Comparison of Phenol and Argon Beam Coagulation as Adjuvant Therapies in the Treatment of Stage 2 and 3 Benign–Aggressive Bone Tumors

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abstract

Argon beam photocoagulation has gained popularity as an adjuvant therapy for the treatment of giant cell tumors of bone and other stage 2 or 3 benign–aggressive bone tumors. Although argon beam photocoagulation has been considered a safe and reasonable adjuvant treatment with acceptable recurrence rates, it has never been directly compared with the commonly described phenol as adjuvant. The purpose of this study was to determine whether argon beam photocoagulation is as effective as phenol in preventing recurrence without affecting functional outcome as an adjuvant to surgical curettage.

We retrospectively reviewed 93 consecutive patients with a minimum 10-month follow-up between 1992 and 2007 who were treated with curettage and either phenol or argon beam photocoagulation. Functional outcomes and complications were recorded. Overall, 16 (17.2%) of 93 patients who were initially treated with 1 of the adjuvants had pathologically confirmed recurrences. No additional recurrences were noted after retreatment, leading to an overall recurrence rate of 17.1% with phenol and 14.8% with argon beam photocoagulation ($P = .726$).

While avoiding the toxic effects of phenol, argon beam photocoagulation provides for statistically equivalent recurrence rates, functional outcomes, and complication rates in the treatment of benign–aggressive bone tumors.

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Benign–aggressive bone tumors represent a diverse group of pathological and clinical tumors and tumor-like lesions that differ in clinical behavior classified by histopathology. Enneking et al. were the first to describe a system for the staging of musculoskeletal tumors adopted by the Musculoskeletal Tumor Society in 1980 to help characterize the locally invasive behavior. Other aspects related to treatment, like surgical margins, also affect local recurrence.

Resection/curettage is now the standard for treatment of giant cell tumor of bone and other benign–aggressive tumors. Resection/curettage is an intralesional procedure with wide exposure and complete unroofing of the cavity that allows for gross removal of the tumor. Giant cell tumors are known for their tendency to recur after simple curettage and bone grafting, with previous studies showing recurrence rates ranging between 12% to 50%. The use of high-speed burs and copious irrigation of the cavity have lowered the local recurrence rates. Various topical adjuvants have been used to treat these benign–aggressive bone lesions, including cryotherapy with liquid nitrogen, hydrogen peroxide, phenol cauterization, polymethylmethacrylate (PMMA), and argon beam photocoagulation. Studies of these varying adjuvant treatments indicate recurrence rates of 6% to 28.6% compared with up to 50% with simple curettage. The use of PMMA polymerization allows for intensive curettage even of large tumor cavities by providing immediate support and is thought to cause a direct thermal or cytotoxic effect on tumor cells.

Phenol has been found to be an effective method of topical adjuvant treatment, with several studies showing the local recurrence rate to be 6% to 25% at a concentration of 85%. It causes protein coagulation and DNA damage, extending the margins of simple curettage, but like other methods, its cytotoxicity can extend beyond the wall of the lesion.

In recent years, argon beam photocoagulation has been used as an adjuvant because its application is more facile, avoiding chemical burns seen with phenol and the extent of tissue necrosis and fractures seen with cryosurgery. The argon beam is a form of high-frequency energy that leads to tissue desiccation and protein coagulation. Giant cell tumors treated with argon beam photocoagulation have a reported recurrence rate of 10%. To our knowledge, no published study has shown a direct comparison of phenol with argon beam photocoagulation in the treatment of stage 2 and 3 lesions. The purpose of this study was to show the equivalency of recurrence rate, function, and complications of argon beam photocoagulation with that of phenol as adjuvant therapy.

**MATERIALS AND METHODS**

After Institutional Review Board approval, all patients who had stage 2 or 3 lesions between 1992 and 2007 at our institution were retrospectively reviewed. The stage 2 or 3 lesions included in this study were giant cell tumors, chondroblastomas, aneurysmal bone cysts, nonossifying fibromas with secondary aneurysmal bone cysts, and chondromyxoid fibromas. For inclusion in the study, the patients had to have (1) a radiologically diagnosed stage 2 or 3 lesion; (2) surgical treatment with curettage; (3) adjuvant therapy with argon beam photocoagulation or phenol; (4) a minimum 10-month follow-up; and (5) a complete medical record.

