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Recommendations in management of head and neck sarcomas

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Oncology in Clinical Practice
2018, Vol. 14, No. 6, 295–301
DOI: 10.5603/OCP.2018.0043
Translation: dr n. med. Dariusz Stencel
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ISSN 2450–1654

ABSTRACT

Sarcomas of the head and neck are rare malignant tumours with incidence 2% of head and neck cancers, 30% of all sarcomas in children and 4–10% of sarcomas in adults. The most common sarcoma in children is rhabdomyosarcoma (RMS) and Ewing sarcoma (ES), in contrary in elderlies there is angiosarcoma; osteosarcoma and chondrosarcoma are the most common bone tumours in head and neck. The typical symptoms are: painless tumour in the head and neck region, difficulty with speaking, hoarseness, dysphagia, nasal obturation, or dysfunction of cranial nerves. The key point of diagnostics is magnetic resonance and computed tomography of the primary tumour. The treatment of patients with sarcoma should be carried out in referral centers, where experienced multidisciplinary team proceed the surgical removal of a primary tumour with reconstructive surgery as well as perioperative systemic therapy (in selected cases). The recommendations were developed by the Head and Neck Sarcoma Group of the Polish Registry of Bone Tumors.

Key words: sarcoma, reference center, multidisciplinary treatment

Oncol Clin Pract 2018; 14, 6: 295–301

Introduction

Head and neck sarcomas (HNS) are rare malignant neoplasms, constituting about 2% of all head and neck cancers, 30% of all sarcomas in children, and 4–10% of sarcomas in adults [1–3]. Data on the prevalence of HNS from American registers (no Polish data) indicate that in the US about 1000 new cases of HNS are diagnosed annually, and the median age of onset is 55–65 years [4]. In children the most common are sarcomas derived from striated muscles — rhabdomyosarcoma (RMS) and Ewing sarcomas (ES). The median age of patients with RMS is 12 years, out of which in about 75% of cases the location of the tumour concerns the epidural and/or orbital area. The median age of Ewing sarcoma patients is 18 years, and the etiology of cancer is unknown. Additionally, in young patients 5% of diagnoses are non-RMS tumours. In the elderly, angiosarcoma (median age: 70 years) most commonly occurs, which is usually located within the skin [5, 6].

Histologically, soft tissue HNS are divided into pleomorphic sarcomas (38%) and less common subtypes, which include: liposarcoma, fibrosarcoma, angiosarcoma, leiomyosarcoma, synovial sarcoma, Kaposi's sarcoma, and malignant peripheral nerve sheaths tumours (MPNST). Synovial sarcoma occurs much less frequently in the region of the head and neck — mainly axial/limb location develops; however, the synovial sarcoma of the head and neck region is characterized by a more aggressive course [7–9].

The most common HNS from bone are osteosarcoma and chondrosarcoma. In children, osteosarcoma of the head and neck account for about 4.8–8% of all diagnoses and most of all relates to the maxillary location in younger children, and the mandible in older children [10].

Most HNS develops *de novo*; hence their etiology is unknown. As with other sarcomas, the risk of disease increases in genetic predisposition syndromes, which include Li-Fraumeni syndrome, neurofibromatosis type I, retinoblastoma, as well as previous exposure to irradiation. In patients infected with HIV (human immunodeficiency virus) and herpes virus (human herpes virus 8), the risk of developing Kaposi's sarcoma increases

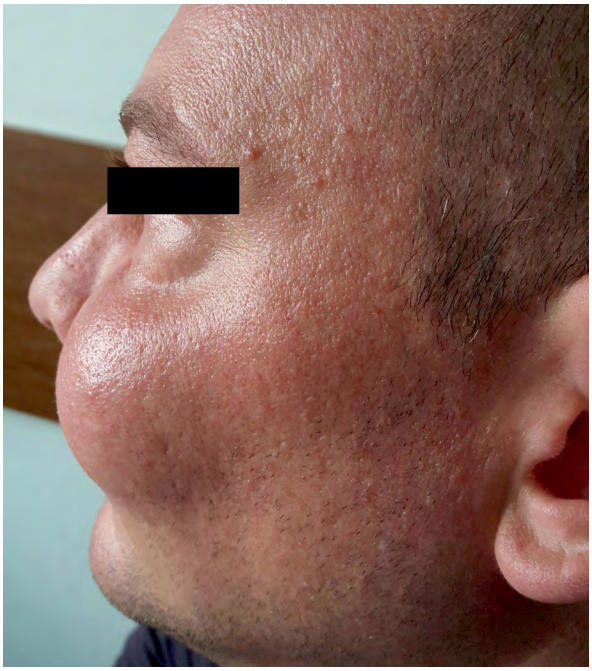

Figure 1. Clinical picture of pleomorphic sarcoma of the left cheek

[11–13], which due to the peculiarity of conduct and the extremely rare occurrence is not the subject of this study.

