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Osteosarcomas

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

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Osteosarcomas

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Compliance rules:

- Guideline
- Conflict of interests

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1 Summary

Osteosarcoma is the most common malignant bone tumor and is characterized by early micrometastasis. The introduction of systemic chemotherapy in addition to tumor resection has significantly improved the prognosis for patients [1, 2]. Multimodal therapy involving neoadjuvant chemotherapy followed by wide tumor resection and adjuvant chemotherapy is now considered the standard of care. This approach can achieve 5-year survival rates of 70% [3]. Any primary metastases must be surgically removed if the goal of treatment is curative. High-dose radiation therapy is indicated only in cases of incomplete tumor resection. In the event of local or systemic relapse, complete resection is of the utmost importance. Second-line chemotherapy for patients in second surgical remission is frequently performed but is not supported by prospective studies.

2 Basics

2.1 Definition and Basic Information

Osteosarcoma is a malignant mesenchymal tumor characterized by the formation of immature bone substance (osteoid). Hematogenous metastasis must be assumed even at the time of initial diagnosis. Predilection sites are the metaphyses of the long bones (especially the knee region with the distal femur and proximal tibia, but also the proximal humerus); involvement of the spine and pelvic skeleton is less common. Most patients present with a solitary tumor lesion [4, 6].

2.2 Epidemiology

Osteosarcoma is rare, with an annual incidence of approximately 0.2–0.3 per 100,000 people (crude incidence rate). In Germany, an average of 180 cases per year were recorded in the state cancer registries and the German Childhood Cancer Registry between 2019 and 2023; in Austria, 23 cases; and in Switzerland, 20–30 cases. Children and adolescents account for about one-third of cases; in this group, osteosarcoma is the most common malignant bone tumor, closely followed by Ewing sarcoma. Overall, about one-quarter of bone malignancies are osteosarcomas.

Among new cases, there is a clear peak in incidence in the second decade of life; beyond the age of 70, the incidence rises slightly again. The overall slightly higher incidence among males (at a ratio of 1.2:1) is primarily due to the significantly higher rates of the disease among those

aged 15 to 24 (Figure 1). The median age at diagnosis is therefore 31 years for men, slightly lower than for women (34 years).

About half of the cases involve the long bones of the lower extremities, although this proportion exceeds 75% in children and adolescents and declines significantly with age. The relative 10-year survival rates exceed 70% for both children and adolescents as well as young adults (up to age 39) and decline significantly in middle and older adulthood (Figure 2).

Figure 1: Annual incidence rates of osteosarcoma in Germany by age and sex (per 100,000 people, 2019–2023)

