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GUEST EDITORIAL

Cryoablation for Breast Cancer: No Need to Turn a Cold Shoulder

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It was not that long ago that it was suggested that mastectomy might not be necessary to treat breast cancer and that lumpectomy and whole breast radiation could be a suitable alternative. When Dr. Fisher and the NSABP first proposed doing a randomized trial of lumpectomy, lumpectomy, and radiation or mastectomy [1], it was met with tremendous skepticism. Many surgeons were quite vocal in their concern regarding local recurrence and the impact it might have on survival. Nevertheless, the trial took place, and today the majority of breast cancer patients in the United States avoid mastectomy. This sort of skepticism is not unusual in surgery. The idea that the gallbladder could be removed via a small umbilical incision, using laparascopic technology, was considered outlandish, and would fade away once an inordinate number of common bile duct injuries were reported. The concept of not diverting the colon after penetrating trauma, of the non-operative management of splenic injuries, of treating vascular disease with stents rather than surgery, or the suggestion of staging melanoma or breast cancer by removing just one or two lymph nodes rather than a complete lymph node dissection are all examples of changes in surgical paradigm that met tremendous resistance when first proposed but became standard surgical practice.

Today, a similar surgical reluctance surrounds the idea of in situ ablation for the treatment of breast cancer, and specifically the use of cryoablation. Cryoablation involves the introduction of a cryoprobe into the center of a tumor under ultrasound guidance in order to freeze the tissue to temperatures between −160 and −190°C. Several small studies have now demonstrated the safety, feasibility, efficacy, and limitations of cryoablation in the treatment of breast cancer [2–5]. Data from these studies, most of which involve cryoablation followed by standard surgical resection, are being used to design larger studies pursuing the ultimate goal of cryoablation; an alternative to lumpectomy. However, the idea of ablating a tumor and leaving it in place, without the opportunity for histological evaluation of the margins, seems like surgical heresy to many surgical oncologists. As with the shift from mastectomy to breast conservation, there is significant concern regarding leaving untreated disease, particularly in situ disease, leading to an unacceptable local recurrence rate. These are highly legitimate concerns, and certainly no one is advocating the immediate introduction of cryoablation as an alternative to lumpectomy. However, there are many potential advantages to cryoablation over lumpectomy that warrant its further investigation.

Cryoablation is technically simple and extremely safe, with minimal discomfort or side effects for the patient [6]. Successful cryoablation requires only moderate proficiency with ultrasound, which is rapidly becoming an essential component of any breast practice [7]. After percutaneous ultrasound guided placement of the probe within the center of the tumor, the procedure involves monitoring the formation of the iceball and occasionally injecting saline between the iceball and the skin to prevent thermal damage. After two freeze-thaw cycles, the probe is removed and a bandage placed over the incision. Because the freezing procedure itself anesthetizes the breast tissue, no local or regional anesthesia is required past the placement of the probe. Patients report minimal discomfort or use of narcotic pain medications afterwards [4]. Compared with lumpectomy, cryoablation would represent a tremendous reduction in the cost and morbidity of breast cancer treatment.

More importantly to the patient, the cosmesis achieved with cryoablation is superior to that obtained with lumpectomy. Even for small tumors, lumpectomy and radiation can be associated with not only a scar, but volume loss and asymmetry, retraction and concavity. Cryoablation leaves a scar no bigger than that of a percutaneous core biopsy. By leaving the frozen tissue in situ for resorption by the body, the breast maintains its natural size and shape, with no resultant volume loss or deformity. The cosmetic appeal of cryoablation is well known both to dermatologists, who use it routinely for the ablation of skin cancers, and breast surgeons, who use cryoablation for the treatment of fibroadenomas. Several studies have now demonstrated the outstanding safety, efficacy, cosmetic outcome, and patient satisfaction with cryoablation as a treatment of benign breast disease [8–10].

