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냉동요법을 이용한 유방암 치료시 발생하는 조직학적 변화

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Histopathological Study of Breast Cancer After Ultrasound Guided Cryotherapy Ablation

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Abstract

배 경: 유방암의 조기발견율의 증가에 의한 유방보존술이 증가하고 있으며 1cm 이하의 병변을 포함하여서 최소침습적 시도에 의한 종양의 제거방법이 다양해지고 있다. 최소침습적 시도 중 냉동요법을 이용한 방법은 아직 많은 보고가 없는 상태이다. 이에 본 연구는 냉동요법을 이용하여서 유방암 조직을 치료하였을 때 유방암 조직의 괴사율과 조직학적 변화를 알아보고자 본 연구를 시작하였다.

방 법: 유방암으로 본원에서 수술을 받은 6명의 환자를 대상으로 하였다. 환자의 평균연령은 63세였으며 종양의 평균 크기는 술 전 초음파 소견상 4.3cm였다. 환자는 정상적으로 유방암 수술을 받았으며 절제한 유방암조직을 가지고 냉동요법을 시작하였다. 3mm크기의 냉동치료를 위한 카테터를 이용하여서 초음파를 이용 종양의 가장자리에 카테터가 위치하도록 하였다. 두 번의 얼리고 녹이는 과정을 반복하였다. 얼리는 시간은 10분 이였고 녹이는 시간은 5분 이였다. 시술을 마치고 H&E 염색을 통해서 조직의 괴사유무 및 종양조직의 유무를 판단하였다

결 과: 냉동요법에 의해서 생성된 냉동된 영역의 지름은 2.8cm이였다. 2명의 환자의 조직에서는 완전괴사가 관찰 되었고 4명의 조직에서는 유방암세포가 여전이 남아 있었다.

결 론: 냉동요법을 이용한 유방암의 치료는 아직까지 많은 연구가 필요하다고 생각한다. 냉동요법을 이용한 유방암의 치료에서 가장 중요한 인자는 종양의 크기이며 2cm 이하의 종양을 대상으로 하여야 할 것으로 생각된다. 여기에 대해서는 많은 연구가 필요하다.

Key words : Cryotherapy; Cryoablation; Breast cancer; Ablative therapies

Introduction

Widespread use of screening mammography and breast cancer awareness is detecting more women at younger ages with earlier stages tumors. Less invasive procedures have been increasingly used for the treatment of breast cancer due to a lack of benefit from more radical forms of therapy. Cryotherapy has been used for ablation of both malignant and benign tumors for a long time. In 1850 treatment of a malignant tumor by cooling to low temperatures was reported for the first time. In 1963 cyrosurgery underwent a renaissance and it has since been used for the treatment of malignant prostate and liver tumors. However, the practice is not new and cryotherapy has been used for more than 30 years in the treatment of small as well as advanced and unresectable breast cancer. Cryoablation destroys tissue through localized freezing. Maximum tissue destruction is achieved through multiple freeze-thaw cycles, which are determined by the size of the tumor. In contrast, fewer studies have been published in breast cancer in humans and few of them have focused on the microscopic lesions of breast cancer and normal breast tissue after cryotherapy. In this study, we analysed the histopathological aspects of tumor in 6 patients who underwent tumorectomy before cryotherapy.

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Material and methods

Between April 2007 and October 2007, 6 patients with ultrasound (US)-visible primary invasive breast cancer were enrolled in the study approved by the local medical ethics committee. All participating patients signed written, informed consent. The clinical characteristics of the patients are listed in table 1. The patients were between 50 and 82years (mean age: 63 years). The diagnosis of invasive breast cancer was made on a large-core needle biopsy before cryotherapy. The mean size of the tumor was 4.7cm on US. There were 6 invasive ductal carcinomas of varied histological grade. They all underwent ultrasound-guided cryoablation after surgical resection. Postoperative radiotherapy and hormonal therapy were later performed according to the general guidelines for breast cancer therapy.