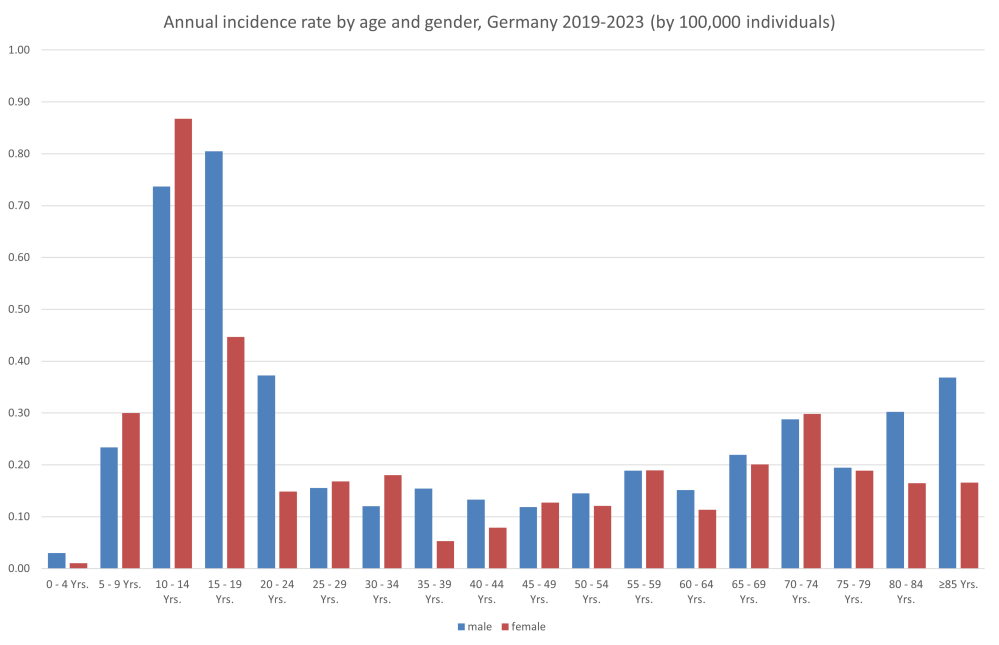
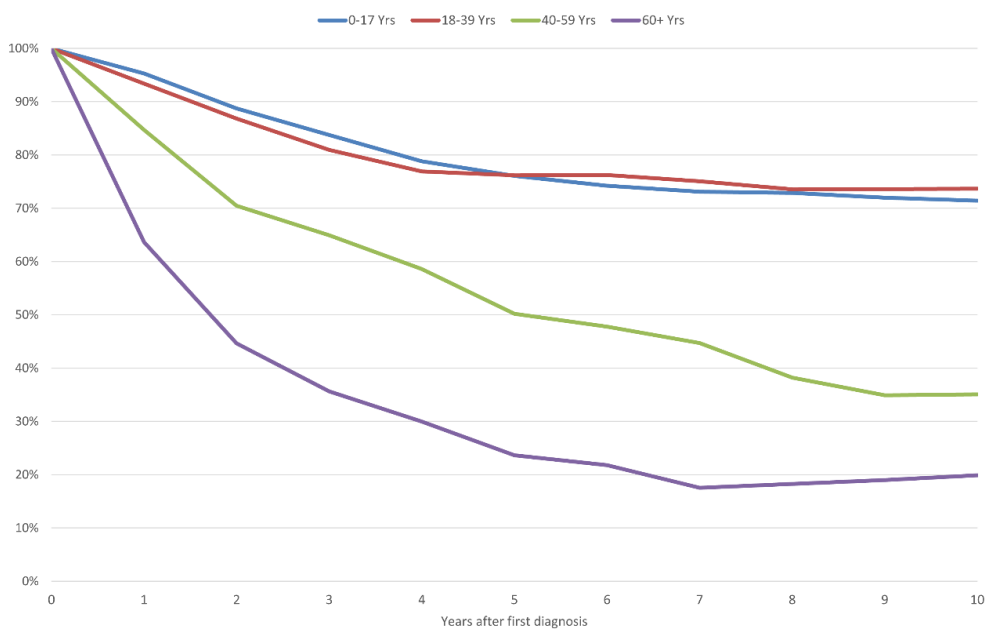


Figure 2: Relative survival rates after diagnosis of osteosarcoma in Germany, by age group, 2014–2023[1]



Legend:

[1] *Results for the 0–17 age group provided by the German Childhood Cancer Registry*

2.3 Pathogenesis

Osteosarcoma is a typically highly aggressive bone-specific sarcoma that originates from pluripotent mesenchymal progenitor cells. Conventional osteosarcomas are mostly characterized by high genomic instability with a complex karyotype and numerous numerical and structural aberrations [8]. Alterations in *TP53, RB1, NF2, PTEN*, and *ATRX* are among the most common recurrent alterations, but they are not specific. Approximately 80% of osteosarcomas also exhibit alterations that are found in cancers with defects in the homologous recombination repair system [9].

2.4 Risk Factors

- Several risk factors for the development of osteosarcoma are known:
- Radiation therapy (typical time interval 12–16 years)
- Chemotherapy (especially alkylating agents)
- *Paget's* disease (in patients over 40 years of age)
- Genetic predisposition syndrome (e.g., TP53 mutation in Li-Fraumeni syndrome, RB1 mutation in retinoblastoma, alterations in various RECQ helicases in Bloom syndrome, Werner syndrome, Rothmund-Thomson syndrome).

For patients with osteosarcoma, genetic counseling and TP53 germline testing should be performed before initiating potentially genotoxic therapies. If a TP53 germline variant is confirmed, radiation therapy should be avoided whenever possible or used only after an interdisciplinary risk-benefit assessment (increased risk of radiation-induced secondary malignancies) [69].

3 Prevention and Early Detection

There is no evidence for effective measures for prevention and early detection in the general population. Exceptions are individuals with a known hereditary predisposition.

4 Clinical characteristics

The leading symptom is pain in the affected region that is often persistent for weeks, progressive, and unrelated to physical exertion. Additionally, swelling or functional impairment may occur. In approximately 10% of cases, a pathological fracture is already present at the time of diagnosis [10]. General symptoms such as fever, weight loss, or a deteriorated general condition usually do not occur. In cases of osteosarcoma in the jaw region, loosening of the teeth and swelling may be early symptoms. In approximately 10–20% of patients, macrometastases can already be detected on imaging at the time of initial diagnosis. The most common target organ is the lung, followed by the bones. In the remaining 80–90% of patients, micrometastasis must be assumed at the time of initial diagnosis. The detection of metastasis at initial diagnosis results in a poorer prognosis [11].

