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Cryoablation Of Breast Cancer

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Abstract:
Cryoablation could be an alternative to surgical excision of breast cancer. The cytotoxic potential of cryosurgery has been seen in both animal models and studies conducted on humans. There are several advantages to be gained from ablation performed at very low temperatures and these include the method's simplicity, lack of pain, low morbidity, cost-effectiveness, and potential for positive cryo-immunologic effects.

Introduction:

Breast cancer is the most common malignant tumor and leading cause of cancer-related mortality in women. Although the problem still remains dangerous, some positive changes in the situation have been observed: due to dynamic development of imaging and population based screening programs there is now in present reduced mortality and the median diameter of tumors has decreased from 2 cm in back in 1990 to 1 cm. [(1)] Another reduction concerns a decrease in the aggressiveness of the local treatment: most patients are suitable candidates for breast conserving therapy (BCT) instead of mastectomy.

Cryotherapy of breast tumors can be a accessible method for the eradication of malignant breast tumors. It has proven value in the destruction of cancer cells within the cryozone in different malignancies (skin cancers, liver and prostate tumors). The procedure can be performed in an outpatient clinic under local anesthesia, without the need for an operating theater and the team usually involved in surgical interventions performed under general anesthesia. Thus, the method is a cost-effective one. Furthermore, there should be no cave within breast parenchyma which usually follows the wide excision of a tumor, which causes breast asymmetry and poor cosmetic results. There is even another advantage of cryosurgery and this concerns its potential to enhance immunological response following cryoablation. [(2)]

Discussion:

The outcome of improved results via the application of low temperatures in the treatment of women with breast cancer were described for the first time in 1850 by Arnott, who used iced saline solutions on women with locally advanced breast tumors[(3)]. The technical development of adiabatic expansion systems introduced new cryogens such as liquid air, nitrogen and oxygen. Eradication of breast tumors through cryoablations seems to be feasible due to the superficial localization of the glands and thus their accessibility for both cryo-probes and imaging devices, and the absence of intervening vital organs within which could be damaged during the procedure leading to serious complications [(4)]. Vessels greater than 5 mm in diameter avoid damage during cryoablation due to their own blood flow [(5)]. According to Kaufman, cryoablation of breast cancer should be reserved for patients with small, unifocal tumors. Criteria for cryoablation exclude invasive lobular cancer as a histo type, an extensive ductal carcinoma in situ (DCIS) component and a tumor diameter larger than 15 mm [(1)]. Sabel et al. describe more than 25% of DCIS in core biopsies as contraindication [(6)]. According to Littrup et al., who performed cryoablation of tumors in clinical stages I-IV with a multi-probe freeze approach, isotherms within cryozones can be accurately controlled and such cryoablation enables the destruction of much bigger lesions, up to 7 cm in diameter [(7)]. Despite the significant cryodestructive potential of the multi-probe freeze approach, we must remember that cryodestruction is not a substitute for mastectomy. In a report on a multi-institutional trial studying cryoablation of early-stage breast cancer, Sabel et al. maintain that "every attempt should be made to exclude patients who may have a significant intraductal component" [(6)]. The procedure can be done either with a single cryoprobe or with more the one, at least two cryoprobes placed percutaneously under local anaesthesia directly into the lesion under US or MRI guidance. In cases of its localization close to the skin, even 1-2 mm from the surface, saline injections enable acquisition of the required 1 cm margin and protect skin from necrosis. Warm bags of saline and vigorous rubbing also prevent ice from penetrating through the skin and possible complications [(7)(8)]. Roubidoux et al. demonstrated good results from the cryoablation of nine malignant breast lesions with ice-balls covering the tumor plus an 8-10 mm margin [(9)]. A study performed on an animal model by Rabin et al. [(9)] showed an even narrower, 5 mm margin to be adequate in the ablation of a sheep breast tumor.

However, there are only a few number of reports concerning the efficacy of malignant breast tumor cryoablation in humans; surgical excision with margins free of cancer cells combined with radiotherapy or mastectomy are the golden standard of locoregional treatment, while systemic therapy is administered depending on the analysis of prognostic factors and comorbidities. Most studies have investigated the effectiveness of very low temperatures in pathological examinations of excised breast tumors after previous cryodestruction. Rand et al described excision of a previously cryoablated tumor. An invasive ductal cancer of a diameter larger than 1.5 cm had been cryodestructed, then excised and examined under a microscope; the authors found no viable cancer cells within the specimen. "Cryolumpectomy" should be effective not only

