Research Paper

Surgical outcomes of extracorporeal irradiation and re-implantation in extremities for high grade osteosarcoma: A retrospective cohort study and a systematic review of the literature

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\textbf{ABSTRACT}

\textbf{Purpose}: To assess the failure rate and mode failure of high-grade osteosarcoma patients who received extracorporeal irradiation and re-implantation (ECIR) in extremities.

\textbf{Patients and Methods}: For the cohort study, patients who had received ECIR at a single institution between January 1996 and December 2014 were retrospectively evaluated. Characteristics of failure and time to failure were recorded and analyzed. In addition, a systematically search of published literatures regarding the use of ECIR for osteosarcoma was conducted. Failure rates and modes of failure were determined from the pooled data.

\textbf{Results}: In the cohort study, the overall reconstruction failure was 46\% (23 of 50 cases) of which 6\% were due to mechanical failure, and 40\% were due to non-mechanical failure. In the systematic review, 164 cases reached the criteria for analysis (50 diaphysis, 97 osteochondral of lower extremity, 6 knee resection, and 11 proximal humerus resection). Among those cases, overall failure rate was 29.9\% (49 of 164 cases) of which 7.9\% were due to mechanical failure, and 22.0\% to non-mechanical failure. Diaphyseal resection with intercalary re-implantation had a significantly lower failure rate than osteochondral reconstruction of lower extremity (OR: 2.7, \(p < 0.02\)), and knee extra-articular resection osteochondral re-implantation (OR: 10.5, \(p < 0.01\)).

\textbf{Conclusions}: Diaphyseal resection and extracorporeal irradiation of intercalary re-implantation offer the most promising outcome among other type of reconstructions. Availability of graft, fewer structural complications, and biological permanence are advantages of this reconstruction method.

1. Introduction

Biological reconstruction is a standard option for malignant bone tumor surgery. It provides permanent structural repair, and seldom requires further surgical revision procedures [1]. Sterilization of tumor-bearing autografts and re-implantation is an optional source of graft. That method has achieved particularly for well-structure maintaining bone tumor including osteosarcoma, chondrosarcoma and Ewing sarcoma [2]. Re-implantation of autograft presents some advantages over allograft implantation including availability of graft material, better osteotomy site match, better graft size match, possibility of soft tissue reconstruction, no disease transmitted problems [3]. The use of other tumor sterilization techniques including autoclaving, pasteurization, soaking in liquid nitrogen has been reported [3–5], but sterilization by extracorporeal irradiation (ECIR) seems to presented a better healing potential in vitro studies [6]. In addition, ECIR does not significantly alter the original mechanical properties of graft [7].

Some concerns have been expressed regarding tumor-bearing autograft re-implantation including locally recurrence, healing of the graft host junction, osteochondral collapse, and fixative device failure. A quantitative comparison of complications is difficult due to the existence of multiple heterogeneous covariables including type of tumor (which determines the biology of the disease and quality of the graft), sterilization techniques, site of reconstruction, status of chemotherapy.

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received. Comparison is further complicated by the fact that previous series have often not adequately defined the relevant characteristics of failures.

To minimize the influence of heterogeneous covariables, this cohort study presents surgical outcome, failure rate and mode of failure exclusively from cases of extracorporeal irradiation and re-implantation in extremities of in case with high-grade osteosarcoma. For the systematic review, a homogenous population was pooled and then analysis. Hypothesis investigated included whether either the type of resection and reconstruction, or maturity of autogenous graft affected to the rate of failure.

2. Patients and methods

2.1. Retrospective study

This retrospective cohort study reviewed osteosarcoma patients treated at a single institute, Chiang Mai University Hospital from 1 January 1996 to 31 December 2014 of osteosarcoma. Osteosarcoma patient data were obtained from musculoskeletal database of OLARN center [8]. This study was approved by Ethics Committee of Chiang Mai University (ORT-2560-04920). Patients who received surgical intervention with ECIR and re-implantation for limb salvage surgery, and follow-up period longer than 24 months were recruited into this study. Exclusion criteria were patients who did not receive standard treatment protocol, those with low grade osteosarcomas, those who received a prosthesis composite, pelvic or scapular reconstruction. Patient characteristics including age at diagnosis, gender, staging, location of tumor, type of resection and reconstruction were recorded. Time to failure and time to follow-up were recorded for survival analysis.

