Original Article

Prospective Evaluation of Argon Gas Probe Delivery for Cryotherapy of Bone Tumours

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Abstract

Introduction: Cryosurgery for tumoural ablation traditionally involves instilling liquid nitrogen into a tumoural bed. The inability to control precise delivery can result in potentially disastrous consequences of skin necrosis and nitrogen gas embolism. In this study, we evaluated a probe-based closed cryosurgical system, which eliminates these risks. Materials and Methods: We performed a prospective evaluation of 36 cases of bone tumours treated with a probe-based cryosurgical system at the National University Hospital, Singapore. Cases consisted of patients with benign aggressive tumours (42%), primary malignant bone tumours (25%) and bone metastases (33%). In primary bone tumours, the aim of therapy was cure. In bone metastasis, the aim of therapy was palliation defined as the relief of symptoms for the patients' remaining lifetime. Results: In the primary bone tumour group, no recurrences were reported. In the metastases group, where the intention was palliation, there were 3 cases of radiological relapses (*P* = 0.02) and 2 clinical relapses. Kaplan-Meier evaluation showed a statistically significant tendency for radiological relapse in metastatic disease versus primary disease (*P* = 0.02). Median time for relapse free survival in the metastatic group was 17 months (*P* = 0.01). There were 4 deaths in the metastatic group due to progression of disease unrelated to the index region of cryosurgical treatment. There were no deaths in the primary bone tumor group. We had 2 complications from this therapy involving fractures through the cryoablated segments. One case healed spontaneously and the other was most expediently managed with a shoulder hemiarthroplasty. There were no skin burns or embolic complications. Conclusion: Good clinical efficacy with probe delivered cryotherapy has been shown in this group of 32 patients with cure in all primary disease. Relapse occurred in only a small proportion of patients with bone metastasis.

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Key words: Cryoprobe, Cryosurgery, Liquid nitrogen, Musculoskeletal tumours

Introduction

Cold therapy has been used for thousands of years by the ancient Egyptians and later Hippocrates. The beginning of cryosurgery in modern medicine was originally proposed by an English physician, James Arnott between 1819 and 1879 who described the use of extreme cold to cause tissue destruction. Arnott combined a mixture of salt and crushed ice ("two parts finely pounded ice and one part of chloride of sodium"), which he applied to tumours. The desired clinical effects of controlling pain and haemorrhage were achieved. He stated that "a very low temperature will arrest every inflammation which is near enough to the surface to be accessible to its influence". He treated breast and uterine cancer as well as some skin cancers. Although palliation was his initial aim, he recognised the potential of cold for curing cancer, stating that the cases he had seen "are therefore, by no means unfavourable to the supposition of the curability of cancer by congelation".

Years later, Marcove and Miller used cryosurgery in an orthopaedic patient. They initially described the 'open technique', which entailed direct contact of liquid nitrogen into a tumour cavity. They had excellent clinical results from this therapy and showed that they were able to achieve local tumour control with minimal bone and functional loss. However, as liquid nitrogen was poured directly into the bone, it was challenging to control the spread of the substance. As a result, significant injury to adjacent

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bony rim, cartilage and soft tissue occurred, resulting in secondary fractures, skin necrosis, infection and temporary neuropraxia. The high complication rates associated with this technique make cryotherapy unpopular. In 1962, Cooper described a cryotherapy unit in which liquid nitrogen was circulated through a hollow metal probe. This closed system allowed the flow of liquid nitrogen to be controlled and also allowed the temperature of the probe to be regulated to the desired range.

The largest study published of recent times used both techniques over the course of 15 years in Israel.[1] Four hundred and forty procedures were carried out. Two-thirds were for benign-aggressive and low-grade malignant lesions and one-third was for primary high-grade bone tumours and metastatic bone tumours. Median follow-up was 7 years. Their local recurrence rate was 8%. Complications included fractures (1%), infections (2%) and skin burns (1.3%). Three cases of transient nerve palsies and 4 cases of late osteoarthritis of an adjacent joint were also reported. They concluded that bone cryosurgery was a safe and effective limb and joint sparing technique and was suitable for all types of bone tumour. We performed an independent evaluation of probe delivery methods in our local Southeast Asian population in treating bone tumours, with particular emphasis on: (i) achieving therapeutic targets of cure in primary bone tumours and palliation in secondary bone tumours and (ii) evaluating the complications of cryotherapy.

