a promising treatment for breast cancer. Pilot and phase II studies have shown RFA to be effective at ablation with few complications or adverse effects experienced by patients. However, complete ablation of tumours is still not achieved in all patients. Conclusion: RFA represents a promising therapeutic modality for breast lesions. However, there is a clear need for further research and refinement of the procedure before it can be offered as a therapeutic alternative to surgical excision for operable breast cancer.

It is well established that breast cancer is the most frequently occurring malignant disease amongst western women (1), with a lifetime risk of 1 in 9 (2). It is unsurprising that nationwide breast screening programmes have been implemented. Furthermore, such screening has resulted in an increased detection of small breast carcinomas. Interestingly, the surgical management for such small breast cancers has changed dramatically over recent years (3). The move from total mastectomy to breast-conserving treatment (BCT) is preferable for both surgeon and patient. The potential for per-cutaneous eradication of breast tumours is an area of great interest. More recently, the use of radiofrequency ablation (RFA) to treat small breast cancers has emerged as a promising non surgical technique (3). This technique uses thermal energy in the form of a high-frequency alternating current which flows from an uninsulated electrode into the surrounding tissue (1). The tissue ions attempt to follow the alternating current and the resultant ‘ion agitation’ is converted by means of friction into heat (4). This generates thermal coagulation necrosis and irreversible protein denaturation, thus destroying the tissue.

Ultrasound-guided Radiofrequency Ablation

It is well established that ultrasound is a key imaging modality in the detection and monitoring of breast disease, both malignant and benign in nature. Furthermore, us-guided techniques, including percutaneous needle biopsy, have proven to be an indispensable tool for the diagnosis of breast cancer. In recent years, us has been employed as part of a new therapeutic intervention, RFA. Although this procedure was initially used for the treatment of metastatic liver disease (5), it was not long before its potential to treat other tumour types including breast cancer was identified.

The first feasibility study for breast RFA was conducted by Jeffrey et al. in1999 (6). They trialled its use in five women with localised (stage III) breast carcinoma. A technique was proposed whereby a multi-pronged electrode was placed into the centre of the lesion. In this initial study, a mean power of 36 W was supplied for 30 minutes. The progress of tissue ablation was tracked via US, where an expanding area of hyperechoicity represents the ablation zone. Immediately after RFA, the tumours were excised by mastectomy. Tissue staining of the tumours with nicotinamide adenine dinucleotide–diaphorase (NADH–diaphorase) revealed the presence of viable tumour cells in one patient, thus giving a success rate of 80%. This study
highlighted one of the principal concerns with RFA i.e. the uncertainty of complete ablation. Unfortunately this problem has not been resolved, although some groups have reported 100% success rates (7-9). The problem is inherent to the technique. It is difficult to accurately determine the three-dimensional proportions of the tumour with US; additionally, matching of the RFA zone to the tumour shape is difficult due to the inability to accurately visualise the zone of ablation. Several solutions to this problem have been proposed.

Electrode design is central in effectively directing the current to all parts of the tumour. It has long been established that a tissue temperature of around 45˚C is required before necrotic cell death occurs (10). The ideal electrode would supply uniform heating to all areas of the tumour. Currently there are two principal designs, the multi array as used by Jeffrey et al. or the single needle with an infusion of cold saline (6). The aim of the single needle set-up is to avoid charring and thus prevent a rise in tissue impedance, allowing greater heat dispersion. The multi-array system is designed to place electrodes evenly throughout the tumour. However, this requires more force and can be technically challenging, resulting in poor electrode distribution (11, 12). An ex vivo model suggested that the single cooled needle system is more efficacious in tumour ablation (13). However, a recent comparative review of ablation techniques found no significant difference in the two designs (14).

To date, a number of RFA studies have suggested that post-ablative core biopsy, US and magnetic resonance imaging might be sufficient for patient follow up (15-17). All three studies demonstrated impressive results, with none of the tumours showing recurrence at between 3-18 months follow-up. A series of studies with a variable delay in tumour resection after RFA, show an increase in the percentage of tumours which showed no residual cancer cells on NADH–diaphorase staining (see Table I). One explanation for these impressive results suggests that tissue thrombosis and hence tissue necrosis and immunological response increase with time.