5 Diagnosis

5.1 Diagnostics

A thorough medical history and complete physical examination form the basis of rational diagnosis. The following diagnostic measures are recommended (see Tables 1, 2, and 3).

Table 1: Diagnostics for Newly Emerged Symptoms

• X-rays of the affected bone and adjacent joints in two planes
• Magnetic resonance imaging (MRI) of the local findings according to a standardized protocol ◦ *Note: During the initial diagnostic workup, the MRI must include a T1-weighted image of the entire tumor-bearing bone in the long axis to detect or rule out skip lesions. Subsequently, a high-resolution coil should be used to image the tumor along with the adjacent joint (small field of view) in order to accurately depict local tumor spread. The slice orientation in the long axis is determined by the anatomy of the adjacent joint (coronal for the hand, shoulder, and hip joints; sagittal for the knee and ankle joints). The following pulse sequences must be performed at a minimum:* ▪ *Long axis: STIR, T1-weighted before and after IV contrast administration (including image subtraction)* ▪ *Short axis: T2-weighted, T1-weighted with fat suppression after IV contrast administration*
• Biopsy ◦ *Note: The biopsy can be performed either as a punch biopsy or as an open biopsy. It is important that sufficient material is obtained and that a surgeon experienced in bone sarcoma therapy is involved in the diagnostic process from the outset. If the suspected diagnosis of osteosarcoma is confirmed by biopsy, staging is indicated (see Table 2). It is based on the most common sites of metastasis in patients with osteosarcoma.*

Table 2: Staging

• Computed tomography (CT) of the thorax
• Bone scan or, alternatively, whole-body FDG-PET/CT, FDG-PET/MRI, or whole-body MRI to detect bone/bone marrow metastases, including skip lesions (if available). For osteoblastic tumors, bone scan or FDG-PET/CT is preferred.

Table 3: Further Diagnostics

Laboratory
• Complete blood count and leukocyte differential • Serum chemistry (including AP and LDH) • Coagulation • Virology (Hepatitis A–C, HIV)
Functional diagnostics
• Echocardiography, ECG • Creatinine clearance • Audiometry • Pulmonary function testing for pulmonary metastases

There are no specific laboratory parameters for osteosarcoma.

Instrumental functional diagnostics are used to assess the patient's ability to undergo treatment prior to chemotherapy and to evaluate organ toxicity during chemotherapy. For patients who still require genetic counseling, fertility-preserving measures should be discussed and implemented at an early stage [72].

5.2 Classification

5.2.1 Histological subtypes

Histological classification is based on the current WHO classification for soft tissue and bone tumors (2020). Most osteosarcomas are high-grade tumors (G3); forms with intermediate (G2) or low malignancy (G1) also occur (see Table 4). The most common are high-grade conventional osteosarcomas (80–90%), which arise within the bone marrow cavity (intramedullary). Parosteal and periosteal osteosarcomas originate from the bone surface. Extraskeletal osteosarcomas are classified as soft tissue sarcomas according to the WHO classification. Multifocal osteosarcoma may rarely occur. In such cases, it can be difficult to distinguish whether the lesions represent multiple, synchronous, primary osteosarcoma foci or metastases. Secondary osteosarcomas occur, for example, in the context of Paget's disease of bone or following radiation therapy and will be listed as a separate entity in the upcoming WHO classification.

Table 4: WHO Classification of Osteosarcomas 2020 (modified)

Grade of malignancy	Osteosarcoma subtype
Grade 1 (low-grade)	• Periosteal osteosarcoma • Low-grade central osteosarcoma
Grade 2 (intermediate)	• Periostal osteosarcoma
Grade 3 (high-grade)	• Osteosarcoma with the following subtypes: ◦ Conventional osteosarcoma* ◦ Telangiectatic osteosarcoma ◦ Small-cell osteosarcoma ◦ High-grade superficial osteosarcoma

Legend:
** In conventional osteosarcoma, osteoblastic, chondroblastic, and fibroblastic types are distinguished based on histological patterns. The WHO classification additionally identifies morphological variants of conventional osteosarcoma, including osteoblastoma-like OS, chondroblastoma-like OS, sclerosing OS, epithelioid OS, giant cell-rich OS, chondromyxoid fibroma-like OS, and undifferentiated pleomorphic sarcoma-like OS.*

5.2.2 Staging

The classification of the extent of the primary tumor and metastasis is based on the TNM criteria of the American Joint Committee on Cancer (AJCC) (see Table 5).

