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Guidelines

Japanese orthopaedic association (JOA) clinical practice guideline on the management of primary malignant bone tumors - Secondary publication☆

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ABSTRACT

Background: In Japan, there are currently no general guidelines for the treatment of primary malignant bone tumors. Therefore, the Japanese Orthopaedic Association established a committee to develop guidelines for the appropriate diagnosis and treatment of primary malignant bone tumors for medical professionals in clinical practice.
Methods: The guidelines were developed in accordance with "Minds Clinical Practice Guideline Development Handbook 2014" and "Minds Clinical Practice Guideline Development Manual 2017". The Japanese Orthopaedic Association's Bone and Soft Tissue Tumor Committee established guideline development and systematic review committees, drawing members from orthopedic specialists leading the diagnosis and treatment of bone and soft tissue tumors. Pediatricians, radiologists, and diagnostic pathologists were added to both committees because of the importance of multidisciplinary treatment. Based on the diagnosis and treatment algorithm for primary malignant bone tumors, important decision-making points were selected, and clinical questions (CQ) were determined. The strength of recommendation was rated on two levels and the strength of evidence was rated on four levels. The recommendations published were selected based on agreement by 70% or more of the voters.
Results: The guideline development committee examined the important clinical issues in the clinical algorithm and selected 22 CQs. The systematic review committee reviewed the evidence concerning each

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CQ and a clinical value judgment was added by experts. Eventually, 25 questions were published and the text of each recommendation was determined.
Conclusion: Since primary malignant bone tumors are rare, there is a dearth of strong evidence based on randomized controlled trials, and recommendations cannot be applied to all the patients. In clinical practice, appropriate treatment of patients with primary malignant bone tumors should be based on the histopathological diagnosis and degree of progression of each case, using these guidelines as a reference.

1. Introduction

Primary malignant bone tumors are extremely rare. Osteosarcoma and Ewing's sarcoma are highly malignant and require drug therapy due to the high rate of pulmonary metastasis; however, there is no effective chemotherapy for chondrosarcoma and chordoma, and the pathology varies depending on the histological type. Furthermore, it is important to maintain motor function during surgery, so appropriate treatment for each case is based on the site of occurrence and the degree of progression.

In Japan, there are currently no general guidelines for the diagnosis and treatment of primary malignant bone tumors. Therefore, the Japanese Orthopaedic Association established a committee to develop guidelines for the appropriate diagnosis and treatment of primary malignant bone tumors.

In the creation of this document, a development committee and a systematic review committee were formed, comprising orthopedic specialists who are at the forefront of diagnosing and treating bone and soft tissue tumors. Furthermore, due to the importance of multidisciplinary treatment, pediatricians, radiologists, and diagnostic pathologists specializing in bone and soft tissue tumors were included in the committee.

Based on an algorithm for the diagnosis and treatment of primary malignant bone tumors, the important clinical issues were examined, and 22 clinical questions (CQs) were identified. Thereafter, the newest evidence for each CQ was reviewed; CQs deemed standard during that process were changed to Background Questions (BQs 1–5), and CQs predicted to be recommended for future research were changed to Future Research Questions (FRQs 1–3). Eventually, 25 questions were published. Based on the overall evaluation of the evidence prepared by the systematic review committee, the guideline development committee drafted statements of recommendation for each CQ, considered the balance between benefits and risks, and discussed and developed the statements of recommendation.

However, since primary bone tumors are rare cancers, multidisciplinary treatment by medical professionals with sufficient knowledge and experience is necessary. Therefore, immediate specialist consultation is recommended when a primary malignant bone tumor is suspected.

2. Methods

2.1. Development of the guidelines

This guidelines were created in accordance with “Minds Clinical Practice Guideline Development Handbook 2014” and “Minds Clinical Practice Guideline Development Manual 2017”. To prevent opinion bias, the guideline development committee and the systematic review committee consisted of orthopedic surgeons, pediatricians, radiologists, and pathologists leading the field of diagnosis and treatment of bone and soft tissue tumors. The development of these guidelines was funded by the Japanese Orthopaedic Association, but the views and interests of the financial contributor did not influence the final recommendations. The conflicts of interest of the development committee were disclosed, based on the standards of the Conflict-of-Interest Committee of the Japanese Orthopaedic Association.

2.2. Algorithm and clinical questions (CQ)

The guideline development committee created an algorithm for the diagnosis of primary malignant tumors (Fig. 1), treatment without distant metastases (Fig. 2), and treatment with metastatic progression (Fig. 3). Thereafter, referring to the algorithm, we developed 25 questions (BQs 1–5, FRQs 1–3, and CQs 1–17) on important decision-making points in the treatment of primary malignant bone tumors (Table 1).

2.3. Literature search and systematic review

Literature searches were conducted on Cochrane, MEDLINE, and the Ichushi database up to August 2020, and 9846 papers were extracted. Of these, 1357 papers were accepted in the primary screening, 417 in the secondary screening, and 154 manually searched papers, which were deemed important, were added. The included literature was cross-sectionally evaluated, based on outcomes, by the systematic review team to generate a body of evidence.

2.4. Development of recommendations and external assessment

After conducting a comprehensive evaluation of the evidence prepared by the systematic review team, the guideline development committee drafted recommendations for each CQ. The committee carefully considered the balance between benefits and risks associated with these recommendations and engaged in extensive discussions. When the implementation/non-implementation of a specific intervention was a subject of discussion, the basic

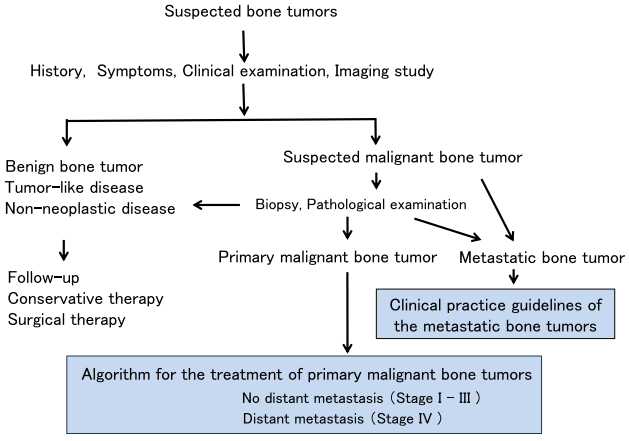

Fig. 1. Algorithm for the diagnosis of primary malignant bone tumors.

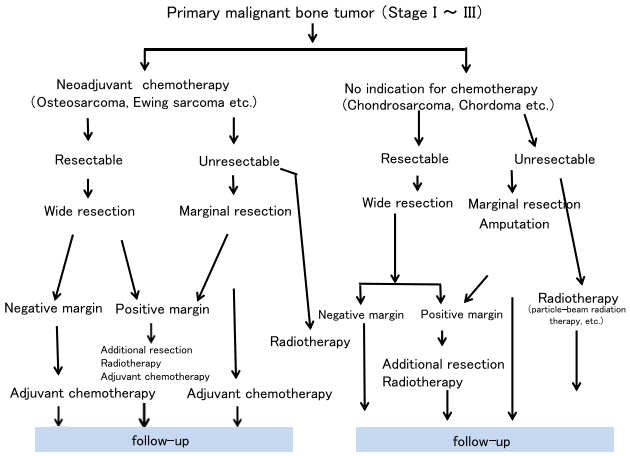

Fig. 2. Algorithm for the treatment of primary malignant bone tumors (Stage I ~ III).

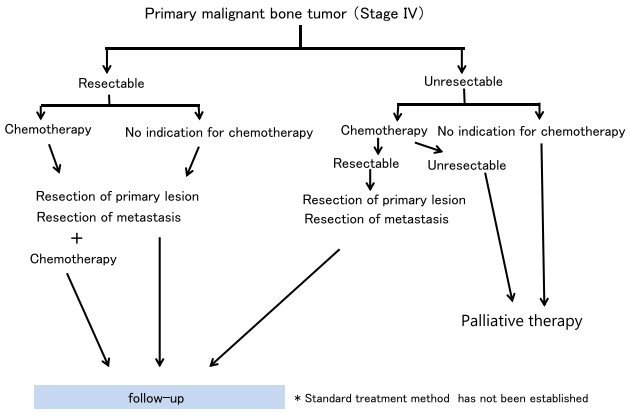

Fig. 3. Algorithm for the treatment of primary malignant bone tumors (Stage IV).

outcomes were "recommended" or "not recommended." The strength of recommendation was as follows: 1. Recommendation to "implement" or "not implement"; and 2. Suggestion to "implement" or "not implement." Recommendations and the strength of the recommendation, were determined by voting (GRADE grid) among the members of the development committee (Tables 2 and 3). For a recommendation to be implemented it required at least a 70% affirmative vote.

A draft of this clinical practice guideline was published on the websites of cooperating academic societies, such as the Japan Society of Clinical Oncology, and public comments were solicited. The collected comments were examined by the development committee and the manuscript was revised accordingly.

3. Results and discussion

3.1. Epidemiology of primary malignant bone tumors

3.1.1. Histology

Bone tumors have histologically been classified based on their differentiation or characteristic features. However, in recent years, genetic alterations have become an important factor in tumor classification, in addition to morphological findings; some tumor groups have even been established based on genetic mutations. The World Health Organization (WHO) classification of bone tumors (2020) has the following categories: 1. chondrogenic tumors, 2. osteogenic tumors, 3. fibrogenic tumors, 4. vascular tumors of bone, 5. osteoclastic giant cell-rich tumors, 6. notochordal tumors, 7. other mesenchymal tumors, and 8. hematopoietic neoplasms of bone [1]. Regarding Ewing's sarcoma, the WHO classification added an independent chapter of undifferentiated small round cell sarcomas of bone and soft tissue, which was subdivided into four tumor groups based on common genetic alterations.