2.2. Osteosarcoma treatment protocols and surgical interventions

All cases suspected osteosarcoma underwent MRI for local staging as well as for incisional biopsy. Systemic staging was performed by CT chest and bone scans within two weeks of the initial pathology report. Neoadjuvant chemotherapy was started the week following receipt of the pathological report. Three courses of neoadjuvant therapy with Adriamycin and Cisplatin were used as the first line therapy for patients older than fifteen years, while Adriamycin, Cisplatin and high dose Methotrexate were used for patients younger than fifteen. Wide resection and reconstruction with ECIR was then conducted. Adjuvant chemotherapy was performed after the wound had healed. Routine follow-up included plain radiography, MRI for locally evaluation, and CT-chest and bone scans for systemic surveilance.

For surgical procedure, a tumor segment was removed from each patient. Tumor was removed using a curette from graft; some capsule and normal ligament were spared for reconstructive proposes in the following step. The autogenous graft was radiated with 50 Gy by using a linear accelerator [3]. The irradiated autologous graft was then soaked in antibiotic solution for 30 min after which it was re-implanted using fixation with plate and screws. Some bony defects were replaced with bone cement; cement substitution was accomplished without disturbing the junction between graft and host bone. Capsule or ligaments from graft was re-implanted at the original site. Muscle flap was used where there was poor soft-tissue coverage. Intravenous anti-biotics was given for two weeks post-operatively. Adjuvant chemotherapy was started within 2–4 weeks after operation. Bracing was applied for 4–6 weeks in case of major ligament reconstruction. Progressive weight bearing ambulation was encouraged depending on the healing between graft and host bone.

2.3. Outcome determination

The system of categorization of the mode of reconstruction failures was adapted from previously published reports on tumor endoprosthesis and the failure modes of biological reconstruction [9–11]. A failed reconstruction was defined as a piece of radiated graft needing to be removed, evidence of local recurrence of tumor, severe osteolysis and loss of skeletal-maintaining function in the upper extremities, requirement for major conversion surgery including tumor endoprosthesis replacement, arthrodesis, rotationplasty or amputation. Modes of failure were classified into two broad categories, “Mechanical failure” and “Non-mechanical failure”. Modes of mechanical failure include (1) Soft-tissue failure (instability, aseptic wound dehiscence), (2) Graft and host non-union, (3) Structural failure (osteochondral collapse, graft fracture, fixative failure, and severe osteolysis and lose skeletal function in upper extremities). “Non-mechanical failure” includes (4) Infection, and (5) Tumor recurrence. This study used MSTS score to determine functional status. The evaluations had been recorded 12-months after the initial operation, an interval after which a stable of reconstructive condition would be expected.

2.4. Systematic review

2.4.1. Selection of studies

The Medline and Scopus database were searched for relevant studies published before 30 June 2017. Search terms included: (Bone neoplasms or Sarcoma or Osteosarcoma) and (Limb salvage or Limb-sparing treatments or Reconstructive surgery or Orthopedic procedure or Biological reconstruction) and (Recycling autograph or Sterile autograph or Homologous or Prosthesis composite reconstruction or Bone transplantation or Osteochondral graft or Intercalary graft) and (Irradiation or Extracorporeal irradiation or Radiotherapy).

Two reviewers (DP and JK) independently performed data extraction Titles, abstracts and full texts were screened following inclusion and exclusion criteria. Inclusion criteria included observational studies (cohort, cross-sectional, case control studies) of high-grade osteosarcoma receiving ECIR. We excluded cohorts with insufficient data to determine outcome, pelvic and scapular reconstruction, prosthesis composites, follow-up time less than two years, and non-English literaturante. Reference lists in the retrieved articles were reviewed to identify additional publications on the same topic. In cases of overlapping cohorts, the report with the largest sample size and the most comprehensive description of outcome was selected. Two independent reviewers (DP and JK) critically appraised study identified using pre-determined criteria; data were extracted using standardized data extraction forms. Patient characteristics, including gender and age at diagnosis were recorded, as well as site tumor, and type of resection and reconstruction. Data on failure and modes of failure were extracted. Discordant judgments were resolved by discussion between the two reviewers. Critical appraisal criteria included disclosure, selection of patients, outcome reporting and assessment, baseline display, and post-operative rehabilitation [12]. This review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (identified CRD42017075059).

