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Minireview

Limb Salvage Using Liquid Nitrogen Treated Autologous Bone Graft in Sarcoma Surgery

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Cryosurgery for Tumor Treatment

The early use of liquid nitrogen in tumor surgery was reported by Cooper [1] in 1962. And then, cryosurgery was applied to manage bone metastasis at the Memorial Sloan-Kettering Cancer Center in the United States in 1969 as a palliative procedure [2]. Hence, cryosurgery has been improved and modified as cryoablation therapy, that has been widely employed for the management of tumors in many specialties, such as renal cell carcinoma, hepatocellular carcinoma, and musculoskeletal neoplasm [3,4].

Because of socio-religious circumstance, allograft bone is not popular in Asia countries. Another unique cryosurgery technique, massive bone frozen and recycling procedure in musculoskeletal malignancies, was developed and reported by Tsuchiya et al. [5] in 2005, preserving tumor bearing affected limb bone. He describes a reconstruction method using tumour-bearing autograft treated by liquid nitrogen in 28 patients. While in the surgery, the excised bone was frozen in liquid nitrogen for 20 minutes, thawed at room temperature for 15 minutes, further thawed in distilled water for ten minutes and finally re-implanted with instrumentation or composite use of a prosthetic replacement. As this has been mainly developed in Asia countries, there are still not many reports published about this procedure [6-11]. A brief summary of those reports is shown in Table 1.

Modification of Liquid Nitrogen Treated Autograft

There are some variations of reconstruction using tumour-bearing massive frozen autograft treated by liquid nitrogen. One is simple re-implantation of the treated bone as “onlay” method. This is usually carried out when the lesion is abutted or invades into the adjacent bone. The most popular method is “intercalary” reposition, treating the affected bone. Composite graft with prosthesis is another option. Those procedures are usually done after excision of the affected bone. However freezing procedure also can be demonstrated while maintaining bone continuity (pedicle freezing procedure). Tsuchiya et al. [12] has developed this procedure and presented 33 cases with good functional results. Shimozak et al. [13] compared pedicle freezing autograft with free freezing autograft on the basis of early bone union and revealed superiority of former procedure. Freezing autograft can also be applied to osteoarticular graft and moreover whole joint freezing is also applicable. Choice of these procedures depends on the site of the lesion and other anatomical condition such as the extent of tumor invasion, intact ligaments and so on.

Bone Union, Function and Complication

As shown in Table 1, bone union is achieved in 80 to 100% of reported cases with the mean follow up of 19.8 to 101 months. As for functional status, mean MSTS functional scores were 75 to 85%. Of course, functional status resulted from not only bone treatment but also the preserved skeletal structure and the type of reconstruction. Therefore, one should be careful enough to interpret those results. Of note is that there was no case that showed local recurrence in grafted bone. However, 7.1 to 12.5% local recurrence rates in adjacent soft tissue were reported.

Recognized complications are infection, fracture, skin sloughing and graft bone osteolysis in those series. Among those, fracture and infection of grafted bone were two major complications with occurrence rate of 7.1 to 25%. According to Igarashi [7] studies, most of them were successfully managed through additional surgery.

Advantage and Disadvantage

The advantages of reconstruction using tumour-bearing massive frozen autograft treated by liquid nitrogen are simplicity, osteoconduction, osteoinduction, a short treatment time, preservation of the cartilage matrix, a perfect anatomical contour, sufficient biomechanical strength, and easy attachment to surrounding soft tissue. In addition, all steps can be carried out within one operating

Table 1. Reports on en bloc frozen autograft bone for musculoskeletal sarcoma surgery