3.1.2. Frequency and age distribution

The incidence of primary malignant bone tumors is extremely low, accounting for only 0.2% of all tumors and occurring at

Table 1
Clinical question.

BQ1	Is plain radiography (X-ray images) useful in diagnosing primary malignant bone tumors?
CQ1	Is computed tomography useful in diagnosing distant metastases of primary malignant bone tumors?
BQ2	Is MRI useful for preoperative planning for primary malignant bone tumors?
CQ2	Is F18-FDG-PET/CT more useful than bone scintigraphy for staging diagnosis in primary malignant bone tumors?
CQ3	Is nuclear medicine study useful for ascertaining the efficacy of preoperative chemotherapy in primary malignant bone tumors?
FRQ1	Is F18-FDG-PET/CT more useful than CT or MRI for the diagnosis of local recurrence in primary malignant bone tumors treated with metallic materials?
CQ4	Is incisional biopsy more useful than needle biopsy for definitive diagnosis of primary malignant bone tumor?
CQ5	Is molecular biological analysis useful for pathological diagnosis of primary malignant bone tumors?
FRQ2	Are nomograms useful for predicting the prognosis of primary malignant bone tumors?
CQ6	Is limb-sparing surgery recommended for pediatric primary malignant bone tumors?
BQ3	What are the limb-sparing surgeries available for primary malignant bone tumors?
FRQ3	Is biological reconstruction useful in limb-sparing surgery for primary malignant bone tumors?
CQ7	Is conventional adjuvant radiotherapy useful for primary malignant bone tumors without metastasis?
CQ8	Is conventional radiotherapy useful for primary malignant bone tumors that are unresectable or are expected to have severe functional impairment after surgery?
CQ9	Is particle-beam radiation therapy useful for primary malignant bone tumors that are unresectable or expected to have severe functional impairment after surgery?
BQ4	Is adjuvant chemotherapy useful for resectable high-grade osteosarcoma?
CQ10	Is drug therapy useful for unresectable recurrent/progressive high-grade osteosarcoma?
BQ5	Is drug therapy useful for localized Ewing's sarcoma?
CQ11	Is intensive drug therapy useful for metastatic Ewing's sarcoma?
CQ12	Is radiotherapy useful for difficult-to-resect localized Ewing's sarcoma?
CQ13	Is intralesional resection useful for central atypical cartilaginous tumors localized in the extremities?
CQ14	Is particle-beam radiation therapy useful for unresectable chondrosarcoma?
CQ15	Is particle-beam radiation therapy useful for chordoma?
CQ16	Is lesion curettage useful as a local treatment for curettable giant cell tumors of bone?
CQ17	Can resection of pulmonary metastases improve the survival prognosis in osteosarcoma cases with lung metastases. ?

Table 2
Strength of recommendation.

1. Strong	To be implemented, or not to be implemented, is recommended.
2. Weak	To be implemented, or not to be implemented, is suggested. Alternatively, is recommended subject to conditions.

Table 3
Strength of evidence.

A. Strong	The evidence of effect is highly convincing.
B. Moderate	The evidence of effect is moderately convincing.
C. Weak	The evidence of effect is weakly convincing.
D. Very weak	The evidence of effect is barely convincing.

approximately one tenth of the incidence of soft tissue sarcomas [2,3]. In North America and Europe, the annual incidence is 0.75/100,000, and all malignant bone tumors are considered "rare cancers". According to the Japanese bone tumor registry (2006–2015), osteosarcoma is the most frequently diagnosed primary malignant bone tumor (34%), followed by chondrosarcoma (21%), plasmacytoma and malignant lymphoma (11% each), Ewing's sarcoma (6%), and chordoma and undifferentiated pleomorphic sarcoma (5% each) [4]. The age-specific frequencies and incidence rates of malignant bone tumors as a group are bimodal. The first well-defined peak occurs during the first two decades of life. The second peak occurs in middle-aged and older adults. Osteosarcoma and Ewing's sarcoma are common in children and adolescents, while chondrosarcoma, myeloma, malignant lymphoma, chordoma, and undifferentiated pleomorphic sarcoma are more common in middle-aged and elderly people.

3.1.3. Localization

Bone tumors have predilections for certain bones and for characteristic locations in an individual bone. Osteosarcoma commonly occurs in the metaphysis of the long bones of the extremities, especially in the distal femur, proximal tibia, proximal humerus, and pelvis. Chondrosarcoma frequently develops in the metaphysis to the diaphysis of the long bones of the extremities, the pelvis, the ribs, and the sternum. Among all chondrosarcomas only clear cell chondrosarcoma has predilections for the epiphyses of long bones. Ewing's sarcoma frequently develops in the diaphyses of the long bones of the extremities and the pelvis. Almost all chordomas occur in central bones, most often in the sacrum, coccyx, and clivus, followed by the cervical and lumbar vertebral bodies. Adamantinoma has a predilection for the tibial shaft. Malignant vascular tumors commonly occur in the long bones of the lower extremities and toes, and often involve multiple bones. The site of occurrence of primary undifferentiated pleomorphic sarcoma is similar to that of osteosarcoma, and secondary undifferentiated pleomorphic sarcoma occurs in accordance with the sites of precursor lesions and radiation fields. Giant cell tumors of bone are eccentrically located in the epiphysis to the metaphysis of the long bones of the limbs. The distal femur, proximal tibia, and distal radius are often affected, while the sacrum is a common site in the spine. Juxtacortical malignant bone tumors include parosteal osteosarcoma, periosteal osteosarcoma, high-grade superficial osteosarcoma, peripheral chondrosarcoma arising from an osteochondroma, peripheral dedifferentiated chondrosarcoma, and periosteal chondrosarcoma.

3.2. BQ1: Is plain radiography (X-ray images) useful in diagnosing primary malignant bone tumors?

Since bone tissue cannot be observed directly from the outside of the body, plain X-ray imaging is routinely used as a screening method for diagnosing bone lesions. This is the starting point for practical treatment. With the exception of limited ultrasonography, it is impractical to perform other imaging studies without plain radiographs in the bone clinic.

More than 100 years have passed since plain radiography was introduced into clinical practice. Since many case experiences have been accumulated, not only for bone tumors but also for bone lesions and injuries, it is possible to obtain primary information, such as the presence or absence of lesions, disease diagnosis, and benign/malignant differentiation only by plain radiography [5]. Furthermore, two-dimensional radiography along the entire length of the affected bone is the most specific test for diagnosing benign or malignant disease, and the importance of plain radiography in determining the presence or absence of bone tumors is unquestionable [1,6]. Moreover, benign lesions are diagnosed by this test alone; no further tests or biopsies are needed, and only if the lesion cannot be determined to be benign should the diagnostic process proceed to the next imaging test [7].

Although other imaging tests provide different information than that of plain radiography, medical costs and inconvenience make it impractical to perform these tests without the initial use of plain radiography for screening.

There have been no observational or interventional studies that directly compare diagnostic accuracy, exposure dose, and medical costs of plain radiography for primary malignant bone tumors. Additionally, there have been no reports with a high level of evidence comparing plain radiographs to other imaging modalities.

However, since there are many reviews and plain radiography can be easily performed in clinical practice, it is routinely performed for primary screening of primary malignant bone tumors in clinical settings. When conducting plain radiography, it is important to keep the range and number of times to a minimum, as well as to avoid unnecessary exposure to radiation through the use of shields, etc. However, it may be appropriate to perform other imaging tests, as necessary, after plain radiography, which can easily obtain two-dimensional information with low exposure.

3.3. CQ1: Is computed tomography useful in diagnosing distant metastases of primary malignant bone tumors?

Statement of recommendation: We suggest performing computed tomography (CT) in the diagnosis of distant metastases of primary malignant bone tumors.

Recommendation strength: 2, Percentage agreement: 91%, Evidence level: C.

Reports related to the usefulness of CT for distant metastases of primary malignant bone tumors were extracted and reviewed. Studies that included soft tissue sarcomas were also considered due to the rarity of primary malignant bone tumors.

Among distant metastases of primary malignant bone tumors, pulmonary metastasis was the most common, accounting for 70.3–100% of advanced cases, followed by bone and bone marrow metastasis; and metastasis to other areas was low at 0–4.7% [8–10]. Respiratory failure has been reported to be the most common cause of death [11], and therefore most of the papers on distant metastases of primary malignant bone tumors have been on pulmonary metastasis. The extracted papers on this subject were about the comparison of early detection and prognosis between plain radiography and CT, the possibility of pulmonary nodules

detected by CT being metastases, and the factors suggestive of metastasis. There were no papers on the medical costs or radiation exposure of CT, and no reports comparing CT with other tests in pulmonary metastasis.

In a randomized prospective study of primary malignant bone tumors, Puri et al. [12] compared the results of chest CTs with plain chest radiographs and reported that although pulmonary metastasis can be diagnosed earlier with chest CT, no difference was noted in the 5-year survival. In contrast, Paioli et al. [13] investigated osteosarcomas with pulmonary metastases, and found that more cases in which all the pulmonary metastases could be resected were found by CT than by plain radiography. Furthermore, 5-year post recurrence survival (PRS) and 5-year overall survival (OS) were also reported to be favorable in cases where CT was used. Kusma et al. [14] reported, through biopsies of pulmonary nodules in patients under 25 years of age, with distant metastases of osteosarcoma or Ewing's sarcoma, that nodules $\leq$5 mm observed on CT were not suggestive of benignity. Heaton et al. [15] reported on patients with pulmonary metastases of osteosarcomas who underwent thoracotomy for pulmonary metastasis resection and had more lesions than were identified by CT. As such, CT was useful, but the results suggest that some lesions are unidentifiable on CT.