Table 5: TNM Classification of Osteosarcoma

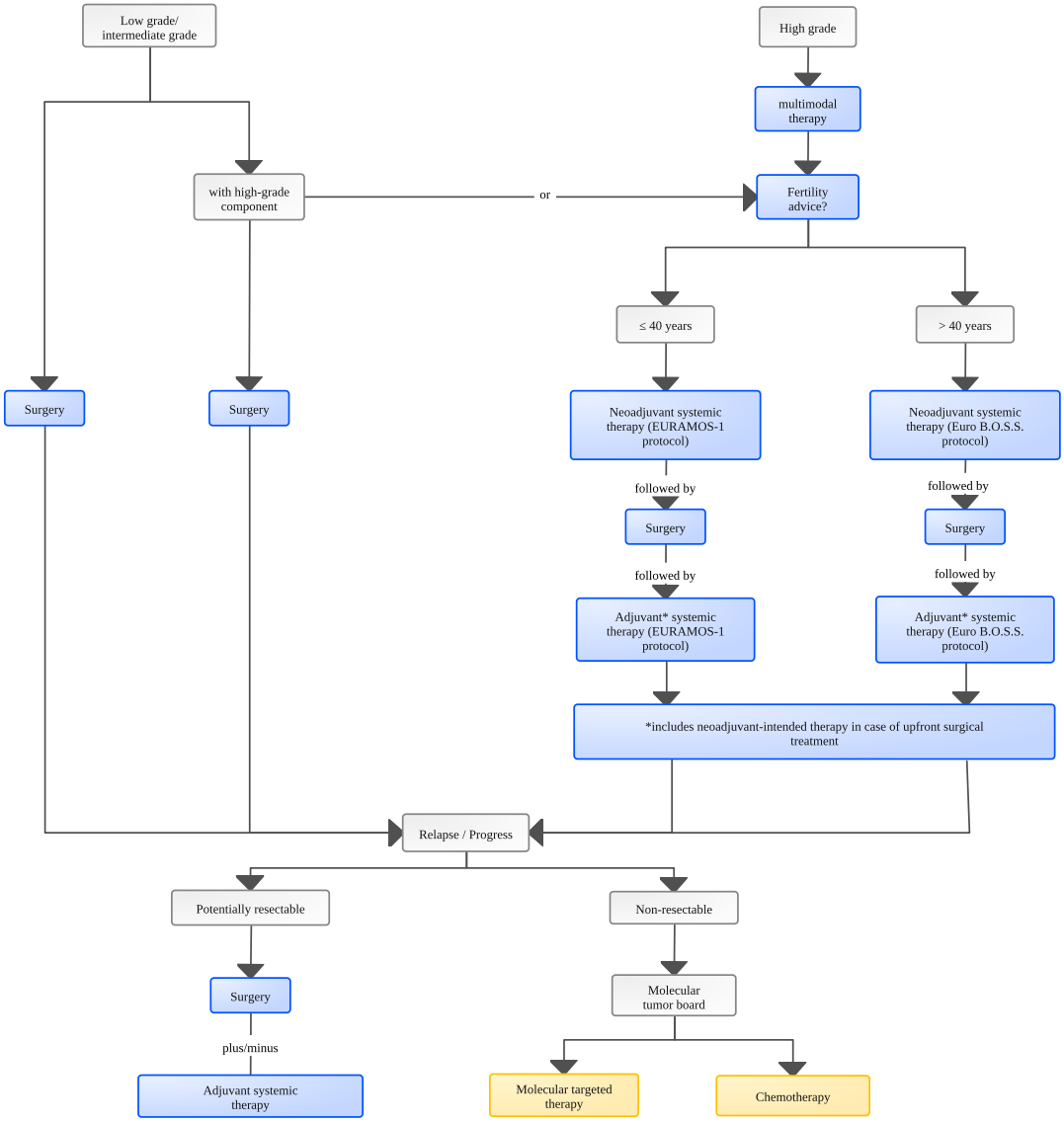
T-Primary tumor			
T1:	≤ 8 cm		
T2:	> 8 cm		
T3:	Discontinuous tumors within the same bone (skip metastases)		
N (regional lymph nodes)			
N0:	No lymph node metastases		
N1:	Regional lymph node metastases		
M (distant metastases)			
M0:	No distant metastases		
M1a:	Metastases only in the lungs		
M1b:	Metastases in other sites (± lungs)		
Staging (simplified according to AJCC)			
IA	T1	N0 M0	G1/GX Low-grade
IB	T2, T3	N0 M0	G1/GX Low-grade
IIA	T1	N0 M0	G2, G3 High-grade
IIB	T2	N0 M0	G2, G3 High-grade
III	T3	N0 M0	G2, G3 High-grade
IVA	any T	N0 M1a	Any G
IVB	every T	N1 or M1b	Any G