Clinical picture and diagnostics

The most frequently observed symptom of HNS is a painless tumour in the area of the head and neck (Fig. 1), sometimes accompanied by changes in the skin, and sometimes there are difficulties in speaking, hoarseness, dysphagia, nasal obstruction, or cranial nerve disorders [14–16]. In children, osteosarcoma is quite often confused with a tooth infection. At the time of diagnosis, distant metastases such as bone, lung, or bone marrow are observed in 15–20% of patients with Ewing sarcoma, in contrast to osteosarcoma, where the presence of metastases at the time of diagnosis is extremely rare [17]. Neoplastic involvement of lymph nodes is also relatively rare (about 10% of patients); however, it increases significantly in cases of RMS and angiosarcoma [18].

Physical examination requires inspection of the oral cavity, lymph nodes of the neck, and upper respiratory tract (supplemented by endoscopic examination in locations not available by direct examination). It is also necessary to conduct a neurological examination. Laboratory tests may show elevated levels of alkaline phosphatase and lactate dehydrogenase (LDH).

The basis of diagnostic imaging is magnetic resonance (MR) and computed tomography (CT) of the affected area. Both tests are necessary in the planning of surgical treatment and reconstruction. In order to determine the oncological stage, the diagnosis should include diagnostic imaging of the chest, abdomen, and pelvis. Other imaging tests, such as positron emission tomography (PET) or skeletal scintigraphy, are performed individually in justified cases. PET is justified in RMS and Ewing sarcomas. The recommendations of the Children's Oncology Group Bone Tumor Committee indicate the need for bone scintigraphy and/or PET testing in all children, adolescents, and young adults with osteosarcoma [19].

In order to establish a diagnosis, a cancer biopsy with histological verification performed by a pathologist specializing in the diagnosis of sarcomas is necessary. Due to the fact that the method of collecting the material for histopathological examination may have a key impact on further surgical treatment, it is recommended that the biopsy be planned by an experienced surgical team after evaluation in imaging studies [20].

Staging

In the case of HNS, the modified TNM classification (T —Tumour, N — Lymph nodes, M — Metastases) is used, which differs from the classification dedicated to head and neck squamous cell carcinomas. In the latest eighth classification by the American Joint Committee on Cancer (AJCC), the HNS classification located in soft tissues also differs from the classification used for limb sarcomas (mainly for T feature); details are presented in Table 1 [21]. In the current classification, no prognostic groups are given, and the histological subtype is not taken into account, although it is considered to play an important prognostic role [18]. The above classification is not applicable for angiosarcoma, embryonal and alveolar rhabdomyosarcoma, and for Kaposi's sarcoma.

AJCC classification for bone sarcoma located in the head and neck area is of limited use. In the eighth edition it was included in the classification concerning also cranial and craniofacial cancers; details are presented in Table 2, while staging classification is presented in Table 3 [22].

Prognostic factors and treatment results

HNS are characterized by a higher rate of local recurrences than in sarcomas of a different location. Data on the results of overall survival are ambiguous due to the relative rarity and heterogeneity of sarcomas. Zagars et al. [23] published the results of treatment of 102 patients with HNS and 1044 patients with limb

or axial sarcomas treated in 1960–1999. The basis for treatment of patients was excision of the primary tumour with complementary radiotherapy (RT). Five-year local relapse-free survival (LRFS) was significantly lower in the group of patients with HNS compared to those with sarcomas in other locations (74% *vs.* 85%), as well as the results of tumour-specific overall survival (DSS, disease-specific survival), which were 64% and 76%, respectively. Data from the Surveillance, Epidemiology, and End Results (SEER) database of 12,000 sarcoma patients who were treated between 1973 and 2010 showed comparable outcomes in patients with sarcomas in both locations. However, DSS in the group of adult patients was significantly lower than in children (66% *vs.* 73%) [4].

Patients with soft tissue and bone sarcomas of head and neck location significantly more often have distant metastases, and the size of the primary tumour almost always exceeds 4 cm. In the case of head and neck sarcomas, the main factors affecting the survival are the possibilities of radical surgical removal of the tumour, taking into account the risk of significant mutilation. In the group of 146 patients with HNS located near the base of the skull, the five-year overall survival was 77%, 43%, and 36%, respectively, in the case of R0 resection with a margin of > 1 mm, R0 with a margin of < 1 mm, and resection R1/2 [16]. In this group, the surgical mar-

Table 1. TNM classification of soft tissue sarcomas located in the head and neck area. Source: AJCC Cancer Staging Manual, 8th edition (2017), Springer International Publishing