As described above, chest CT can be useful for early detection of pulmonary metastases of primary malignant bone tumors, but its effect on improving prognosis is still being debated. However, in the future, with advances in treatment technology, early detection of distant metastasis by CT may become increasingly important for improving prognosis.

3.4. BQ2: Is MRI useful for preoperative planning of primary malignant bone tumors?

Magnetic resonance imaging (MRI) of primary bone tumors is widely performed and used for pretreatment staging and evaluation of the effect of preoperative chemotherapy. There have been a few studies on treatment plans and tumor ranges, but they are limited to osteosarcoma and Ewing's sarcoma. Here, we selected and examined five pieces of literature regarding preoperative MRI evaluation.

In a study that investigated whether epiphyseal line preservation is possible in osteosarcoma (n = 47) and Ewing's sarcoma (n = 18) [16], there were more false positive cases than false negative cases, but there were no false negative cases with combined CT and MRI. The accuracy of MRI is as high as 90.3%, and the epiphysis can be safely preserved if there is no invasion of the growth plate. A comparative study of dynamic MR angiography, T1-weighted imaging, and short tau inversion recovery (STIR) [17] showed histological progression to the epiphysis in 20 of the 40 cases. Both T1-weighted imaging and STIR were 100% sensitive in detecting tumors or edema; however, the specificity was 60% for T1-weighted imaging and 40% for STIR. For tumor detection only, the sensitivity was 95% for STIR and 90% for T1-weighted imaging, and the specificity was 90% for T1-weighted imaging and 70% for STIR. In conclusion, T1-weighted imaging was more accurate than STIR in detecting the presence of a tumor. The receiver-operator characteristic (ROC) analysis showed 0.94 for T1-weighted images and STIR, but 0.90 for dynamic MR angiography. In addition, there is a piece of literature that states that microscopic infiltration can be distinguished from normal bone marrow by evaluating the gradient in dynamic imaging [18]. Of the six cases of osteosarcoma that underwent tumor resection, microscopic infiltration was observed in five cases. Another study investigated the detection of residual tumor after preoperative chemotherapy, using dynamic contrast-enhanced MRI combined with subtraction in 21 cases of osteosarcoma or Ewing's sarcoma [19]. The interval between the arrival of the bolus of contrast agent in the artery and the onset of the contrast enhancement effect of the tumor was used to evaluate the presence of residual tumor; early enhancement on MRI reflected the feeder artery and residual tumor. In a report comparing preoperative MRI with resected specimens of 26 bone tumors (four of which were benign bone tumors), tumor extent was accurately evaluated, except in two cases of Ewing's sarcoma. Decrease in signal intensity and tumor size reflected changes due to preoperative chemotherapy [20].

T1-weighted imaging and STIR are expected to provide high diagnostic accuracy for evaluating the extent of tumor progression with MRI, while dynamic imaging is also useful for detecting microscopic infiltration, particularly for distinguishing between edema and infiltration. In contrast, there have been studies reporting that dynamic imaging is less accurate than T1-weighted imaging and STIR, and there is room for further investigation as to whether it is necessary. It should be noted, that in all the literature reviewed on this question the number of included cases was small, there were no reports with strong evidence and the included studies were at least 20 years old. As a result, the assessments are based on equipment that is inferior in performance to current MRI technology. In the future, it is expected that applicability will be improved through the development of hardware, such as the improvement of the static magnetic field strength, and the development of software that eliminates metal artifacts. It will be necessary to report on further evidence for individual application in the future.

3.5. CQ2: Is F18-FDG-PET/CT more useful than bone scintigraphy for staging diagnosis in primary malignant bone tumors?

Statement of recommendation: F18-FDG-PET/CT is conditionally useful for diagnosing the stage of primary malignant bone tumors, compared with bone scintigraphy; therefore, we suggest the use of F18-FDG-PET/CT.

Recommendation strength: 2, Percentage agreement: 100%, Evidence level: C.

Nine articles comparing F18-FDG-PET (PET)/CT and bone scintigraphy for the staging of primary malignant bone tumors were selected. Other than review articles, they were limited to the imaging assessment of bone metastasis [21–25]. The targets were Ewing's sarcoma, osteosarcoma, or both.

All the papers concluded that the diagnostic performance of PET/CT was excellent, and the accuracy was either high[22-24)] or equivalent25). The difference in sensitivity was particularly large [22,24,25]. The superiority of PET/CT is clear, and there is an argument [21] that if Ewing's sarcoma is an osteolytic lesion, there is no point in adding bone scintigraphy. However, PET/CT is inferior to bone scintigraphy for cranial lesions [23]. There are also reports that combining PET/CT and bone scintigraphy improves accuracy [24.25], so they can complement each other. Since there are technical limitations in PET/CT, depending on the facility, it is necessary to avoid relying on it and delaying the evaluation. Bone scintigraphy has the same or better detection capability than PET/CT for sclerotic bone lesions [21], so the appropriate examination method should be selected according to the case and lesion site.

The evaluation of pulmonary metastases is essential for staging primary malignant bone tumors. However, PET/CT images have the disadvantage of a higher radiation dose and relatively inadequate ability to detect pulmonary metastases. Therefore, evaluation of pulmonary metastases by PET/CT alone is considered insufficient.

PET/CT is superior to bone scintigraphy for staging primary malignant bone tumors. However, there are sites that are difficult to detect using PET/CT. As such, both tests are considered complementary as their combination improves diagnostic accuracy. Due to

restrictions on the distribution of imaging devices, there are cases where sufficient examinations cannot be obtained, resulting in some differences in indications in order to proceed smoothly with overall treatment. Comparing bone scintigraphy and CT combination images (SPECT-CT) is an issue for future research, but equivalent diagnostic performance can be expected, especially for sclerotic lesions, for which bone scintigraphy has higher sensitivity.

3.6. CQ3: Is nuclear medicine studies useful for ascertaining the efficacy of preoperative chemotherapy in primary malignant bone tumors?

Statement of recommendation: We could not make a definite recommendation on the indication for nuclear medicine studies to evaluate the efficacy of preoperative chemotherapy.

Recommendation strength: No recommendation, Percentage agreement: -, Evidence level: C.

The Response Evaluation Criteria in Solid Tumors (RECIST) is widely used in clinical studies and clinical trials to assess therapeutic efficacy in solid tumors. However, with primary bone tumors, it is not possible to adequately evaluate therapeutic effects based solely on changes in tumor mass. In the histological efficacy criteria, which are the gold standard for assessing therapeutic efficacy for primary malignant bone tumors, the presence or absence of $\leq$10% residual viable tumor cells in the maximum section of the resected specimen is used to ascertain the therapeutic effect. It serves as a criterion for assessing the superiority or inferiority of image diagnosis.

In this systematic review, we included 45 papers on treatment effect assessment and prediction using nuclear medicine imaging in preoperative chemotherapy. The papers accepted for review were 14 papers on Tl-201 (TI), 5 papers on Tc-99 m-MIBI (MIBI), and 28 papers on PET.

For Tl and MIBI, the indicators of the tumor extent before chemotherapy are compared with postoperative histopathological tissue to determine whether they decreased during or after treatment. For Tl, eight original papers with more than 15 cases [26–28]) found sensitivities of 79%–100% (87 ± 6.4%) and specificities of 71%–100% (85 ± 11.4%) for assessing histological response, and accuracy ranged from 76% to 97% (86 ± 6.8%). For MIBI, four papers [26,30], covering more than 15 cases, found sensitivities of 81%–100% (87 ± 7.8%), specificities of 69%–100% (86 ± 14.2%), and accuracy of 78%–90% (87 ± 5.0%). Both had the same diagnostic ability, even during preoperative chemotherapy [27–29]. The diagnostic performance of Tl and MIBI was almost the same, but in a study [28] where the two were directly compared, the diagnostic accuracy of MIBI was slightly higher.

Typical PET indicators were the standardized uptake value (SUV) after treatment, the ratios of the SUV values before and after treatment, and the rate of change in SUV values. In the 14 original papers [30–33], with more than 15 cases studied, sensitivity was 59–100% (82 ± 11.3%), specificity was 25–100% (71 ± 18.6%), and accuracy was 69–100% (78 ± 9.0%). The diagnostic accuracy was slightly lower than that of Tl and MIBI. It was thought that residual viable cells after treatment, post-treatment inflammatory changes, reactive fibrosis, and accumulation of immature granulation tissue and fibrous pseudotumor capsules were some of the causes of false positives. There was also a review article that compared its ability to ascertain the therapeutic effect on osteosarcoma and Ewing's sarcoma and found it slightly inferior for Ewing's sarcoma. However, it has been reported that diagnostic ability can be maintained by altering the diagnostic criteria for each tumor.

Based on the above, nuclear medicine evaluation of the effect of preoperative chemotherapy on primary malignant bone tumors is useful to predict the histological effect. However, it is currently uncommon to use MIBI, which is not covered by the National Health Insurance in Japan for bone and soft tissue tumors, and it may be reasonable to use Tl as the first choice for large extremity lesions and PET for small trunk lesions and cases without pretreatment imaging studies. Furthermore, it was not possible to provide a definitive recommendation regarding the optimal choice between nuclear medicine, non-nuclear image diagnosis (such as plain radiography, CT, and MRI), or abstaining from conducting an image assessment to evaluate the efficacy of preoperative chemotherapy.

3.7. FRQ1: Is F18-FDG-PET/CT more useful than CT or MRI for diagnosing local recurrence in primary malignant bone tumors treated with metallic materials?

