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Role of ablation in the treatment of breast cancer: A review

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Abstract

Breast cancer surgical treatment has evolved from the days of the radical mastectomy to breast conservation surgery. In recent years, there has been much interest in percutaneous treatment modalities for breast cancer, instead of surgery. There are several different methods of percutaneous treatment of breast cancer. These include cryoablation, radiofrequency ablation, microwave ablation, laser ablation, and ultrasound ablation. The advantages of these techniques include an outpatient or office procedure, with local anaesthesia; minimal scarring, which is only from introducing the percutaneous instrument into the breast, instead of a surgical incision; and minimal recovery time, as the procedure does not involve surgery or general anaesthesia. Disadvantages relate mainly to pathologic evaluation, in that the true size of the breast cancer has to be estimated from the pre-procedure imaging, and all molecular profiling must be obtained from the biopsy specimen. In addition, long term patient satisfaction with cosmesis after adjuvant radiotherapy has not been studied. We review these percutaneous ablation modalities in this paper, as well as their individual techniques, associated advantages, and disadvantages. We also review current clinical trials, exploring these methods of breast cancer treatment.

Key words: Breast cancer; Cryoablation; Radiofrequency ablation; High frequency ultrasound ablation

Core tip: This paper seeks to provide updated literature on percutaneous ablation modalities in the treatment of breast cancer. We review the technical aspects and literature, including ongoing clinical trials for the following percutaneous treatment techniques: cryoablation, radiofrequency ablation, microwave ablation, laser ablation, and ultrasound ablation.

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INTRODUCTION

The treatment of breast cancer has evolved over time to include minimally invasive approaches. Earlier detection of breast cancer results in smaller lesions being detected, and thus have made them amenable to minimally invasive approaches. Several ablative modalities have emerged in recent years, which include cryoablation, radiofrequency ablation, microwave ablation, laser ablation, and ultrasound ablation. The purpose of this article is to review current clinical trials,

and past literature on various ablation techniques. Current reviews are not updated with recently completed or ongoing clinical trials[1,2].

CRYOABLATION

Cryoablation is a percutaneous technique in which a probe is inserted into the breast, and the tumor is treated through a freezing process. The benefits of cryoablation include the ability to perform the procedure in the office and with the use of local anesthesia, making it an attractive option for those patients with multiple co-morbidities. The probe is inserted through a small incision in the breast resulting in minimal scarring. Due to the fact that this is an ablative technique and does not involve removal of tissue, the cosmetic outcome is excellent.

Interestingly, there is also thought to be an immunological response to cryotherapy[3]. Cytokines are postulated to be released, and to modulate the immune response to the breast cancer. T cells are thought to stimulate cytotoxic lymphocytes and kill circulating metastatic cells. In a recent study presented at the 2014 American Society of Clinical Oncology Breast Cancer Symposium, 18 patients were divided into three study cohorts. One group was treated with cryotherapy, one with ipilimumab, a monoclonal antibody, and the final group with both cryotherapy and ipilimumab. T-cell tumor lymphocyte infiltrating density was assessed in each of these patients, and ranged from 2%-30%. Systemic immune response was measured by elevations in plasma interferon gamma, and a marker of CD 4 T cells. A greater than two times increased response in these two markers was considered positive. There were elevations in the group that received both the cryoablation and the ipilimumab, although two patients who received the ipilimumab alone also had elevated immune responses[4]. The author concluded that further studies with larger numbers are necessary to evaluate this finding, but it reinforces the idea that there is a clear systemic immune response to cryoablation.

Established criteria for treatment of breast cancers with ablation techniques are still evolving. A national phase Ⅱ clinical trial is still underway, evaluating cryoablation in the treatment of early stage breast cancers. Criteria for cryoablation of breast cancers include tumors less than 2 cm, unifocal cancers, and the absence of a significant intraductal component[5,6].