6 Therapy

6.1 Treatment structure

The treatment plan for patients with osteosarcoma should be determined by an interdisciplinary tumor board at a center with experience in treating osteosarcoma patients. Since subclinical metastasis must be assumed even at the time of initial diagnosis in cases of localized high-grade osteosarcoma, neoadjuvant chemotherapy is typically administered, followed by resection and subsequent adjuvant chemotherapy. If the primary tumor has already been resected, the entire course of chemotherapy is administered as adjuvant therapy. The algorithm for first-line therapy is shown in Figure 3.

Figure 3: Treatment of Osteosarcoma



Legend:
= curative-intent therapy, = palliative therapy
**also includes neoadjuvant therapy if primary surgery has been performed*

6.1.1 First-line therapy

6.1.1.1 Low-grade osteosarcomas

For low-grade osteosarcomas (periosteal and low-grade central osteosarcoma), treatment is primarily surgical due to the low potential for metastasis. However, if a high-grade component (dedifferentiation) is detected, chemotherapy may be considered [12]. Smaller areas of dedifferentiation in low-grade central osteosarcoma do not yet constitute a clear indication for chemotherapy [13].

6.1.1.2 Periostial osteosarcoma

In patients with periosteal osteosarcoma (intermediate risk), the benefit of chemotherapy has not been demonstrated [13, 14, 15].

6.1.1.3 High-grade osteosarcoma

6.1.1.3.1 Chemotherapy

The importance of chemotherapy for high-grade osteosarcomas starting at the time of the primary diagnosis is undisputed. Although no survival benefit has been formally demonstrated for the combination of neoadjuvant and adjuvant chemotherapy compared to adjuvant chemotherapy alone [16], neoadjuvant/adjuvant chemotherapy is preferred. The histopathological response to neoadjuvant chemotherapy is considered an important prognostic factor. It has been shown that the 5-year survival rates for patients with a good histopathological response (>90% necrosis rate) are significantly higher than for patients with a poorer response (50–90% or <50% necrosis rate) [6, 19, 21]. Retrospective case series also suggest that a good histological response is associated with an increased likelihood of limb-sparing resections as well as improved local tumor control [35, 57].

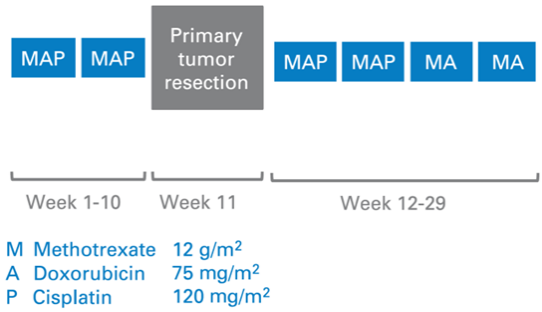
Doxorubicin, cisplatin, high-dose methotrexate (HD-MTX), and ifosfamide have demonstrated antitumor efficacy in osteosarcoma and are used as part of first-line therapy. Different chemotherapy regimens are recommended depending on the patient's age. HD-MTX at a dose of 12 $^{g/m^2}$is used as standard only in younger patients (≤ 40 years) due to its higher toxicity and is replaced by ifosfamide in older patients. In cases of poor response to therapy, there is the option of supplementing HD-MTX with a slightly lower dose of 8 $^{g/m^2}$ in older patients (see below). Retrospective data have shown that the time interval between tumor resection and the start of adjuvant chemotherapy influences the prognosis [22]. Adjuvant chemotherapy should therefore, if possible, be initiated within 21 days of resection. Patients in whom metastasis is already detected at initial diagnosis have a poorer prognosis than patients with locally confined disease. Lung metastases are associated with a more favorable prognosis compared to bone metastases. Nevertheless, even in these patients, long-term survival rates of 10–50% can be achieved through the use of multimodal therapy combining chemotherapy and resection (primary tumor and metastases) [23, 25]. Regarding the choice of chemotherapy, patients with primary metastasis are treated in the same manner as patients with localized osteosarcoma.