Plain radiography, CT, MRI, and F18-FDG-PET (PET/CT) are used to evaluate local recurrence after treatment of primary malignant bone tumors. When the patient has endoprostheses, as well as other metallic materials, assessment by CT and MRI may be difficult due to metal artifacts. It is an important clinical issue to clarify the usefulness of PET/CT for detecting local recurrence in cases with metallic materials.

In a study involving eight recurrent cases of pediatric osteosarcoma following endoprosthetic reconstruction, PET/CT imaging revealed solid uptake patterns (five cases) and peripheral/nodular uptake patterns (three cases) of recurrent tumors. The SUVmax ranged from 3.0 to 15.7 (median value of 6.7) [34]. CT scans confirmed the presence of a soft tissue mass or asymmetric swelling in five cases. However, in three out of four cases where MRI was used, the diagnosis could not be made due to metal artifacts. Plain radiography revealed soft tissue swelling or a mass in four of the seven cases identified by PET/CT. Compared to CT and MRI, which are limited by metal artifacts, PET/CT provided a clear confirmation of the complete extent of local recurrence.

In 15 cases of primary malignant bone tumors, PET/CT imaging conducted after limb salvage surgery involving metallic materials demonstrated continuous uptake at soft–tissue interfaces with endoprostheses, allografts and internal fixation devices. FDG uptake was minimal or absent at cemented endoprostheses–bone interfaces. SUVmax at margins of endoprostheses ranged from 1.4 to 5.7 [35]. In four cases of endoprostheses, minimal artifacts were observed in the attenuation-corrected PET images, without affecting image interpretation. Among the other 11 cases that underwent CT attenuation correction, artifacts resulting from the attenuation correction were not detected.

Although it is unknown whether metal materials were used, PET/CT evaluation of 109 patients with osteosarcoma showed that SUVmax was 4.7–7.7 (median: 5.8) in nine cases of local recurrence, and 2.4–4.6 (median: 3.5) in those without recurrence [36]. Recurrence was observed in 7 of 13 cases whose SUVmax was >4.6 and increased by 75% or more from the initial examination (which was 3 months after surgery), with a sensitivity of 78%, specificity of 94%, and accuracy of 93%. Another study, which examined both local and distant metastases, reported that PET/CT imaging for suspected recurrence in 53 cases of Ewing's sarcoma demonstrated a sensitivity of 95%, specificity of 87%, and an overall accuracy of 91.5% [37].

PET/CT was less affected by metal artifacts and more useful than other modalities in diagnosing osteosarcoma recurrence. PET/CT was also useful in diagnosing the recurrence of Ewing's sarcoma. However, there was no comparison with other modalities because it was unclear whether metal materials were used. Due to the lack of evidence at this time, we cannot recommend PET/CT for the diagnosis of local recurrence in patients with metallic materials. The usefulness of PET/CT is a Future Research Question.

3.8. CQ4: Is an incisional biopsy more useful than a needle biopsy for a definitive diagnosis of primary malignant bone tumor?

Statement of recommendation: For a definitive diagnosis of primary malignant bone tumors, we suggest performing an incisional biopsy rather than a needle biopsy when the tumor is deep in the sacrum or when the extra-osseous lesion is small.

Recommendation strength: 2, Percentage agreement: 90%, Evidence level: C.

None of the prospective studies compared needle biopsy with incisional biopsy for primary malignant bone tumors; all papers on this topic were retrospective case series. In a study involving 117 patients under the age of 21 with suspected malignant bone tumors, 90 percutaneous needle biopsies and 27 open biopsies were performed [38]. The percutaneous biopsy demonstrated a diagnostic yield of 95.5%, an accuracy of 96.2%, and an efficacy of 89.3%. There was no statistical difference compared to open biopsy. Another study, included 142 biopsies in 105 patients (median age 13.4) diagnosed with osteosarcoma or Ewing's sarcoma family of tumors [39]. The incisional biopsy resulted in a successful specimen in 94.1% of cases, while the percutaneous procedure had a success rate of 73.1%. The odds of obtaining a successful diagnostic specimen were 7.8 times higher with an open approach. Additionally, in a study involving 60 patients with sacral tumors, 25 percutaneous needle biopsies and 54 open biopsies were performed [40]. The accuracy rate for needle biopsy was 44%, while the incisional biopsy had an accuracy rate of 87%. Diagnosis could not be achieved in 12 out of 21 needle biopsy cases and 2 out of 39 incisional biopsy cases ($p < 0.0001$) [40].

None of the reports indicated any differences between needle biopsy and incisional biopsy for bone and soft tissue tumors [41–45]. Even when focusing only on data related to bone tumors, the following results were obtained: for 33 needle biopsies, the diagnostic sensitivity, specificity, and accuracy were 100%, 100%, and 100%, respectively; for 15 incisional biopsies, the corresponding values were 95.5%, 100%, and 100%, respectively [41]. In another study, CT-guided needle biopsy demonstrated an accuracy of 89.4% for 20 benign cases and 86.4% for 45 malignant cases, incisional biopsy showed an accuracy of 92.7% for 14 benign cases and 77.8% for 27 malignant cases [42]. In yet another study, needle biopsies of 14 benign and 20 malignant cases had an accuracy of 71.4% and 75%, respectively, while incisional biopsies of 80 benign and 49 malignant cases had an accuracy of 97.5% and 87.8%, respectively [43]. No significant differences were reported in any of these studies.

One report indicated that there was no difference in the incidence of complications during biopsy between CT-guided needle biopsy (0.9%) and incisional biopsy (4.7%) for bone and soft tissue tumors ($p = 0.14$) [42]. Other reports only listed complications, and there were no serious complications.

The diagnostic accuracy of incisional and needle biopsy in bone tumors was comparable except for sacral bone tumors. However, there was a possibility that the localization of the tumor and the size of the extra-osseous lesions had been biased in the selection of the cases. The incidence of complications tended to be slightly higher in incisional biopsies, but none were serious, and all were acceptable. In terms of cost, incisional biopsy was 3.3 times [38] or 6.5 times [44] more expensive than needle biopsy because it included the cost of surgery and hospitalization.

In the definitive diagnosis of primary malignant bone tumors, it is recommended to perform an incisional biopsy instead of a needle biopsy if the tumor is located deep in the sacrum or if the extra-osseous lesion is small. Needle biopsy is inexpensive and can be performed immediately, but there may be cases where diagnosis is not possible due to insufficient tissue collection. With this in mind, it would be best to attempt needle biopsy first if a system for early incisional biopsy is in place. Needle biopsy, which is less invasive, is the first procedure attempted for spinal tumors and metastatic bone tumors.

3.9. CQ5: Is molecular biological analysis useful for pathological diagnosis of primary malignant bone tumors?

Statement of recommendation: Molecular biological analysis is suggested for pathological diagnosis of primary malignant bone tumors.

Recommendation strength: 2, Percentage agreement: 100%, Evidence level: C.

With the advances in molecular biological analysis techniques, including whole-genome analysis, many tumor-specific gene mutations have been reported in primary malignant bone tumors [46,47]. Fluorescent In Situ Hybridization (FISH) analysis, using a break-apart probe of the first intron of the TP53 gene, revealed that translocation signals were observed in 20 of 37 osteosarcomas (54%), but not in 80 non-osteosarcoma or benign bone tumors (100% specificity) [48].

It has been reported that approximately 60% of conventional chondrosarcomas have isocitrate dehydrogenase (IDH) type 1 or type 2 mutations. In addition, somatic mutations in the IDH1/IDH2 genes were found in conventional chondrosarcomas or chondromas, but not in other tumor [49]. The IDH1/IDH2 gene abnormality was not observed in osteochondromas, or secondary chondrosarcomas caused by EXT1 or EXT2 gene abnormalities.

In Ewing's sarcoma, the EWSR1 gene on chromosome 22 forms a fusion gene with the FLI-1 gene on chromosome 11 or the ERG gene on chromosome 21. Identification of chromosomal translocations by FISH [50], or fusion gene identification by RT-PCR [51], is widely used for the pathological diagnosis of Ewing's sarcoma. In the past 10 years, among Ewing's sarcoma-like small round cell sarcomas, Ewing's sarcoma-like tumors such as CIC-rearranged sarcoma [52], BCOR-rearranged sarcoma [53], and EWSR1-non-ETS family fusion gene tumors have been identified as a result of genetic analysis [54]. In the diagnosis of these Ewing's sarcoma-like tumors, in addition to morphological diagnosis, immunohistological analysis and molecular biological analysis are indispensable.

As can be seen from these cases, molecular biological analysis is useful for improving the accuracy of pathological diagnosis of malignant bone tumors and has great significance, such as the definition of new tumors based on the results of the analysis [55]. However, in order to translate the results of molecular biological analysis to actual clinical practice, it is also important to conduct the analyses with appropriate quality control to ensure reliability and accuracy.

3.10. FRQ2: Are nomograms useful for predicting the prognosis of primary malignant bone tumors?

To appropriately treat malignant tumors and predict the prognosis of each patient, it is extremely important to select treatment according to risk, to follow up appropriately, and to provide patients with accurate information.

A nomogram is a statistically based technique that yields more accurate predictive values from a multifactor mathematical model. Unlike staging, which is defined only by basic tumor parameters at diagnosis, nomograms can incorporate more individual factors, such as detailed clinicopathologic characteristics, patient demographics, and response to therapy, into the predictive model. For these reasons, nomograms are expected to be able to predict the clinical course of individual cases more precisely than staging.