Another unique feature of cryoablation that may be exploited is the immunologic response initiated by the absorption of the frozen tissue. The uptake of intact tumor antigens by antigen presenting cells and the release of proinflammatory cytokines, both of which are hallmarks of cryoablation, represent the perfect equation for initiating a tumor-specific immune response. The ''cryoimmunologic'' response has been well documented in both pre-clinical and clinical investigations [3,11,12]. The use of immunotherapy in the treatment of breast cancer is fraught with challenges, and cryoablation alone, or more likely in combination with immune adjuncts, may overcome these obstacles [13,14]. It is feasible that this aspect may elevate cryoablation beyond lumpectomy in terms of local or distant recurrence. This may also further support the role of cryoablation in other aspects of breast cancer therapy, such as the treatment of primary tumors in the face of stage IV disease, the eradication of chest wall recurrences, or the ablation of metastatic foci as an alternative to metastatectomy.

Of course, none of this potential means anything if cryoablation of primary malignant disease is associated with an unacceptably high rate of local recurrence. The importance of local recurrence in the

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management of breast cancer, and its potential impact on survival, is increasingly clear [15–17]. But the present limitations or concerns regarding cryoablation do not argue against further evaluation, but rather the importance of well-designed clinical trials to optimize patient selection and identify patients who may not have had a complete response. Initial trials clearly demonstrate that patients with lobular carcinoma or an extensive intraductal component (EIC) are poor candidates due to the discordance of imaging findings with pathologic findings [4]. Tumor size is also an issue with present technologies, although this may be easily overcome with modifications to the equipment. The biggest objection to cryoablation, and by far the largest obstacle to be overcome, is the fact that with today's imaging, even the patient with a small, ductal carcinoma, who seems ideal for cryoablation, could harbor occult disease outside the iceball. Critics would argue that this disease would be missed by in situ ablation but recognized by histological analysis of the lumpectomy specimen (although the local recurrence rate after lumpectomy alone, even with negative margins, clearly demonstrates that even pathology misses much of this disease). However, this is not an indictment of cryoablation, but of our present ability to image invasive and in situ disease of the breast.

Our current imaging capabilities are the limiting factor with cryoablation, but as imaging technologies improve, so too will our ability to select appropriate patients and identify residual disease after treatment. Magnetic resonance imaging (MRI) may already be the key to this [5,18]. Pre-treatment MRI may select out patients with tumor extension beyond the predicted iceball, and post-treatment MRI (with or without biopsies from the periphery of the ablation zone) may identify patients who have residual disease, separating those that can proceed to radiation from those who should have lumpectomy. The role of MRI and cryoablation is the subject of ongoing and planned clinical trials. However, even if MRI is not the answer, it is only a matter of time before more sophisticated imaging can identify patient populations for whom in situ ablation is appropriate.

In the movie The Matrix, as the protagonist Neo is forced in front of an oncoming train, he is asked by his would-be killer, ''Do you hear that sound, Mr. Anderson? That is the sound of inevitability.'' Although Neo obviously escapes, surgeons have not always been that fortunate. There are several examples where surgeons failed to embrace promising new technologies, only to see the management of ''surgical'' diseases lost to other fields. One needs look no further than the fields of cardiac or vascular surgery. The shift from mastectomy to lumpectomy, from node dissection to sentinel node biopsy, from whole breast radiation to partial breast radiation, and from excisional biopsy to percutaneous biopsy all demonstrate the direction breast cancer management is moving; equally effective but less drastic forms of treatment. Cryoablation of breast disease is the next logical step. Cryoablation of primary prostate or renal cell carcinoma is already accepted therapy. In breast cancer, almost all essential information can be obtained from a core biopsy, including genomic analysis, precluding the need for surgical resection for prognostic information. Widespread screening has already greatly reduced the median size of breast tumors and it is predicted that soon over half of all new breast cancers will be less than 1 cm, ideal candidates for cryoablation. Further improvements in both cryoablative and breast imaging technologies will only expand the applicability of this approach. If we fail to establish ourselves as leaders in this field, and guide the clinical trials and basic science research that establish its efficacy and proper implementation, then radiologists certainly will. To avoid being left behind in the management of another ''surgical disease,'' surgeons should embrace this new technology, and not give it the cold shoulder.

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