Materials and Methods

This is a prospective evaluation of patients in a single centre adopting probe-based cryotherapy in the management of bone tumours. All patients with primary and secondary bone tumours who underwent argon cryotherapy from March 2007 to September 2010 were included. The Ministry of Health provided a grant to evaluate the probe-based cryosurgical system (Cryohit®, Galil Medical, Israel). This is the only device of its kind used in Southeast Asia and relies on the use of high pressure circulated argon to produce a hyperfreeze effect to as low as –200°C (Fig. 1). Bone necrosis occurs at temperatures below –21°C. Cryotherapy uses low temperature to induce tissue necrosis via 4 processes: freezing, holding of freeze, thawing and repetition of these cycles. Slow cooling to –10 to –15°C results in extracellular ice formation. The intracellular compartment remains unfrozen due to the presence of high molecular weight solutes, and the resultant hyperosmolar extracellular space encourages the transport of water from the intracellular compartment via osmosis. This causes cell shrinkage, membrane damage and enzyme dysfunction. Rapid cooling (within a few millimeters of the probe) induces intracellular ice formation at temperatures below –150°C. The frozen tissue is subjected to mechanical shear forces resulting in cell injury. Intermittent thawing causes recrystallisation, which increase vascular permeability and oedema, and hence further cellular damage. After the tumour excision is completed, cryotherapy is used to extend the oncological margins by effecting tissue necrosis in the peri-tumoural reactive zone.

All patients underwent diagnostic procedures and treatment at our institution. Diagnostic procedures included roentgenograms and magnetic resonances imaging of the region of interest and nuclear isotope (Technetium 99) bone scans and contrast enhances computerised axial tomograms of the chest in the work up of malignant disease. Only primary tumours perceived to be of benign aggressive and low grade malignant type at stage 1 or 2 A (American Musculoskeletal Tumor Society surgical staging system) and metastatic tumours requiring cryosurgical control were included. Technically, cavities with a wall thickness of at least 75% of the original; and at least 1 cm of subchondral bone remaining over the joint surfaces after curettage and burr drilling were considered for this therapy to avoid local mechanical failure post procedure.

Meller's operative technique was employed. Standard orthopaedic approaches were taken. This included a tourniquet where possible to avoid the countercurrent heat-sink effect and to prevent bleeding into the operative field. Wide retraction with protection of tissues and neurovascular structures were carried out. A large cortical window was opened away from vital structures. This window was large enough to allow efficient instrumentation. The tumour was excised with curettes and high speed burring of the walls of the cavity. Care was taken not to allow embolisation of tumour material into the systemic system via argon-beam coagulation of the cavity wall.

The probe-based cryosurgical system (Cryohit®, Galil Medical, Israel) was used for cryoablation using lignocaine gel as the interface for uniform freezing. This system comprised a monitor and control panel (Fig. 1). Argon is used for freezing and helium for thawing. Probes with cryotherapeutic zones of 2 cm long by 1 cm diameter were used in our study. Combinations of these probes accomodated the geographic variability inherent to the specific tumour for treatment. Probes, as described earlier, delivered argon gas, which does not come into contact with the ablated tissue. The default temperature for freezing was –200°C. Using the same probes, the thawing effect of helium is translated into the frozen cavity. Default temperature of a helium containing probe is 20°C. Three cycles of freezing to –70°C and thawing were undertaken, with thermocouples to monitor the intracavity temperature. The thermocouple is able to detect a limit of –70°C although the temperature is known to fall lower than this. During ablation, the surrounding soft tissue was irrigated with warm saline to

