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CORR Insights®: Freezing Nitrogen Ethanol Composite May be a Viable Approach for Cryotherapy of Human Giant Cell Tumor of Bone

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Where Are We Now?

The goal of cancer care is to target the neoplasm and spare uninvolved tissues. We exploit the differential effect of our various therapies on tissues to achieve better local and systemic control of

tumors. Despite progress in our ability to ablate tumors and preserve functional anatomy, diseases still relapse locally and our therapies cause collateral damage, compromising patient function. Adjuvant therapies promise to improve tumor control and minimize damage to uninvolved tissue. For that reason alone, oncologic surgeons and patients need adjuvants.

Cryotherapy remains controversial despite more than 50 years of clinical advocacy and application in orthopaedics. This adjuvant exploits both mechanical and biologic mechanisms. Practitioners have a poor understanding of how it actually works and how to best apply it. Since cryotherapy may

cause both beneficial and detrimental effects, many surgeons are leery about its use.

Where Do We Need To Go?

Refinement of the tumor ablation technique and better protection of innocent tissues is needed if this adjuvant is to persuade skeptics and achieve its clinical promise. The absence of clinical trials with relevant control groups leaves many practitioners dubious of the value of cryosurgery as an effective adjuvant. Therefore, we need to pursue: (1) Professional education, (2) technical refinement, and (3) comparative outcomes research.

We must rectify the widespread misunderstanding of how cryosurgery works by educating surgeons and investigators (Fig. 1). The oft-cited mechanical sequence that intracellular ice crystals disrupt organelles and rupture the frozen cells themselves is an incomplete and temporally inconsistent explanation [2]. This simplistic

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mechanical sequence fails to consider the unique chemical characteristics of water and the physical- and protein-chemical changes involved. Cryosurgery causes intra and intercellular dehydration, changing the Gibbs–Donnan equilibrium of solutes in the cell (which is the equilibrium governing the sometimes-uneven distribution of charged particles across a semipermeable membrane, such as a cell membrane). Accentuating the dehydration effects, intracellular ice crystals bind free water. There is gross disruption of cellular permeability, solute concentration, osmolarity, pH, and other aspects of cellular physiology. These lethal effects occur in the cell before there is any cell rupture from the ice crystal itself. In central areas of thermal damage, the cells are killed. Toward the periphery of the frozen tissue, the cells are not killed immediately and necrosis doesn't occur. The effects are partial and slower to evolve. They are further influenced by endothelial damage and tissue scarring. We need to educate the orthopaedic community about the biology of this technique, and for that matter, all new techniques that we want to translate into practice.

The second goal should be to define and refine the technical aspects of the treatment. Cryobiology has been worked out commercially in daily life such as with frozen foods [4], but hasn't been well defined in vivo as a

Mechanism of Cryodestruction

Fig. 1 Geographic representation of the temperature and necrosis profile of cryosurgery is shown. Commonly used cryosurgery probes deliver liquid nitrogen at a temperature of -155°C . Liquid nitrogen itself is less than -195.79°C and may be directly applied to the tumor. (Published with permission from John Healey MD, FACS).

surgical adjuvant. We know it works to kill tumor cells and can extend the surgical margin beyond what can be done mechanically by curetting, burring, or resection. The refinement of using a freezing nitrogen ethanol composite to distribute freezing more uniformly is one method that holds

promise. The investigation by Wu and colleagues elegantly assesses the extent of apoptosis in tumors subjected to cryotherapy in vitro. However, the geographic distribution of the areas of necrosis and apoptosis in a frozen tumor were not explored and remain unknown. The temporal relationship of

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the freeze-thaw cycle is also inadequately defined. Experimental and clinical data are lacking to shed light on the ideal rates of freezing and thawing, even though it is well recognized that a rapid freeze and slow thaw is needed for cryodestruction and that the reverse is needed for cryopreservation of tissue. It is this damaged-but-not-destroyed area where the cells may undergo apoptosis rather than necrosis, or evade the ablative treatment altogether. It is also the area where the revascularization is compromised by the cryosurgery. Many other intrinsic and extrinsic variables influence these effects, such as how repetitive freezing injury affects the tissue (we know that thermal conductivity is much greater during the second freeze than the first) and what the ideal time might be between each freeze. We don't know how to optimize the effects nor minimize the damage to adjacent innocent tissues. These areas require bench and clinical research.

Comparative outcomes research is sorely needed and requires controlling the methodology and establishing common outcome measures. Variations in technique must be reconciled so that we use and test a consistent therapeutic maneuver. The clinical priority must be agreed upon. Is it to avoid local recurrence? Or is it improving clinical function by preserving the adjacent joint? What about

reducing the development of late osteoarthritis, or some other outcome measure? All are worthy goals that need to be pursued.

How Do We Get There?

The specialty societies such as the Musculoskeletal Tumor Society (MSTS) and the International Society of Limb Salvage need to provide education for the membership about this technique, as well as for all other new adjuvant strategies as they are developed. Since the first MSTS meeting when Dr. Marcove demonstrated the open-pour method for cryosurgery to his astonished audience of leading surgical oncologists, most of the education has focused on the phenomenon and not the science. A more discerning, in-depth coverage of the topic is needed and should be easy to provide. For example, it would be desirable to establish a workshop between the MSTS and the Society for Cryobiology, or have a joint publication on the topic with the journal *Cryobiology* and *CORR*®. Inviting speakers to our meeting to review recent advances would be an easy springboard to improve our understanding of cryoablation [1].

The MSTS can encourage research on the topic of improving the theoretic and practical aspects of using this adjuvant. Specifically, it could

advertise a request for research proposals on cryobiology. Collaboration with other specialties working the other side of the coin, cryopreservation, could also be possible. Setting adjuvant therapies as a Society priority will encourage investigators to enter the field and encourage granting agencies to set this work at a higher priority.

Collaboration among centers is usually the best way to have the tightest control of variables and best collection of relevant data for clinical outcomes studies. Society-sponsored investigation is also possible, but often cumbersome and always expensive. New approaches to clinical research in oncology may benefit us. For example, the National Surgery Quality Improvement Program database will collect and maintain from every participating center in this American College of Surgeons database. It has a focus more geared to oncology than to general orthopaedics. It is particularly suited to assess early quality measures [3]. Complications such as fracture, neuropathy, thromboembolic complications, among others, and oncologic outcome will be accessible to participating centers with approved research questions. Such anonymous databases can reduce the logistical challenges of requiring individual IRB approval at every center.

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Finally, interest in methods like cryotherapy has increased now that there is more understanding of the immune system and research into how tissues can autoimmunize [5]. Understanding the basic science of cryobiology may translate into new methods that when combined with immunomodulation, could introduce a new strategy to treat local and systemic disease.

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