2.5. Statistical analysis

Survival analysis of failed reconstruction was estimated using Kaplan–Meier curves. Cox’s regression analysis was performed for comparison between each type of reconstruction. As part of systematic review, data on the prevalence, type of reconstructions, and mode of failure were pooled. Logistic regression analysis was performed using STATA version 14.0. Statistically significant difference was set at $p < 0.05$.

3. Results

3.1. Patient characteristics and functional score

A total of 63 of osteosarcoma underwent ECIR and re-implantation.
Of those, 50 (79.0%) reached the criteria for analysis (13 were excluded: 3 prosthesis composites at the hip joint, 4 follow-up time less than 24 months, 1 low-grade osteosarcoma, 5 insufficient data). The median age was 17.5 years (range 10–46 years) with a male: female ratio of 1.5:1. MSTS scores could be evaluated for 36 cases (72%). Thirteen cases were determined to have failed before the time of evaluation, and one had passed away. The median of MSTS score was 87 (range 40–97.6). The patient whose reconstruction had failed (n = 10) had an MSTS score at one year significantly lower than the 26 patients with good reconstruction results: 67.1 (40.0–94.0) and 84.4 (64.9–97.6), respectively, p < 0.05. Characteristics of the study group are shown in Table 1.

### Table 1

| No. | Age-Gender | Site | Resection and reconstruction | Reconstruction outcome | Follow up<sup>a</sup> (months) | MSTS | Oncological outcome | Follow up<sup>b</sup> (months) |
|-----|------------|------|------------------------------|------------------------|-------------------------------|------|-------------------|-------------------------------|
| 1   | 25-M       | Femur| DF-OC                        | Good                   | 265                           | 83   | Survive           | 265                           |
| 2   | 15-F       | Femur| DF-OC                        | Good                   | 257                           | 87   | Survive           | 257                           |
| 3   | 31-F       | Femur| DF-OC                        | Good                   | 221                           | 87   | Survive           | 221                           |
| 4   | 17-F       | Femur| DF-OC                        | Good                   | 53                            | 87   | Survive           | 53                            |
| 5   | 15-F       | Femur| DF-OC                        | Good                   | 56                            | 94   | Survive           | 56                            |
| 6   | 22-F       | Femur| DF-OC                        | Good                   | 244                           | 83   | Survive           | 244                           |
| 7   | 21-F       | Femur| DF-OC                        | Good                   | 98                            | 83   | Survive           | 98                            |
| 8   | 17-M       | Femur| DF-OC                        | Good                   | 26                            | 87   | Death             | 26                            |
| 9   | 24-M       | Femur| DF-OC                        | Good                   | 35                            | 94   | Death             | 35                            |
| 10  | 18-M       | Femur| DF-OC                        | Good                   | 22                            | 94   | Death             | 22                            |
| 11  | 14-F       | Femur| DF-OC                        | Good                   | 6                             | NR   | Death             | 6                             |
| 12  | 19-M       | Femur| DF-OC                        | Failed                 | 44                            | 60   | Survive           | 173                           |
| 13  | 13-M       | Femur| DF-OC                        | Failed                 | 28                            | 60   | Survive           | 97                            |
| 14  | 32-M       | Femur| DF-OC                        | Failed                 | 14                            | 43   | Survive           | 106                           |
| 15  | 17-M       | Femur| DF-OC                        | Failed                 | 35                            | 60   | Survive           | 118                           |
| 16  | 16-M       | Femur| DF-OC                        | Failed                 | 24                            | 70   | Survive           | 370                           |
| 17  | 11-F       | Femur| DF-OC                        | Failed                 | 18                            | 87   | Death             | 25                            |
| 18  | 19-M       | Femur| DF-OC                        | Failed                 | 10                            | NR   | Death             | 18                            |
| 19  | 16-M       | Femur| DF-OC                        | Failed                 | 6                             | NR   | Death             | 26                            |
| 20  | 46-M       | Femur| DF-OC                        | Failed                 | 12                            | NR   | Death             | 53                            |
| 21  | 23-F       | Tibia| PT-OC                        | Good                   | 164                           | 87   | Survive           | 164                           |
| 22  | 15-F       | Tibia| PT-OC                        | Good                   | 224                           | 83   | Survive           | 224                           |
| 23  | 14-F       | Tibia| PT-OC                        | Good                   | 257                           | 94   | Survive           | 257                           |
| 24  | 34-M       | Tibia| PT-OC                        | Good                   | 29                            | 94   | Survive           | 29                            |
