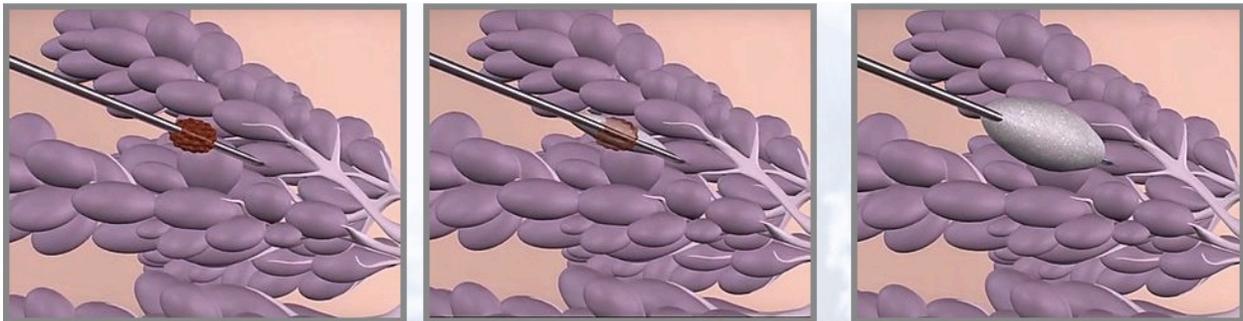


Breast Cancer Care During A Pandemic: The Right Time for Cryoablation

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The COVID-19 pandemic has placed a tremendous burden on the healthcare system, resulting in the postponement of elective surgical procedures to preserve limited hospital resources and minimize viral transmission. The American College of Surgeons, the American Society of Breast Surgeons, and multiple other surgical and cancer societies have endorsed a policy that recommends at least a 1.5-4 month delay of surgery for conditions that are not immediately life-threatening, including most cases of breast cancer. In place of surgery, the societies recommend a 6-12 month course of pre-operative anti-estrogen medications for most women with estrogen-sensitive breast cancer as a way of reducing cancer extent or preventing further cancer growth while withholding surgery until after the pandemic has ended. This recommendation potentially impacts the care of 70% of women diagnosed with breast cancer today.

Although surgery delays of a few months are unlikely to reduce breast cancer survival, an unfortunate consequence of surgical delay is the tremendous amount of patient anxiety caused by the postponement of surgery for several months. Anxiety might also be caused by fear that surgery delays might lead to further tumor growth or spread, and well as by uncertainty about how long the pandemic will last. Will this pandemic be followed by yet another cycle of widespread infections that might cause additional delay of elective surgery? When the pandemic ends, will the national backlog of elective surgery further delay the scheduling of breast cancer operations, and what will determine the order of priority of elective surgery for patients awaiting surgery—date of diagnosis, tumor stage, patient age, level of insurance, or some subjective factor? Will financially-strapped hospitals remain open and sufficiently staffed to handle the backlog of elective cases? Will the new requirement of coronavirus testing before surgery and persistent uncertainty about the accuracy of coronavirus testing cause additional delay? If elective surgery is available in one community but not another, will a patient have the freedom of movement, personal financial means, and insurance coverage to travel to another community for breast cancer surgery that might not be available to her locally?

Completely missing from the discussion about the management of breast cancer during the pandemic is cryoablation or tumor freezing. Although cryoablation has yet to be adopted as a standard treatment option for breast cancer, unconventional times call for unconventional measures, like the unprecedented policy to postpone elective breast cancer surgery. By these new standards, cryoablation warrants special consideration as a practical, non-operative, healthcare resource-saving strategy for treating breast cancer.