Primary tumour (T)	
Tx	Primary tumour cannot be assessed
T1	Primary tumour ≤ 2 cm
T2	Primary tumour > 2 do ≤ 4 cm
T3	Primary tumour > 4 cm
T4a	Primary tumour infiltrates the orbital cavity, the base of the skull, the craniofacial bones, the wing muscles, and the parapharyngeal space with large vessels
T4b	Cancer infiltrates brain tissue, the internal carotid artery, pre-vertebral muscles, or central nervous system by perineural spread
Regional lymph nodes (N)	
N0	Regional lymph nodes cannot be assessed or no locoregional lymph node metastasis
N1	Locoregional lymph node metastasis
Distant metastasis (M)	
M0	Distant metastases — absent
M1	Distant metastases — present

Table 2. TNM classification of osteosarcomas located in the area of the head and neck. Source: AJCC Cancer Staging Manual, 8th edition (2017), Springer International Publishing

Primary tumour (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Primary tumour ≤ 8 cm
T2	Primary tumour > 8 cm
T3	Infiltration of adjacent bones and metastases "leaping" within the original bone
Regional lymph nodes (N)	
N0	Regional lymph nodes cannot be assessed or no locoregional lymph node metastasis
N1	Locoregional lymph node metastasis
Distant metastasis (M)	
M0	Distant metastases — absent
M1a	Metastases to the lungs
M1b	Metastases to bones and other organs

Table 3. Classification of the stage of osteosarcoma located in the area of the head and neck. Source: AJCC Cancer Staging Manual, 8th edition (2017), Springer International Publishing (G — histological grade)

Primary tumour (T)	Lymph node (N)	Metastases (M)	Histological malignancy grade	Stage
T1	N0	M0	G1 or GX	IA
T2	N0	M0	G1 or GX	IB
T3	N0	M0	G1 or GX	IB
T1	N0	M0	G2 or G3	IIA
T2	N0	M0	G2 or G3	IIB
T3	N0	M0	G2 or G3	III
Any T	N0	M1a	Any G	IVA
Any T	N1	Any M	Any G	IVB
Any T	Any N	M1b	Any G	IVB

gin was the only and the most important independent prognostic factor in HNS.

The relationship between higher risk of locoregional recurrence and the size of the primary focus (> 10 cm) (HR, hazard ratio — 6.13, 95% CI 1.84–20.5) as well as with higher histological malignancy (HR for death 5.52, 95% CI 1.51–20.21) was confirmed [18]. In adult patients, unfavourable prognosis is associated with the following histological subtypes: fibrosarcoma, pleomorphic sarcomas (five-year results of treatment are 60–70%) and MPNST, osteosarcoma, and angiosarcoma (five-year treatment results are 50%). In children with RMS, the factors of poor prognosis are unfavourable histopathology (alveolar subtype), II and III group according to the IRS, unfavourable location (e.g. orbital location with bone infiltration, epidural, limb, bladder, or prostate tumours), tumour size greater than 5 cm, age over 10 years, metastases to the lymph nodes, and distant metastases. Although RMS in children is an aggressive sarcoma, the survival results are 75% due to combination therapy [24].

General principles of management

Treatment of patients with head and neck sarcomas should be performed in reference centres due to the need for a multidisciplinary approach based on the surgical removal of the primary tumour, often with reconstructive surgery and post-operative supportive care. The team of specialists looking after patients with HNS should be a maxillofacial surgeon, ENT specialist, neurosurgeon, clinical oncologist, radiotherapist, plastic surgeon, oncology surgeon, and a child surgeon. Physiotherapists, a speech and swallowing therapist, dietitian, physiotherapist, and psychologist also play important roles in the treatment process.

The basis for the radical treatment of adult patients with HNS is radical surgery with a margin of healthy tissue > 5 mm in soft tissues and at least 2 cm in bone. In most cases, the maintenance of the above margins is difficult due to the anatomical complexity of the craniofacial structures and difficulties in precise histological interpretation of the surgical material [25]. Nevertheless, the desire for radical resection (R0) is the most important goal of the surgeon in HNS resection. In the case of extensive tissue defects after HNS resection, simultaneous reconstructive treatments with the option of using vascularised flaps from distant parts with microsurgical vascular anastomosis, 3D modelling of bone reconstruction, and the use of other reconstruction techniques to improve the radicality of treatments and achieve a better aesthetic and functional effect are necessary. An additional limitation of the extent of the resection is the need to maintain important activities dependent on head and neck organs, i.e. breathing, chewing, swallowing, speech, and sight. Distortions of the face and head after treatments have a severe impact on the quality of life. Due to the rare occurrence of regional metastases, elective removal of non-enlarged neck lymph nodes is not recommended.