| 25  | 18-M       | Tibia| PT-OC                        | Good                   | 34                            | 94   | Survive           | 34                            |
| 26  | 11-M       | Tibia| PT-OC                        | Failed                 | 41                            | 64   | Death             | 41                            |
| 27  | 30-M       | Tibia| PT-OC                        | Failed                 | 260                           | 87   | Survive           | 260                           |
| 28  | 14-M       | Tibia| PT-OC                        | Failed                 | 211                           | 87   | Survive           | 211                           |
| 29  | 12-M       | Tibia| PT-OC                        | Failed                 | 28                            | 63   | Survive           | 40                            |
| 30  | 13-F       | Tibia| PT-OC                        | Failed                 | 5                             | NR   | Survive           | 299                           |
| 31  | 11-M       | Tibia| PT-OC                        | Failed                 | 6                             | NR   | Survive           | 31                            |
| 32  | 15-F       | Tibia| PT-OC                        | Failed                 | 14                            | 40   | Survive           | 133                           |
| 33  | 19-F       | Tibia| PT-OC                        | Failed                 | 4                             | NR   | Survive           | 173                           |
| 34  | 24-M       | Tibia| PT-OC                        | Failed                 | 5                             | NR   | Death             | 6                             |
| 35  | 19-M       | Tibia| PT-OC                        | Failed                 | 6                             | NR   | Death             | 156                           |
| 36  | 26-M       | Tibia| PT-OC                        | Failed                 | 8                             | NR   | Death             | 34                            |
| 37  | 32-M       | Tibia| PT-OC                        | Failed                 | 8                             | NR   | Death             | 70                            |
| 38  | 24-F       | Tibia| PT-OC                        | Failed                 | 3                             | NR   | Death             | 82                            |
| 39  | 16-M       | Femur| D-I                         | Good                   | 149                           | 97.6 | Survive           | 149                           |
| 40  | 12-F       | Tibia| D-I                         | Good                   | 144                           | 83.3 | Survive           | 144                           |
| 41  | 23-M       | Femur| D-I                         | Good                   | 137                           | 76.6 | Survive           | 137                           |
| 42  | 18-F       | Femur| D-I                         | Good                   | 132                           | 75.3 | Survive           | 132                           |
| 43  | 12-M       | Femur| D-I                         | Good                   | 125                           | 96.9 | Survive           | 125                           |
| 44  | 20-F       | Femur| D-I                         | Good                   | 143                           | 70   | Survive           | 143                           |
| 45  | 26-M       | Tibia| D-I                         | Good                   | 21                            | 73.3 | Death             | 21                            |
| 46  | 14-M       | Tibia| D-I                         | Failed                 | 25                            | 94   | Survive           | 35                            |
| 47  | 13-F       | Tibia| D-I                         | Failed                 | 21                            | 94   | Survive           | 315                           |
| 48  | 16-F       | Tibia| KE-OC                        | Good                   | 46                            | 87   | Death             | 28                            |
| 49  | 10-M       | Tibia| KE-OC                        | Failed                 | 1                             | NR   | Survive           | 24                            |
| 50  | 22-M       | Humerus| PH-OC                  | Failed                 | 6                             | NR   | Death             | 46                            |

<sup>a</sup> Follow up time of reconstruction.

<sup>b</sup> Follow up time of survival, NR: unable to evaluate, DF-OC: distal femoral resection and osteochondral graft replacement, PT-OC: proximal tibia resection and osteochondral graft replacement, D-I: diaphyseal resection and intercalary replacement, PH-OC: proximal humerus resection and osteochondral graft replacement, KE-OC: knee extraarticular resection and osteochondral graft replacement.

### 3.2. Oncological outcomes

The five- and ten-year overall survival of patient (n = 50) are 70.4% and 65.4%, respectively, Fig. 1(A). Eighty-two percent (41 from 50 patients) presented with stage IIB, and 18% (9 from 50 patients) with stage III. Forty-two percent of Stage IIB (17 from 41 patients) developed systemic metastasis after surgery. There was 36% of all cases available for tumor necrosis data after neoadjuvant chemotherapy. Good chemo-responsive patient (tumor necrosis ≥ 80%: n = 10) significantly showed a better overall survival rate than poor chemo-responsive patients (tumor necrosis < 80%: n = 8), Fig. 1(B). There was 87.5% (7 from 8 patients) presented systemic metastasis and 25% (2 from 8 patients) presented local recurrence in a poor responsive group. On the other hand, 50% (5 from 10 patients) presented systemic metastasis and 10% (1 from 10 patients) presented local recurrence in a
good responsive group. Oncological characteristics of patients were listed in Supplementary Table 2.

