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Review

European standard clinical practice recommendations for children and adolescents with primary and recurrent osteosarcoma

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ABSTRACT

Osteosarcoma is a challenging disease requiring multidisciplinary management in expert centers for optimal outcome. There are no current international protocols or guidelines specific for pediatric and adolescent osteosarcoma. The European Standard Clinical Practice (ESCP) project is a collaboration between ERN PaedCan and SIOP Europe's Clinical Trial Groups to develop approved clinical recommendations reflecting current best practice. This manuscript is a summary of the full ESCP guideline for patients with osteosarcoma. The manuscript provides evidence graded recommendations for diagnosis, staging, management, response evaluation and follow-up. The methodology as defined in the standard operating procedures of the European Society for Medical Oncology (ESMO) was applied. Experts of the Fight OsteoSarcoma Through European Research (FOSTER) consortium contributed. In summary, the ESCP provides guidance on low-grade, but has a focus on high-grade osteosarcoma. In high-grade osteosarcoma the outcomes of most recent trials for clinical subgroups (e.g., metastatic vs. non-metastatic, resectable vs. non-resectable) are discussed, for treatment-naïve as well as for recurrent/refractory disease. An overview of current evidence also highlights the need for further therapeutic development as patients with primary metastatic or recurrent/refractory high-grade osteosarcoma still have a poor prognosis. Intensified collaborative research is identified as a prerequisite to increase survival and to limit long-term toxicities.

1. Introduction

Osteosarcoma is a malignant tumor arising from primitive mesenchymal bone precursor cells. Production of osteoid and/or bone matrix and the proliferation of malignant mesenchymal tumor cells are key histopathological features [1,2]. Osteosarcoma is the most common primary sarcoma of the skeleton [1,2].

In 2021, a comprehensive clinical practice guideline on bone sarcomas was published by the European Society for Medical Oncology (ESMO) in collaboration with ERN PaedCan (European Reference Network for Paediatric Oncology), GENTURIS (genetic tumor risk syndromes) and EURACAN (European Network for Rare Adult Solid Cancer) representatives [3]. The ESMO-PaedCan-GENTURIS-EURACAN clinical practice guideline was an important update on current therapeutic strategies. Here, we describe detailed clinical practice guidance for the treatment of children and adolescents with osteosarcoma, based on most recent published evidence, as part of the ERN PaedCan-SIOPE European Standard Clinical Practice (ESCP) project.

2. Methodology

This ESCP guideline has been drafted by RE and NH in accordance with ESMO's standard operating procedures for Clinical Practice Guidelines development (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). SB and LK have supervised the development of the draft version. Recommended interventions and regimens are intended to correspond to 'standard' approaches, according to current consensus among the European expert multidisciplinary sarcoma community. Experts involved in the finalization of this guidance document were recruited from the recently established FOSTER ('Fight OsteoSarcoma Through European Research') consortium. The relevant literature has been selected by the authors. Levels of evidence and grades of recommendation have been applied following the system shown in Table 1. Statements without grading were considered standard clinical practice justified by the experts.

3. Presentation, diagnosis and initial work-up

The World Health Organization (WHO) describes conventional osteosarcoma (OS NOS, ICD-O: 9180/3) as an intramedullary high-grade sarcoma in which the tumor cells produce bone. Telangiectatic and small cell osteosarcoma are mentioned as histologic subtypes. Conventional osteosarcoma is further subdivided according to the predominant matrix: osteoblastic, chondroblastic or fibroblastic, but bone formation is required to set the diagnosis. Specific osteosarcoma entities comprise low-grade central osteosarcoma (LGCOS, ICD-O: 9187/3), parosteal osteosarcoma (ICD-O: 9192/3), periosteal osteosarcoma (ICD-: 9193/3) and high-grade surface osteosarcoma (ICD-O 9194/3) [1,2]. The International Incidence of Childhood Cancer investigators reported that bone sarcomas constitute approximately 4.7% and 7.8% of all cancers in children (0–14 years) and adolescents (15 – 19 years), respectively [4]. The total estimated number of cases per year in Europe across all age groups is 1135 with a peak incidence of 0.5 cases per 100.000 between 15 and 24 years [5].

The *etiology* of osteosarcoma is unknown. The incidence of osteosarcoma is increased in children and adolescents with certain cancer predisposition syndromes, such as hereditary retinoblastoma, Li-Fraumeni, Rothmund-Thomson type II, Werner and Bloom syndrome as well as Diamond-Blackfan anemia [6–8]. More recently, in patients with osteosarcoma, rare pathogenic variants were found to be enriched in DNA repair genes like *BRCA1*, *BRCA2*, *RAD51*, *ATM*, etc. [9]. This indicates that failures in the maintenance of genome integrity play an important role in the pathogenesis of this malignancy. Other factors include genotoxic therapies, most importantly radiotherapy [10], and growth/hormonal factors [7].

Clinically, children and adolescents with osteosarcoma present with localized swelling, pain, and limitations of joint movement due to local expansion of and tissue destruction by the tumor. The metaphyses of the long bones proximal and distal of the knee are the most frequent tumor locations, present in up to two thirds of the patients. This localization is followed by the proximal humerus and, less frequently, the axial skeleton [11,12]. Children are most commonly diagnosed during adolescence, with a higher prevalence in boys (approx. ratio 1.3:1) [13–17].

Table 1
Levels of evidence and grades of recommendation.

Levels of evidence	
I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs…), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

In case of suspected diagnosis of a bone sarcoma, the first investigation is conventional radiography of the primary tumor in at least two planes. A combination of bone destruction and osteoid formation is suggestive of osteosarcoma with a typical, but not specific, phenomenon of a "Codman triangle" [18,19]. In case of a suspected bone tumor, an MRI covering the whole anatomical compartment and the adjacent joints is indicated to evaluate the primary tumor (size), its relationship with surrounding tissues, the presence of skip lesions and the relationship to joints, which are all essential to guide the later surgical treatment approach. MRI is the modality of choice and should include T1, T2, fat sat and post-contrast sequences. A CT scan may be of added value in less common sites like the skull [18,20–25].