In the case of enlargement of the lymph nodes of the neck above 1 cm, a selective treatment is recommended, limited only to the anatomical group of the nodes in which neoplastic lesions were found.

In the case of soft tissue sarcomas, radiotherapy has broad indications as a complementary treatment for surgery. It should always be used when the safe margin is not precisely defined or when it is < 5 mm in the soft tissue area. Radiation therapy is also used in the case of chondrosarcomas with R1 or R2 resection. The total irradiation dose should be 66–70 Gy under conventional fractionation conditions. Due to frequent proximity of critical organs, especially in tumours around the base of the skull, there are preferences for proton radiotherapy. The use of radiotherapy has a dubious effect on overall survival [4], but it significantly improves local cure, especially in the case of R1 resection [26–28]. Radiotherapy can also be used as an exclusive treatment in some inoperable cases of soft tissue sarcoma (in the absence of features of skin invasion, subcutaneous tissue, and critical organs). The wider application of radiotherapy concerns small cell sarcomas (RMS in embryonic form, Ewing sarcomas). Irradiation is also the treatment of choice for advanced, inoperable chondrosarcomas located above Ohngren's line (preference for proton radiotherapy). In these cases, a total dose of 70 Gy should be applied under conventional fractionation conditions (2 Gy 5 × weekly), which is often difficult due to the immediate proximity of critical organs. Radiotherapy is not routinely used for osteosarcoma.

The place of chemotherapy is not conclusive due to the lack of data from randomized clinical trials in this group of patients. In the case of soft tissue sarcomas of limbs, the results of meta-analysis justify the use of complementary chemotherapy in sarcomas with a higher degree of histological malignancy, also in the context of local cure. The chemotherapy regimen should be adapted to the sarcoma subtype. For this reason, in selected clinical situations in high-risk HNS from soft tissues it is justified to use complementary chemotherapy (also neoadjuvant) to reduce the risk of local recurrence of disease or to induce a response before the planned surgery. If chemotherapy is used in the neoadjuvant sequence, the early (within 2 second course), assessment of the therapeutic response is critically important. If there is no answer, patients should be operated immediately. Wider, routine indications for chemotherapy as a component of combination therapy exist in small cell sarcomas (RMS embryonic form, Ewing sarcomas) as

recommended for locations in other regions. Induction chemotherapy as well as complementary surgery can be considered for osteosarcoma. Treatment of patients at the dissemination stage is the same as recommendations for sarcomas located outside the head region.

In children, the treatment of sarcomas of the head and neck area does not differ from the principles of treatment for sarcomas in other locations. Because of long-term complications, radiotherapy in children under one year of age is used only in exceptional cases; its use is possible in justified cases in children between one and three years of age. In this age group the golden standard is preoperative chemotherapy, consecutive surgical treatment, followed by chemotherapy with or without radiation therapy. In some patients (mainly Ewing sarcoma patients) high-dose chemotherapy with subsequent autologous bone marrow transplantation is also applied. The use of preoperative chemotherapy usually leads to a reduction in tumour size, improves the ability to perform a radical operation, and reduces the risk of a mutilating procedure. In children, it is a mistake to perform mutilation procedures at the beginning of treatment.

Osteosarcoma

Osteosarcoma in the area of head and neck organs is most often located in the mandible, less often in the jaw. A tumour is observed clinically, often accompanied by a swelling of the cheek, periodically the patient reports pain, and there may be problems with dentition. Osteosarcoma of the head and neck less commonly gives distant metastasis than osteosarcoma in the limb location [29–31]. After confirming the histopathological diagnosis, *en bloc* excision is recommended with the greatest possible surgical margin and simultaneous reconstruction of the mandible with the vascularized flap, usually fro m the fibula bone. In the case of postoperative confirmation of R1 resection, first of all the possibility of reoperation for the purpose of radicalisation should be considered. If reoperation is impossible or surgical margin after reoperation is still positive, there are indications for postoperative radiotherapy. Based on the results of osteosarcoma treatment with axial or limb location confirming sensitivity to chemotherapy, cisplatin can be added to radiation therapy as a radiosensitiser. In the case of a negative margin, only adjuvant chemotherapy based on anthracyclines and cisplatin is recommended, in accordance with general recommendations (e.g. ESMO) and retrospective analyses. The therapeutic option, like the existing standard for other locations, is neoadjuvant two or three drug chemotherapy (based on doxorubicin with cisplatin) with an early (after two cycles) assessment of the response so as not to overlook the possibility of tumour resection. In the case of low-grade osteosarcoma, the use of adjuvant treatment has limited justification.