Cryoablation an outpatient, office-based, minimally-invasive procedure performed under local anesthesia the reduces burden on the healthcare system by eliminating the need for a patient to undergo surgery. Using a handheld, needle-like instrument and liquid-nitrogen, breast cancers are typically treated with cryoablation in two freeze-thaw cycles in as little as 30-45 minutes, reaching a central temperature of -180 C. As an alternative to surgery, cryoablation reduces the side effects, psychological burden, and cosmetic impact of breast cancer treatment. Women are spared the cost, discomfort, and potential complications of general anesthesia and breast cancer surgery. Breast appearance and patient satisfaction are likely to be superior with cryoablation given that the incision is small (~3 mm) and no breast tissue is removed that could alter breast size or shape. Furthermore, the cryoablation procedure is essentially painless due to the pain-relieving effect of cold temperatures. Women are able to return to non-strenuous activities the day after the procedure. All things considered, cryoablation might be the perfect compromise that balances the goals of early cancer detection and treatment of breast cancers with the desire for a less invasive, less morbid, and less healthcare resource-intensive approach to managing breast cancer.

Breast cancer cryoablation builds on a significant body of preliminary data and historical experience in the use of cryoablation for the treatment of benign and malignant breast tumors. The largest published study about cryoablation was the American College of Surgeons Oncology Group (ACOSOG) Z1072 trial, which sought to determine the rate of successful tumor freezing in 99 women with stage I breast cancer treated initially with cryoablation followed 4 weeks later by lumpectomy or mastectomy. The Z1072 trial documented complete tumor kill in 100% of tumors <1 cm and 92% of lesions \leq 2 cm, and these findings later influenced the design of the FROST Trial (currently enrolling, www.clinicaltrials.gov, #NCT011992250) and the Ice3 Trial (active, non-enrolling, www.clinicaltrials.gov, #NCT02200705). These two U.S. clinical trials are currently examining the use of cryoablation for stage I breast cancer treated without subsequent lumpectomy or mastectomy. Interim results of both trials demonstrated 1.1% and 1.4% local recurrence rates with 1-year short-term follow-up. In Japan, a clinical trial of stage I invasive ductal carcinomas managed with cryoablation, sentinel node biopsy, anti-estrogen medication, and whole breast radiotherapy without subsequent surgical removal reported a 0.98% local recurrence rate among 304 women with 6 years of follow-up. The Japanese results provides confidence in the ability of cryoablation combined with radiation and/or anti-estrogen medications to achieve long-term local control similar to lumpectomy in eligible patients. As with lumpectomy, there is a risk of cancer recurrence in the vicinity of the cryoablation. The fact that invisible, microscopic cancer cells might remain around the borders of the cancer tumor is why radiotherapy and/or drug therapy remain important in the overall management of most women treated with either cryoablation or lumpectomy.

In the context of non-operative management of breast cancer, opportunities also exist for the non-operative management of the lymph nodes. Since 2016, the Society of Surgical Oncology's "Choosing Wisely" Campaign, an initiative of the American Board of Internal Medicine, has encouraged surgeons to avoid "routine sentinel node biopsy in clinically node-negative women \geq 70 years of age with hormone receptor-positive, HER2/neu-negative (stage I) invasive breast cancer." This recommendation is based on the low estimated risk of lymph node metastasis in this group of women as well as the low rate of lymph node recurrence when lymph node surgery is omitted among these patients. Whereas selective omission of sentinel node biopsy is now widely accepted in women \geq 70, withholding sentinel node biopsy is more controversial in younger women for whom the status of the axilla has remained a key factor in evaluation the need for chemotherapy. However, the importance of the lymph nodal stage has been gradually eroded by growing confidence in the ability of tumor genomic assays likely Oncotype Dx and MammaPrint as tools for assessing the benefit of chemotherapy, regardless of patient age or

tumor size. For example, the Oncotype Dx and MammaPrint tests are now capable of identifying women that benefit little from chemotherapy despite the presence of high-risk cancer features, including positive axillary nodes, further reducing the need for lymph node surgery and the use of related healthcare resources.

Applications of Cryoablation

Although there is a lack of long-term evidence supporting the unrestricted use of cryoablation, there is considerable preliminary and anecdotal data to warrant consideration of cryoablation as a definitive or temporary, stopgap measure in specific women with the following conditions who are anxious about delaying surgery or who simply refuse traditional surgery.