Table 1. Summary of clinical, imaging and pathological data of patients before cryotherapy

Patiet No.	Age (yr)	Tumor Type	Histologic Grade	Tumor Localization	Clinical Size(cm)	Ultrasound Size(cm)
1	65	IDC	G2	Rt upper	5.0	5.0
2	60	IDC	G3	Lt upper	6.0	5.5
3	50	IDC	G3	Rt lateral	2.0	2.0
4	82	IDC	G2	Rt lower lateral	6.0	6.0
5	50	IDC	G3	Lt lower lateral	2.0	2.0
6	50	IDC	G2	Lt upper	6.0	6.0

IDC, invasive ductal carcinoma; Histologic Grade, Elston&Ellis Classsification of Histologic Grade

Cryoablative procedure

Cryotherapy was done at resected breast cancer specimen containing surgical safe margin. Cryotherapy was performed using a CRYO-HIT TM System-3 (Galil Medical, Yokneam, Israel). It is a gas system using argon as the cooling agent, which was designed to create probe temperatures of −180℃. One cryotherapy needles were inserted in the tumor under US guidance. The tip of the cryoprobe was placed via the centre of the lesion at the opposite margin of the tumor (Fig. 1).

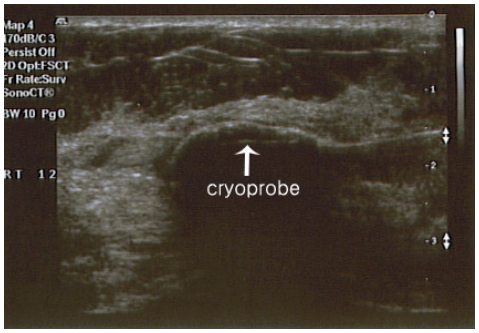

Fig. 1. Ultrasound-image of the final position of the cryoprobe

One needle was used for tumors <1.2Two freeze cycles with durations of 20min were performed and separated by a 5min thaw cycle. The target freeze temperature was −180℃ according to the setting of the cryoprobe. US control was performed during the thaw cycle and after the second freeze cycle.

Histological analysis

Tumorectomy specimens were fixed in 4% formaldehyde. They were then sliced to grossly determine the dimensions of the region exposed to cryosurgery and photographed. The cryoablation region and surgical margins were sampled, embedded in paraffin, and sections stained with Hematoxylin-Eosin (HE). Tumor destruction or residual invasive and/or in situ carcinoma was documented. Staging of the residual tumor was based on TNM/AJCC staging system (6th ed.)

Results

In 2cases, the targeted tumor area was completely included in the cryozone. The cryozone or "iceball" is a well defined yellow round lesion with a central hemorrhagic core. In this case, the tumor, a white stellate mass with irregular borders is found adjacent to the cryozone. Residual tumor in the cryozone is illustrated in Fig.ure 2.

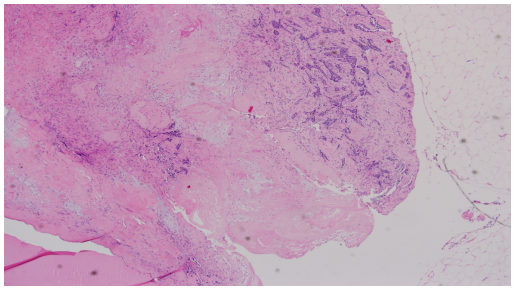

Fig. 2. post cryotherapy histology. Hyaline necrosis with hemorrhage in the centre of the cryo lesion Tumor area was replaced by dense fibrosis partly admixed with coagulative necorsis, usually without recognizable tumor parts.(H&E stain, x40)

Tumor response

The pathological evaluation of the tumor after cryotherapy is summarized in Table2. The tumor response after cryotherapy was very variable. In 2 cases, there was no evidence of residual invasive carcinoma (IC) or ductal carcinoma in situ (DCIS). In those cases, the tumor area was replaced by dense fibrosis partly admixed with coagulative necrosis, usually without recognisable tumor parts. In 4 cases, there was evidence of residual IC of various sizes with or without DCIS (inside or outside the cryozone).

Table 2. Summary of histopathological evaluation of tumors after cryotherapy

Patient No	Residual invasive carcinoma type	Size (cm)	Histology in Tumor area	DCIS inside cryozone	DCIS outside cryozone
1	Yes	2	No tumoral necrosis	Yes	No
2	Yes	3.5	No tumoral necrosis	Yes	No
3	No	0	Fibrinoid necrosis	No	No
4	Yes	3.5	No tumoral necrosis	Yes	No
5	No	0	Fibrosis and fibrinoid necrosis	No	No
6	Yes	3.5	No tumoral necrosis	Yes	No

DCIS, ductal carcinoma in situ.