In children, the procedure of choice after biopsy is the inclusion of neoadjuvant chemotherapy based on anthracyclines (A; 75 mg/m^2 per course), cisplatin (P; 120 mg/m^2 per course), and methotrexate (MTX, 12 g/m^2 per course). AP courses (every 21 day) are alternatively administered interleaved with a weekly MTX administration in a two-week sequence. After 10 weeks of treatment, an operative procedure is performed, followed by adjuvant chemotherapy based on the same cytostatics. Radiotherapy is not normally used to treat osteosarcoma in children. Sometimes it is applied (currently mainly proton therapy) in cases of a non-radical procedure or lack of the possibility of surgery [32].

Ewing sarcoma

In children, the treatment of Ewing sarcoma is combined — after the biopsy, the first stage of treatment is the administration of multi-drug neoadjuvant chemotherapy containing vincristine, doxorubicin, ifosfamide, and etoposide. Subsequent surgery is performed, followed by adjuvant chemotherapy with or without radiotherapy (RT). In some patients high-dose chemotherapy is additionally used followed by autologous bone marrow transplantation. The type of further chemotherapy, as well as its duration, depends on the result of histopathological examination from the removed primary lesion (percentage of tumour cell necrosis, radicality). As part of surgical treatment, radical operation should be performed according to the oncological evaluation, confirmed by histopathological examination, because it largely determines the final result of the therapy. A good histopathological response means finding, in a histological examination of the primary tumour after induction CHT, over 90% of the dead cells. Poor histopathological response is defined as the presence of less than 90% necrosis in the tumour after pre-operative CHT. Currently, surgical removal of the primary focus as a complementary treatment of chemotherapy and radiotherapy is thought to prolong the survival time. In the absence of the possibility of surgical treatment, after the initial chemotherapy, radiotherapy is applied, and the remaining therapeutic procedures are continued [33].

Chondrosarcoma

Chondrosarcoma occurs less frequently than osteosarcoma, mainly localized in the bones outside the jaw and mandible, in the larynx is the most common sarcoma [33, 34]. Men suffer from chondrosarcoma of the head and neck three times more often than do

women [35]. Histologically 81% of chondrosarcoma are conventional subtype, 10% are myxoid subtype, and 9% are mesenchymal type [36]. The basis for treatment of patients with chondrosarcoma is radical tumour resection. The extent of resection depends on the location and histological malignancy. In the case of chondrosarcoma with low malignancy, the procedure may involve removing the tumour and adjoining parts of the bone [20]. In undifferentiated tumours, it is particularly important to provide a wide bone margin. Due to unfavourable prognosis in the mesenchymal chondrosarcoma subtype, surgical treatment should be supplemented with neoadjuvant or adjuvant multi-drug chemotherapy. Chondrosarcoma, except for the possibility of radical removal, is an indication for radiotherapy — especially proton therapy (this is the therapy recommended by AOTMiT and financed in our country).

Angiosarcoma

Angiosarcoma is an aggressive tumour derived from cells that form blood or lymph vessels. The head and neck region is the most common location of this sarcoma in adult patients. It accounts for about 15% of all head and neck sarcomas and 1% of all soft tissue sarcomas [37, 38]. Angiosarcoma mainly occurs in older patients, with a median age of 65–70 years, with male dominance, and 5–20% of patients have previously used radiotherapy in this location.

In children, angiosarcoma is extremely rare, and the prognosis is poor [39–42]. In the clinical picture there is a blue-purple, ulcerated, bleeding lesion, which can be multifocal, located mainly on the scalp or face, and the disease lasts for several months. Cancerous involvement of lymph nodes takes place in about 10% of cases [43].

As for other HNS, surgical treatment is also the basis for therapy of angiosarcoma patients. Due to the risk of tumour cell infiltration, preoperative or post-operative RT is recommended in almost all patients. Supplementary chemotherapy is used in selected patients, taking into account the risk factors, general condition, and co-morbidities. Pre-operative chemotherapy with taxanes can be used to reduce the tumour mass and increase the chance of radical surgery. The five-year survival rate is about 40%, and is significantly lower than other subtypes of sarcomas due to much more frequent distant metastases [44–46]. The most important unfavourable prognostic factors in angiosarcoma are size > 5 cm, no resection R0, epithelioid subtype, and age over 70 years [47, 48].

In children, the cornerstone of angiosarcoma treatment is radical surgery with or without subsequent radiotherapy. In the case of non-surgical tumours, multi-drug chemotherapy is used, which includes anthracyclines, alkylating drugs, vinca alkaloids, and sometimes taxanes.

Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is mainly found in children; 35–40% of sarcomas are located in the area of the head and neck: 25% in the area of orbital cavity, 50% in the area of the sinuses, nasopharynx, and ears. The most common subtypes of RMS are embryonal RMS (frequent in orbital cavity) and alveolar. Clinical symptoms of RMS include tumour, runny nose, headache, nausea, vomiting, and impaired hearing, vision, swallowing, and breathing, as well as other symptoms resulting from cranial nerve involvement. The prognosis depends on risk factors, including the stage of advancement and the patient's age. The basis of RMS treatment is combination therapy based on surgery, RT, and multi-drug chemotherapy — before and after surgery, which includes drugs similar to angiosarcoma (anthracyclines, alkylating drugs, vinca alkaloids, and sometimes taxanes). In patients with cancer cells in cerebrospinal fluid, simultaneous intrathecal treatment is sometimes used. The duration and type of chemical treatment depends on the presence or absence of the risk factors described above. The use of radiotherapy also dependents on the patient's age. The five-year survival rate in patients with RMS is 50–75%, with the prognosis depending on the stage and age of the patient [24].

This work was developed by the Head and Neck Sarcomas Group of the Polish Bone Tumor Register (grant from the funds for the statutory activity of the Maria Sklodowska-Curie Institute — Oncology Center in Warsaw: *Comparison of the results of treatment of adult patients with Ewing sarcoma with the results of treatment in children, based on data from two reference centres in Poland)*.

References

1. Kraus DH, Dubner S, Harrison LB, et al. Prognostic factors for recurrence and survival in head and neck soft tissue sarcomas. Cancer. 1994; 74(2): 697–702, indexed in Pubmed: 8033050.
2. Hoffman HT, Robinson RA, Spiess JL, et al. Update in management of head and neck sarcoma. Curr Opin Oncol. 2004; 16(4): 333–341, indexed in Pubmed: 15187888.
3. Potter BO, Sturgis EM. Sarcomas of the head and neck. Surg Oncol Clin N Am. 2003; 12(2): 379–417, indexed in Pubmed: 12916461.
4. Peng KA, Grogan T, Wang MB. Head and neck sarcomas: analysis of the SEER database. Otolaryngol Head Neck Surg. 2014; 151(4): 627–633, doi: 10.1177/0194599814545747, indexed in Pubmed: 25135525.
5. Fletcher CDM, Chibon F, Mertens F. Undifferentiated/unclassified sarcomas. In: WHO classifiction of tumours of soft tissue and bone, 4th, Bridge JA, Hogendoorn PCW, Mertens F (Eds), IARC, Lyon 2013. p. 236.
6. Freedman AM, Reiman HM, Woods JE. Soft-tissue sarcomas of the head and neck. Am J Surg. 1989; 158(4): 367–372, indexed in Pubmed: 2802043.
7. Mattavelli D, Miceli R, Radaelli S, et al. Head and neck soft tissue sarcomas: prognostic factors and outcome in a series of patients treated at a single institution. Ann Oncol. 2013; 24(8): 2181–2189, doi: 10.1093/annonc/mdt126, indexed in Pubmed: 23562930.