We identified 134 patients and excluded 41 patients for the following reasons: 24 patients had resection as primary treatment without adjuvant therapy; 7 patients did not have >10-month follow-up and were therefore excluded from data regarding recurrence rates; 5 patient received cryosurgery as adjuvant; and 5 patients were without complete and adequate medical records, such as type of adjuvant, length of follow-up, and Musculoskeletal Tumor Society (MSTS) score, thereby excluding them from assessment.

Ninety-three patients fit the criteria and were included in the study. Fifty-seven men and 36 women had a mean age of 25.9 years (range, 5–66 years). Follow-up was computed from the last clinic visit. Average follow-up was 55 months (range, 10-184 months) (Table 1). Histological diagnosis and anatomic locations are summarized in Table 2. Perioperative medical records, office visit notes, and radiographs and their respective reports were reviewed. Surgical complications and local recurrences were recorded.

All patients included in the study were treated with curettage and high-speed burring of the lesion to remove the macroscopic tumor; with further high-speed burring, attempts were made to remove residual microscopic tumor, thus enlarging the remaining cavity prior to adjuvant therapy. After irrigation with pulsatile lavage or bulb syringe, phenol (Figure 1) or argon beam photocoagulation (Figure 2) was applied as adjuvant.

Prior to the year 2000, patients were treated with phenol as per surgeon preference in our institution. When phenol was the adjuvant of preference, it was applied meticulously with a cotton swab at a concentration of 85% (Figure 1); contact time was approximately 1 minute, after which contact time was extended as needed to ensure complete coagulation.
the cavity was irrigated with Lactated Ringer's solution. Petroleum gauze was used to prevent the phenol from leaking into the soft tissues surrounding the lesion. With the addition of a second fellowship-trained musculoskeletal oncologist, a transition occurred in practice that led to an increasing number of patients being treated with argon beam photocoagulation. When argon beam photocoagulation was used, the thermal coagulation was applied throughout the curetted cavity (Figure 2). Throughout all procedures, the argon beam coagulator was set to 100 watts, with an average time of coagulation to each part of bone being 8 to 10 seconds, after which the area of bone being treated with argon turned black. After curettage and adjuvant therapy was performed, the cavity defects were reconstructed with PMMA cementation, autograft, or allograft bone. In addition, critical defects were treated with internal fixation using Steinmann pins, limited-contact dynamic compression plate, or a locking compression plate.

Stage; complications such as recurrence, infections, physeal arrest, and postoperative fractures; and functional outcome data were obtained from patient examinations and review of their respective radiographs and histology slides. The benign–aggressive bone tumors were staged according to the staging system developed by Enneking et al. Based on radiographs assessed by the 3 senior authors (J.B., F.R.P., K.S.B.), 0 stage 1 lesions, 38 (37.2%) stage 2 lesions, and 64 (62.3%) stage 3 lesions existed (Table 2).

Table 2

<table>
<thead>
<tr>
<th>Recurrence</th>
<th>Phenol</th>
<th>Argon</th>
<th>Total</th>
<th>( P )</th>
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<tr>
<td>By tumor histology</td>
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<td></td>
</tr>
<tr>
<td>GCT</td>
<td>3/14</td>
<td>3/30</td>
<td>44</td>
<td>.929</td>
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<tr>
<td>GCT + ABC</td>
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<td>2/3</td>
<td>7</td>
<td>.371</td>
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<tr>
<td>ABC</td>
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<td>2/12</td>
<td>21</td>
<td>.811</td>
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<tr>
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<td>1/5</td>
<td>14</td>
<td>.604</td>
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<td>9/61</td>
<td>102</td>
<td>.726</td>
</tr>
<tr>
<td>(17.1%)</td>
<td>(14.8%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>By tumor location</td>
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<td></td>
</tr>
<tr>
<td>Proximal tibia</td>
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<td>2/14</td>
<td>4/24</td>
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<td>Distal femur</td>
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<td>3/16</td>
<td>4/23</td>
<td>.648</td>
</tr>
<tr>
<td>Humerus</td>
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<td>1/5</td>
<td>2/14</td>
<td>.604</td>
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<tr>
<td>Distal tibia</td>
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<td>1/5</td>
<td>2/8</td>
<td>.893</td>
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<td>Proximal femur</td>
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<td>0/6</td>
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<tr>
<td>Total</td>
<td>7/41</td>
<td>9/61</td>
<td>16/102</td>
<td>.726</td>
</tr>
</tbody>
</table>