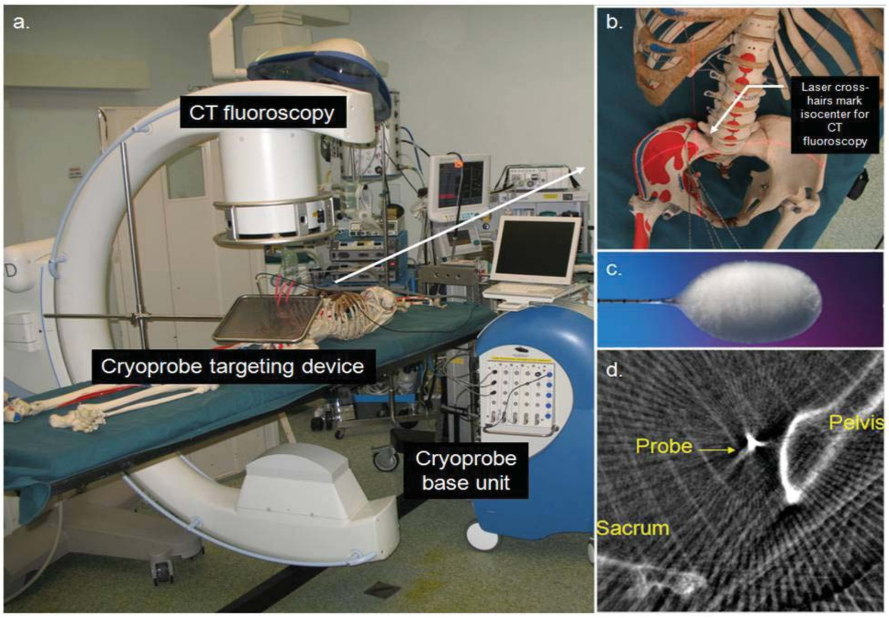


Fig. 1(a). CT fluoroscopy, Cryoprobe targeting device and base unit. Fig. 1(b). Cryoprobe zone of ablation. Fig. 1(c). Cryoprobe. Fig. 1(d). Fluoroscopy picture of probe in position within the pelvis.

limit thermal injury. At the end of the therapy, the defects were then thoroughly washed with saline, and the cavity filled with bone cement or other substitutes. In this series, all the cavities were filled with cement and fixation was achieved with plates, screw or joint replacement except for pelvic lesions which are small and did not participate in weigh bearing. All the surgeries were performed by the senior author (SSN).

Postoperatively, patients continued on intravenous antibiotics for 72 hours. Normal weight bearing was not permitted for 6 months. This period of rest presumably allowed bone remodelling. The cautions reintroduction of mobility would also avoid uncontrolled torque to the limbs, which would predispose to fracture. A review of all clinical charts and investigations was performed. Patient's demographics, nature of disease, procedure performed and complications were evaluated. The outcome parameters included the status at last follow up, relapse (radiological or clinical) and need for revision surgery. Outcome data was analysed using the Fisher Exact test and Kaplan-Meier Method on SPSS 16 for Windows XP. A *P* value of less than 0.05 was considered significant.