We systematically reviewed whether nomograms were useful in the treatment of primary malignant bone tumors, with outcomes

such as predicting prognosis, improving treatment outcomes, and reducing medical costs. Five papers (four papers [56–59] on osteosarcomas and one paper [60] on chondrosarcoma) were evaluated and all of them demonstrated the high prognostic accuracy of nomograms. However, it remains unclear whether nomograms improve prognostic accuracy in other primary malignant bone tumors, such as Ewing's sarcoma, or in malignant bone tumors overall. In addition, it is unclear whether the use of nomograms improves treatment outcomes, and there are no studies examining medical costs.

In conclusion, nomograms are useful for predicting the prognosis of patients with osteosarcomas and chondrosarcomas; however, prediction of the prognosis of other malignant bone tumors remains unclear, and the improvement of treatment results by nomograms has not been clarified. The usefulness of nomograms for predicting prognosis in patients with primary malignant bone tumors is a Future Research Question.

3.11. CQ6: Is limb-sparing surgery recommended for pediatric primary malignant bone tumors?

Statement of recommendation: Limb-sparing surgery is suggested for pediatric primary malignant bone tumors.

Recommendation strength: 2, Percentage agreement: 78%, Evidence level: C.

Currently, limb-sparing surgery is indicated in many cases of pediatric malignant bone tumors of the extremities. There are various methods, such as artificial joint replacement, autologous bone graft, allogenic bone graft, processed bone graft, and hyperthermia therapy. The National Comprehensive Cancer Network (NCCN) guidelines state that limb-sparing surgery has been successfully performed in more than 90% of cases of osteosarcoma and has become established as a general treatment method [61–66]. However, amputation and rotationplasty are still performed in some cases [62,64,66,67]. There are no randomized controlled trials (RCTs) on these surgeries, and limb salvage is performed in patients with safe surgical margins. It is presumed that amputation was performed in patients with more advanced tumors, and the preoperative-patient-selection conditions were different.

There are two papers that directly compare OS between limb-sparing surgery and amputation, and there was no difference in the survival rate in either case [65,66].

Regarding postoperative function, three studies have directly compared limb-sparing surgery with amputation or rotationplasty, and the functionality of limb-sparing surgery is good [62,64,65].

There are studies that show no difference between limb-sparing surgery and amputation or rotationplasty in terms of quality-of-life. However, it should be noted that rotationplasty and amputation are treated as the same category [68,69].

There are two papers comparing limb-sparing surgery and amputation regarding the occurrence of adverse events [65,66]; as such, limb-sparing surgery tends to require additional surgery to correct leg length discrepancies and to address complications. However, the risk of bias is high because the original disease stage is likely to differ from that of the RCT, including comparisons of survival time and function.

For younger patients, it should be noted that multiple surgeries, including additional surgeries for leg length discrepancies, are unavoidable, and that the affected limb function is inadequate. In particular, limb-sparing surgery for osteosarcoma in children under the age of 5 poses many problems, which include complications and postoperative function [68,69].

It has been reported that limb-sparing surgery often entails the use of artificial joints which drives up medical expenses [65]. However, looking at long-term progress, prostheses will also need to be replaced, and amputation would be more costly in terms of the development of the functionality of the prosthesis in the future [65].

Overall, although patients who are candidates for limb-sparing surgery may have an earlier disease stage than those who are candidates for amputation, there have been no reports of deterioration in prognosis after limb-sparing surgery, and limb function is good.

3.12. BQ3: What types of limb-sparing surgeries are available for primary malignant bone tumors?
FRQ3 Is biological reconstruction useful in limb-sparing surgery for primary malignant bone tumors?

Various reconstructive methods have been devised in limb-sparing surgery. There are many papers on the topic; however, they are only retrospective observational studies, and there are various biases in determining surgical indications. The reconstruction methods are broadly classified as reconstruction using an artificial material, such as an artificial joint, after extensive excision of the tumor, and biological reconstruction methods that can be expected to regenerate bone, such as the use of autologous bone, processed bone, and allogeneic bone. It is difficult to uniformly compare and study each reconstruction method as there are various influencing factors, such as tumor site, reconstruction method, age, and tissue type. Various limb-sparing surgeries exist for various sites including the knee, hip, pelvis, ankle, and shoulder joints, where osteosarcoma frequently occurs [70–81].

In a Japanese study on the distal femur, a retrospective analysis showed no significant differences between the post-joint replacement Musculoskeletal Tumor Society (MSTS) functional score of 74 ± 18% and biological reconstruction score of 68 ± 17% [71].

Regarding improvement of the survival rate, 5- and 10-year survival rates of 50–80% and 30–70%, respectively, have been reported for limb-sparing surgery for osteosarcoma. There are no reports that the survival rate of limb-sparing surgery is inferior to that of amputation [67,68]. Even in patients with pathological fractures, if wide resection is possible, there are many cases in which the affected limb can be preserved [73].

A high rate of local recurrence, and deterioration in life prognosis, have been reported in patients with positive resection margins, regardless of whether limb-sparing surgery or amputation were performed [72].

Regarding adverse events, there are different complications, depending on the reconstruction method. However, deep infection is a frequent and important complication of any kind of reconstruction. In particular, in long-term follow-up studies of joint replacement, the incidence of infection increased over time, to 10% at 5 years, 16% at 10 years, 22% at 20 years, and 27% at 30 years, and 13.5% eventually led to amputation [74]. No significant differences in complications such as infection, fracture, and loosening, between biological reconstruction and reconstruction with artificial joints for tumors, have been reported [71]. However, a higher complication rate was reported with biological reconstruction [75]. It has been reported that five of 13 cases of limb-sparing surgery that required revascularization led to amputation due to complications [77].

Regarding the usefulness of biological reconstruction, in cases where bone healing is finally achieved and the articular surface is preserved, good function can be expected to be maintained over the long term. In Japan, where obtaining allogeneic bone is difficult, there have been reports of good mid-to long-term results with reconstruction methods that use heat-treated bone, intraoperatively irradiated bone, and cryopreserved bone. It was judged that this would be a Future Research Question, as future research on

the evaluation of its usefulness and the selection of appropriate cases is desired [79–81].

3.13. CQ7: Is conventional adjuvant radiotherapy useful for primary malignant bone tumors without metastasis?

Statement of recommendation: Conventional adjuvant radiotherapy is suggested for primary malignant bone tumors without metastasis.

Recommendation strength: 2 Percentage agreement: 100%, Evidence level: C.

A literature search was conducted to clarify the usefulness of adjuvant radiaotherapy, with emphasis on the outcomes of reduction in local recurrence, improvement in OS, occurrence of adverse events, and worsening of quality of life (QOL).

In a study on Ewing's sarcoma, the recurrence rate was lower when both surgery and radiotherapy were performed as local treatment than surgery-only, suggesting the contribution of radiotherapy [82]. Another study found no significant difference in the local recurrence rate between surgery and surgery + radiotherapy in peripheral neuroectodermal tumor/Ewing's sarcoma of the bone [83]. A study on the usefulness of postoperative adjuvant radiotherapy for Ewing's sarcoma showed significantly better local control compared with surgery-only ($p = 0.02$) [84]. There was no significant difference in overall survival between the two groups. Regarding reports on tumors other than Ewing's sarcoma, there was no significant difference in the local control rate with the use of adjuvant radiotherapy for osteosarcoma compared to the non-radiotherapy group [85].

It has been reported that 69% of patients with Ewing's sarcoma [86] in the surgery + radiotherapy group and 75% of patients in the surgery-only group had adverse events. Regarding osteosarcoma, it has been reported that six of 72 patients (8%) had adverse events after surgery and radiotherapy [85]. No paper has reported on the deterioration of QOL.

Adjuvant radiotherapy for non-metastatic primary malignant bone tumors may be of limited benefit in Ewing's sarcoma, whereas there was no evidence that it is useful for other tumors. Patients with Ewing's sarcoma, which could not be treated by surgery-only, may wish to receive adjuvant radiotherapy. In addition, the fact that conventional radiotherapy is covered by insurance makes it easier for patients to receive treatment.

Based on the aforementioned, conventional adjuvant radiotherapy is suggested for primary malignant bone tumors without metastasis.

3.14. CQ8: Is conventional radiotherapy useful for primary malignant bone tumors that are unresectable or are expected to cause severe functional impairment after surgery?

Statement of recommendation: Conventional radiotherapy is suggested for patients with primary malignant bone tumors that are unresectable or expected to cause severe functional impairment after surgery.

Recommendation strength: 2, Percentage agreement: 100%, Evidence level: D.

A literature search was conducted to ascertain the usefulness of conventional radiotherapy for primary malignant bone tumors that were unresectable or expected to cause severe functional impairment after surgery, with an emphasis on the outcomes of the improved local control, improved OS, and the occurrence of adverse events.

In an analysis of metastatic Ewing's sarcoma, the 5-year local control rate with radiotherapy-only was 68% and surgery-only was 50%, and the 5-year survival rate was 45% with radiotherapy-only and 0% with surgery-only [87].

The 5-year local control rate for osteosarcoma was 22% with radiotherapy-only and 48% with radiotherapy and surgery. The 5-year survival rate for radiotherapy-only was 26% and radiotherapy + surgery was 62% [88].

In an analysis of Ewing's sarcoma of the lower extremities [89], there was no difference in the survival rate in the radiotherapy-only group compared with the surgery + radiotherapy group, but the local control rate was lower in radiotherapy-only group ($p = 0.03$). In a Children Oncology Group study for Ewing's sarcoma [90], among the surgery group, radiotherapy-only group, and surgery + radiotherapy group, local control was significantly worse in the radiotherapy-only group ($p < 0.01$), and radiotherapy was an independent risk factor in multivariate analysis (hazard ratio 2.40, $p < 0.01$). In a study of patients with Ewing's sarcoma under the age of 40 years, using the National Cancer Database [91], radiotherapy-only tended to have a poor prognosis compared to the surgery-only, and surgery + radiotherapy groups ($p = 0.07$).