Results from several studies have suggested that complete tumour ablation may be dependent on tumour size. An RFA study using the single cooled needle method, evaluated ablation efficacy in 20 patients with tumours ≥2 cm and 29 patients with tumours ≤2 cm (20). They found complete tumour ablation rates of 30% and 86% respectively. Similar results were seen in a second study of 14 patients with tumours ≤2 cm and 11 patients with tumours >2 cm (21). These findings agree with numerous other studies where tumour sizes of <2cm showed ablation rates of between 90-100% (7, 8, 18-19). The strong concordance between the good success rates in the <2 cm groups suggests that RFA may be more appropriate for smaller tumours.

Two studies have demonstrated particularly good results when RFA is used in elderly patients (mean ages 80.5 and 81 years) (15, 16). These studies both reported no viable malignant tissue at 3 and 18 months respectively. However, neither of the studies performed consequent surgical excision of the tumours therefore it is difficult to objectively assess tumour ablation. Since RFA is performed under local anaesthesia, it has the potential to be the therapeutic intervention of choice in frail elderly patients unfit for general anaesthesia and open surgery.

Across multiple studies, increased tumour impedance has been shown to reduce the effectiveness of RFA. High impedance is associated with an increased fat content of tumours due to the high electrical resistance of fat. Within the elderly population, age-related breast atrophy results in a lower tumour fat content compared to younger groups. Thus, RFA may be more successful amongst this group as a direct result of reduced resistance to thermal energy.

MRI-Guided Radio frequency Ablation

The use of MRI for screening, diagnosis and management of breast cancer is gaining popularity. It has long been established that MRI is highly sensitive for the detection of benign and malignant abnormalities that are often concealed on other imaging modalities such as mammography and US (22). Furthermore, due to the sensitivity of MRI to temperature changes, it is exceptionally suited to guide RFA. MRI can potentially allow monitoring of the ablation process in real time. This has the benefit of the continuous intraprocedural assessment of the completeness of ablation (22). The majority of RFA studies to date have used real time US to monitor the ablation process. However, many authors question the true accuracy of US for this procedure (24). Specifically, the combination of the hyperechogenicity of heated breast tissue and US shadowing can make it difficult to differentiate between residual breast tumour and the ablated tissue (22). Therefore, malignancy may be left behind unknowingly in these patients.

