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Foot Tumor: Comprehensive Collation and Evaluation

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Abstract

Background: Considerable evidence showed that foot tumors can cause severe harm to people across various age groups, though they have relatively low incidence rate. Currently, substantial research articles provide thorough discoveries among diagnosis, treatment, reconstruction, and other related areas. However, a comprehensive literature evaluation of current study findings is required. ***Methods:*** A search approach implementing the PICOS principle was utilized to acquire the literature from mainly three databases—PubMed, NCBI and SpringerLink. All the included studies underwent independent screening and evaluations of quality and risk of bias. The outcomes covered evaluation and comparison of various tumor kinds, diagnostic techniques, treatment modalities, and reconstructive procedures. ***Results:*** The location of the foot is characterized by the presence of three primary bone tumor types — osteosarcoma (OS), chondrosarcoma (CDS) and Ewing sarcoma (ES)— and four forms of soft tissue tumor—Synovial sarcoma (SS), epithelioid sarcoma (EPS), clear cell (CC) sarcoma and melanoma. Diagnosis involves the utilization of four approaches—CT, MRI, X-ray and biopsy, either singly or in combination. Out of all the options, biopsy is the most effective and accurate. Surgery and immunotherapy are widely used to treat foot tumor. The advancement of immunotherapy can significantly improve the efficiency and effectiveness of foot tumor treatment due to its specific targets and better established adjustment mechanism. Combining various types of immunotherapy with additional medicines such as chemotherapy and radiotherapy can help improve the progression of foot tumor treatment. For the reconstruction methods, Structural allograft Plastic surgery is widely used for bone tumor and soft tissue sarcoma respectively. ***Conclusion:*** The clinical significance of foot tumors is attributed to their infrequency, resulting high possibility of delayed detection and difficulties in proper treatment. The text that provides a comprehensive discussion and analysis of the diagnostic, therapeutic tactics, and repair approaches for the foot tumor can be highly beneficial to the development of foot tumor in the medical area. The methodical collation on characteristics, data of foot tumor categories is therefore equally significant. By obtaining and analyzing such information, researchers and physicians can better identify certain pattern in foot tumor. For the treatment, Immunotherapy stands out among the existing methods since it has the highest potential to selectively target certain types of foot tumors depending on their distinct needs. The evaluation of immunotherapy and reconstruction methods still contain some limitations due to the lack of the latest and adequate research.

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1. Introduction

Soft tissue sarcomas (STS) are uncommon and varied mesenchymal tumors that exhibit intrinsic heterogeneity (Bourcier et al., 2019). The condition can arise from any anatomical site inside the human body and impact individuals at both ends of the age spectrum. The Neoplasms originating from various tissues such as skeletal muscle, adipose tissue, blood, lymphatics, connective tissue, and peripheral nerves can exhibit a wide range of clinical manifestations, ranging from non-cancerous lipomas to highly invasive angiosarcomas that spread to other parts of the body (Popovich et al., 2023). There exist about 70 distinct varieties of it. The 10-year relative survival rate for STS among patients aged 20 was 70%, but around 50% among patients aged 65 or older (Bourcier et al., 2019). A bone tumor starts in a bone when bone cells undergo excessive proliferation. While primary bone cancer is commonly of unknown cause, there are many risk factors that may bring significant results (Clevel & Clinic, 2021).

In the location of the foot, benign tumors and tumor-like lesions are the major tumors that occurred, while malignant tumors, particularly malignant bone tumors of the foot, are rare. Though having a non-universality, malignant tumors are the major drivers that affect people's lives, as they have a worse survival rate than benign tumors (Mascard et al., 2017). These malignant tumors of bone and soft tissue are generally characterized based on matrix production and differentiation (Morley & Paintal et al., 2019). Through radiographic and pathologic research, it finds that: For malignant bone tumors on foot, the common subtypes include osteosarcoma (OS), chondrosarcoma (CDS) and Ewing sarcoma (ES). Whereas common foot malignant soft tissue tumors are Synovial sarcoma (SS), epithelioid sarcoma (EPS), clear cell (CC), sarcoma and melanoma (Angelini et al., 2023).

While different types of tumors may require specific diagnostic, therapeutic, and reconstructive procedures, they all adhere to the fundamental principles of these strategies. The diagnosis encompasses several crucial procedures: a physical examination consisting of inspection, palpation, and a comprehensive neurovascular examination; an imaging approach that includes Computed Tomography (CT) for detailed bone analysis, Magnetic Resonance Imaging (MRI) for specified soft-tissue analysis, and X-rays that are comprehensive for both types of tumors (Angelini et al., 2023; Bos GD. et al., 2002). It is then followed by biopsy which is a crucial procedure. A biopsy that is sufficient ensures that the tissue obtained is both representative and viable, allowing for a reliable diagnosis (Angelini et al., 2023).

The standard therapies for these bone malignancies involve the application of chemotherapy, radiation therapy, and surgical excision, which entails the removal of the adjacent muscle, bone, and other tissues, depending on the location, mass and condition of the tumor (Frazier M et al., 2021). In addition, novel and effective approaches such as cryosurgery and immunotherapy have also been utilized in the treatments (Chen C et al., 2017; Panagi M et al., 2022).