The site for a *biopsy,* either core needle or open, incisional biopsy, should be planned in collaboration with an orthopedic surgeon and/or experienced dedicated interventional radiologist, with future resection of the biopsy tract in mind. Performing the biopsy in a center of expertise leads to fewer local relapses and better outcomes [26–28].

Pathological diagnosis should be performed according to the WHO 2020 [1–3]. The identification of neoplastic bone formation seen on hematoxylin/eosin staining is the defining feature of the histopathological diagnosis. A permeative growth pattern of the tumor is usually identified, with replacement of bone marrow and destruction of pre-existing trabecula. Typically, the tumor cells demonstrate severe anaplasia and pleomorphism with abundant atypical mitotic figures [1,2]. In cases of diagnostic uncertainty, DNA methylation and copy number profiling can support the diagnosis, but cannot replace the defining morphologic features [29]. To date, no treatment-stratifying biomarkers have been identified.

In confirmed high-grade osteosarcoma, *staging* should include a high-resolution chest CT to evaluate for the presence of pulmonary metastatic disease [30,31]. Despite superior detection to conventional radiographs [18,32,33], studies comparing CT to open thoracotomies show that CT still misses an important number of metastatic lesions [34,35]. Concerning the definition of imaging-classified lung metastases, studies have shown no specific criteria, neither size nor morphological characteristics can clearly distinguish benign from malignant nodules [33,36,37]. The EURAMOS-1 investigators have arbitrarily defined lesions as "certain" pulmonary metastases if one or more pulmonary/pleural nodule(s) have a diameter of 1 cm or more; or if three or more nodules of 0.5 cm or larger maximum diameter are detected. Fewer or smaller lesions are defined as "indeterminate" but should be considered "possible" metastatic disease and pathological assessment is advised particularly if these lesions persist after neoadjuvant chemotherapy [38]. No prospective studies with sufficient patient number have been performed showing that a higher detection rate will translate into improved survival.

In high-grade osteosarcoma, metastases to the bone or, even more so, to other tissues than the lung are rare [31]. Nevertheless, staging should include a body-wide screening. The current recommended modality is - at least - a bone scintigraphy. Where available, [18 F]2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET)-CT or PET-MRI, whole-body(WB)-MRI, are increasingly utilized [39–44]. Some studies, retrospective and of limited size, have shown better detection of non-pulmonary metastases by [^{18}F]FDG PET-CT as compared to conventional imaging (bone scintigraphy) [43,45]. No prospective studies with sufficient number of patients have been performed to show that a higher detecting rate translates to improved survival.

In conclusion, staging should include conventional radiographs and an MRI of the primary tumor, a chest CT and whole-body imaging. Imaging should be performed closely, and no longer than 28 days before start of chemotherapy to prevent misclassification of response on neoadjuvant therapy.

Before initiation of chemotherapy, baseline organ function should be evaluated, see **supplement 1**. The outline of the proposed therapy as well as expected and specific side-effects including possible infertility and options of fertility preservation in line with international guidelines [46,47] should be discussed with the patient and family..

4. Management of primary high-grade, resectable, osteosarcoma

High-grade (central) osteosarcoma is the most common bone sarcoma of childhood [13–17]. High-grade surface osteosarcoma should be similarly treated [51,52]. In early multi-institutional trials, introduction of systemic chemotherapy showed a drastic improvement of survival, with 2-year survival rates rising from ~20% to ~65% [53,54]. Over the following decades, study groups such as the North American Children's Oncology Group (COG), the Cooperative Osteosarcoma Study Group (COSS), the European Osteosarcoma Intergroup (EOI), the French Bone Sarcoma group (SFCE and GSF-GETO) and the Scandinavian Sarcoma Group (SSG) have made international collaborative efforts [55–62]. For patients with localized disease, recent prospective clinical trials have achieved five-year event-free (EFS) and overall survival (OS) rates of 60% and 70–80%, respectively. Patients with known primary metastatic disease fare worse with 5-year EFS rates of ~30% and 5-year OS of ~45% [38,55,56,62,63]. Unfortunately, treatment intensification by addition of more chemotherapeutic agents did not yield improved survival in the investigational arms of the latest randomized clinical phase III trials [55,56].

Current management of high-grade osteosarcoma combines neoadjuvant multi-agent chemotherapy followed by aggressive surgery aiming for complete resection with wide margins followed by adjuvant chemotherapy. The number of patients and cumulative chemotherapy dose of each protocol is summarized in Table 3. A combination of three drugs seems superior in terms of efficacy and/or toxicity as compared to regimens containing either 2 [64], 4 [65], or 5 drugs [55,66]. The EURAMOS-1 trial has been the largest international phase III trial where the standard arm including methotrexate, doxorubicin and cisplatin (MAP) [56] (based on the COG INT-0133 trial [67,68]) was non-inferior to investigational arms. Other regimens have shown efficacy, e.g., the French Sarcome/OS2006 approach based on methotrexate, ifosfamide and etoposide (M-EI). This study aimed to limit long-term toxicities of doxorubicin and cisplatin [62]. Furthermore, the efficacy of other combination regimes omitting methotrexate, such as the St. Jude OS99 [69] and the API-AI regimen [70] might provide alternatives in case of methotrexate-intolerability or contraindications.

4.1. *EURAMOS −1*

EURAMOS-1 was an open-label, international, randomized and controlled phase III trial running between 2005 and 2011. The trial included children and adults below the age of 40 with high-grade,

Table 2
Diagnostic recommendations.

Level of evidence and grade of recommendation		Ref
In case of suspected bone sarcoma, early patient referral to a reference center for diagnostic work-up and management of disease is recommended.	IV, A	[26,27]
In case of suspected bone sarcoma, plain radiographs and an MRI of the primary tumor (including the whole compartment and adjacent joints) are recommended prior to biopsy.	III, A	[19,22,23,25]
It is recommended to plan and perform a biopsy in collaboration with an oncology-experienced orthopedic surgeon and/or interventional radiologist. Histopathological diagnosis is recommended to be performed according to the WHO 2020 guidelines.	IV, A	[26–28]
In confirmed high-grade osteosarcoma, a high-resolution chest CT is recommended for evaluation of pulmonary metastatic disease.	III, A	[30–32,34,35]
Whole body staging is recommended to screen for non-pulmonary metastases with at least bone scintigraphy. If available [^{18}F]FDG PET-CT, [^{18}F]FDG PET-MRI, whole body MRI are recommended modalities.	III, A	[31,39,41, 43–45,48–50]

Table 3
Number of patients and cumulative chemotherapy doses per treatment protocol.