6.1.1.3.1.1 Patients ≤ 40 years

Treatment is administered in accordance with the standard arm of the EURAMOS-1 protocol using HD-MTX (12 $^{g/m^2}$), doxorubicin, and cisplatin (MAP chemotherapy; Figure 4). The first 2 cycles of MAP are administered neoadjuvantly. Postoperatively, 2 additional cycles of MAP are

followed by 2 cycles of HD-MTX and doxorubicin (MA). Additions or intensification of chemotherapy based on histological response within the EURAMOS-1 study did not result in improved treatment outcomes but did contribute to increased toxicity [10, 26, 27].

Figure 4: MAP chemotherapy protocol



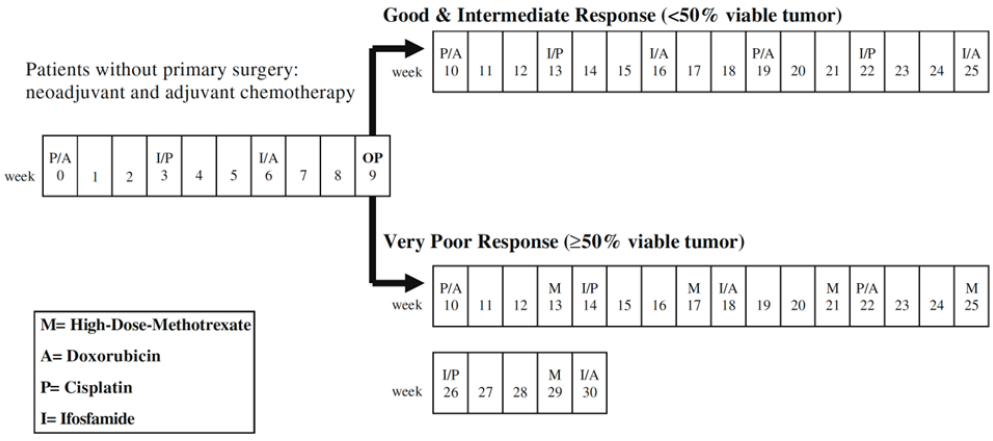
In cases of contraindications to anthracyclines (e.g., pre-existing cardiac conditions, reaching the cumulative dose limit due to prior treatments), the French M-EI regimen (HD-MTX – etoposide/ifosfamide) offers an alternative [59, 70].

Based on the results of a randomized American study, which demonstrated a benefit for overall survival (OS) following the addition of the immunomodulator liposomal muramyl tripeptide phosphatidyl ethanolamine (L-MTP-PE) to postoperative chemotherapy, this was approved in combination with chemotherapy for the treatment of completely resected, localized osteosarcoma patients < 30 years in Europe (but not in the United States) [28]. However, according to various European and American osteosarcoma groups, these data are insufficient to recommend the routine use of this substance outside of controlled trials due to a complex study design [29].

6.1.1.3.1.2 Patients > 40 years

Due to the poorer tolerability of high-dose MTX in this age group, treatment is administered in accordance with the Euro-B.O.S.S. protocol using doxorubicin, cisplatin, and ifosfamide (Figure 5) [30]. A poor histological response is also considered a negative prognostic factor in older patients. The addition of HD-MTX at a reduced dose (8 g/m²) offers an additional option in this case (< 50% necrosis or Salzer-Kuntschik grade 5–6); however, an independent prognostic benefit of this addition cannot be assessed due to the study design [30].

Figure 5: Euro-B.O.S.S. protocol



6.1.1.4 High-grade craniofacial osteosarcomas/jaw osteosarcomas

Although the risk of distant metastasis is considered somewhat lower, the treatment of high-grade craniofacial osteosarcomas/jaw osteosarcomas should be conducted in a manner analogous to that of high-grade osteosarcomas in other locations [7]. The prognosis in combination with pre- and/or postoperative chemotherapy is considered good [30, 33].

6.2 Local therapy

6.2.1 Surgery

Surgery should be performed exclusively by surgeons experienced in bone sarcoma surgery who are also proficient in the necessary reconstructive procedures. Achieving an R0 resection is the defined goal of the surgery. In most cases, a limb-sparing approach is possible for osteosarcomas of the extremities and pelvis. The goal should be to perform the osteosarcoma biopsy at the same center where the subsequent tumor resection will take place. A large retrospective analysis of data from the Cooperative Osteosarcoma Study Group (COSS) showed that the risk of local recurrence after a biopsy performed outside the center is more than twice as high as when the biopsy is performed at the center [35]—a shocking finding when one considers that the development of a local recurrence is associated with a dramatic decline in the probability of survival. The same analysis further underscored the importance of treating patients at experienced centers, as limb-sparing surgery was achieved in 70% of patients at high-volume clinics, compared to 51% at low-volume clinics [35]. These limb-sparing rates are now outdated; today, >90% of resections are performed with limb-sparing intent [64]. Depending on the extent of bone destruction, particularly in the long bones, there is a risk of pathological fracture [35], which is slightly increased following open biopsies in particular. To reduce the risk of pathological fractures in the long bones during neoadjuvant chemotherapy, temporary partial unloading or even complete unloading of the affected lower extremity through a may be advisable.