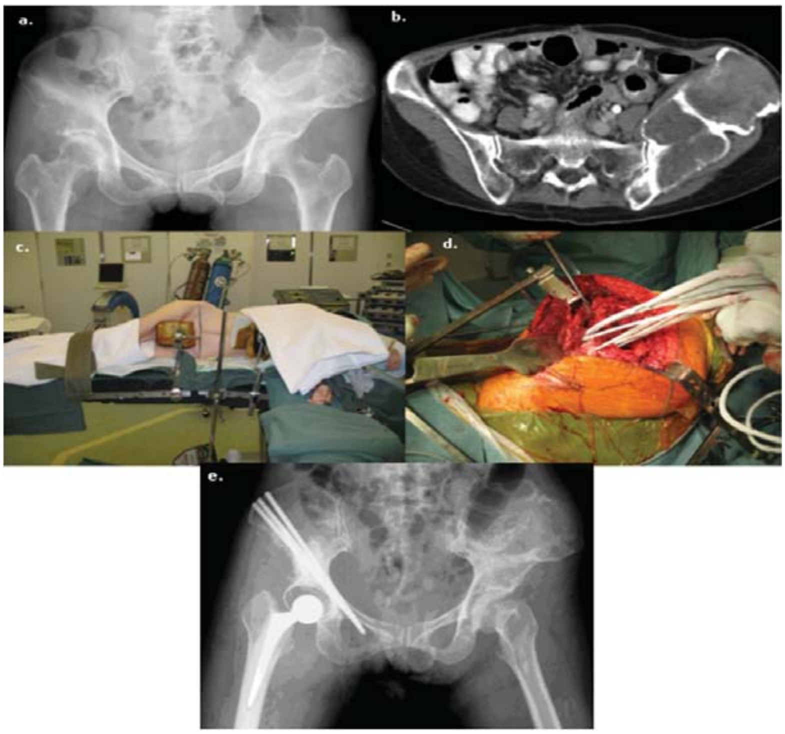
Results

From March 2007 to September 2010, we performed 36 procedures in 32 patients. Demographics and tumour characteristics are summarised in Table 1. Median age in this group was 48 years (range, 17 to 70). There were 16 (50%) females and 16 (50%) males. There were 19 (60%) Chinese, 2 (6%) Malay, 7 (22%) Indian and 4 (12%) other nationalities.

There were 15 (42%) benign, and 9 (25%) malignant tumors comprising 6 low grade chondrosarcomas, 1 osteosarcoma, 1 giant cell sarcoma and 1 mesenchymal sarcoma. To clarify the inclusion of the 1 case of giant cell sarcoma and 1 case of osteosarcoma, we should point out that both cases presented as benign aggressive tumours reminiscent of giant cell tumours of the bone. The former patient had a malignant variant of giant cell tumour on final histology and was included for analysis. In the latter case, the patient had an initial diagnosis of giant cell tumour on a diagnostic biopsy. However, following cryotherapy, the histology was revised to high-grade osteosarcoma and the patient was subsequently treated as per standard of care. These 2 cases provided valuable information on the safety profile of the procedure as well as an evaluation of remnant disease as they both underwent an en bloc resection of the cryoablated disease-bearing segment of bone.

Table 1. Demographics and Tumor Characteristics

Parameters		
Age (median)		48 years (range, 17 to 70)
Follow-up		16.5 ± 11.9
Gender		**No. of patients**
	Male	16
	Female	16
Total no. of patients		32
Tumor Characteristics		**No. of cases**
	Benign (with features of aggressiveness)	
	Malignant	
	Primary	9
	Secondary	12
Total no. of cases		36



Figs. 2(a) & (b). Patient had metastatic pelvic hemangiopericytoma, with large expansile lytic lesions in both iliac wings and right femoral head and neck seen on x-ray and CT. Fig. 2(c). The patient is positioned in a lateral position, and after intralesional tumour excision. Fig. 2(d). Cryo probes are inserted into the cavity followed by application of repeated cycles of freezing and thawing to effect cryonecrosis. Fig. 2(e). Radiographs showing the reconstruction employing a total hip replacement reinforced with a Harrington procedure (application of rods to augment the acetabular wall).

The remaining 33% of patients in our series were in the bone metastasis group. We highlight an unusually rare case of a patient with a metastatic retroperitoneal haemangiopericytoma presenting as a large expansile lytic lesion in both iliac wings and right femoral head as shown in Figure 2. This patient had a poor quality of life preoperatively with constant pain requiring high dose painkillers and immobility. The patient underwent cryotherapy and a reconstruction consisting of a total hip replacement, with rod and cement augmentation. Following this, the patient had immediate pain relief and was able to ambulate independently. In another case, cryotherapy was used as an adjunct rather than primary therapy to conserve bone in order to place a megaprosthesis for the patient. This patient returned with pain in her right hip secondary to renal metastasis. We subsequently administered cryotherapy percutaneously which gave her excellent pain relief (Fig. 3).