Complications of cryotherapy

Skin ulceration and/or necrosis were seen in five patients. The cryozone was in contact with the skin. No other complications were reported.

Discussion

The present study demonstrates that cryotherapy is a feasible procedure in the treatment of breast cancer without severe complications.[1] In this study, cryotherapy allowed variable and unpredictable tumor destruction. Only two patients (33%) had a complete response without remnants of viable tumor cells. Four patients (66%) had partial response with some degree of tumor downstaging. In previous studies of breast cancer cryoablation, the technique has been reported as being more successful in destroying invasive carcinoma (IC) rather than ductal carcinoma in situ (DCIS) as well as destroying smaller (<1.5tumors.[2, 3, 4] In their latest study in 2005, Pfleiderer et al. studied cryoablation under ultrasound guidance on 30 breast tumors. The tumor diameter was 15or smaller (mean: 12mm). The tumors were resected within 6 weeks of cryoablation. In five patients, there was remnant of DCIS beyond the margin of the cryozone. In 24 patients, no viable tumor cells were found. No severe side effects were observed.[5, 6] Cryoablation induces tissue destruction through at least three important mechanisms: intracellular ice formation and osmotic injury, both direct effects; and ischemia, an indirect mechanism.[7, 8] A possible theory might be a greater sensitivity of IC to hypoxia-ischemia, which as mentioned above is the dominant injury mechanism of cryotherapy. Hypoxia-inducible factor-1 (HIF-1) activates the transcription of many genes controlling glucose and high-energy phosphate metabolism, growth factors, erythropoiesis, heme metabolism, iron transport, vasomotor regulation, and nitric oxide synthesis and, thus, may increase the survival of tumor cells under hypoxic conditions.[9] Also, as in chemo or radiotherapy, the stage of the cell cycle can also influence cryosensitivity. Besides these biological factors, the location of DCIS in "the tumor" might also explain to some extent it's apparent greater resistance to cryosurgery.[10] Indeed, in many cases the DCIS is more often located in the peripheral area, which is

further away form the cryoprobe and thus less sensitive to cryoinjury.[11, 12]

In cases where the procedure does not destroy the whole tumor (for example in tumors >1.5cm), cryotherapy (with sublethal temperature) might behave similarly to chemotherapy, destroying susceptible clones and allowing cryoresistant clones that produce stress-induced protective (cold shock or HIF-1 like) proteins to survive.[13]Besides tumoral destruction due to direct and indirect damage, cryoablation might also have additional antitumor effects.One of the principal advantages of cryoablation over conventional treatment and other ablative techniques is that cryosurgical destruction of tumor could elicit an antitumor response and improve localized or secondary destruction of tumor cells (cryoimmunology).[14, 15]Because nearly all ablation studies are retrospective and have been coupled with postprocedure resection in order to evaluate the efficiency of cryotherapy, the natural history of the primary tumor after cryoablation, with or without tumoral response, is not known and can be only guessed from the tumor response to cryotherapy on tumorectomy specimens.[16] Although cryotherapy does not achieve complete tumor ablation in every case, even partial tumor sterilization might still be satisfactory because adjuvant radiotherapy might destroy the residual tumor cells.[17]In the literature, there is only one report of a cryotherapy treatment not followed by surgical excision. It could have been of interest to correlate local destructionof the tumor by the cryotherapy with imaging studies and with precise temperature measurement within the tumor or around it using thermosensors. In cryotherapy and other ablatives techniques used for small tumors, ablated tissues remain in the breast for resorption over time. Hence, the ability to pathologically examine the specimen is compromised.[18] Therefore, histopathological and biological information regarding the tumor must be obtained in advance using tissue biopsy and imaging techniques which usually give enough morphological and biological informations about the tumor. A better knowledge and definition of the pathological response of the tumor to cryotherapy in lumpectomy specimens will also provide a base whether a post cryotherapy biopsy or lumpectomy is necessary in order to evaluate residual or recurrent disease.

Conclusion

Cryotherapy allows variable tumoral destruction which is not influenced by tumor size or other histological parameter. Cryotherapy of breast cancer is an attractive minimally invasive technique which might be used as an adjuvant or neoadjuvant treatment or to guide lumpectomy; however, as with all ablative techniques, prospective randomised trials are needed to determine its long-term effectiveness on breast cancer.

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