8. Kartha SS, Bumpous JM. Synovial cell sarcoma: diagnosis, treatment, and outcomes. Laryngoscope. 2002; 112(11): 1979–1982, doi: 10.1097/00005537-200211000-00013, indexed in Pubmed: 12439166.
9. Mallen-St Clair J, Arshi A, Abemayor E, et al. Factors Associated With Survival in Patients With Synovial Cell Sarcoma of the Head and Neck: An Analysis of 167 Cases Using the SEER (Surveillance, Epidemiology, and End Results) Database. JAMA Otolaryngol Head Neck Surg. 2016; 142(6): 576–583, doi: 10.1001/jamaoto.2016.0384, indexed in Pubmed: 27100936.
10. Daw NC, Mahmoud HH, Meyer WH, et al. Bone sarcomas of the head and neck in children: the St Jude Children's Research Hospital experience. Cancer. 2000; 88(9): 2172–2180, indexed in Pubmed: 10813731.
11. Eeles RA, Fisher C, A'Hern RP, et al. Head and neck sarcomas: prognostic factors and implications for treatment. Br J Cancer. 1993; 68(1): 201–207, indexed in Pubmed: 8318414.
12. Sale KA, Wallace DI, Girod DA, et al. Radiation-induced malignancy of the head and neck. Otolaryngol Head Neck Surg. 2004; 131(5): 643–645, doi: 10.1016/j.otohns.2004.05.012, indexed in Pubmed: 15523441.
13. Yeang MS, Tay K, Ong WS, et al. Outcomes and prognostic factors of post-irradiation and de novo sarcomas of the head and neck: a histologically matched case-control study. Ann Surg Oncol. 2013; 20(9): 3066–3075, doi: 10.1245/s10434-013-2979-5, indexed in Pubmed: 23604715.
14. Farhood AI, Hajdu SI, Shiu MH, et al. Soft tissue sarcomas of the head and neck in adults. Am J Surg. 1990; 160(4): 365–369, indexed in Pubmed: 2221235.
15. Ketabchi A, Kalavrezos N, Newman L. Sarcomas of the head and neck: a 10-year retrospective of 25 patients to evaluate treatment modalities, function and survival. Br J Oral Maxillofac Surg. 2011; 49(2): 116–120, doi: 10.1016/j.bjoms.2010.02.012, indexed in Pubmed: 20416997.
16. Gil Z, Patel SG, Singh B, et al. International Collaborative Study Group. Analysis of prognostic factors in 146 patients with anterior skull base sarcoma: an international collaborative study. Cancer. 2007; 110(5): 1033–1041, doi: 10.1002/cncr.22882, indexed in Pubmed: 17614334.
17. Lilian M, Janeway G, Janeway K, et al. Sarcoma: Bone lesion. Pediatric head and neck tumors. Springer New York. 2014.
18. Park JT, Roh JL, Kim SO, et al. Prognostic factors and oncological outcomes of 122 head and neck soft tissue sarcoma patients treated at a single institution. Ann Surg Oncol. 2015; 22(1): 248–255, doi: 10.1245/s10434-014-3870-8, indexed in Pubmed: 25001093.
19. Meyer JS, Nadel HR, Marina N, et al. Imaging Guidelines for Children With Ewing Sarcoma and Osteosarcoma: A Report From the Children's Oncology Group Bone Tumor Committee, Pediatr Blood Cancer. 2008; 51: 163.
20. National Comprehensive Cancer Network. Bone Cancer (Version 2.2018). http://www.nccn.org/professionals/physician_gls/pdf/bone.pdf (April 9, 2018).
21. O'Sullivan B, Maki RG, Agulmik M, et al. Soft tissue sarcomas of the head and neck. In: AJCC Cancer Staging Manual, 8, Amin MB, (Eds), American Joint Committee on Cancer, Chicago 2017. p. 503.
22. Kneisl J, Rosenberg A, Anderson P, et al. Bone. AJCC Cancer Staging Manual. 2016: 471–486, doi: 10.1007/978-3-319-40618-3_38.
23. Zagars GK, Ballo MT, Pisters PWT, et al. Prognostic factors for patients with localized soft-tissue sarcoma treated with conservation surgery and radiation therapy: an analysis of 1225 patients. Cancer. 2003; 97(10): 2530–2543, doi: 10.1002/cncr.11365, indexed in Pubmed: 12733153.
24. Affinita MC, Ferrari A, Milano GM, et al. Long-term results in children with head and neck rhabdomyosarcoma: A report from the Italian Soft Tissue Sarcoma Committee. Pediatr Blood Cancer. 2018; 65(3), doi: 10.1002/pbc.26876, indexed in Pubmed: 29115716.
25. Balm AJ, Vom Coevorden F, Bos KE, et al. Report of a symposium on diagnosis and treatment of adult soft tissue sarcomas in the head and neck. Eur J Surg Oncol. 1995; 21(3): 287–289, indexed in Pubmed: 7781799.
26. Mendenhall WM, Mendenhall CM, Werning JW, et al. Adult head and neck soft tissue sarcomas. Head Neck. 2005; 27(10): 916–922, doi: 10.1002/hed.20249, indexed in Pubmed: 16136585.
27. Barker JL, Paulino AC, Feeney S, et al. Locoregional treatment for adult soft tissue sarcomas of the head and neck: an institutional review. Cancer J. 2003; 9(1): 49–57, indexed in Pubmed: 12602768.