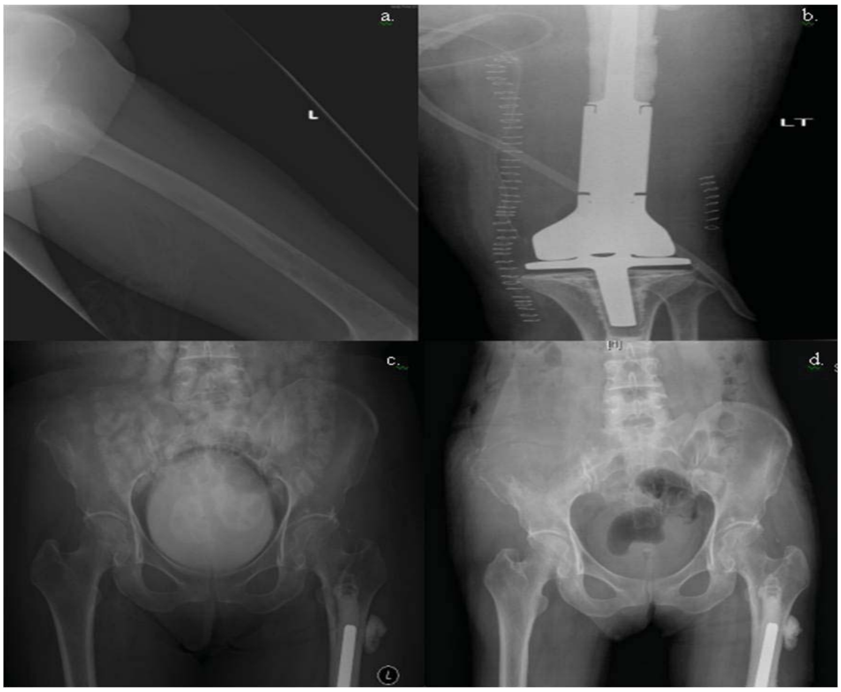


Fig. 3(a). Lytic lesion seen in the distal femur. Fig. 3(b). Megaprosthesis. Fig. 3(c). Lytic lesion right iliac wing. Fig. 3(d). Post cryotherapy radiograph of pelvis showing tumour destruction.