	Number	Doxorubicin	Cisplatin	Methotrexate	Etoposide	Ifosfamide	Carboplatin
EURAMOS-1 (GHR)[a]	716	450 mg/m^2	480 mg/m^2	144 g/m^2			
EURAMOS-1 (PHR)[b]	618	450 mg/m^2	480 mg/m^2	144 g/m^2	1500 mg/m^2	60 g/m^2	
OS 2006 (GHR/L/R)[c]	212			228 g/m^2	1200 mg/m^2	60 g/m^2	
OS 2006 (PHR/M+/U)[c]	164	375 mg/m^2	600 mg/m^2	144 g/m^2	600 mg/m^2	24 g/m^2	
OS 2006 API-AI (GHR)[d]	106 *	420 mg/m^2	500 mg/m^2			54 g/m^2	
OS 2006 API-AI (PHR/M+/U)[d]		300 mg/m^2	300 mg/m^2		1500 mg/m^2	90 g/m^2	
St Jude OS99	72	375 mg/m^2				63,6 g/m^2	8 * AUC 8 mg/ml x min
ISG/OS-2	194	420 mg/m^2	600 mg/m^2	120 g/m^2		60 g/m^2	

GHR: good histological response; PHR: poor histological response; L: localized; R: resectable; M+ : metastatic disease; U: unresectable disease
[a] RCT randomizing the addition of Interferon alfa-2b to patients with good histological response following neoadjuvant chemotherapy
[b] RCT randomizing the addition of ifosfamide and etoposide in patients with poor histological response following neoadjuvant chemotherapy
[c] RCT randomizing the addition of zoledronate
[d] 106 patients were included in the analysis of the OS 2006 API-AI regime

resectable, non-metastatic and metastatic, osteosarcoma of the extremity or axial skeleton, including those arising as second malignancies, between 2005 and 2011. Following neoadjuvant MAP chemotherapy, the histologic response of the primary tumor was stratifying for different randomizations. Poor histological response was defined as 10% or more viable tumor cells present at histological assessment. In case of good histologic response, the addition of Interferon alfa-2b [71] and, in case of poor histologic response, the addition of ifosfamide and etoposide, to MAP adjuvant treatment were investigated. 716 patients with a good histologic response showed no statistically significant survival benefit of adding Interferon alfa-2b maintenance [56]. However, a considerable proportion of patients never started Interferon alfa-2b or stopped prematurely. 618 patients with a poor histologic response showed no survival benefit of the addition of ifosfamide and etoposide [55]. Post-analyses of the full cohort, n = 2186, with 93% of patients with a conventional osteosarcoma and a median age of 14 years were published sequentially with a median follow-up of 54 months [38]. For the full registration cohort, 5-year EFS was 54% (95% confidence interval (CI): 52–56%) and 5-year OS was 71% (95% CI: 68–73%). In localized disease 5-year EFS and OS were 60% (95% CI: 57–62%) and 76% (95% CI: 74–78%), respectively. In metastatic disease, 5-year EFS and OS rates were 28% (95% CI: 23–33%) and 45% (95% CI: 39–50%), respectively. The most common event was the detection of new metastases (53% of events). In non-metastatic patients who achieved complete surgical remission 3–6 months after diagnosis, the 5-year EFS and OS were 64% and 79%, respectively [38]. Acute toxicities led to dose reductions in 58% of all patients treated with MAP, and 86% experienced a grade 4/5 toxicity. Most important acute non-hematological toxicities were electrolyte disturbances, acute kidney injury and elevated bilirubin. Left-ventricular cardiac dysfunction grade 1/2 was identified in 15% of patients and hearing problems in 25% of patients [55]. Long term toxicity data is currently not available for the EURAMOS study.

4.2. The French OS 2006 study

The French OS 2006-study was a multicenter national study for patients with high-grade osteosarcoma, which included a phase III randomized trial investigating the impact on outcome of adding zoledronate to the standard treatment (NCT00470223) [62]. First results showed no added benefit of zoledronate [63]. The study also aimed to identify an alternative to MAP with similar survival but less long-term toxicity [72] in a sub-cohort of young patients with high-grade osteosarcoma by reducing exposure to doxorubicin and cisplatin. The neoadjuvant chemotherapy in patients aged < 18 years (and in a selected group of 55 patients aged between 18 and 25 years) consisted of 7 courses of high-dose methotrexate (HD-MTX) (vs. 4 courses in EURAMOS-1), and two courses of etoposide and ifosfamide followed by surgery. Postoperative chemotherapy consisted of M-EI in patients with good histologic response, and MAP in patients with poor histologic response, limiting cisplatin and doxorubicin to patients with poor prognostic markers. All adults above 25 years of age were treated with a combination of doxorubicin, cisplatin and ifosfamide (API-AI). For patients aged between 18 and 25 years, centers decided at the start of the study which regimen would be used, i.e., the methotrexate based M-EI or the API-AI regimen.

Between 2007 and 2014, 522 patients were enrolled. Safety and efficacy were reported for all patients up to 25 years of age treated according to the M-EI regimen. 409 patients were analyzed with a median follow-up of 4.8 years. Reported 5-year EFS was 56% (95% CI: 51–62%) and 5-year OS 71% (95% CI: 66–76%). After 14 weeks neoadjuvant M-EI (vs 10 weeks EURAMOS-1) 73% of these young patients (up to 25 years vs up to 40 years EURAMOS-1) achieved good histologic responses [62]. The outcome of a total of 187 young patients with localized completely resected high-grade osteosarcoma treated with M-EI were reported with median follow-up of 4.8 years [62]. However, analysis of long-term outcome and toxicity is still ongoing. M-EI may be considered for individuals who do not tolerate doxorubicin or cisplatin.

4.3. The ISG/OS 1 and 2 study

The Italian Sarcoma Group Trial ISG/OS-1 was a multicenter randomized trial comparing neoadjuvant therapy with or without ifosfamide added to MAP, including 246 patients with nonmetastatic osteosarcoma of the extremity. Neoadjuvant ifosfamide did not translate in a higher rate of good histologic response, but did increase hematological toxicity. Survival was not different between the different arms. The study was not designed to answer whether adjuvant ifosfamide in patients with poor histological response improved survival [73].