Regarding adverse events, a study investigating patients with Ewing's sarcoma without distant metastasis [92] indicated secondary cancer is observed in 1.6%, but there was no difference in incidence between the group with use or non-use of radiotherapy.

Considering that many reports do not solely analyze inoperable cases, radiotherapy may be useful for inoperable Ewing sarcoma cases. Patients with inoperable Ewing's sarcoma may prefer conventional radiotherapy. Additionally, this treatment is covered by insurance. On the other hand, there is little evidence of its usefulness for other primary malignant bone tumors. Therefore, if the target is limited to Ewing's sarcoma, it can be conditionally recommended.

Based on the aforementioned, conventional radiotherapy is suggested for patients with primary malignant bone tumors that are unresectable or are expected to cause severe functional impairment after surgery.

3.15. CQ9: Is particle-beam radiation therapy useful for primary malignant bone tumors that are unresectable or expected to cause severe functional impairment after surgery?

Statement of recommendation: Particle-beam radiation therapy is suggested for patients with primary malignant bone tumors that are unresectable or expected to cause severe functional impairment after surgery.

Recommendation strength: 2, Percentage agreement: 100%, Evidence level: D.

A literature search was conducted to ascertain the usefulness of particle-beam radiation therapy for primary malignant bone tumors that were unresectable or expected to have severe functional impairment after surgery with emphasis on the outcomes of improved of local control, improved OS, maintenance of QOL, and occurrence of adverse events.

In a report from Japan, carbon ion radiotherapy for 188 patients with sacral chordoma showed a 5-year local recurrence-free survival rate of 77.2%, an OS rate of 81.1%, and adverse events were grade 3–4 skin disorders in three cases and grade 3 neuropathy in six cases [93]. Proton therapy for 96 patients with primary bone sarcoma (chordoma, chondrosarcoma, and osteosarcoma) showed a 5-year recurrence-free survival rate of 71.1%, an OS rate of 75.3%, and ≥grade 3 adverse events in nine patients [94]. Carbon ion radiotherapy for 48 patients with sarcomas originating in the

vertebral body, including 13 osteosarcomas and seven primary bone malignant fibrous histiocytomas, showed a 5-year recurrence-free survival rate of 79%, an overall survival rate of 52%, and vertebral compression as adverse events was observed in seven cases [95]. Concerning carbon ion radiotherapy for pediatric osteosarcoma, the 5-year local recurrence-free survival rate was 62.9% and the overall survival rate was 41.7% [96].

Regarding reports from overseas, a report on heavy particle therapy in Germany showed a 3-year control rate of 81% for chordoma and 100% for chondrosarcoma, and a 3-year overall survival rate of 91% for chordoma and chondrosarcoma of the head and neck in patients with chordomas and chondrosarcomas in the cranial region, spine, and sacrum. There were no grade 4-5 adverse events [97]. In a study from Italy, reporting on the safety of proton therapy in 21 patients with chordoma and chondrosarcoma originating from the base of the skull and sacrum, grade 1 adverse events were noted in 18 cases and grade 2 in four cases [98].

Few studies evaluated the maintenance of patient's QOL.

For tumors with poor radiosensitivity, such as chordoma and osteosarcoma, patients may wish to receive particle radiotherapy for difficult-to-operate tumors in the trunk. On the other hand, there are few facilities where it can be performed, and it may not be easy for patients to access.

Based on the aforementioned, particle-beam radiation therapy is suggested for patients with primary malignant bone tumors that are unresectable or expected to cause severe functional impairment after surgery.

3.16. BQ4: Is adjuvant chemotherapy useful for resectable high-grade osteosarcoma?

The usefulness of adjuvant chemotherapy for non-metastatic high-grade osteosarcoma was established in the early 1980s by an RCT called the Multi-Institutional Osteosarcoma Study (MIOS). MIOS targeted patients without metastasis, younger than 30 years old with histologically high-grade osteosarcoma of extremities which had been resected with negative margin. The results verified that relapse-free survival in the adjuvant chemotherapy group (high-dose methotrexate, doxorubicin, cisplatin, bleomycin, cyclophosphamide, and actinomycin D) was significantly longer than that of the follow-up group [99]. The 2-year relapse-free survival rate in the follow-up group was 17 ± 9% (±SE), while that in the adjuvant chemotherapy group was 66 ± 13%, showing a significant difference in the log-rank test ($p < 0.001$). Furthermore, in the long-term follow-up results of the same RCT [100,101], the 6-year overall survival rate in the follow-up group was 50%, while that in the adjuvant chemotherapy group was 71%, with a significant difference in the log-rank test in terms of overall survival ($p = 0.037$).

In a report comparing a group in which adjuvant chemotherapy was administered before and after surgery with a group in which adjuvant chemotherapy was administered only after surgery [102], the significance of neoadjuvant chemotherapy before surgery was not clarified because the limb-sparing rate was almost 50% in both groups and no significant difference in relapse-free survival was observed.

Adjuvant chemotherapy may cause adverse events, such as cytopenia, nausea/vomiting, mucositis, febrile neutropenia, cardiotoxicity, deafness, renal dysfunction, and fertility disorders.

In MIOS, although there was a small risk of bias, the benefit of adjuvant chemotherapy for improving overall survival was large, and it is judged that the benefit is commensurate with the adverse events. Adjuvant chemotherapy for resectable high-grade osteosarcoma appears to be used by almost all clinicians who treat osteosarcoma and is considered a standard treatment.

3.17. CQ10: Is drug therapy useful for unresectable recurrent/advanced high-grade osteosarcoma?

Statement of recommendation: Drug therapy is suggested for unresectable recurrent/advanced high-grade osteosarcoma.

Recommendation strength: 2, Percentage agreement: 100%, Evidence level: C.

3.17.1. Background of this CQ as an important clinical issue

Adjuvant chemotherapy improved the initial outcome of patients with non-metastatic osteosarcoma, but about 40% of these patients relapsed after the initial treatment and more than 80% of them died. In addition, patients with metastatic disease at the time of initial diagnosis had worse outcomes. Clarity on whether drug therapy is useful for unresectable recurrent/advanced high-grade osteosarcoma is expected to be of great help in selecting treatment in daily clinical practice.

3.17.2. Collection of evidence

A total of 49 papers, including some retrieved through manual searches, were used as evidence. There were no phase III trials, and all the results were from exploratory phase II trials. There were two placebo-controlled randomized phase II trials.

3.17.3. Assessment of evidence

In the 1990s, ifosfamide alone [103,104], combined with etoposide (IE) [105,106], or combined with etoposide and carboplatin (ICE) [107], were tried as drug therapy for recurrent/advanced high-grade osteosarcoma. The ifosfamide dose ranged from a 6 g/m2/course to high doses of 14 g/m2/course. Response rates ranged from 15.6% to 62.5%, and complete responses (CR) occurred in 5.3%–37.5%. However, its toxicity, mainly myelosuppression, is severe, with frequent febrile neutropenia, severe nonhematologic toxicity such as nephrotoxicity and neurotoxicity, and treatment-related death in a small number of cases [106,107]. Although the evidence is weak because there are no comparisons with no treatment, achievement of CR in a certain number of patients has been reported. Considering the high demand for treatment, high dose ifosfamide can be weakly recommended as the main drug therapy for unresectable, recurrent, and advanced high-grade osteosarcoma.

Combination therapy with gemcitabine hydrochloride and docetaxel hydrate [108,109] has been reported to have a response rate of 7.1–17.1%. Although hematologic toxicity is weak, nonhematologic toxicity, such as allergic reactions, pneumonitis, edema, and skin disorders have been reported.

Phase II trials have been conducted with small molecule compounds, and response rates ranging from 0% to 43.2% have been reported. Mild hematologic toxicity has been observed, but nonhematologic toxicity is common. In two placebo-controlled phase II studies using regorafenib [110,111] as the test drug, nonhematologic toxicity, mainly diarrhea and hypertension, occurred; however, progression-free survival (PFS) was prolonged by about 3 months. Further treatment development is expected, but the current evidence is weak.

Results of the trials using immunotherapy have been reported, but the response rate was low.

At present, the beneficial outcomes of drug therapy for unresectable, recurrent, advanced high-grade osteosarcoma cannot be said to outweigh the harmful outcomes. However, considering that the main patient demographics are children and the Adolescents and Young Adults (AYA) generation, there may be many situations in which a slight benefit can be expected even if a certain degree of harm is assumed; as such, high-dose ifosfamide monotherapy, IE therapy, and ICE therapy can be suggested.