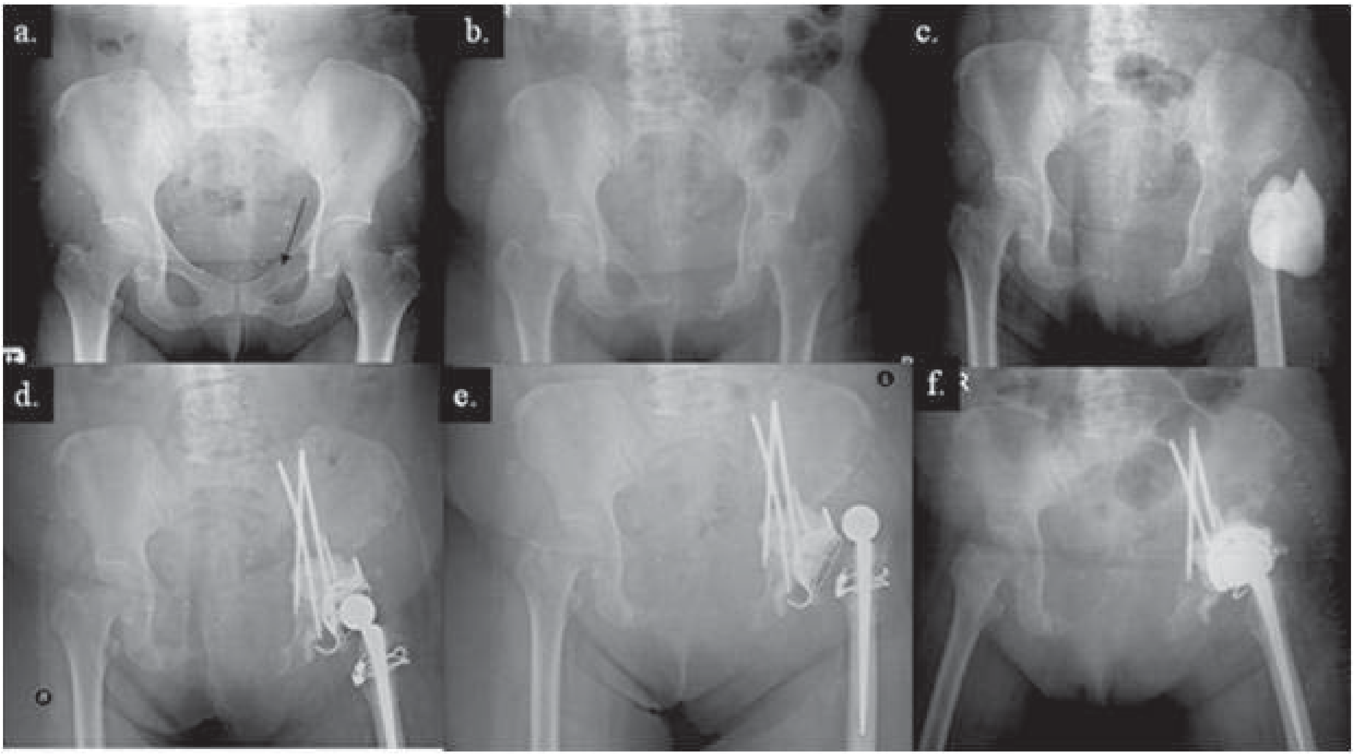


Fig. 4(a). This patient underwent 5 parotid resections over a 5-year period for pleomorphic adenoma. Fig. 4(b). Underwent 20Gy radiotherapy but developed metastatic disease. Fig. 4(c).- Pelvic metastatic lesions were initially resected with intraoperative blood loss. Fig. 4(d). Cryosurgery and staged reconstruction through a posterior approach was taken subsequently. Fig. 4(e). Postoperative complication include traumatic implant fracture and dislocation. Fig. 4(f). Revision of hip with a constrained cup followed by successful relocation of hip.

Mean follow-up time was (16.5 ± 11.9) months. There were 2 clinical relapse amongst 3 cases of radiological relapse. One of the patient required hip revision surgery (Fig. 4). Relapses occurred only in the metastatic group (P = 0.01). Kaplan-Meier evaluation (Fig. 5) indicated a statistically significant tendency for relapse to occur in metastatic disease as opposed to primary disease (benign and malignant) (P = 0.02) which had a durable long-term control. Median time to relapse was approximately 17 months. The 4 deaths in our series occurred in patients with metastatic disease with no local relapse. We had 2 complications from this therapy. Both were fractures. One fracture occurred through a proximal tibial cryoablated defect with calcium sulphate cementation alone. This healed uneventfully with protected weight bearing. The second was a fracture through a metal rod-augmented calcium sulphate filled defect in the proximal humerus. This was most expediently treated with a proximal humeral hemiarthroplasty. There were no skin burns or embolic phenomenon in this series.

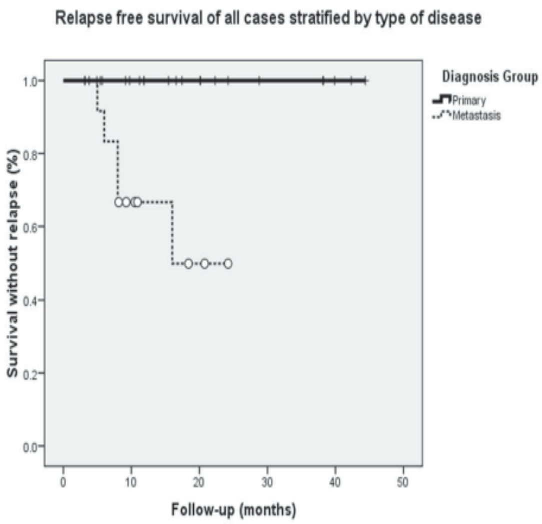


Fig. 5. Kaplan-Meier Curve; Relapse free survival of all cases stratified by type of disease.

Discussion

In our cases series of 32 patients, cryotherapy appeared to be effective in the treatment of a range of primary and secondary bone tumours. Our objective in the management of primary bone tumours and bone metastasis were different. We intended to treat and cure patient with benign aggressive bone tumours as well as primary bone cancers and in some instances, we had utilised cryotherapy as an adjunct to the management of bone cancer. However, in bony metastasis, which is usually associated with pain and dysfunction, our aim was palliative. Complications were also evaluated and reported as part of the study objective.

Cryotherapy has been shown to have improved cure rate for primary bone tumour. Chondrosarcoma has also been treated with adjuvant cryotherapy. Ahlmann et al[2] reported no recurrence in a series of 10 patients treated with cryotherapy with an average follow up of 38.5 months. Marcove et al[3], Schreuder et al[4] and Souna et al[5] also reported no recurrence in their series with a follow-up of 78, 27.4 and 96 months respectively. We thus implemented adjuvant cryotherapy in our centre. In our mean follow up of (18.7 ± 13.4) months, there were no tumour recurrences in our 23 patients (24 cases) with primary disease. However, we did have 3 relapses in our metastatic group of 9 patients (12 cases) after a mean of (12.1 ± 6.2) months. These relapses were manifested as hip instability secondary to progression of pelvic lesion.