The ISG/OS-2 was a phase 2 multicenter uncontrolled trial with the objective to evaluate treatment according to a risk-adapted chemotherapy regimen based on ABCB1/Pgp expression, including 194 patients. The lack of a control group limited the interpretation of the results. Furthermore, the trial was not designed to answer whether mifamurtide had an effect in the Pgp positive patients [74].

4.4. The St. Jude OS99

The OS99 protocol may be considered in young patients who do not tolerate HD-MTX. This protocol included patients under the age of 25 years with a non-metastatic, resectable, high-grade osteosarcoma in a single-center study between 1999 and 2006. It combined ifosfamide, doxorubicin and carboplatin. 72 patients were enrolled with a median age of 13.4 years. The median follow-up was 5.1 years with a 5-year EFS of 66.7% ± 7.0% and 5-year OS of 78.9% ± 6.3, respectively [69].

4.5. The INT-0133 trial

The INT-0133 trial was a randomized phase III trial in patients with

high-grade localized osteosarcoma. The aim was to investigate ifosfamide and the addition of liposomal mifamurtide, L-MTP-PE, to MAP in a two-by-two factorial design. 677 patients below the age of 30 years were included. In a first analysis, there was no added value of the addition of ifosfamide, with a 3-year EFS rate of 68% in the group that received a combination of mifamurtide and MAP and a rate of 78% for those who received mifamurtide combined with MAP and ifosfamide. An interaction between ifosfamide and mifamurtide and no significant benefit for mifamurtide were reported [67]. Subsequently, with different analysis cut-off points (i.e., 6-years OS), the investigators reported improved overall survival rates in patients who were randomized to receive mifamurtide [68]. The results of this trial, however, were confounded by a possible interaction between ifosfamide and mifamurtide. Currently, it remains questionable if mifamurtide can really help to improve outcomes in patients with high-grade osteosarcoma [75–77]. Therefore, the US Food and Drug Administration (FDA) did not approve the drug. Mifamurtide, however, received marketing authorization in the EU by the EMA for patients aged 2–30 years with newly diagnosed, non-metastatic osteosarcoma [75].

4.6. Surgery

Surgery of the primary tumor and metastatic lesions with wide resection margins is essential if treatment is to be for curative intent [78–81]. The timing of surgical resection of the primary tumor is preferably performed after neoadjuvant chemotherapy for pathologic response assessment and optimal planning of surgery. Concerning efficacy, no differences in survival or potential for limb salvage between direct surgery and surgery after 10 weeks of neoadjuvant chemotherapy were reported [82].

The optimal surgical approach for lung metastases is part of ongoing discussion. Historically, thoracotomy with palpation of the lung was advised. With the availability of high-resolution CT scans smaller lung metastases are identified by imaging. There might, therefore, be a role for minimally-invasive surgical techniques in oligo-metastatic disease. Up to one third of the surgeons approach oligo-metastatic disease by video-assisted thoracoscopy [83]. A retrospective analysis of 202 pediatric patients (thoracotomy (n = 154) or thoracoscopy (n = 48)) showed no difference in EFS. The findings, however, are limited by significant selection bias [35]. A prospective trial comparing thoracotomy versus thoracoscopy by COG is currently ongoing in upfront and recurrent/refractory osteosarcoma.

4.7. Prognostic factors

Metastatic disease, inadequate surgical margins, non-extremity osteosarcoma, proximal osteosarcoma, male gender, older age, a large tumor volume (mostly > 8 cm or $\geq 1/3$ of the involved bone diameter) and a poor histological response after neoadjuvant chemotherapy were consistently associated with poor outcomes [38,55,56,62,63,84–86]. International staging systems, like the American Joint Committee on Cancer (AJCC), Enneking Musculoskeletal Tumor Society (MSTS), and Vanderbilt Osteosarcoma staging system all seem to perform similarly well [87–89].

4.8. Conclusion

Combined with tumor surgery, intensive chemotherapy has led to approximately 70% 5-year survival rates for patients with resectable high-grade osteosarcoma. Large-scale clinical trials have unfortunately not resulted in significantly improved survival rates over the last four decades. Based on current available evidence, the MAP regimen from the EURAMOS-1 trial could be considered the standard of care in osteosarcoma. The French M-EI approach reported similar outcomes in a smaller group of patients [55,56,62,90]. While analyses of both long-term outcomes and toxicities of M-EI are still ongoing (gonadotoxicity, nephrotoxicity and induction of secondary leukemia/MDS), M-EI might be an alternative for patients with pre-existing hearing loss or cardiac disease.

Current standard systemic therapy is a 3-drug chemotherapy regimen [3,66,91]. Stratification and treatment intensification according to currently known prognostic factors have not overcome the observed stagnation. It remains essential to establish novel stratification strategies to identify those patients eligible for dose reductions and to introduce novel therapies for those patients known to have poor prognostic features. A fact worth mentioning is that a gap between intended and received chemotherapy intensity seems to be associated with poorer survival [92]. Furthermore, insight into chemotherapy resistance and pharmacogenomics will hopefully allow for more individually tailored chemotherapy regimens in the future [65,93,94].

The use of mifamurtide is a matter of ongoing debate among clinical and regulatory experts [75,95]. Unfortunately, a definitive prospective randomized trial comparing MAP versus MAP with mifamurtide was not supported by industry. Trials like the current French Sarcome-13/OS2016 randomized phase II trial (NCT03643133) and the ISG/OS-2 single-arm trial (NCT01459484, NCT04383288) [74] were not designed to address the question of the added value of mifamurtide. Further prospective, randomized trials are urgently needed.

5. Management of primary high-grade, unresectable osteosarcoma

As described for the management of resectable osteosarcoma, surgery aiming for wide margins of the primary tumor and complete metastasectomy are the cornerstones of curative treatment. Therefore, osteosarcoma where complete resection of either the primary tumor or metastases is not feasible is particularly challenging. This includes synchronous multifocal osteosarcoma [99].