### 3.3. Failure rate of ECIR

There was a total of 23 cases of reconstruction failure (46%). The one, three and five-year survival time of reconstructive procedures was 75.0%, 60%, and 55% respectively (Fig. 1(A)). Of the failure cases, nine (39.1%) had subsequently undergone corrective surgery with arthrodesis. Those patients had indicated satisfaction with the results, reporting that the limb was painless and stable. One failure case (4.2%) was revised with tumor endoprosthesis which achieved good results (Table 2). Subgroup analysis found that diaphyseal resection and intercalary re-implantation (D-I) had a lower failure rate than any other type of reconstruction. Distal femoral resection and osteochondral re-implantation (DF-OC) had a lower failure rate than proximal tibial resection and osteochondral reconstruction (PT-OC), and other types of reconstruction, but the difference was not statistically significant (Fig. 1(B)).

### 3.4. Systematic review of ECIR in osteosarcoma patients

For the systematic review of ECIR in osteosarcoma patients, 523 studies were identified from Medline database and 379 from the Scopus database. Flow chart study is shown in Fig. 2. Of these, nine studies were relevant and critically appraisal. Twenty-two percent of studies were level III evidence and most of others were level IV evidence. Fifty-six percent reported that patient selection criteria were based on age and quality of autogenous bone graft. All studies showed a proper report of included base line characteristics, outcome assessment, and complications. In one study reported that all cases in series had good results without descriptions to other parameters. The critical appraisal of systematic review is shown in Fig. 3. There were 164 cases which provided sufficient data for individually analysis [13–20] (Supplement Table 1). Characteristics of data, failure rate, mode of failure and surgical conversion is shown in Table 3.

#### Table 2

The list of procedures related failure, and following conversion procedures.

| Type of procedure | Number (%) | Overall failure (%) | Soft tissue | Non-union | Structure | Infection | Local recurrence |
|------------------|------------|---------------------|-------------|-----------|-----------|-----------|-----------------|
| DF-OC            | 20(40.0)   | 9                   | –           | –         | –         | 2         | 5               | 2               |
| PT-OC            | 18(36.0)   | 10                  | –           | –         | –         | 2         | 8               | –               |
| D-I              | 9(18.0)    | 2                   | –           | –         | –         | –         | –               | –               |
| KE-OC            | 2(4.0)     | –                   | –           | –         | –         | –         | –               | –               |
| PH-OC            | 1(2.0)     | 1                   | –           | –         | –         | –         | –               | –               |
| Total (%)        | 50(100.0)  | 23(46.0)            | –           | –         | 4(8.0)    | 15(30.0)  | 4(8.0)          |

| Type of surgical conversion | Number (%) | Conversion procedure according to type of failure |
|-----------------------------|------------|-----------------------------------------------|
| Amputation/rotationplasty   | 11(47.8)  | –                                             | 9 | 2 |
| Arthrodesis                 | 9(39.1)   | –                                             | 3 | 6 |
| Endoprosthesis              | 1(4.3)    | –                                             | 1 | – |
| Refuse for surgery          | 2(8.6)    | –                                             | – | 2 |
| Total                       | 23(100.0) | –                                             | 4 | 4 |
failure than LE–OC with OR 2.7, \( p = 0.02 \), and KE–OC with OR 10.7, \( p = 0.01 \). No significant differences were found from other paired comparisons due to the relatively low power of sample. Bone maturity was categorized into two groups: immature (age \( \leq 13 \) years) and mature (age > 13 years) [21]. No significant differences in failure rate between the two age groups was identified.