28. Le Vay J, O'Sullivan B, Catton C, et al. An assessment of prognostic factors in soft-tissue sarcoma of the head and neck. Arch Otolaryngol Head Neck Surg. 1994; 120(9): 981–986, indexed in Pubmed: 8074826.
29. Jasnau S, Meyer U, Potratz J, et al. Cooperative Osteosarcoma Study Group COSS. Craniofacial osteosarcoma Experience of the cooperative German-Austrian-Swiss osteosarcoma study group. Oral Oncol. 2008; 44(3): 286–294, doi: 10.1016/j.oraloncology.2007.03.001, indexed in Pubmed: 17467326.
30. Huh WW, Holsinger FC, Levy A, et al. Osteosarcoma of the jaw in children and young adults. Head Neck. 2012; 34(7): 981–984, doi: 10.1002/hed.21850, indexed in Pubmed: 21853501.
31. DeAngelis AF, Spinou C, Tsui A, et al. Outcomes of patients with maxillofacial osteosarcoma: a review of 15 cases. J Oral Maxillofac Surg. 2012; 70(3): 734–739, doi: 10.1016/j.joms.2011.03.020, indexed in Pubmed: 21778010.
32. Vogel J, Both S, Kirk M, et al. Proton therapy for pediatric head and neck malignancies. Pediatr Blood Cancer. 2018; 65(2), doi: 10.1002/pbc.26858, indexed in Pubmed: 29058370.
33. Raciborska A, Bilska K, Drabko K, et al. Validation of a multi-modal treatment protocol for Ewing sarcoma — a report from the polish pediatric oncology group. Pediatr Blood Cancer. 2014; 61(12): 2170–2174, doi: 10.1002/pbc.25167, indexed in Pubmed: 25163763.
34. Kozelsky TF, Bonner JA, Foote RL, et al. Laryngeal chondrosarcomas: the Mayo Clinic experience. J Surg Oncol. 1997; 65(4): 269–273, indexed in Pubmed: 9274792.
35. Chin OY, Dubal PM, Sheikh AB, et al. Laryngeal chondrosarcoma: A systematic review of 592 cases. Laryngoscope. 2017; 127(2): 430–439, doi: 10.1002/lary.26068, indexed in Pubmed: 27291822.
36. Koch BB, Karnell LH, Hoffman HT, et al. National cancer database report on chondrosarcoma of the head and neck. Head Neck. 2000; 22(4): 408–425, indexed in Pubmed: 10862026.
37. Wanebo HJ, Koness RJ, MacFarlane JK, et al. Head and neck sarcoma: report of the Head and Neck Sarcoma Registry. Society of Head and Neck Surgeons Committee on Research. Head Neck. 1992; 14(1): 1–7, indexed in Pubmed: 1624288.
38. Weber RS, Benjamin RS, Peters LJ, et al. Soft tissue sarcomas of the head and neck in adolescents and adults. Am J Surg. 1986; 152(4): 386–392, indexed in Pubmed: 3766868.
39. Albores-Saavedra J, Schwartz AM, Henson DE, et al. Cutaneous angiosarcoma. Analysis of 434 cases from the Surveillance, Epidemiology, and End Results Program, 1973-2007. Ann Diagn Pathol. 2011; 15(2): 93–97, doi: 10.1016/j.anndiagpath.2010.07.012, indexed in Pubmed: 21190880.
40. Lydiatt WM, Shaha AR, Shah JP. Angiosarcoma of the head and neck. Am J Surg. 1994; 168(5): 451–454, indexed in Pubmed: 7977971.
41. Fury MG, Antonescu CR, Van Zee KJ, et al. A 14-year retrospective review of angiosarcoma: clinical characteristics, prognostic factors, and treatment outcomes with surgery and chemotherapy. Cancer J. 2005; 11(3): 241–247, indexed in Pubmed: 16053668.
42. Maddox JC, Evans HL. Angiosarcoma of skin and soft tissue: a study of forty-four cases. Cancer. 1981; 48(8): 1907–1921, indexed in Pubmed: 7197190.
43. Morrison WH, Byers RM, Garden AS, et al. Cutaneous angiosarcoma of the head and neck. A therapeutic dilemma. Cancer. 1995; 76(2): 319–327, indexed in Pubmed: 8625109.
44. Willers H, Hug EB, Spiro IJ, et al. Adult soft tissue sarcomas of the head and neck treated by radiation and surgery or radiation alone: patterns of failure and prognostic factors. Int J Radiat Oncol Biol Phys. 1995; 33(3): 585–593, doi: 10.1016/0360-3016(95)00256-X, indexed in Pubmed: 7558947.
45. Köhler HF, Neves RI, Brechtbühl ER, et al. Cutaneous angiosarcoma of the head and neck: report of 23 cases from a single institution. Otolaryngol Head Neck Surg. 2008; 139(4): 519–524, doi: 10.1016/j.otohns.2008.07.022, indexed in Pubmed: 18922337.
46. Patel SH, Hayden RE, Hinni ML, et al. Angiosarcoma of the scalp and face: the Mayo Clinic experience. JAMA Otolaryngol Head Neck Surg. 2015; 141(4): 335–340, doi: 10.1001/jamaoto.2014.3584, indexed in Pubmed: 25634014.
47. Lahat G, Dhuka AR, Hallevi H, et al. Angiosarcoma: clinical and molecular insights. Ann Surg. 2010; 251(6): 1098–1106, doi: 10.1097/SLA.0b013e3181dbb75a, indexed in Pubmed: 20485141.
48. Aust MR, Olsen KD, Lewis JE, et al. Angiosarcomas of the head and neck: clinical and pathologic characteristics. Ann Otol Rhinol Laryngol. 1997; 106(11): 943–951, doi: 10.1177/000348949710601110, indexed in Pubmed: 9373085.