3.18. BQ5: Is drug therapy useful for localized Ewing's sarcoma?

Ewing's sarcoma is a small round cell sarcoma that develops in the bones and soft tissues of children and adolescents. Among malignant bone tumors occurring in children and the AYA generation, it is the second most frequent disease after osteosarcoma. Multimodal therapy, consisting of multidrug chemotherapy, surgery, and radiation, has recently improved the outcome of localized Ewing's sarcoma. In a comparative study [112] in which 398 patients with localized Ewing's sarcoma were randomized into a VDC group receiving doxorubicin, vincristine, and cyclophosphamide; and a VDC-IE group receiving VDC, ifosfamide, and etoposide; the 5-year survival rate was 61% in the VDC group and 72% in the VDC-IE group, with a significantly superior result in the VDC-IE group ($p = 0.01$). In a trial [113] in which 478 patients were randomized into two groups: one receiving 30 weeks of intensive VDC-IE therapy with higher doses of cyclophosphamide and ifosfamide; and another receiving 48 weeks of standard VDC-IE therapy; the 5-year survival rate was 77% in the enhanced group and 80.5% in the standard group, showing no significant difference. In a randomized study [114] in which VDC-IE alternating therapy was administered either every 3 weeks or every 2 weeks to 587 patients, the 5-year survival rate was 83% in the every 2 weeks group and 77% in the standard, every 3 weeks group, but the difference was not statistically significant. In a study [115] that stratified by high risk (HR)for tumors with a volume ≥100 ml or a primary site on the central axis, and standard risk (SR) for others, 241 of 301 patients were treated with vincristine, actinomycin D, ifosfamide, doxorubicin (VAIA) for HR, and the others were treated with a regimen using cyclophosphamide instead of ifosfamide (VACA) for SR. The 5-year overall survival rate was 57%. In a recent comparative trial in which 640 patients with Ewing's sarcoma, which included 26% of cases with metastases, were randomized to the US regimen of VDC-IE and the European regimen with VAI or VAC after an introduction with VIDE, the US regimen was superior in both event free survival and OS [116]. Regarding adverse events, 12 treatment-related deaths were observed in the entire study, seven of which were due to infection1). The other four deaths, due to cardiotoxicity, were all in the VDC group. A total of seven cases of secondary cancers (three in the VDC group and four in the VDC-IE group) were also observed. Based on the above, there have been no clinical trials to verify the difference in treatment outcomes for Ewing's sarcoma with or without drug therapy. However, drug therapy is recommended for localized Ewing's sarcoma because of the improved results in clinical practice and the improved treatment results compared to historical controls. Adverse events associated with drug therapy are unavoidable, and extreme caution is needed in implementation.

3.19. CQ11: Is intensive drug therapy effective for metastatic Ewing's sarcoma?

Statement of recommendation: It is suggested that intensive drug therapy should not be performed for metastatic Ewing's sarcoma.

Recommendation strength: 2, Percentage agreement: 77%, Evidence level: B.

Metastatic cases at the time of initial diagnosis of Ewing's sarcoma account for 20–25% of the overall cases, and the prognosis is extremely poor. The 5-year survival is about 20%, and the prognosis has not improved for more than 30 years. A comparative study [117] was conducted in which 120 patients with metastatic Ewing's sarcoma were randomized into a VDC group that received doxorubicin, vincristine, and cyclophosphamide; and a VDC-IE group that received VDC, ifosfamide and etoposide. The 8-year survival rate was 32% in the VDC group and 29% in the VDC-IE group, showing no statistically significant differences between the two regimens. Combined metastatic and localized tumors with a tumor volume of ≥100 ml are considered high-risk cases, and according to the report of an RCT [118] in a group that received treatment with VAIA, and a group that added etoposide to VAIA (EVAIA), a subgroup analysis of metastatic cases showed that no statistically significant differences occurred between the VAIA and EVAIA groups. In a report of a single-arm study in which 60 patients with metastatic Ewing's sarcoma underwent intensive VDC-IE therapy with higher doses of doxorubicin, cyclophophamide, and ifosfamide [119], the 6-year survival rate was 29%, which was not better than the results obtained to date. Another study [120] found an overall 3-year survival rate of 34% for 281 patients with metastatic Ewing's sarcoma, enrolled in the R3 study of the Euro-Ewing 99 trial, who received local therapy, high-dose drug therapy, and autologous stem cell transplantation, after receiving six courses of VIDE and one course of VAI. None of these studies have shown that intensive drug therapy is effective in improving survival in metastatic Ewing's sarcoma. Regarding adverse events, it has been reported that Grade 3 or 4 leukopenia, a decreased platelet count, and infections were significantly more frequent in the EVAIA group to which etoposide was added[2)]. There are also reports of treatment-related deaths in two patients in the VDC group and four patients in the VDC-IE group [112]. In these studies, there were many ≥ Grade 3 adverse events, and treatment-related deaths were also observed, so the occurrence of adverse events is inevitable. Based on the above, there is no evidence that intensifying drug therapy for metastatic Ewing's sarcoma would improve overall survival. Furthermore, there was no improvement in the survival rate with different drug regimens. At present, we do not recommend intensifying drug therapy for metastatic Ewing's sarcoma, but the development of new treatment methods is desired moving forward.

3.20. CQ12: Is radiotherapy useful for difficult-to-resect localized Ewing's sarcoma?

Statement of recommendation: Radiotherapy is suggested for difficult-to-resect localized Ewing's sarcoma.

Recommendation strength: 2, Percentage agreement: 77%, Evidence level: D.

Multidisciplinary therapy, including drug therapy, surgery, and radiotherapy is essential for the treatment of localized Ewing's sarcoma. Surgery is the basic local treatment, but radiotherapy can be administered if complete resection is difficult, or if resection would result in significant functional disability when the disease affects the pelvic bone, skull, or spine. According to a report [121] on Ewing's sarcoma originating in the bone in 612 cases, using the Surveillance Epidemiology and End Results (SEER), an analysis of all the cases showed that surgery-only significantly prolonged OS; however, in cases with lesions localized to the intraosseous or subperiosteal areas, and lesions outside the extremities and pelvis, radiation alone was not inferior to surgery-only. In contrast, a large-scale analysis of 1031 cases of Ewing's sarcoma originating in bone, using the National Cancer Database (NCDB) [91], showed that patients treated with radiotherapy-only had significantly inferior survival rates at 2, 5, and 10 years compared with those treated with surgery-only and those treated with surgery + radiotherapy. In a case series study [122] of 85 cases of pelvic Ewing's sarcoma at a single institution, 54 cases received radiotherapy-only, 21 underwent surgery, and 10 had surgery + radiation as local treatment. Surgery cases had the highest OS, while surgery + radiation had the lowest, but no significant differences were noted. A study investigating relapse rates analyzed the data of 956 patients with Ewing's sarcoma enrolled in the INT-0091/INT-915/AEWS0031 trial in the United States [90] and found that the 5-year relapse rate was 7.3% in

all patients and 15.3% in those who received radiation alone. The relapse rate was significantly higher with radiation alone, as it was 3.9% for surgery-only, and 6.6% for surgery + radiation. In particular, the incidence of local recurrence after radiotherapy-only was significantly higher in cases involving the extremities and pelvis, but there was no significant difference in cases involving the trunk (ribs, scapula, etc.), spine, and soft tissue. Regarding adverse events, it was reported that eight of 674 patients (1.2%) developed secondary cancers [123]. Four had acute myeloid leukemia, one had myelodysplastic syndrome, and the remaining three had sarcoma, all of which occurred in the radiation field. In addition, there is a report [124] that all cases of sarcoma that developed as secondary cancers occurred within the irradiation field. A positive correlation was observed between irradiation doses and the occurrence of secondary sarcomas. Based on the above, although there are no studies comparing the use or non-use of radiotherapy for difficult-to-resect localized Ewing's sarcoma, the benefit of radiotherapy in terms of improving OS is significant when the tumor is difficult to resect, and no other local therapy options are available. However, since adverse events, such as the onset of secondary cancer may occur, it is important to conduct a thorough examination before implementation.

Radiotherapy is currently the only available method for improving local control of localized difficult-to-resect Ewing's sarcoma, and its use may be considered.

3.21. CQ13: Is intralesional resection useful for central atypical cartilaginous tumors localized in the extremities?

Statement of recommendation: Intralesional resection may be considered for central atypical cartilaginous tumors localized in the extremities.

Recommendation strength: 2, Percentage agreement: 100%, Evidence level: D.

According to the WHO classification, revised in 2020, tumors previously classified as grade 1 chondrosarcoma occurred in long and short bones in the extremity are now termed atypical cartilaginous tumor and classified as intermediate [1]. Wide excision has been the standard surgical procedure for chondrosarcoma, but in recent years, curettage with local adjuvants such as phenol, alcohol, and liquid nitrogen may be considered for central atypical cartilaginous tumors. In this CQ, we performed a systematic review on the clinical effects of intralesional resection of central atypical cartilaginous tumor over wide resection focusing on disadvantages such as a reduction in local control rate and disease-specific survival, and on advantages such as a reduction of adverse events and an improvement of limb function.

In most studies, curettage with an adjuvant for central atypical cartilage tumors did not result in an increase in the local recurrence rate compared to wide excision [125–128]. Most of them were observational studies with shortcomings, such as including grade 2 and 3 cases, determining the application of curettage based on radiological evaluation, and not setting a wide resection group as a control for curettage. All the reported systematic reviews analyzed only observational studies, so the level of evidence was low.

In observational studies on OS, no distant metastasis or tumor specific death occurred in either group and there was no significant difference in risk for events between the two groups [129,130]. These were retrospective studies on a small number of cases, and the evidence level was low. In systematic reviews, the overall survival rate was not set as an outcome due to the rarity of events, but there was no significant difference in the risk of metastasis between the two groups [125–128].

Many observational studies and systematic reviews showed that the curettage group had significantly better postoperative function and fewer adverse events [125,126,128]. The results were based on observational studies which had shortcomings, such as the inclusion of benign lesions, the application of curettage based on radiological evaluation, and the absence of a wide resection group as a control. Therefore, the level of evidence was low.

Currently, there is no strong evidence demonstrating a disadvantage of curettage with respect to local recurrence and OS. On the other hand, although the evidence level is low, curettage significantly reduces adverse events and improves postoperative function. It is expected that many patients will choose this method due to of its superior outcomes. Therefore, we declare that intralesional resection for intraosseous atypical cartilaginous tumors may be considered.