Abbreviations: ABC, aneurysmal bone cyst; GCT, giant cell tumor.
A recurrence was defined as a histologically confirmed tumor at the initial site. The MSTS functional scoring system was used to evaluate all patients at latest follow-up for the upper or lower extremity.\textsuperscript{28}

To assess the effect of individual factors and the clinical outcomes on recurrence-free survival, statistical analysis was performed via univariate analyses using log-rank tests and univariate Cox proportional hazards models; a factor was considered significant if the corresponding $P$ value was <.05. In addition, a Kaplan-Meier survival curve was created to show the recurrence-free survival for phenol and argon beam coagulation.

**RESULTS**

Overall, 16 (17.2\%) of the 93 patients who were initially treated with 1 of the 2 adjuvants had pathologically confirmed recurrences, with 7 (17.9\%) recurrences in 39 patients initially treated with phenol and 9 (16.6\%) recurrences in 54 patients treated with argon beam coagulation. Statistical analysis revealed no significant difference in recurrence rates between the 2 adjuvant groups ($P = .672$) (Table 3).

Of the 7 recurrences initially treated with phenol, repeat surgery included 2 patients with curettage and cementation with phenol, 2 patients with curettage and cementation with argon beam coagulation, and 2 patients with resection and conversion to an endoprosthesis; in addition, 1 clavicular recurrent lesion initially treated with curettage and phenol eventually had a wide resection performed at revision (Table 3). Of the 9 recurrences initially treated with argon beam coagulation, repeat surgery included 5 patients with curettage and cementation with argon beam coagulation and 4 patients with resection and conversion to an endoprosthesis (Table 3).

This led to a total of 102 procedures using adjuvant therapy, with 41 procedures using phenol and 61 procedures using argon beam coagulation. Patients treated for recurrence remained disease-free, with no additional recurrences noted, leading to an overall recurrence rate of 17.1\% and 14.8\%, respectively ($P = .726$).

The study group was classified according to the Enneking staging system. Of the 41 patients treated with phenol, 15 were stage 2 lesions and 26 were stage 3 lesions, where 2 and 5 patients had recurrences, respectively (Table 2). Of the 61 patients treated with argon beam coagulation, 23 were stage 2 lesions and 38 were stage 3 lesions, where 3 and 6 patients had recurrences, respectively. No statistically significant difference was found in overall recurrence when comparing stage 2 and 3 lesions ($P = .4042$).

Patients were then grouped by the use of 3 methods of reconstruction with or without internal fixation: PMMA, bone grafting (autograft or allograft), or bone grafting with PMMA. Groups of patient recurrence with method of reconstruction after initial adjuvant therapy are summarized in Table 4. No statistical difference in recurrence rate was found in lesions treated with or without internal fixation ($P = .646$). No statistical differences in recurrence rates were found based on method of reconstruction using PMMA, bone grafting, or bone grafting with PMMA ($P = .913$). Statistical analysis comparing recurrence rates with argon beam coagulation and phenol and the abovementioned reconstruction methods revealed no statistical significance.

A Kaplan-Meier survival curve showed the recurrence-free survival for phenol and argon beam coagulation (Figure 3). The 5-year recurrence-free survival was 73.4\% (95\% confidence interval [CI], 73.8\%-98.11\%) for argon beam coagulation and 77.0\% (95\% CI, 72.21\%-97.22\%) for phenol. No statistical differences in recurrence rates were found based on type of adjuvant used, histological group, or Enneking stage (Table 2).

The average MSTS functional score at follow-up was 27.4 (range, 13-30), with an average of 28.1 (range, 23-30) for lesions treated with phenol and an average of 27.1 (range, 13-30) for those treated with argon beam coagulation. No significant difference was found in functional outcomes in both groups ($P = .1898$).

Postoperative complications were seen in 12 (11.8\%) of the 102 procedures, 6 (14.6\%) in those treated with phenol and 6 (9.8\%) in those treated with argon beam coagulation. Complications seen after the use of phenol included 1 deep infection, 2 phyleseal arroses, 1 case of synovitis, 1 case of arthrofibrosis, and 1 case of bursitis. Complications seen after the use of argon beam coagulation included 1 postoperative fracture, 1 postoperative fracture in the setting of local recurrence, 1 phyleseal arrest, 1 case of synovitis, 1 case of bursitis, and 1 case of joint instability (Table 5).