In our patients with metatstasis, treatment with cryotherapy allows local control with less extensive resection, allowing patient more rapid recovery and thus preserving the quality of life for the patient. Callstrom et al[6] reported significant reduction in worst pain and pain interference with activities of daily living using radiological guided cryoablation of osseous metastases. In our series, pain was sufficiently controlled for patients with secondary bone tumours to allow daily activities.

The main complications associated with cryoblation include fracture, skin necrosis, transient nerve injuries, and infection.[3,4,7-9] Probe-based therapy in our hands seems to have eliminated all complications except fractures. These reported complications of cryotherapy were secondary to the uncontrolled nature of liquid nitrogen leading to tissue necrosis.[10] Since the introduction of cryosurgery by James Arnott in the 18th century, cryosurgery has advanced from using pouring techique, to using liquid nitrogen spray and finally cryoprobe. Marcove et al[9,11] has advocated a "direct pour" technique of delivering liquid nitrogen through a stainless steel funnel into the tumor cavity after excision and curretage. However, this method is associated with side effects, including damage to adjacent rim of bone, cartilage, and soft tissue exposed to liquid nitrogen, increased rate of skin necrosis (2.9% to 8%), and secondary fracture rates (5.9% to 25%).[7,9,11] Although it was found that liquid nitrogen spray has a more profound freezing effect[12] than a cryoprobe, cryoprobe can give a more precise and controlled delivery of freezing and thawing agents. Cryoprobe allows such controlled delivery that percutaneous radiological guided cryotherapy has been introduced.[13] As such, we adopted the use of cryoprobe for cryotherapy in our centre. Since the advocation of cryotherapy in our centre, there were no soft tissue complications in all our patients who have undergone cryotherapy.

With this technique, we reported 2 (6%) peri-implant fracture and fracture through a cement filled tibial defect. These complications arise secondary to osteonecrosis after cryotherapy. Risk of fracture after cryotherapy was reported as from 1% to 20%.[1,14] The risk of fracture is due to osteonecrosis from cryoablation.[2] Fisher et al[15] showed that liquid nitrogen therapy weakens the bone, the effect of which is maximal around 6 weeks. Pogrel et al[10] advocate autogenous bone grafting for defect greater than 4 cm, or for defect with only cortical bone remaining after ablation. Ahlmann et al[2] criteria for placing internal fixation and cementation were any lesion involving a lower-extremity weightbearing bone or a large cortical window in an upper extremity greater than 5 cm. In our centre, any lesion with a wall thickness of less than 75% of the original or 1 cm of subchondral bone remaining over the joint surfaces after curettage and burr drilling will be filled with cement or supplemented with internal fixation. This practice has resulted in a relatively low fracture complication rate of 6% in our study.

Cryosurgery has the advantage of lower morbidity, less neurological deficit, improved speed and ease of surgical procedure, less potential blood loss, preservation of spinal and pelvic continuity, and lower tumour recurrence rates. In our series, we showed no soft tissue complications using cryotherapy and 2 bony complications of fractures. There were no relapse in the primary bone tumour group and pain was well controlled in the secondary bone tumour patients. We showed that cryotherapy in selected patients was able to achieve our therapeutic target with acceptable rate of complications.

With the success that we have enjoyed, it is important to remember that this remains to be a provisional study evaluating probe-based therapy on 3 pathological entities. It does not allow us to compare different therapies. Although the follow-up period is relatively short, complications of cryotherapy are immediate thus this study allows us to report the complication rate of our 32 patients treated with cryotherapy. In addition, the sample size is small as bone tumours are relatively rare. However, even in this limited study, clinical efficacy with this therapy has been demonstrated with no recurrences in our primary group and improvement in the quality of life for our patients with metastatic disease.

Conclusion

Bone cryosurgery has been successfully used in the treatment of bone tumours of benign aggressive and low malignant variants whilst conserving bone and joints. The use of a more controlled form of cryotherapy with the argon probe has obliterated most complications associated with the use of liquid nitrogen. In our 36 cases, good clinical efficacy has been proven with a relapse in only a small proportion of patient in the metastatic group only (end point being palliation of symptoms and not cure).

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