Initial research of cryoablation in the treatment of breast cancer involved cryoablation followed by excision of the cancer in a multi-institutional phase Ⅰ pilot study[5]. This study examined twenty-nine patients with invasive breast cancer. All the patients had tumors less than or equal to 2 cm. Twenty seven patients underwent cryoablation of their tumors, followed by surgical resection 4-6 wk later, consisting of either partial mastectomy (breast conservation) or mastectomy. The median age in this study was 52.5 years, with a range of 34-77 years old.

When the specimens were evaluated by the pathologists, 23 patients out of 27 patients had no evidence of invasive cancer. Four patients had residual DCIS surrounding the ablative zone. The study concluded that the size of the cancer was an important factor in terms of residual disease. There was no residual disease found in the eleven patients in the study who had tumors less than 1 cm. Sixteen patients had tumor less than 1 cm, and of these, 10 patients had no residual cancer. In three out of the five patients with either invasive lobular cancer or colloid cancer, there was residual invasive cancer. The size of the cancer was found to be larger on final pathologic evaluation than the original size estimated by preoperative imaging in these cases. With these findings, a phase Ⅱ study was recommended eliminating surgical excision. The criteria for inclusion were size of tumor less than or equal to 1.5 cm and those patients with less than 25% DCIS on the biopsy specimen. Additionally, the study concluded that those patients with a significant non-calcified DCIS component should be excluded from treatment with cryoablation.

Subsequently, a multicenter phase Ⅱ trial, ACOSOG Z-1072, has been completed. This study evaluated the use of cryotherapy in early stage breast cancer. Inclusion criteria included invasive breast cancers less than or equal to 2 cm. The study sought to evaluate the overall efficacy of cryoablation in invasive breast cancer, as well as to assess how well magnetic resonance imaging (MRI) can identify residual cancer after ablation[7]. Patients underwent cryoablation, followed by a contrast enhanced MRI within 2 wk, followed by surgery. Radiation and appropriate adjuvant systemic therapy were given according to standard clinical practice. Eighty-seven cancers were treated in this trial. Sixty (70.9%) showed no residual cancer, while 27 (31%) had residual DCIS or early stage breast cancer. 100% of patients with tumors less than 1 cm in size treated with cryoablation had no residual invasive cancer on pathologic examination of the specimen[7]. MRI showed no enhancement in 66 breasts, (75.9%). Interestingly, there were 21 (24.1%) failures, defined as residual invasive cancer and or DCIS, with no MRI enhancement after ablation.

In a study examining the efficacy of cryoablation without excision, Littrup *et al*[8] examined 11 patients, who had previously refused surgery. The patients had stage 1 to stage 4 breast cancers, and had 22 different foci of breast cancer. Tumor size ranged from 0.5 cm to 5.8 cm. The average age was 62.5 years old. The authors did not find any local complications to the skin or chest wall. Five of the patients who were included in the study had recurrent breast cancer. At a mean follow-up time of 18 mo, there were no local recurrences. Pain after the procedure was also evaluated. The mean pain scale rating was 0.3 on a scale of 0-10 at 24 h. Successful tumor treatment was measured by 1 cm of ice beyond the tumor. This was assessed using a combination of ultrasound, computed tomography, and

MRI imaging modalities, which was observed in all of the patients.

A national multicenter, clinical trial evaluating cryoablation without subsequent excision, is beginning to enroll patients. This trial is evaluating cryoablation in luminal a breast cancers, without excision, in women 65 years old or greater. This trial is predicated on the ACOSOG Z1072 trial, with the exception that the cancers are not subsequently excised. Adjuvant treatment is at the discretion of the treating physician. Local recurrence rates and disease free survival are being evaluated, as well as quality of life. This should provide important information as to the use of cryoablation alone in the treatment of breast cancer.

In summary, the current clinical trial evaluating luminal A breast cancers treated with cryoablation only, should provide important information about recurrence rates with this modality.