However, unloading is also associated with muscle atrophy and secondary osteopenia, so it cannot be recommended across the board. Since no risk score exists for the development of pathological fractures, the question of whether partial or complete unloading is necessary should be discussed individually with the orthopedic surgeon or trauma surgeon performing the primary biopsy.

In the case of a pathological fracture, internal osteosynthesis should be avoided prior to oncological resection due to the risk of tumor seeding. External splinting or immobilization is preferred. A pathological fracture does not necessarily constitute an indication for amputation. Primary neoadjuvant chemotherapy may be used to reduce the extent of the fracture hematoma and subsequently allow for a wide, limb-sparing resection including the affected soft tissues [67].

Given the frequent metaphyseal location of osteosarcoma in the extremities, defect reconstruction using tumor endoprostheses is the predominant approach. Advantages include rapid return to full weight-bearing on the affected extremity and good functional outcomes. In a historical cohort, the failure rate for all locations was 24.5% [61].

The most common reason for secondary amputation is local recurrence (63%), followed by periprosthetic infection (34%) [36]. In very young patients (< 5 years), the amputation rate is significantly increased due to limited reconstruction options. For osteosarcomas in the femur and proximal tibia in young patients, reverse plasty is a sensible alternative to amputation or the implantation of growth-adjustable prostheses in slightly older children. Reverse plasty is generally a one-time surgical procedure. With the appropriate prosthetic fitting, patients are functionally and emotionally virtually on par with the general population [37].

6.2.2 Radiation therapy

Radiation therapy may be considered for primary tumors that are initially unresectable or as adjuvant therapy in cases of high risk of local recurrence and when R0 resection is not feasible. Osteosarcoma is considered relatively radiation-resistant. Therefore, modern, highly conformal radiation therapy techniques such as IMRT or particle therapy with protons or heavy ions should be considered, particularly when curative intent is the goal, in order to achieve high local doses while sparing healthy tissue as much as possible. Although the evidence for radiation therapy is limited and is based primarily on results from retrospective, non-randomized studies with small case numbers and often heterogeneous cohorts, these findings support the role of radiation therapy [4, 58, 60, 65]. In the case of an R0 resection, there is no indication for adjuvant radiation therapy. Radiation therapy can also be used in a palliative treatment approach as an alternative to Surgery and on a symptom- or need-based basis for the treatment of metastases.

6.2.3 Local treatment of metastases

Treatment of patients with primary metastatic osteosarcoma can follow the same principles as for patients without metastasis. For patients with exclusively pulmonary metastases, in whom all lesions could be surgically removed, the 5-year survival rate was 44%. If other regions were also affected, the 5-year survival rate was only 19% [38]. For palliative treatment of metastases in cases of fracture risk or pain, local radiation therapy may be considered. Since L-MTP-PE (mifamurtide) did not result in any survival benefit in this patient group, it should not be used outside of clinical trials in this setting either [39].

6.3 Special Situations

6.3.1 relapse

Treatment in the event of a relapse or metastasis depends on the time interval since primary therapy as well as on the number and location of the metastases [38]. It should also be considered whether radiation therapy was already administered during primary therapy. For example, a disease-free interval > 18–24 months, ≤ 2 lung metastases, and unilateral pulmonary involvement without pleural involvement are considered favorable prognostic factors. Treatment should preferably be performed at an experienced center.

6.3.1.1 Potentially resectable disease

Treatment is primarily surgical, provided that complete removal of the local relapse and/or metastases can be achieved. Approximately one-third of patients survive longer than 5– -years after a second surgical remission [40]. This also applies to recurrent relapses. If surgery is not possible, alternative procedures such as (stereotactic) radiotherapy, radiofrequency ablation (RFA), or cryotherapy can be used to treat lung metastases [7]. RFA and (stereotactic) radiotherapy can also be used as options for treating bone metastases [41]. The role of repeat adjuvant chemotherapy after achieving a second surgical remission is not clearly established. Retrospective analyses exist that show either no benefit, a benefit only in a subgroup (e.g., patients with ≥ 3 lung metastases), or a small benefit [38, 40, 42]. We recommend considering second-line chemotherapy in patients with early relapse (within 12 months), multiple metastases (≥ 3 lung metastases), or pleural involvement, in addition to resection of all manifest tumor foci. The agents used include carboplatin and etoposide, high-dose ifosfamide alone or in combination with etoposide, gemcitabine and docetaxel [43, 45], as well as cyclophosphamide and topotecan [46]. Based on current knowledge, patients with a late, solitary pulmonary relapse do not benefit from additional salvage chemotherapy [47]. Further treatment in the

form of maintenance therapy is not part of the standard of care during second complete remission.