It is unknown whether neoadjuvant chemotherapy, as recommended for resectable osteosarcoma, can increase resectability in terms of tumor reduction [82,100–102]. However, delineation of the tumor's boundaries might be improved in patients with a good response to chemotherapy [103,104].

In case of definitively unresectable localized or oligo-metastatic osteosarcoma, intensive radiotherapy with doses of 70 gray (Gy) or higher is recommended for local therapy, whereas debulking surgery does not appear to confer a survival benefit and should only be considered to improve quality of life (for example primary tumor resection in case of

Table 4
Recommendations for high-grade, resectable osteosarcoma.

Level of evidence and grade of recommendation		Ref
Patients with high-grade osteosarcoma should be treated with three-drug chemotherapy in combination with aggressive surgery aiming for wide resection margins.	I, A	[53–56,62,65, 67,68]
Patients with primary resectable metastatic high-grade osteosarcoma should be treated following the same principles as non-metastatic osteosarcoma plus complete surgical resection of all metastatic sites.	I, A	[53–56,62,65, 67, 68]
Surgery of the primary tumor and metastatic lesions with wide resection margins is essential if treatment is to be with curative intent.	III, A	[78–81]
The MAP regimen (methotrexate, doxorubicin and cisplatin) could be considered a standard for current osteosarcoma treatment.	I, A	[55,56,67,68]
The M-EI regimen (methotrexate, etoposide and ifosfamide) might pose an alternative to the MAP regimen in patients with a contra-indication for cisplatin or doxorubicin.	III, B	[62,72]
In case of a contra-indication to methotrexate, the St. Jude OS99 and the API-AI regimens provide reasonable alternative treatment approaches.	III, C	[69,70,96]
Due to lack of clear evidence for a benefit of additional mifamurtide, this is not a part of current standard treatment.	II, C	[67,68,75,97, 98]

pain) [105,106]. Evidence is based on non-randomized studies with limited patient numbers, where heavy-ion and proton beam therapy are considered to be the modalities of choice, and sometimes are combined [105,107–111]. In series describing the treatment of unresectable osteosarcoma, with very high-dose radiotherapy, 5-year OS of 67% was reported [105,111,112]. However, current evidence only includes case-series, as summarized by North American and European radiation oncologists [113]. In case of multi-metastatic osteosarcoma treatment is often not curative. Case series describe longer symptom control with radiotherapy to metastatic sites in symptomatic patients [114]. In those cases, hypofractioned or stereotactic radiotherapy may be considered [115,116]. We consider individually balanced use of chemotherapy, radiotherapy and (palliative) surgery to be useful focusing on quality of life.

6. Management of recurrent or refractory high-grade osteosarcoma

Recurrent/refractory osteosarcoma remains a major challenge, occurring in around one third of the patients[38, 55, 56], with a dismal 5-year OS below 30% (range 13%−57%). Most patients present with metastatic disease with lung metastases in up to 80%. Achieving a second surgical remission strongly improves the chance for survival [119–123].

The management depends on the localization of the relapse (local vs metastatic), the time of the relapse, the number of metastases, and the metastatic sites. Early relapses (in most studies defined $\leq$ 18 months) have a worse prognosis than late relapses [120,121,124–128]. Survival of patients with two or less pulmonary lesions at relapse is better compared to disseminated relapse [119,121], or in patients with bone metastases [119,121,123]. When treating recurrent/refractory osteosarcoma, the chance of cure has to be balanced with the toxicity of the intended treatment [129,130].

Aggressive surgery should be performed where feasible, including re-surgery in case of subsequent relapses [30]. Complete removal of all lesions, including locally recurrent/refractory osteosarcoma or osseous metastases should be attempted [131]. In case of any inoperable lesions or in case of preference for non-thoracotomic approaches in multi-repetitive recurrent patients or as part of palliative treatment, stereotactic RT [114,132,133] or thermo-ablation (including radiofrequency or microwaves) [134,135] might be alternatives for local control.

The benefit of chemotherapy or radiotherapy in recurrent osteosarcoma remains debatable, as randomized controlled clinical trials in this situation are lacking. The optimal systemic treatment approach for recurrent osteosarcoma therefore remains ill-defined. Retrospective analyses showed either no improved outcome with chemotherapy added to surgery [119,128,136–138] or demonstrated only a moderately improved outcome [48,121,139–142]. Regarding the choice of second-line systemic therapy, exposure to previous agents frequently precludes the use of doxorubicin and cisplatin. Ifosfamide or cyclophosphamide, often combined with etoposide or carboplatin, are best studied [120,121,143–145]. Conflicting results are published concerning the combination of gemcitabine with docetaxel [146–149]. In current expert view, ifosfamide (9–14 g/m^2/cycle) with or without etoposide (300–500 mg/m^2/cycle), are the most often used second-line regimens.

No new agents have been evaluated in phase 3 trials in recurrent/refractory osteosarcoma. Phase 2 trials with tyrosine kinase inhibitors (TKIs) have demonstrated some clinical efficacy, including regorafenib (median-PFS of 3.6 months vs 1.7 months in placebo [150]; 8-week PFS of 65% vs 0% [151]), sorafenib (4-month PFS of 46% [152]), cabozantinib (4-month PFS of 71% [153]), apatinib (4-month PFS of 57%, 6-month PFS of 37% [154]), and lenvatinib (4-month PFS of 33%) [155]. In search of improved efficacy, such TKIs have been combined with everolimus [156]) or chemotherapy [155,157]. The use of different trial designs with different endpoints in predominantly single arm studies prohibits direct cross trial comparisons, and results did not translate yet in a phase 3 trial [150–152,156].

6.1. Conclusion

Recurrent/refractory osteosarcoma is challenging to treat. Surgery aiming for a renewed surgical remission of all tumor-sites is essential for a curative intent. It is highly recommended to include affected patients into clinical trials. Chemotherapy, most often ifosfamide ± etoposide or other combinations dependent on previously given therapies (e.g., IE or CE after MAP or AP after M-EI), is recommended in the absence of clinical trials in patients with early local or metastatic relapses.

7. Craniofacial osteosarcoma

Craniofacial osteosarcoma is a rare subset of osteosarcoma (approx. 5%), where dedicated clinical trials are lacking. The peak incidence of this specific disease is reported to be between ages 30 and 40 years [159]. In the COSS registry, which mainly caters to pediatric centers, the median age was only 19.7 years [160].