Author (year)	Case	Site	Methods	Follow-up months (mean)	Functional Score (MSTS)	Union (%)	Grafted Bone Recurrence	Local Recurrence (%)	Complications (%)
Tsuchiya (2005) [5]	28	Femur 13 Tibia 5 Humerus 4 Pelvis 4 Radius 1 Sacrum 1	OAG CGP	10 – 54 (19.8)	71.4% excellent 10.7% good 7.1% fair	26 (92.8)	0	2 (7.1)	Infection 3 (10.5) Fracture 2 (7.1)
Rahman (2009) [6]	10	Femur 8 Tibia 2	OAG 4 ICG 6	34 – 69 (54)	Mean 82.4%	9 (90)	0	0	Skin sloughing 1 (10)
Igarashi (2014) [7]	36	Femur 15 Tibia 9 Humerus 3 Pelvis 6 Radius2 Sacrum 1	ICG 8 OAG 16 CG 7	16 – 163 (101)	72.2% excellent 19.4% good 8.3% fair	30 (83)	0	4 (11)	Infection 4 (11.1) Fracture 7 (19)
Ogura (2015) [8]	5	Femur 4 Tibia 1	ICG 5	25 – 75 (44.8)	Mean 85%	4 (80)	0	0	Infection 1 (20)
Paholpark (2015) [9]	12	Femur 3 Tibia 6 Humerus 2 Ilium 1	OAG 8 ICG 4	12 – 86 (32)	Mean 79%	12 (100)	N/A	1 (8.3)	Infection 3 (25) Fracture 2 (13.8) Graft osteolysis (8.3)
Li (2016) [10]	8	Femur 8	ICG 8	37 – 71 (48.7)	Mean 95%	8 (100)	0	1 (12.5)	Fracture 1 (12.5)
Gede (2017) [11]	4	Tibia 4	OAG 4	36 -	Mean 75%	4 (100)	0	0	none

OAG: osteoarticular graft, ICG: intercalary graft, CGP: composite graft with prosthesis, MSTS: Musculoskeletal Tumor Society

room. Yamamoto et al. [14] documented the effectiveness of treatment with liquid nitrogen on osteosarcoma cells, both in vitro and in vivo, and also found that frozen autografts had adequate biomechanical properties. Takata1 et al. [15] suggested that bone morphogenetic activity was superiorly preserved in frozen autografts than in those treated with autoclaving and pasteurisation. The immunological effects of cryosurgery were another expectation. Nishida et al. [16] reported the possible induction of a systemic anti-tumour immune response induced by re-implantation of destroyed tumour tissue treated with liquid nitrogen in a murine osteosarcoma model.

The disadvantages of this method include degeneration of the cartilage over long period, the difficulty of histological analysis of the whole lesion and difficulty in histological evaluation of surgical margin. Allograft implantation shares the similar characters. Frozen autograft should be contraindicated in tumours with apparently broad osteolysis.

Igarashi [7] presented seven late fractures without any biological augmentation. Ogura [8] and Li [10] have utilized fibular inlay graft and showed minimal fracture rate. We also have experienced an osteoarticular graft fracture (Figure1), that did not have fibular graft enforcement. Although there is no definitive report on it, to our experience, onlay graft seems to show the best bone union (Figure 2).

Controversies

One of controversies on this freezing method is whether the tumor cells after single cycle of freezing and thawing are completely devitalized. In common cryoablation technique in tumor surgery, freezing and thawing is repeated several times to secure tumor death [4]. However, there is not such report that a local recurrence occurred in grafted bone. The single cycle method was ensured on basis of in vitro and in vivo studies of the effects of liquid nitrogen on the proliferation of osteosarcoma cells [14].

Figure 1. 67-year-old male who underwent osteoarticular freezing autograft and intramedullary nailing of his distal femur. A grafted bone fracture occurred seven years after surgery.

Figure 2. 61-year-old female had wide resection surgery for soft tissue sarcoma, using onlay freezing autograft of the lateral femoral cortex. Complete bone graft union was acquired`. (left: immediate after surgery, right: five years after surgery).

Ogura et al. [8] mentioned the combination of frozen autograft and vascularized fibular graft showed earlier bone union than pasteurized autograft, whereas Igarashi [7] showed almost similar results without vascularized fibular graft. Considering the possibility of late fracture, composition with vascularized fibular graft seems to be necessary whenever possible

Optimal Use in Limb Salvage Surgery

The limb reconstruction will be possible by other several techniques, including free or vascularized bone graft, allograft, prosthetic replacement, distraction osteogenesis, autoclaved bone, irradiated bone, pasteurized bone, and combinations of those procedures. Surgeons should well understand those alternatives and should determine which is the most preferable for each individual patient. If possible the optimal use of liquid nitrogen treated bone graft should be done as "onlay" method. Pedicle graft is also another good selection hopefully as composition with vascularized fibular graft.

Conclusions

Although various biological and nonbiological techniques are available, there is still no gold standard technique for reconstruction after tumour resection of malignant bone tumor. Liquid nitrogen treated autologous bone graft in musculoskeletal surgery is now definitely one of unique reconstruction procedures. Before reconstruction, one should carefully consider both advantages and disadvantages of variety of this technique to accomplish the optimal result.

Declaration of Conflicting Interests

The authors declared no potential conflict of interest with respect to the research, authorship and/or publication of this article.

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