RADIOFREQUENCY ABLATION

Radiofrequency ablation (RFA) is another percutaneous tumor ablation modality, which utilizes heat to produce an area of cell death[9]. Advantages of the technique are the same as the other ablation techniques, including an office based procedure. Disadvantages of the technique are the pain associated with it. In a pilot study of seventeen patients, RFA and then excision was performed on invasive breast cancers that measured less than or equal to 1.5 cm[10]. Of the fifteen patients who ultimately completed the trial, three patients had positive margins. One patient had a tumor that was completely missed by the RFA. Similarly, Fornage *et al*[11] found that out of 21 patients who underwent RFA and then surgical excision, one patient had residual tumor beyond the zone of ablation. However, this patient initially had a 4 cm lesion, and underwent neoadjuvant chemotherapy. The authors concluded that patients who received neoadjuvant chemotherapy were not eligible for RFA.

Radiofrequency ablation has also been used to create an additional area of tumor sterilization, in a phase Ⅱ clinical trial, after local excision[12]. This study sought to examine whether radiofrequency ablation could reduce the rate of re-excisions for close margins, to possibly provide adequate local control, and obviate the need for adjuvant radiotherapy. One hundred patients were included in this study, with tumor sizes ranging from Tis to T3. Seventy-eight patients had margins that were considered negative, which was defined as a margin less than 2 mm. Twenty-two patients had margins which were less than or equal to 2 mm. Twelve of these patients had close margins, and three had focally positive margins. Seven patients underwent mastectomy for positive margins, and 2 patients subsequently chose mastectomy electively after RFA. Sixty-eight percent of all patients in the study with close or positive margins did not have re-excisions. Of the 100 patients, 24 patients underwent adjuvant radiotherapy. In the subset of patients who did not receive adjuvant radiotherapy, the mean follow-up was 62 mo ± 24 mo. During this time there were 2 recurrences near the tumor bed; two recurrences in a separate location in the same breast; and three recurrences along the biopsy track. The study also examined five year disease free survival and overall survival, which were 88% and 93%, respectively. Interestingly, the disease free and overall survival with adjuvant radiotherapy was 83%. The authors concluded that this is a safe method of treatment of small breast cancers.

In a prospective study, fourteen patients with invasive ductal carcinoma were treated with RFA and sentinel node biopsy. Breast MRI was performed 1 wk prior to RFA, and then 3 wk afterwards[13]. The goal of the study was to assess for residual lesions. The tumors were surgically excised one week after RFA. Five patients had areas of enhancement on post-RFA MRI, which was irregular. In two patients, enhancement of the initial lesion was noted, which signified failure of the RFA to ablate the cancer. Seven patients had no enhancement on post-RFA MRI. Interestingly, the patients with larger tumors had complete ablation, and no residual enhancement on post-RFA MRI. The authors concluded that breast MRI is able to detect residual abnormalities after RFA.

In summary, longer follow-up of patients treated with RFA is needed to assess for recurrence rates and for the appropriate imaging modality used for follow-up, but it holds promise as a minimally invasive treatment for breast cancer, possibly obviating the need for surgery.

MICROWAVE ABLATION

Microwave ablation is an additional percutaneous modality for treatment of breast cancer. Heat is made *via* tissue water agitation, achieved by electromagnetic frequencies of 900-2450 MHz[14]. Advantages of this technique are similar to other ablation techniques and include ability to treat lesions using local anaesthesia and good cosmetic outcomes. In a pilot study of 41 patients, Zhou *et al*[14] performed microwave ablation for breast cancers less than or equal 3 cm, followed by mastectomy. Eligibility criteria for the study included a unifocal tumor, with at least one centimeter between the skin and the tumor, and the tumor and the pectoralis muscle, as well as a limited intraductal component. The mean age of the patients was 55.5 years old. All of the patients had either invasive ductal carcinoma or DCIS. The pathologic analysis showed that 37 out of 41 cases were successfully ablated, when analyzed using alpha-NADH-diaphorase staining. There were 3 injuries to the skin and pectoralis muscle secondary to heat. The authors concluded that in small, unifocal cancers, microwave ablation may be a feasible option. However, since mastectomies were performed in all of the patients, there is no data from

this study on recurrence rates. Additionally, patients in this study underwent general anesthesia, so patient tolerance of the procedure was not assessed. Further studies are needed in larger groups of patients to determine patient tolerance and recurrence rates.