4. Discussion

Surgical outcomes of biological reconstruction in tumor surgery depends on several factors including characteristics of graft, fixative technique, biology of the disease, chemotherapy receiving, and host status [22]. Comparative evaluation between series was difficult due to the heterogeneities in the data and clarity regarding determination of cause of failure. Henderson et al. introduced a failure mode classification for tumor endoprosthesis [9], as well as a modified classification system for biological reconstruction and pediatrics [10]. An endpoint determination is the most important concern for selecting case into this analysis. Some series were excluded from study if authors do not provide adequate end-point outcomes. Soft-tissue laxity presented in various degree in ECIR reconstruction. Failure solely from soft-tissue laxity is rarely seen in DF–OC or PT–OC, although it has been frequently reported in KE-OC. Surgical conversion is performed mostly in case presenting with severe joint laxity accompanied by osteochondral collapse. In case of delayed union between host and graft junction, healing which can be enhanced with a bone graft substitute or with minor revision of the fixative device has not been considered as failure. Local recurrence would be the major concern for sterile tumor-bearing autogenous graft. However, systematic review was unable to determine the definite site of recurrence whether occurred in graft or surrounding soft-tissue therefore causative of locally recurrence could not be specified in this study.

Diaphyseal resection and intercalary reconstruction showed better results than other type of reconstructions in both the cohort study and in the systematic review. Intercalary reconstruction by using ECIR also showed a relatively lower failure rate than allograft and endoprosthesis reconstruction. In systematic review, the overall failure from I–I was
16% (8 of 50 cases), all from non-mechanical failure. A higher failure rate from intercalary endoprosthesis reconstruction at tibial bone was reported at 44.4% (8 in 18 patients), of which 11.1% were from non-mechanical and 33.3% from mechanical failure [23]. Recently reported results of modular intercalary endoprosthesis of the femur, tibia and humerus showed an overall failure rate at 29% (13 of 41 patients) of which 3% were from non-mechanical failure and 26% were from mechanical failure [24]. Intercalary reconstruction by using allograft reported in a multicenter study had an overall failure rate of 17% (13 of 87 patients), 6.9% from non-mechanical failure, and 10.1% from mechanical failure [25]. Interestingly, mechanical complications seemed to be the major cause of failure in both endoprosthesis and allograft, a result that was not found in ECIR in the systematic review. Good bone healing at the host-bone and graft junction had a healing time of around 7.3 months (range 3–28 months) [18]. Technical advantages play an important role in good healing. Completely fit at the osteotomy site enhances primary healing between host and graft junction. Authors perform chevron cut since it helps anatomical fit, increasing contact area, and using compression technique via plate and screw system. An example of healing potential of 1-t is shown in Fig. 4. Preserving osteoinductive proteins from irradiated bone graft has also been shown to be beneficial in both experiment and clinical study [6,26]. Good healing of a biological construct creates a permanent stability, and reduces the failure rate in long term follow-up. Sterilization techniques for tumor bearing autograft in diaphyseal reconstruction from other sterile techniques including pasteurization, liquid nitrogen need to be further explored. In spite of potential challenges such as availability of graft, good healing potential, and permanent biological construct, sterile autograft might be the treatment of choice for diaphyseal reconstruction to achieve maximize benefits.

Osteochondral re-implantation around the knee had a high complication rate 34.0% (33 in 97 cases) from ECIR procedures. Of those, 8.2% were mechanical failure, and 25.8% were non-mechanical failure (19.6% infection and 6.2% locally recurrence). Systematic review in outcome of osteochondral allograft implantation around knee showed an overall failure rate of 35.4%: 18.4% graft fracture, and 14.6% infection [11]. Reconstruction with tumor endoprosthesis presented a lessor failure rate of 29.0%: 14% mechanical failure and 15% non-mechanical failure (10% of infection and 5% was local recurrence). The rate of non-mechanical failure due to infection in ECIR was relatively high compared to allograft and endoprosthesis (4.6% and 9.6%, respectively). There was a similar rate of mechanical failure between ECIR and endoprosthesis. The high infective rate with ECIR is a significant drawback. The longer operative time required for graft sterilization and for fixative processes might increase risk of infection. The relatively larger operative exposure for plate and screws fixation is a good chemos-responsive group showed a lower percentage of local another concern. Identify risks and modifying processes could potentially help reduce infection rates.