Although no postoperative fractures were noted in the phenol group, 2 patients initially treated with argon beam coagulation...
tion sustained postoperative fractures, 1 of which was associated with recurrence. The postoperative fracture due to giant cell tumor recurrence was revised with open reduction and internal fixation, whereas the other fracture underwent nonoperative treatment with casting. No statistical significant difference in complication rate was found in those treated with argon beam coagulation or phenol as adjuvant (P = .853); specifically, no statistical significant difference was found in postoperative fractures in the 2 groups (P = .355).

**DISCUSSION**

Surgical curettage is the standard of care for the treatment of stage 2 and 3 bone lesions. The use of high-speed burrs and irrigation of the cavity has reduced the incidence of recurrence compared with simple curettage. With extended curettage, the use of adjuvants such as PMMA, phenol, cryosurgery, and argon beam photocoagulation appear to further reduce recurrence.21

Historically, cementation rather than bone grafting has been method of choice for reconstruction. Blackley et al2 reviewed patients with giant cell tumors treated with curettage with use of high-speed burr and reconstruction with autogenous bone graft with or without allograft bone. Internal fixation was used when stability was required. They concluded that risk of local recurrence after curettage with high-speed burr and reconstruction with autogenous graft with or without allograft bone is similar to that observed after use of cement and other adjuvant treatment. It is likely that the adequacy of the tumor removal rather than the use of adjuvant modalities is what determines the risk of recurrence.5 The current study showed no statistical difference in recurrence rate in those lesions treated with or without internal fixation or based on method of reconstruction using PMMA, bone grafting, or bone grafting with PMMA.

Several studies have reported the role of these adjuvants on stage 2 and 3 recurrence rates. O’Donnell et al15 reviewed patients who were treated with curettage, high-speed burring, phenol, and/or packing with PMMA and reported that the highest rate of recurrence was seen in patients who did not have adjuvant therapy in the form of high-speed burr or phenol.
prior to the use of PMMA; those treated with high-speed burr, phenol, or both had a recurrence rate of 17%. Similarly, Durr et al\textsuperscript{12} reported that patients treated with curettage and phenol as adjuvant had a lower recurrence rate (9.1%) compared with those who did not receive adjuvant therapy (42.9%). Another recent study examined giant cell tumors specifically treated with PMMA, PMMA with phenol, or phenol or other toxins (alcohol, cyclophosphamide, or cauterization without PMMA).\textsuperscript{5} The study found that when no adjuvants were used, the recurrence rate was 49%, whereas recurrence rate with PMMA was 22%, with PMMA after treatment with phenol was 27%, and with phenol or other toxins was 15%, thereby confirming results of previous studies.

Malawer et al\textsuperscript{25} studied patients who were treated with cryotherapy by direct pour technique using liquid nitrogen. Overall, the recurrence rate was 7.9%, with a lower recurrence rate seen in patients presenting with a primary lesion (2.3%). They concluded that cryotherapy may be used as an adjuvant to curettage for most giant cell tumors of bone.\textsuperscript{25,29,30} Previous studies by Marcove\textsuperscript{26} and Marcove et al\textsuperscript{29} showed recurrence rates of 2% to 28%, with improvement in recurrence rates seen with refinement of procedure. Complications associated with cryosurgery included pathologic fractures (6% to 25%), partial skin necrosis, and significant degenerative changes.\textsuperscript{25,26,29}

With the emerging understanding of argon beam photocoagulation as an effective surgical adjuvant, Lewis et al\textsuperscript{19} studied its role in preventing local recurrence in benign–aggressive bone tumors, showing a local recurrence rate of 10%. The data suggested that argon beam photocoagulation is associated with a lower rate of local recurrence and is a reasonable adjuvant therapy choice, with a low risk of complications, compared with recurrence rates from 12% to 50% using curettage and bone grafting alone.\textsuperscript{2,4-11} The current study revealed a similar recurrence rate to that of Lewis et al\textsuperscript{19} as well as to those of other studies comparing varying adjuvant therapies.