Craniofacial osteosarcoma is most frequently sporadic, but can also be associated with a tumor predisposition syndrome (e.g., hereditary retinoblastoma, Li-Fraumeni syndrome) [161,162]. It can also rarely occur as a malignant transformation from fibrous dysplasia[163,164], or secondary after radiotherapy in case of retinoblastoma or rhabdomyosarcoma [162,165–169]. Craniofacial osteosarcoma most commonly affects the jaws. Extragnathic craniofacial osteosarcoma is a negative predictive factor [160,170,171]. Craniofacial osteosarcoma has a lower propensity to metastasize than its extremity counterpart, but it is generally more difficult to obtain permanent local tumor control [172].

Table 5
Recommendations for high-grade, unresectable, osteosarcoma.

Level of evidence and grade of recommendation		Ref
• Diagnostic work up and staging is similar to resectable osteosarcoma.	III, A	[19,22,23, 25]
• Neoadjuvant chemotherapy and radiotherapy can be considered in an attempt to achieve resectable disease.	IV, B	[117,118]
• High-dose radiotherapy can be considered as local therapy in definitively unresectable local or oligo-metastatic disease. Chemotherapy, as recommended for resectable osteosarcoma, should be administered if the approach is curative.	IV, B	[105, 107–110]
• In multi-metastatic unresectable osteosarcoma, therapies considered should be balanced with quality of life.		

Table 6
Recommendations for high-grade refractory or recurrent osteosarcoma.

Level of evidence and grade of recommendation		Ref
Surgery and, if necessary, re-surgery is strongly recommended in resectable, recurrent/refractory osteosarcoma.	II, A	[30,119–121]
Chemotherapy might be considered in multi-metastatic, unresectable relapses or in early relapses.	III, B	[120,121,128, 140–142]
Chemotherapy or experimental therapies should preferably be given in the context of osteosarcoma-specific clinical trials.	V, B	[57,158]
Tyrosine kinase inhibitors (sorafenib, regorafenib, cabozantinib, lenvatinib, apatinib) have demonstrated some efficacy in small phase II trials and might be of added value. They require further studies.	III, B	[150–154,156]
In unresectable disease or in multi-repetitive recurrent patients, high-dose radiotherapy or radio-frequency ablation might be considered in order to achieve local and/or metastatic control.	IV, B	[114,132–135]

The standard-of-care is largely identical to extra-axial osteosarcoma. Chemotherapy, as described above, together with complete surgery has been considered effective [173–178], also in the case of craniofacial osteosarcoma secondary to retinoblastoma treatment [166]. However, non-response to chemotherapy with the risk of local progression during neoadjuvant chemotherapy is a concern [178,179]. Primary surgery followed by adjuvant chemotherapy might be preferred in selected patients. This seems particularly advisable if resectability is possible [180]. Inoperability and incomplete resection are more frequent than in extra-axial osteosarcoma. While photon-beam radiotherapy at conventional doses cannot be recommended, such craniofacial osteosarcoma should be candidates for high-dose radiation. Heavy-ions have a higher biological efficacy and seem to be better confined to the target volume [111,172]. In craniofacial osteosarcoma, some locations seem to have a lower tendency to metastasize. Therefore, in some patients, systemic treatment might be omitted. Examples of patients eligible for expert discussion are patients with an osteosarcoma of the jaw [181] or craniofacial osteosarcoma associated with a tumor predisposition syndrome.

8. Management of low-grade and intermediate-grade osteosarcoma

Low-grade osteosarcomas encompass low-grade central osteosarcoma, which accounts for 1–2% of osteosarcomas, and parosteal osteosarcoma, which accounts for about 4% of osteosarcomas. Low-grade osteosarcoma has a peak incidence in the third decade of life, amplification of 12q13-q15 involving *MDM2* and *CDK4* is often observed. While low-grade osteosarcoma can be cured by surgery alone, this must be with wide margins to prevent both local recurrence and dedifferentiation into high-grade osteosarcoma [182]. Parosteal low-grade osteosarcoma can be radiographically difficult to distinguish from high-grade osteosarcoma, hence, careful histopathological work-up is mandatory [183].

In up to 25% of low-grade osteosarcoma, a clinical challenge is posed by foci of dedifferentiation. Here, one retrospective study suggested that low-grade osteosarcoma with up to 50% of high-grade dedifferentiation might be treated by surgery alone [184]. This was corroborated by Norwegian registry data which indicated 5-year overall survival rates > 90% when treatment was surgery alone [185]. Low-grade osteosarcoma with > 50% high-grade dedifferentiation might be treated with adjuvant high-grade osteosarcoma-type chemotherapy. The benefit of such an approach is at present unclear, as metastatic relapse rates similar to those observed in exclusively surgically treated patients have been observed [184–188].

Periosteal osteosarcoma (ICD-O 9193/3) is an intermediate grade bone-forming sarcoma. It typically affects the diaphyses of the femur or tibia. Periosteal osteosarcoma accounts for 2% of all osteosarcomas. It has its peak incidence in the second decade of life [1]. Marrow involvement is rare and may predict a more aggressive behavior. Wide surgical excision is essential. Chemotherapy is not routinely recommended [3].

Table 7
Recommendations for craniofacial osteosarcoma.

Level of evidence and grade of recommendation		Ref
In general, use the same diagnostic procedures (including staging) and treatment modalities as for other high-grade osteosarcomas.	IV, A	[173–177]
Consider primary surgery instead of neoadjuvant chemotherapy even in case of resectability, thereby omitting the risks of associated with potential tumor progression and, consequently, unresectability. This might be particularly relevant in older patients.	IV, B	[180]
Favor proton/heavy-ion radiotherapy over photon therapy for the management of unresectable/incompletely resected craniofacial osteosarcoma.	V, B	[111,172]

9. Osteosarcoma and tumor predisposition syndromes

Germline predisposition can nowadays be identified in at least 8% of childhood cancers [190–193]. Recent guidelines have suggested evaluation for pediatric tumor predisposition syndromes (modified Jongmans criteria) [192,194]. Osteosarcoma is overrepresented among pediatric cancers with known germline predisposition. Approximately 10% of patients with osteosarcoma harbor germline mutations of *TP53*, and potentially over 25% of patients harbor any germline pathogenic or likely pathogenic mutation in cancer-susceptibility genes [9], making osteosarcoma an index malignancy that should raise suspicion for tumor predisposition.