The risk of tumor recurrence from a sterile tumor-bearing autograft has become an issue of concern. Many factors play a causative role in locally recurrence including resection margin, biology of tumor, and adjuvant chemotherapy received. Sterility of tumor-bearing grafts has been studied and proven effective in animal model. In those studies, tumor cells were completely killed with 50 Gy irradiated condition [7]. Furthermore, clinical data from this study found relatively little

| Type of surgical conversion | Number (%) | Conversion procedure according to type of failure |
|----------------------------|------------|-----------------------------------------------|
| Amputation/rotationplasty  | 19(38.8)   | 13                                          | 6              |
| Arthrodesis                | 11(22.4)   | 2                                           | 1              |
| Endoprosthesi             | 8(16.3)    | 5                                           | 1              |
| Refuse for surgery         | 2(4.1)     | 1                                           | 2              |
| No data           | 9(18.4)    | 4                                           | 3              |
| Total (%)                | 49(100.0)  | 11                                          | 11             |

Table 4
Analysis extracted data from systematic review of reconstructive failure of ECIR of extremities for high grade osteosarcoma.

| Reconstructon | Overall  | Mechanical failure | Infection | Tumor progression |
|---------------|----------|--------------------|-----------|-------------------|
|               | n   | OR (95% CI) | p | n   | OR (95% CI) | p | n   | OR (95% CI) | p |
| D-I (50)     | 8   | 1.5(0.52–6.22) | 0.36 | 6   | 1.6(0.47–5.45) | 0.45 |
| LE-OCa (97) | 33  | 2.7(1.14–6.43) | 0.02 | 7   | 0.6(0.18–1.79) | 0.34 |
| KE-OC (6)   | 4   | 10.5(1.64–67.33) | 0.01 | 0   | 0  | 0  | 0  |
| UE-OCb (11) | 4   | 3.0(0.71–12.69) | 0.14 | 1   | 1  | 1  | 1  |
| Skeletal mature status | 14   | 1.90(0.87–4.17) | 0.11 | 6   | 1.50(0.55–4.26) | 0.42 | 10  | 1.6(0.47–5.45) | 0.45 |

| Immature (34) | 35   | 1.80(0.52–6.22) | 0.36 | 16  | 1.50(0.55–4.26) | 0.42 | 10  | 1.6(0.47–5.45) | 0.45 |

a LE-OC: lower extremity of osteochondral re-implantation.
b UE-OC: upper extremity of osteochondral re-implantation.
different in the mode of recurrence from endoprosthesis and ECIR reconstruction in a population which were primarily osteosarcoma patients [9]. However, chemo-receiving status is an interesting issue that needs to be further explored. A long-term study of oncological outcome in 101 cases of ECIR looked at the differences in histology between Ewing sarcoma, osteosarcoma and chondrosarcoma. That study reported no local recurrence of osteosarcoma (0 of 34 cases), 2.9% of Ewing sarcoma (1 of 35 cases), and 20% of chondrosarcoma (4 of 20 cases). A higher local recurrence rate was presented in chondrosarcoma patients most of which did not receive adjuvant chemotherapy [2]. From our study, a good chemo-responsive group showed a lower local recurrence rate than a poor chemo-responsive group however it's not statistically significant. Tumor-bearing autograft might be a factor in immunity activation. Tumor antigens remaining in autogenous graft might be recognized by T-lymphocytes and then play a role of immune surveillance [27]. Murakami et al. used frozen tumor-bearing autograft inside a cage for reconstruction in total En bloc spondylectomy, and found increased antitumor immunity at post-operative follow up [28].

The present study was unable to demonstrate whether bone maturity status affects the reconstruction failure rate. Gender status was not fully collected from pooled data, therefore thirteen years old was the estimated cut off for both gender of overall data [21]. The number of immature bone status was less frequent. It is possible that suitable alternative procedures had been selectively performed on very young patients. The use of prosthesis composite was also reviewed in this study. A common procedure was proximal femur resection with prosthesis composite replacement which resulted in excellent outcomes. Prosthesis composite around the knee also had good results. Determination of failure in prosthesis composite with autogenous graft is not equivalent to exclusively biological reconstruction. Additionally, there was only a small group (n = 19) in pooled data. For those reasons, prosthesis composite reconstruction was excluded form analysis. The limitation of analysis was the inability to determine time to failure as this information was poorly defined in the recruited series.

5. Conclusion

Diaphyseal resection and intercalary re-implantation by using ECIR shows promise for achieving favorable outcomes. Among the advantages of D-I reconstruction are availability of graft material, fewer structural complications, and biologically permanence. Osteoarticular re-implantation around the knee presents with mechanical complications similar to tumor endoprosthesis but has been shown to have higher rate of complications from infection.

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Conflict of interest

The authors declare that there are no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jbo.2018.100210.

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