Although phenol has been a preferred method of adjuvant treatment in the past 2 decades, its application is not without risk. In fact, meticulous application of the phenol via a swab is required because spillage, dripping, or inadvertent application of phenol may result in chemical skin burns and necrosis of nearby fatty and connective tissue.\textsuperscript{31} Higher-than-recommended concentrations of phenol may also increase the risk of necrosis of normal tissue, therefore requiring irrigation.\textsuperscript{32} In addition, phenol is known to be carcinogenic and flammable and is commonly not readily available for distribution to practicing physicians from pharmacies at all institutions. Other methods that are safer and at least equal in efficacy should be considered for adjuvant treatment of benign–aggressive bone tumors.

Recently, argon beam photocoagulation has been shown to be an effective alternative to phenol in the treatment of benign–aggressive bone tumors because of its precision, ease of use, and low complication rate.\textsuperscript{17,23} However, difficulties seen with argon beam photocoagulation may include difficulty with resection edge application and currently unknown long-term exposure complications. Some studies report that argon beam photocoagulation may cause progressive joint degeneration due to causing tissue necrosis at a depth that has been sparsely studied.\textsuperscript{19} This issue has been examined in ovarian carcinoma studies, concluding that the depth of necrosis is linearly correlated with the time interval of interaction,\textsuperscript{33} whereas Heck et al\textsuperscript{18} reported that the depth of necrosis in cancellous bone can be controlled by the power of the argon beam and the location of the tumor. We recommend, along with others, long-term follow-up to evaluate for complications such as degenerative joint disease with the use of this adjuvant.\textsuperscript{18,19}

The purpose of our study was to directly compare argon and phenol in terms of effectiveness in reducing recurrence rates and minimizing complications in benign–aggressive bone tumors. Whereas Lewis et al\textsuperscript{19} noted a slightly lower, although comparable, recurrence rate for giant cell tumors treated with argon beam photocoagulation than in other studies, to our knowledge no study has directly compared its effectiveness to older, well-known adjuvants such as phenol in 1 patient population. Our study resulted in comparable recurrence rates for argon (14.8%) and phenol (17.1%) reported in the literature, but no

<table>
<thead>
<tr>
<th>Complication</th>
<th>Phenol No.</th>
<th>Argon No.</th>
<th>Total No.</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
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<td>9</td>
<td>16/102</td>
<td>.726</td>
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<tr>
<td>Infection</td>
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<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Fracture</td>
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<td>1</td>
<td>1</td>
<td></td>
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<tr>
<td>Fracture with recurrence</td>
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<td>1</td>
<td></td>
</tr>
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<td>Physeal arrest</td>
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<td>3</td>
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<tr>
<td>Synovitis</td>
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<td>6/41 (14.6%)</td>
<td>6/61 (9.8%)</td>
<td>12/102 (11.8%)</td>
<td>.853</td>
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</tbody>
</table>
statistically significant difference existed in recurrence between the 2 ($P=.726$). Likewise, our study demonstrated an average overall MSTS score of 27.4, and the phenol and argon beam photocoagulation subgroups individually had an average MSTS score of 28.1 and 27.1, respectively. These scores indicate that our phenol and argon beam photocoagulation subgroups are comparable when assessing functional outcomes, and these scores have also been found to be comparable with previous outcomes seen in other studies. Intra- and postoperative complications can also compromise functional outcomes. In our study population, no intraoperative complications were noted with either studied adjuvant. Although comparable rates of postoperative complications were noted with phenol (14.6%) and argon beam photocoagulation (9.8%), more postoperative fractures were seen in patients treated with argon beam photocoagulation, which was not statistically significant ($P=.355$).

One of the limitations of retrospective studies is the comparison of patients with different histologies, varying tumor sites, and varying tumor grades, although with similar stages (2 and 3). Although no comparable difference was found in these groups, these factors may hinder our ability to draw better conclusions from our study. In addition, 7 patients were lost to follow-up due to having a length of follow-up <10 months, and 5 patients were excluded due to incomplete records, limiting a larger patient population from being studied. Although we agree that a 10-month follow-up later in the course of this study, further changes in technique may have occurred with time. Additional variation in technique may have existed amongst the 3 surgeons involved in this study, although all were trained in musculoskeletal oncology.

While avoiding the difficulties in handling the toxic effects of phenol, argon beam photocoagulation provides for statistically equivalent recurrence rates in the treatment of benign–aggressive bone tumors. Further studies on the longer-term complications of argon may be warranted.

REFERENCES


24. DiCaprio MR, Boyle J, Gibbs CP. Use of the argon beam coagulator as an adjuvant for