LASER ABLATION

Laser ablation is an additional percutaneous technique in which light is delivered into the tissue[15]. It has been evaluated mainly in terms of patient safety in various pilot studies. In a meta-analysis, Zhao *et al*[2] found a 13%-70% complete ablation rate of breast cancer utilizing laser ablation in the literature[1]. Dowlatshahi *et al*[16] studied 54 patients with invasive breast cancer. Median age was 60 years old, with a range of 42-80. The mean tumor size was 12 mm. Fifty patients had an invasive breast cancer, and four patients had DCIS. They were all treated with laser ablation, followed by standard surgical resection, 1 to 8 wk afterwards. The study found that the complete ablation rate was 70%. The authors concluded that it was feasible and appropriate to ablate breast cancers that were mammographically detected.

An additional study of laser ablation evaluated fourteen patients who were treated with laser ablation instead of surgery[17]. Three patients had stage 4 disease, and the treatment was for palliative therapy. Local control was demonstrated in five patients, with a disease free survival of 19-60 mo, in those patients without evidence of metastatic disease. The authors concluded that laser ablation was feasible for tumors less than 2 cm, with ductal histology, without exensive intraductal components, and vascular invasion. One patient had a skin burn, and one had a localized pneumothorax. Further large scale studies are needed to evaluate the local control rates, as well as complication rates.

HIGH INTENSITY FOCUSED ULTRASOUND ABLATION

High intensity focused ultrasound (HIFU) ablation differs from other ablation techniques in that it does not employ an incision in the skin or insertion of a probe into the breast for treatment. There is very limited data about the use of high frequency ultrasound ablation in breast cancer. In a phase Ⅱ randomized trial of HIFU ablation and breast cancer, 23 patients underwent HIFU ablation, with a mean tumor size of 3.1 cm[18]. All of the patients underwent HIFU ablation, followed by modified radical mastectomies. Complete ablation was demonstrated in 100% of patients. Small skin burns occurred in one patient. In a phase Ⅲ trial, 22 patients with breast cancer underwent HIFU ablation, followed by standard adjuvant therapy[18]. The study found that the recurrence free survival rate was 89%, and the five year disease free survival rate was 95%. The authors concluded that HIFU could be safe and feasible in the treatment of localized breast cancer, but that further clinical trials are needed.

In a study of 22 patients, with 23 breast cancers, 100% of post-procedural biopsies showed necrosis of the entire tumor[19]. Follow-up over 55 mo showed a 9% local recurrence rate, with one death. The five year disease free survival rate was 95%. Overall, larger numbers of patients need to be studied in order to determine the clinical use of this modality.

CONCLUSION

In summary, various modalities exist for the percutaneous treatment of breast cancer, which hold promise for the minimally invasive treatment approach for breast cancer. Larger clinical trials are needed for wide-spread applicability of these treatments to more advanced stage patients. Current clinical trials include the use of cryoablation without subsequent excision in the treatment of early stage breast cancers. Advantages of ablative techniques include percutaneous technique, minimal scarring, and an office procedure, thus avoiding taking the patient to the operating room. Disadvantages include inability to assess margin width and estimate of staging of breast cancer only by imaging. Additionally, hormone receptor status must be assessed on preoperative biopsy. Additional concerns include long term patient satisfaction with cosmesis, especially after adjuvant radiation, as percutaneous ablation modalities do not obviate the need for radiation, as well as other adjuvant treatment. As further research accumulates, ablation modalities may play a significant role in the future treatment of breast cancer.

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