10. Supportive care

We refer to local practice, national recommendations and international guidelines for general aspects of supportive care in pediatric oncology [196–198]. Due to osteosarcoma biology and chemotherapeutic treatment at maximum tolerated doses, several aspects of supportive care warrant special attention.

Local pain at diagnosis due to swelling, infiltrative growth or, in rare cases, pathologic fractures can cause significant pain. In the latter case, brace or cast immobilization can be employed [199].

HD-Methotrexate therapy requires the capacity of rapid MTX plasma concentration measurements. Major HD-MTX toxicities are often mediated by reduced drug-excretion and include acute kidney injury (AKI), severe myelosuppression, hepatotoxicity, mucositis, and CNS toxicity [200]. To prevent MTX-mediated AKI, hyperhydration and urine alkalization are essential. Non-renal toxicities can be prevented by antagonizing MTX with the antidote leucovorin, commonly initiated 24 h after the MTX-infusion. As long as renal excretion of methotrexate is not impaired, leucovorin rescue is sufficient to prevent life-threatening toxicities [201,202]. If severe MTX-related AKI is suspected, the use of glucarpidase should be considered, which can rapidly decrease MTX serum concentrations.

Cisplatin is directly toxic to the (proximal) renal tubule which actively transports cisplatin [203–205]. Tubular damage can lead to a Fanconi-like syndrome, characterized by a loss of reabsorption capabilities and resulting in losses of sodium, potassium, magnesium, calcium, glucose, bicarbonate (renal tubular acidosis) and protein [206–208]. Cisplatin-associated nephrotoxicity can be reduced by adequate pre-hydration and by prolonged cisplatin infusion rates [209,210]. As cisplatin-induced hypomagnesaemia can increase nephrotoxic effects, magnesium supplementation during and immediately following cisplatin administration is recommended [211–215]. Ototoxicity is another major concern related to cisplatin-based chemotherapy. However, due to concerns of reduced cisplatin efficacy (that have so far not been assessed sufficiently in osteosarcoma), prophylactic administration of the otoprotective sodium thiosulfate can currently not be recommended in osteosarcoma[216–219].

Doxorubicin is known to be cardiotoxic. In order to monitor cardiotoxicity, echocardiography should be performed at baseline and prior to each doxorubicin course (at least with cumulative doses of >225 mg/m^2) [220]. To reduce cardiotoxicity, prolonged continuous infusion of doxorubicin of 6 h or longer are advised based on data in adults, with

Table 8
Recommendations for low-grade and intermediate-grade osteosarcoma.

Level of evidence and grade of recommendation		Ref
Diagnostic work-up, including staging, and follow-up should be the same as for high-grade osteosarcoma.	V, B	[184–189]
Surgery, with wide margins, is the treatment of choice.	IV, A	[184–188]

Table 9
Recommendations concerning tumor-predisposition syndromes in osteosarcoma.

Level of evidence and grade of recommendation		Ref
Consider hereditarity in all osteosarcoma cases.	V, A	[192–194]
Consider referral for genetic counselling, in line with (inter) national guidelines, for cancer predisposition syndromes in case of clinical suspicion, a positive family history, or when genetic tumor analysis reveals a lesion suggesting germline predisposition.		
Take into consideration potentially increased toxicity and secondary cancers with genotoxic treatment (e.g., chemotherapy and radiation therapy).	V, B	[195]

need for more studies in children [221]. Current international supportive care guidelines made a moderate recommendation that in patients intended to receive 250 mg/m^2 or more doxorubicin the benefits of dexrazoxane outweigh the risk [222]. Dexrazoxane, if considered, should be given intravenously 30 min prior to doxorubicin, starting with its very first dose [223]. If dexrazoxane is not used pre-emptively, it should be considered if the LVEF shows a confirmed reduction of $>10\%$ within the normal range or if the FS shows a similar fall.

Ifosfamide can cause renal tubular damage [224–226]. Kidney damage might be reduced by prolonged infusions and by adequate intravenous hydration. Urothelial damage leading to hemorrhagic cystitis is due to the ifosfamide metabolite acrolein. It has to be prevented by administering the antioxidant sodium 2-mercaptoethane sulfonate (MESNA) [227]. Ifosfamide can also cause encephalopathy, clinically spanning from confusion to coma [228]. The most important intervention is stopping further ifosfamide administration. Administration of methylene blue (methylthioninium) has been described as an effective antidote in case series [229–232]. Expert consensus in ESMO-EONS-EANO clinical practice guideline do not recommended the routine use of methylene blue in the prevention or treatment of ifosfamide induced central neurotoxicity, based on very limited data [233].

11. Response assessment and long-term follow-up

11.1. Imaging response evaluation on therapy

Pre-operative imaging is essential to guide surgery and to assess radiologic response. In localized disease, MRI of the primary tumor and radiograph or CT of the chest is recommended to be performed preoperatively. In metastatic disease, appropriate imaging of the metastatic site(s) is mandatory. In pulmonary metastatic disease or indeterminate pulmonary nodules, this includes a preoperative chest CT. Due to its calcified matrix, complete or partial imaging-response to preoperative chemotherapy is rarely seen in osteosarcoma [234]. The definition of progressive disease prior to surgery, measured as a one-dimensional increase of more than 20% according to RECIST 1.1, is associated with poor survival [235]. It is recommended to classify progressive disease in the context of clinical features of progression, such as increased pain, inflammatory signs, rising alkaline phosphatase, as increases in tumor size might also reflect delay between staging and start of therapy or a result of hemorrhagic/necrotic changes indicating response to therapy (pseudoprogression). Furthermore, restaging should be performed (chest CT and whole body imaging) in case of local progression to evaluate possible metastatic progression.

Various studies have investigated the value of functional quantitative imaging indices in [^{18}F]FDG-PET, diffusion-weighted MRI and dynamic contrast-enhanced MRI [236–245]. All these quantitative measurements require larger prospective studies.