To date, only two main studies have evaluated MRI-guided RFA in humans (Table II). Van der Bosch et al. (24) treated three female breast cancer patients with MRI-guided RFA. In this study, the MRI guided technique allowed four areas to be closely monitored throughout the procedure: i) the breast tumour undergoing ablation; ii) normal breast parenchyma away from the region to be ablated; iii) retro-mammary fascia at the breast/chest wall border; iv) subcutaneous tissue along the probe tract (24). The initial results from this preliminary study were promising. All three patients tolerated the procedure well, with no complications or burning reported post procedure. Within a week following RFA, two patients had a lumpectomy and one patient had a mastectomy. The ablated and surrounding tissue underwent histopathological analysis to determine the success of
Table 1: Comparison of US guided RFA studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Technique</th>
<th>Stage</th>
<th>Number</th>
<th>Age</th>
<th>Tumour size (cm)</th>
<th>Ablation technique</th>
<th>Power (W)</th>
<th>Temperature</th>
<th>Tip time</th>
<th>Ablation power (Ω)</th>
<th>Impedance</th>
<th>Complications</th>
<th>Definitive treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Kinoshita 2010</td>
<td>Cool tip</td>
<td>T1-2</td>
<td>49</td>
<td>61 median</td>
<td>0.5-3.0</td>
<td>30 (61)</td>
<td>55 max</td>
<td>15-25</td>
<td>3-18</td>
<td>195.1 mean skin burns</td>
<td>3x muscle burns</td>
<td>2x Superficial Surgery</td>
<td>Surgery</td>
</tr>
<tr>
<td>2 Medina-Franco 2008</td>
<td>Saline infused</td>
<td>Invasive</td>
<td>25</td>
<td>55.3</td>
<td>0.9-3.8</td>
<td>19 (76)</td>
<td>50 max</td>
<td>70-90</td>
<td>9-15</td>
<td>-</td>
<td>-</td>
<td>3x Superficial skin burns</td>
<td>Surgery</td>
</tr>
<tr>
<td>3 Izzo 2003</td>
<td>Multiple array</td>
<td>T1-2</td>
<td>26</td>
<td>57 median</td>
<td>0.7-3.0</td>
<td>13 (92.8)</td>
<td>80 max</td>
<td>-</td>
<td>-</td>
<td>6-24</td>
<td>95 mean initial</td>
<td>1x Full thickness burn</td>
<td>1x Late absciss at 9 months</td>
</tr>
<tr>
<td>4 Marcy 2007</td>
<td>Saline cooled</td>
<td>T1 invasive</td>
<td>5</td>
<td>80.5</td>
<td>1.8-2.3</td>
<td>25 (96)</td>
<td>80 max</td>
<td>45 mean</td>
<td>15</td>
<td>14</td>
<td>-</td>
<td>-</td>
<td>No surgery</td>
</tr>
<tr>
<td>5 Fornage 2004</td>
<td>Multiple array</td>
<td>T1 Invasive</td>
<td>20</td>
<td>56</td>
<td>0.6-2.0</td>
<td>20 (100)</td>
<td>15-20</td>
<td>95</td>
<td>3-16</td>
<td>91-192</td>
<td>145 mean</td>
<td>None reported</td>
<td>Surgery</td>
</tr>
<tr>
<td>6 Hayashi 2003</td>
<td>Multiple array</td>
<td>T1</td>
<td>19</td>
<td>73 median</td>
<td>0.5-2.6</td>
<td>12 (64)</td>
<td>20 all cases</td>
<td>95</td>
<td>15-20</td>
<td>15 median</td>
<td>-</td>
<td>1x Superficial skin burn</td>
<td>Surgery 1-2 weeks later</td>
</tr>
<tr>
<td>7 Wiskell 2003</td>
<td>Saline cooled</td>
<td>Unifocal tumour</td>
<td>31</td>
<td>64</td>
<td>0.6-2.2</td>
<td>26 (84)</td>
<td>-</td>
<td>85</td>
<td>7-11</td>
<td>9.5</td>
<td>8-12</td>
<td>-</td>
<td>Surgery</td>
</tr>
<tr>
<td>8 Susini 2007</td>
<td>Cool tip</td>
<td>T1 ductal</td>
<td>3</td>
<td>81</td>
<td>1.0-1.3</td>
<td>3 (100) confirmed by core biopsy and MRI at 18 months</td>
<td>-</td>
<td>90</td>
<td>8-12</td>
<td>10.3</td>
<td>-</td>
<td>-</td>
<td>No surgery</td>
</tr>
<tr>
<td>9 Garbay 2008</td>
<td>Multiple array</td>
<td>T1-3</td>
<td>10</td>
<td>50</td>
<td>1.0-2.2</td>
<td>7 (70)</td>
<td>32 mean</td>
<td>-</td>
<td>5-16</td>
<td>10</td>
<td>-</td>
<td>2x Minimal bruising</td>
<td>2x Superficial burn</td>
</tr>
<tr>
<td>10 Imoto 2009</td>
<td>Multiple array</td>
<td>T1</td>
<td>30</td>
<td>36-76</td>
<td>0.9-2.4</td>
<td>24 (87)</td>
<td>45 mean</td>
<td>-</td>
<td>4-42</td>
<td>136 median</td>
<td>18</td>
<td>2x Skin burn</td>
<td>7x Muscle burn</td>
</tr>
<tr>
<td>11 Barak 2003</td>
<td>Multiple array</td>
<td>T1</td>
<td>10</td>
<td>54</td>
<td>0.8-1.6</td>
<td>9 (90)</td>
<td>36</td>
<td>20-60</td>
<td>14</td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>No surgery</td>
</tr>
<tr>
<td>12 Jeffrey 1999</td>
<td>Multiple array</td>
<td>Local stage III</td>
<td>5</td>
<td>38-66</td>
<td>4.0-7.0 on mammography (0.8 to 1.8 cm, Ablation zone)</td>
<td>4 (80)</td>
<td>47-70</td>
<td>36</td>
<td>20-60</td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>No surgery</td>
</tr>
<tr>
<td>13 Oura 2007</td>
<td>Cool tip</td>
<td>T1</td>
<td>52</td>
<td>55</td>
<td>0.5-2.0</td>
<td>52 (100) no recurrence at 15 months</td>
<td>-</td>
<td>89</td>
<td>5-25</td>
<td>12</td>
<td>-</td>
<td>1x Skin burn</td>
<td>No Surgery</td>
</tr>
<tr>
<td>14 Noguchi 2006</td>
<td>Multiple array</td>
<td>Early invasive/ non-invasive</td>
<td>10</td>
<td>54</td>
<td>0.5-2.0</td>
<td>-</td>
<td>-</td>
<td>89</td>
<td>5-25</td>
<td>12</td>
<td>-</td>
<td>None reported</td>
<td>Surgery</td>
</tr>
<tr>
<td>15 Earashi 2007</td>
<td>Multiple array</td>
<td>Local invasive</td>
<td>17</td>
<td>38-66</td>
<td>0.8-1.5</td>
<td>13 (92.8)</td>
<td>35 mean</td>
<td>15-25</td>
<td>21 mean</td>
<td>218 mean</td>
<td>2x Skin puckering</td>
<td>Surgery – after 4 weeks</td>
<td></td>
</tr>
<tr>
<td>16 Khatri 2007</td>
<td>Cool tip</td>
<td>Local invasive</td>
<td>14</td>
<td>63</td>
<td>&lt;2.00</td>
<td>(97)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Surgery</td>
</tr>
<tr>
<td>17 Manenti 2009</td>
<td>Cool tip</td>
<td>Local invasive</td>
<td>34</td>
<td>53</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Surgery</td>
</tr>
</tbody>
</table>
ablation in each case. In the first patient, pathological analysis illustrated necrotic ablated tissue and no viable tumour cells. However, in the second patient, analysis of the lumpectomy specimen revealed residual invasive ductal carcinoma and in this case only 50% of the tumour had been successfully ablated with RFA. In the final patient, only 33% of the tumour had been ablated; post mastectomy specimen analysis also revealed residual infiltrating ductal carcinoma and an insitu ductal carcinoma in this patient. While the authors clearly demonstrated the accuracy of MRI in identifying breast cancer and the ability to monitor various regions during the procedure itself; successful ablation was only achieved in one patient.