3.22. CQ14: Is particle-beam radiation therapy useful for unresectable chondrosarcoma?

Statement of recommendation: Particle therapy may be considered for unresectable chondrosarcomas.

Recommendation strength: 2, Percentage agreement: 83%, Evidence level: D.

The standard treatment for chondrosarcoma is wide excision; therefore, the outcomes of treatment for unresectable chondrosarcoma have been poor. In recent years, the outcomes of particle beam radiation therapy for chondrosarcoma have been reported, and it has been established as a new treatment modality. A systematic review was conducted on the usefulness of particle-beam radiation therapy for unresectable chondrosarcoma in terms of improvement in the local control rate, OS rate, and maintenance of QOL as advantages, and the occurrence of adverse events and increased medical costs as disadvantages.

Four papers were analyzed regarding improvements in local recurrence rates and OS rates94, [131–133]. All were retrospective studies, and most were single-arm. In addition, there was a risk of bias due to the lack of uniformity in tumor location, irradiation dose, tumor size, and grade; however, they suggested the efficacy of particle-beam radiation therapy.

Three papers were analyzed regarding the occurrence of adverse events [131,132,134]. Adverse events in the particle-beam radiation therapy group included collapse in the pelvis, femoral head necrosis, and dermatitis. A direct comparison was not possible because adverse events such as infection, implant dislocation, and nerve palsy, which occurred in the resection cases of the control group, were essentially different from those in the particle-beam radiation therapy group.

Although there were no reports directly evaluating QOL, the particle-beam radiation therapy group was superior to the surgery group in terms of MSTS score and maintenance of gait function [132,134].

No papers have examined the increase in medical costs.

The options for unresectable cases are limited, and the opportunity to select an effective treatment is considered to be a benefit worth the effort (cost) of seeking the limited number of institutions offering this treatment modality. Therefore, there is a high possibility that patients would prefer to receive particle-beam radiation therapy; however, the scarcity of institutions currently available for treatment may affect patient decision making.

3.23. CQ15: Is particle-beam radiation therapy useful for chordoma?

Statement of recommendation: Particle-beam radiation therapy is suggested for local control of chordoma that is not indicated for resection.

Recommendation strength: 2, Percentage agreement: 100%, Evidence level: D.

A systematic review was conducted on the usefulness of particle-beam radiation therapy for chordoma, with reduction in the local relapse rate, improvement of OS (period), and maintenance of QOL, as positive outcomes, and the occurrence of adverse events and increase in medical costs as negative outcomes. Regarding the reduction of the local recurrence rate, the 5-year local control rate for 188 unresectable sacral chordoma cases treated with heavy particle beam was 77.2% [93], and the 3-year local control rate for 56 cases of sacral chordoma treated with the intensity modulated radiation therapy (IMRT) combination was 53% [135]. In comparison with surgery, local recurrence occurred in three of 10 patients who underwent surgery, but no recurrence occurred in seven patients who underwent heavy particle radiation therapy [136]. Regarding proton beam therapy, the 4-year local control rate of 34 cases of vertebral chordoma was 67% [137], and the 5-year local control rate of 71 cases of vertebral chordoma was 62% [138]. The 5-year local control rate for 100 cases of vertebral chordoma was 63% [139], and the 5-year local control rate for 72 cases of cranial base and vertebral chordoma was 68.4%[94)]. The 5-year local control rate for 40 spinal and sacral chordomas was 85.4% [140], and the local progression-free survival rate for 33 sacral chordomas was 89.6% [141]. The 5-year overall survival rate for unresectable sacral chordoma was reported to be 81.1% [93] and the 3-year OS rate was 100% [135]. In a comparison between heavy particle radiation therapy and surgery, two of seven cases who underwent heavy particle radiation therapy and one of 10 cases who underwent surgery died from the tumor [136]. Regarding proton beam therapy, the 5-year overall survival rates were 81% [138,139], 75.5% [94], and 81.9% [140], and the 3-year overall survival rate was 92.7% [141]. In terms of maintenance of QOL, 45.5% of patients treated with proton beam therapy showed improvement in pre-treatment pain [133], and when comparing heavy particle radiation therapy and surgery, there were no cases of bladder and rectal function deterioration in the heavy particle radiation therapy group, whereas 60% of patients treated with surgery showed deterioration. The MSTS score was 75% for the heavy particle radiation therapy group and 55% for the surgery group, indicating that the heavy particle radiation therapy group was superior [136]. Regarding the occurrence of adverse events in the heavy particle radiation therapy group, grade 3 peripheral neuropathy was observed in 3.2% and grade 4 skin toxicity was observed in 1.1% of cases that received heavy particle radiation therapy. However, it has been reported that 97% of cases maintained gait [84], and there was also a report that $\geq$ grade 3 toxicity was not observed in the heavy particle radiation therapy group [135]. In proton beam therapy, tissue necrosis requiring surgery was observed in 4%, vertebral body fracture in 2%, and chronic urinary tract infection in 2% [137]; and $\geq$grade 3 toxicity was reported in 11% [139]. We did not find any articles on the cost of particle-beam radiation therapy for chordoma.

3.24. CQ16: Is lesion curettage useful as a local treatment for curettable giant cell tumors of bone?

Statement of recommendation: Lesion curettage is suggested as local treatment for curettable giant cell tumors of bone.

Recommendation strength: 2, Percentage agreement: 100%, Evidence level: D.

Regarding the usefulness of lesion curettage as a local treatment for curettable giant cell tumors of bone, a systematic review was performed with reduction of the local relapse rate and improvement in the OS rate (period) as positive outcomes, and deterioration in postoperative function, occurrence of adverse events, malignant progression, and increased medical costs as negative outcomes. Regarding the decrease in the local relapse rate, it has been reported that curettage combined with local adjuvant therapy tended to have a slightly higher local recurrence rate than resection, but without a significant difference [142–144]. In contrast, there was a report that the relapse rate was lower in the group in which resection was performed rather than curettage [145], and that local control by curettage was difficult in the case of Campanacci classification Grade 3 [146]. In addition, as local adjuvant therapy for curettage, liquid nitrogen treatment [147] and phenol treatment [148] have been reported to be useful in preventing relapse. There is a report [149] that the use of denosumab as adjuvant therapy did not affect the reduction of the local relapse rate. In contrast, there was also a report of a high relapse rate in the denosumab group, and that the use of denosumab increased the relapse rate [150]. Regarding improvements in OS rates, an analysis of 46 cases with pulmonary metastases found a 5-year OS rate of 94.4% [151]. Furthermore, in the analysis of giant cell tumors of the spine, it was also reported that local recurrence was strongly associated with death [152]. Postoperative functional deterioration was reported to be significant in relapse cases [145]. Regarding the occurrence of adverse events, it was reported that the incidence was significantly lower in the curettage group than in the resection group[144)]. Regarding malignant transformation, two cases of malignant transformation after curettage and bone grafting have been reported [153]. The first case was a proximal tibial case with a second relapse 15 years after the initial surgery, and the histopathological diagnosis at that time was a malignant fibrous histiocytoma. The second case involved the distal femur, with recurrence after 13 years, and the histopathology at that time was reported to be osteosarcoma. Both cases did not receive radiotherapy.

We could not find any papers on the cost of curettage as a local treatment for curettable giant cell tumors of bone. The cost seems to depend largely on adjuvant therapies, such as denosumab, and reconstructive materials, such as artificial joints.

3.25. CQ17: Can resection of pulmonary metastases improve the survival prognosis in patients with pulmonary metastases of osteosarcoma?

Statement of recommendation: Resection of pulmonary metastases was conditionally suggested for osteosarcoma with pulmonary metastases.

Recommendation strength: 2, Percentage agreement: 82%, Evidence level: C.

Pulmonary metastasis is the most important prognostic factor in patients with osteosarcoma. Therefore, complete resection of pulmonary metastases can improve prognosis for these patients [154–158]. For this CQ, a systematic review was conducted on the usefulness of resection of pulmonary metastases, with improvement of prognosis as a positive outcome, and the occurrence of adverse events and increased medical costs as negative outcomes. All previous studies were observational. RCT have not been conducted to evaluate the differences of clinical outcomes between resection and non-resection of pulmonary metastases in osteosarcomas. However, surgery is essential since long-term survival has not been reported in osteosarcoma patients without resection of pulmonary metastases.

In total, 6 articles were included [155,159–163]. Relapse and death occurred in 112 of 151 patients (74.2%) after pulmonary metastasis resection and in 87 of 93 patients (93.5%) without metastasis resection. The cumulative survival rates, after initial resection of pulmonary metastases, were 28–60% at 3 years and 19–47% at 5 years [154,156,149,158,162,164–166]. The cumulative

survival after second and subsequent resections of pulmonary metastases was similar to that of primary surgery. Therefore, if pulmonary metastases can be completely resected in the second and subsequent surgeries, a life prognosis equivalent to that of the first surgery can be expected [154,155,157].

There were no articles reporting on the costs and necessary resources for the surgical resection of pulmonary metastases. Factors related to good prognosis after resection of pulmonary metastases were unilaterality, three or fewer metastases, and complete resection [155,156,164].

The frequency of adverse events ranged from 0 to 12%. Hemopneumothorax was the most common. Empyema was also reported. These adverse events were improved with indwelling chest drainage for approximately 2 weeks. No fatal cases have been reported [156,165,166].

Future research should include minimally invasive surgery using radiofrequency ablation. It is necessary to verify its usefulness in comparison to pulmonary metastasis resection. In conclusion, complete resection of pulmonary metastases is conditionally proposed to improve survival in patients with pulmonary metastases of osteosarcoma.

Declaration of competing Interest

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