through destruction of tumor cells; rather, excision of the frozen tumor encompassed by an ice-ball could prevent spillage of cancer cells within the tumor bed [10]. The frequency of local recurrences in the cryoablated group (80 patients) was much lower than in the group of patients who underwent lumpectomy without cryosurgery (76 patients): 1.3% vs. 9.2%. The 3-year overall survival in the first group was 85.7% compared to 65.0% in the second, control group [11]. Tafra et al. described a similar situation after they had excised frozen breast tumors. Furthermore, they showed cryo-assisted localisation (CAL) to be an interesting and effective alternative to hook-wire localisation of non-palpable breast cancers. Excision of palpable ice-ball encompassing tumors is much easier for the surgeon than resection with use of the hook wire, often displaced during manoeuvres in the fatty tissue of the breast. Furthermore, in this study margins were free from cancer cells, while the volume of the resected breast parenchyma was lower compared to the traditional method [12]. In another study, Tafra et al. compared CAL with needle-wire localisation in 310 patients: positive margin status was similar in both groups (28% vs. 31%), while the volume of the specimens was significantly lower in the CAL group (49 vs. 66 mL). CAL was easier to perform, the quality of the specimen was better, short term sampling and patient satisfaction were better in the first group. Although invasive cancer positive margin rates were lower in the CAL group (11% vs. 20%), there were higher ductal in situ positive margin rates (30% vs. 18%) [13]. Pfleiderer et al. performed cryodestruction of 16 breast cancers with the use of one cryoprobe for each lesion and observed no major side effects. Mean tumor diameter was 21±7.8 mm, and the diameter of the cryoprobe was 3 mm. The authors used one cryoprobe for each tumor, placed under US guidance. There were two freeze/thaw cycles; the median diameter of the ice ball was 28±2.7 mm. The lesions were further excised within 5 days following cryoablation. Rand et al. treated one patient with ductal cancer of a diameter larger than 1.5 cm (1 cm × 2 cm), which was cryoablated, then excised and examined under a microscope. No viable cancer cells were found in the specimen [10]. abel reported the effectiveness of cryoablation of 100% of tumors which were not larger than 10 mm and those of a diameter less than 15 mm but without in situ components. Cryoablation was not effective in tumors larger than 15 mm. The procedure was performed with the use of a single cryo-probe for each case [6]. Roubidoux et al. performed cryosurgery of nine malignant tumors followed by excision 2-3 weeks after cryoablation. The mean size of the tumors was 12 mm (range: 8-18 mm). Seven of nine patients had no residual disease, while there was one small invasive focus in one case and extensive multifocal ductal in situ neoplasm in another one. These residual lesions were localised at the posterior margins of the cryodestructed tumors; their visibility is lower in US. The extensive intraductal component was occult in US [14]. There are also studies describing the effect of cryoablation in cases when tumors have been left for follow-up without excision. A case report published by Staren described cryoablation of two separate but proximate synchronic tumors (0.8 and 0.5 cm in diameter; invasive lobular carcinoma in histology) present in the same breast and their total necrosis; the place of cryoablation was further assessed in pathologic examination of the specimen obtained through core biopsies. There were no viable cancer cells 12 weeks post procedure [15]. Littrup et al. described cryodestruction of 22 cancer foci in 11 patients in clincal stage I-IV, who refused surgery. Tumors were larger than those cryoablated in the forementioned studies: mean lesion diameter was 1.7±1.2 cm (range: 0.5-5.8 cm). There was also another difference concerning the number of cryo-applicators used for ablation. The authors performed multiprobe placement (with an average of 3.1 probes) under visualisation of cryoprobe position and ice-ball in US and computed tomography (CT). There were no significant complications following the procedure and, most importantly, there were no local cancer recurrences within breast MRI imaging follow-up lasting 18 months. Cryoablation was well-tolerated by patients: the average value of pain self-assessment was 0.4 on a 10-point scale, with the highest value 4 in two cases. Pain was well controlled with analgesics. There were no breast distortions after treatment [7]. Cryotherapy has been described in the treatment of patients with locally advanced and/or disseminated breast carcinoma. The application of very low temperatures, either with a cryo-probe or spray provides benefit by inhibiting bulky tumor growth and decreasing odor, cryodestruction is much more than the last method of palliative treatment performed for psychological reasons. The positive effect of cryoablation on inoperable cancers was described by Tanaka in four out of nine patients. He reported not only relief of pain and bulk reduction, but also prolonged survival [16]. Neel reported tumor-specific immunity in an animal model to be consistently higher after cryoablation than when measured after surgical excision [16]. It seems that both stimulation and suppression can be triggered as a response to cryoablation. According to Sabel, the effect depends not only on the tumor type, but also on the technique: method of freezing (the length of time the lowest temperature is maintained, number of freeze/thaw cycles and the rates of the particular phases), volume of cancer frozen and the time of assessment [17]. This shows cryosurgery to be especially attractive for patients with dissemination to skin, chest wall recurrences and/or bulky tumors [18].

Conclusion:

1- Cryoablation of malignant breast tumors can be an attractive alternative to surgery for patients not suitable for the standard form of treatment due to general contra-indications and/or a lack of consent for surgery.
2- Proper staging allows cases with extensive intraductal components to be identified and excluded. The procedure is cost-effective and can be performed in an outpatient clinic.
3- The lack of need for general anaesthesia and the short recovery period could be highly attractive, especially for women with comorbidities which might increase the risk of perioperative complications.

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