More recently, Yamamoto et al. conducted a pilot study on 26 patients using MRI guided breast RFA (25). The ablated tumours were histologically evaluated using hematoxylin-eosin (H&E) and nicotinamide adenine dinucleotide (NADH) diaphorase staining. The results illustrated that 92% of the patients (24 out of 26) had complete ablation of the tumour, since no viable tumour cells were found on histological analysis (25). The authors report complications in four patients: three patients suffered small diameter grade three burns to the skin (two to the outside of the thigh from grounding pad and one to the breast skin itself). In addition, one patient was noted as having a significant adverse breast lesion similar to chronic granulomatous mastitis as a result of overreaction of the ablated zone. This larger study compared to that conducted by Van der Bosch et al. suggests that MRI-guided RFA could potentially an accurate and safe application for patients with small breast tumours. These encouraging results could be attributed to the larger cohort of patients recruited in this study. In addition, Yamamoto et al. adopted a shorter ablation time but with a higher temperature (25). However, in order to establish whether this technical difference is significant in terms of ablation success, further studies would need to be carried out.

RFA of Benign Breast Tumours

The management of benign breast tumours encountered on percutaneous biopsy has also been at the centre of recent debates i.e. surgical excision versus follow up. Furthermore, strong data to aid the decision are lacking within this particular field (26). The development and introduction of breast conserving treatments including RFA, offers a potentially different route from the conventional surgical excision of benign lesions. In addition, due to the benign nature of these tumours, the issues surrounding RFA for small breast tumours i.e. the concern of incomplete ablation is not a primary concern in benign breast disease. It is clear that further research is required in this particular field, since, to date, no studies have been carried out to evaluate the potential role of RFA in benign breast disease.

Conclusion

RFA is emerging as a promising treatment for breast cancer. Studies to date have illustrated complete ablation in the majority of patients. However, in order for RFA to be considered as a definitive treatment for breast cancer further studies are required to delineate suitable patients groups for successful RFA intervention (tumours <2 cm, at least 1 cm away from skin and chest wall). Unfortunately, comparison between studies is challenging due to the heterogeneity of treatment protocols between groups. In our opinion, the greatest potential of RFA lies in the treatment of small tumours (<2 cm) and older patient groups and those otherwise unfit for major surgical intervention. Vacuum-assisted core biopsy post-ablation could represent the modality of choice for evaluating completeness of ablation and margins prior to radiotherapy.

References


Received May 4, 2010
Revised June 29, 2010
Accepted July 6, 2010