6.3.1.2 Unresectable disease

In patients with unresectable local recurrence or extensive metastasis, treatment is provided with palliative intent. For these patients, referral to a molecular tumor board should be considered (see below). Depending on the patient's general condition and previous chemotherapy, the same treatment regimens as described in Chapter 6.3.1.1 may be considered. In addition to classic chemotherapies, the use of targeted agents (alone or in combination) for which a prolongation of the progression-free interval has been observed in Phase I/II studies may also be considered (e.g., sorafenib with or without everolimus [48, 49], gemcitabine/sirolimus [50], regorafenib [51, 52], cabozantinib [53].

For regorafenib, randomized Phase II data are available for metastatic, previously treated osteosarcoma showing significantly prolonged progression-free survival (PFS) compared to placebo. A significant OS benefit was not demonstrated in the available data. Additionally, data from 2025 on regorafenib as maintenance therapy following doxorubicin-based therapy showed a PFS benefit (the study was not powered to detect an OS benefit). In a single-arm Phase II study in patients with previously treated, advanced osteosarcoma, cabozantinib demonstrated a clinically relevant 6-month non-progression rate of 33%. Activity was confirmed in a multicenter real-world cohort published in 2023 (median PFS in the range of a few months). These agents remain off-label/individualized options and should preferably be used within the context of clinical trials or following a multidisciplinary/molecular tumor board decision [52, 62, 63, 66].

6.3.1.3 Molecular profiling/rare targets

Current studies are also examining the use of immune checkpoint inhibitors (ICIs) in patients with advanced or metastatic osteosarcoma. If microsatellite instability (MSI-H), mismatch repair deficiency (dMMR), or a high tumor mutation burden (TMB-H) is detected, treatment with pembrolizumab or with nivolumab/ipilimumab. In cases of unresectable/metastatic disease, expanded molecular profiling (e.g., NGS-based tumor profiling, including fusion diagnostics) should be considered to identify rare alterations that may be amenable to targeted therapy (e.g., NTRK fusions; overall very rare in bone tumors). Therapies with appropriate targeted agents (e.g., TRK inhibitors for NTRK fusions) should preferably be administered in this setting within the framework of clinical trials or following a tumor board decision [63, 68].

7 Rehabilitation

Surgery, radiation therapy, and systemic tumor therapy can lead to treatment-related complications of varying severity that require targeted rehabilitative measures. Added to this are the specific psychological and social impacts of cancer in adolescents and young adults. Patients should be informed at an early stage about the options for outpatient and inpatient rehabilitation measures as well as other entitlements arising from social welfare law. Regarding the choice of rehabilitation clinic, the patient's wishes should be taken into account (§9 SGB IX). Nevertheless, a recommendation should be made for a clinic with an oncology focus that also has specific experience with the age group of patients with osteosarcoma. Furthermore, experience with patients following major tumor surgeries of the skeletal system is advisable to ensure targeted physical therapy.

8 follow-up

The goal of follow-up care is the early detection of local recurrence or metastasis, with the possibility of initiating specific therapy, as well as the assessment of long-term effects of the therapy. Follow-up care (Table 6) includes a physical examination, a chest X-ray or, alternatively, a low-dose chest CT (HR-CT), a conventional X-ray and MRI of the primary tumor region, as well as assessment of long-term effects. Imaging intervals are every 3 months for the first 2 years, every 6 months from the 3rd to the 5th year, and annually thereafter for at least 10 years following the primary diagnosis [73]. In cases of suspected recurrence, an FDG-PET/CT or FDG-PET MRI may be helpful in individual cases [67]. In cases of confirmed Li-Fraumeni syndrome, structured follow-up is performed, including regular whole-body MRI examinations [71].

Table 6: Follow-up Protocol

Modality	**Time/Interval (months)**		
	0–24	**24–60**	**>5 years**
	Every 3 months	**Every 6 months**	**Once a year**
Chest X-ray or HR-CT of the chest	x	x	x
X-ray of primary tumor region	x	x	x
MRI of the primary tumor region	x	x	x

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15 Disclosure of Potential Conflicts of Interest

according to the rules of DGHO, OeGHO, SGH+SSH, SGMO

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