A. Stage I invasive breast cancer

Patients with stage I (≤ 2 cm) breast cancer may undergo cryoablation of the breast cancer a definitive therapy with optional surgical removal of the cryoablation site for women who may later require surgery for other reasons, such as for removal of suspicious lymph nodes.

B. Stage II invasive breast cancer

Based upon experience with stage I breast cancer, patients with Stage II (2cm-5 cm), low-risk, lymph node-negative breast cancer may receive upfront cryoablation for management of breast cancer combined with anti-estrogen medication if the tumor is estrogen sensitive. Lymph node surgery with or without surgical removal of the cryoablation site may be performed when it can be conveniently scheduled. Lumpectomy or mastectomy can be performed at a later date if follow-up breast imaging suggests the presence of residual or recurrent disease.

C. Stage III invasive breast cancer

Drawing on experience from liver tumor cryoablation, patients with breast cancers more than 5 cm may undergo cryoablation using multiple overlapping cryoablation treatments in a single session to treat the cancer plus a surrounding margin of normal tissue. Cryoablation might eliminate the need for surgery in patients refusing breast surgery or provide temporary control of tumor growth until the patient is able to conveniently undergo mastectomy with or without breast reconstruction. The need for anti-cancer medications (e.g. chemotherapy and/or endocrine therapy), radiotherapy after surgery, or radiation after cryoablation should be guided by the cancer extent and/or cancer biology.

D. Stage 0, ductal carcinoma in situ (DCIS)

As an office-based procedure typically performed under ultrasound-guidance, cryoablation is usually restricted to cancers that are visible by ultrasound. DCIS is usually visible by mammography, but not usually visible by ultrasound. However, an area of DCIS detected by mammography can be converted to an ultrasound-visible target for cryoablation by the insertion, under mammographic guidance, of one or more ultrasound-visible biopsy site markers into the area of DCIS.

E. Recurrent breast cancer

Similar to primary breast cancer, a recurrence of invasive breast cancer or DCIS following prior lumpectomy or cryoablation can be managed with cryoablation if breast imaging studies confirm that the recurrence is limited to a small area.

F. Stage IV breast cancer

The debate continues regarding the benefit of lumpectomy or mastectomy in the setting of stage IV breast cancer. However, cryoablation may be offered as a low-risk solution to control the breast tumor while drug therapy and possibly radiotherapy are administered to control the distant metastatic site(s).

G. Positive lymph nodes

The current standard of care for patients with positive lymph nodes is the surgical removal of affected lymph nodes, the goal of which is to reduce the risk of recurrence in the lymph node area, eliminate the lymph nodes as a source of cancer spread, and to allow complete cancer staging by counting the number of positive lymph nodes. However, with the biology of the primary tumor playing an increasingly important role in predicting the risk of distance recurrence and the response to systemic therapy, the actual number of positive axillary lymph nodes is not as important as it used to be. Furthermore, the ability of radiotherapy to effectively control microscopic cancer in the lymph nodes provides an opportunity to limit the extent of lymph node surgery or cryoablation to the grossly-abnormal axillary nodes in situations when complete removal of lymph nodes with surgery is either infeasible or refused by the patient. Appropriate caution must be applied when ablating lymph nodes near large nerves and veins in the armpit.

Conclusion

Recent national policies recommended the delay of elective breast surgery to preserve limited hospital resources and to decrease transmission of COVID-19. Although short-term surgery delay is unlikely to reduce breast cancer survival, delay of breast cancer surgery has the capacity to greatly increase the psychological burden of a woman diagnosed with breast cancer. Breast tumor cryoablation is an outpatient, minimally-invasive procedure that is already emerging as a substitute for surgery in early-stage invasive breast cancer. It can serve as a stand-alone treatment for some patients and a temporary, stopgap measure for others until surgery can be conveniently scheduled. Access to cryoablation would be greatly aided by relaxation of current insurance coverage restrictions that now form a barrier to the inclusion of cryoablation in the comprehensive management of breast cancer. In the meantime, cryoablation can expedite treatment in some women, minimize the risk of further tumor growth, reduce the anxiety of prolonged surgery delay, and save limited-healthcare resources.