In patients with either localized or metastatic disease who achieved complete surgical remission, further imaging is focused on potential disease recurrences. After surgery, the primary tumor site can be followed using conventional radiographs, with added value of CT or MRI in case of a suspected local relapse. In case of prostheses or surgery including osteosyntheses, specific CT or MR protocols are advised [246]. Of note, it must be verified with the prosthesis manufacturer whether an MRI is still possible. Certain length-adaptable prostheses might be damaged by such a procedure. Chest radiographs are recommended for follow-up of pulmonary metastases with a chest CT at end of therapy. MRI is recommended for the follow-up of unresectable bone metastases. In patients with bone metastases achieving surgical remission, bone-scintigraphy [247], [^{18}F]FDG PET-CT imaging [248], or WB-MRI might be considered at the end of therapy.

In patients with either localized or metastatic disease where surgical remission cannot be achieved, response assessment might support decision making. No studies have systematically investigated the value of functional imaging like [^{18}F]FDG PET-CT to guide local or systemic treatment in these patients.

11.2. Pathology

To evaluate the (surgical) remission status, tumor margins should be assessed in conformity with the MSTS system or the margin distance method. Wide resections are essential to reduce local recurrence risks [78,249]. The histologic response of the primary tumor to preoperative chemotherapy is assessed after surgery. The percentage of viable tumor is assessed, as this has prognostic value. Less than 10% viable tumor cells is used to indicate a good response [250]. This histologic response correlates with survival [38,62,74]. In the setting of neoadjuvant MAP therapy, two courses of cisplatin/doxorubicin and 2–6 methotrexate courses are recommended to best interpret the prognostic value of histologic response, in line with guidance in the EURAMOS-1 study.

11.3. Follow-up after therapy

Apart from diagnosing and managing toxicities known to affect quality-of-life (ototoxicity, cardiotoxicity, nephrotoxicity, secondary malignancies) [251–253] and the function after (reconstructive) surgery, the main goal of surveillance is the detection of disease recurrences. There is a lack of prospective studies investigating the optimal follow-up schedule. Generally, imaging is recommended to be performed at least up to 10 years after primary or recurrent disease, with more frequent screening in the first years post-therapy. In cases of doubt and particularly with suspected disease recurrences, a complete restaging and a biopsy of suspected recurrence are strongly recommended.

In patients achieving complete surgical remission, regular radiographs of the primary tumor site are recommended. For screening of recurrent pulmonary disease, EURAMOS-1 advised chest radiographs for non-metastatic patients, whereas the COG imaging guidelines favor the use of chest CT [18]. No randomized studies investigating whether the use of chest CT leads to better post-recurrence survival rate in osteosarcoma are available. In non-metastatic high-grade bone sarcoma ($n = 352$, disease type and treatment not further specified), a randomized study did show that chest radiography as an imaging modality did not lead to worsened 3-year survival and was not inferior to CT scan in terms of detecting pulmonary metastasis [254]. Researchers from the Rizzoli Institute reported better outcomes in patients who developed lung metastases when the metastases were detected via CT-scans ($N = 112$ patients; 5-year post-relapse survival (PRS) 49%), when compared to patients whose metastases were detected via chest radiograph ($N = 119$; 5-year PRS 30%) in a retrospective study [255].

The recommended surveillance frequencies after completion of chemotherapy are: every 2–3 months for the first 2 years, every six months for years 3–5, every 6–12 months thereafter [3]. We recommend performing chest radiographs and conventional radiographs of the primary tumor in primary non-metastatic patients that achieved complete surgical remission status on therapy. Awaiting future studies, chest CT during follow-up remains of debate and should be performed according

to institutional practice. In line with the EURAMOS-1 protocol, we recommend performing chest CT in primary pulmonary metastatic patients that achieved complete surgical remission status on therapy every 6 months for a minimum of 2 years. In case of residual disease at end of therapy, imaging should include the site of residual disease (no specific recommendations for modalities). In case of recurrent disease, we recommend to start the surveillance over again every 2–3 months for the first 2 years.

12. Future perspectives

Outcomes for patients with osteosarcoma have not improved during the last decades. This might partially be explained by the heterogeneous and complex biology of osteosarcoma. Ongoing preclinical and clinical research needs to elucidate patient-specific aspects of osteosarcoma biology and immunology to foster rational development of urgently needed novel therapeutic approaches. Progress requires international collaboration due to the limited number of patients. Within an international consortium, translational research should complement clinical evaluation of new therapies in frontline and recurrent/refractory disease. The role of maintenance therapy, the optimal backbone in recurrent osteosarcoma, the potential of multi-tyrosine kinase inhibitors, be it in upfront or relapse therapy, as well as the role of immunotherapy are some important questions to be addressed. The development of oncological treatment should be accompanied by research in supportive care to optimize oncological efficacy while at the time minimizing acute and long-term toxicities.

13. Conclusion

This guideline provides the current standard-of-care in frontline, refractory and recurrent osteosarcoma, with a focus on but not limited to high-grade osteosarcoma. Treatment at specialized centers that can guarantee optimal work-up, chemotherapy delivery, surgery, and supportive care is essential to achieve best oncological outcome and manage treatment-related complications.

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Declaration of Competing Interest

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Table 10
Recommendations on supportive care in osteosarcoma.

Level of evidence and grade of recommendation		Ref
Adhere to general local, national and international guidelines.		
Treat pathological fractures conservatively.	IV, B	[199]
High-dose MTX should only be administered at experienced centers, and glucarpidase should be rapidly available.	V, A	[201,256, 257].
Consider supplementation of magnesium with cisplatin therapy.	II, A	[211–215]
Cardiotoxicity should be monitored with echocardiography at baseline and at least following cumulative doxorubicin doses > 225 mg/m^2.	V, B	[220]
To prevent cardiotoxicity, dexrazoxane can be considered with expected cumulative doxorubicin dose higher than 250 mg/m2, ideally starting with the first administration of doxorubicin or after fall in left ventricular function.	I, B	[222,223, 258]
During ifosfamide treatment, MESNA supplementation to prevent hemorrhagic cystitis is mandatory.	II, A	[227]
Methylene blue can be considered to treat severe ifosfamide-induced neurotoxicity.	V, D	[229]

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejcped.2023.100029.

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