The reconstruction methods are responsible for the recovery after the tumor resection surgery. It is also challenging for orthopedic surgeons to select appropriate techniques for different bone defect conditions. Currently, structural allografts and plastic surgical reconstruction methods are widely considered to be the reliable reconstruction methods for bone defect and soft tissue defect respectively (Ayerza, M.A. et al., 2016; Ring A. et al., 2016). In addition, Masquelet technique and Vascularized grafts of fibular or pelvis bone are also mentioned in the case report related to the foot defect reconstruction (Giannoudis, P. V. et al., 2011; Toma, C. D. et al, 2007; Kurvin, L. A. et al., 2008). However, the majority of these cases are individual and include varying patient conditions, therefore rendering these procedures lacking in universality, authority, and clarity.

2. Epidemiology and Pathology

2.1 Bone Tumor

2.1.1 Osteosarcoma (OS)

OS is a pathological disorder marked by the abnormal growth of osteoblasts in the skeletal system (Pullan, J.E et al, 2022). Several mutations associated with the development of OS include RB protein and the p53 protein (Rickel, K et al, 2017). It is a rare occurrence in the foot, representing approximately 0.5 to 1.3% of all cases of OS in the human body. But it is the most common bone tumor on foot. OS occurring in the foot tend to manifest in slightly older age groups compared to OS found in other parts of

the body. This difference in age distribution can potentially result in decreased clinical suspicion and a delay in making a diagnosis. Moreover, the occurrence of this tumor is more prevalent in males as compared to females. Around a quarter of patients with OS had lung metastases at the time of diagnosis, while 60-70% of patients acquire metastases within 5 years of receiving main treatment (Angelini et al, 2023; Bos GD et al, 2002).

2.1.2 Chondrosarcoma (CDS)

It is the second most prevalent primary bone tumor, acting as slow-growing malignancies and affecting adult and elderly individuals who are primarily in the age range of 40 to 60 years. It can be distinguished by the tumor cells' capacity to generate a cartilage matrix. Unlike other CDS, which typically remain limited to the metadiaphysis, CDS in the feet affect a significant portion of the bone's length. When compared to other parts of the body such as the pelvic bones, femur, and chest wall, CDS are relatively rare in the foot, which account for approximately 0.1% of all cases. It impacts adult and elderly individuals, primarily in the age range of 40 to 60 years (Angelini et al, 2023; Bos GD et al, 2002).

2.1.3 Ewing Sarcoma (ES)

ES is a type of tumor that consists of small round cells and can develop in both bone and soft tissue. It has the ability to differentiate into neuro-ectodermal cells and can affect any area of the skeleton (Mascard et al, 2017). It occurs rarely in the foot, but compared to other bone tumors, it brings more effect on more children and adolescents (Pullan, J.E. et al, 2022). This bone tumor is the second most prevalent malignant tumor in children, with 80% of patients being under the age of 20 (Mascard et al., 2017). In the location of foot, its five-year survival is approximately 45%, with improved survival rates with smaller masses or forefoot lesions (Bos GD et al., 2002).

2.2 Soft Tissue Tumor

2.2.1 Synovial Sarcoma (SS)

It is the commonest malignant soft-tissue sarcoma seen in the foot, comprising 8% of all primary malignant soft-tissue tumors (Angelini et al., 2023). The primary group affected by SS consists predominantly of young to middle-aged adults. The highest occurrence rate is observed in individuals aged between their second and fifth decades, which is earlier compared to patients with other types of soft-tissue sarcomas. (Bos GD et al., 2002). The etiology of the tumor is revealed to relate to 2 different forms of chromosomal translocations—fusion type SYT-SSX1 and SYTSSX2. They are also related to the survival rate: The 5-year overall survival rate for the SYT-SSX2 and SYT-SSX1 is 13.7 years, 73% and 6.1 years, 53% respectively (DeGroot, 2008, p. 174).

2.2.2 Epithelioid Sarcoma (EPS)

EPS is an uncommon malignancy, representing less than 1% of all STS (Angelini et al, 2023). The majority of patients are young people, with 75% of instances occurring in individuals under the age of 40, however children and elderly individuals may also be affected. Men are more frequently impacted than women. The tumor might manifest as a compact, solid, superficial or profound nodule, or as a concentrated group of nodules. Approximately 50% of the tumors are non-painful（DeGroot, 2008, p. 174). The 5-year survival rate ranged from 60% to 80% after the primary treatment. However, it still has a high local recurrence rate of about 35% and metastases rate of 40–50%. (Angelini et al., 2023)

2.2.3 Clear Cell (CC) Sarcoma

CC in foot constitutes 34% of such tumor types (Bos GD et.al, 2002). Besides, clear-cell sarcomas account for 33-43% of all the cases in the foot. The tumor manifests in individuals aged 20 to 40 years, with a higher incidence in females. The presentation often involves the gradual development of a tiny mass, which is often accompanied by discomfort and soreness in around 50% of cases. CC sarcoma typically occurs in deep tissues and is frequently connected to aponeuroses and tendons (Mascard et al, 2017). The reported 5-year survival rates range from 47 to 75%, and the survival is most likely to be improved by having a smaller tumor volume and receiving an early diagnosis. (Angelini et al., 2023)

2.2.4 Melanoma

Around 15% of melanomas are discovered on the foot, and it is a frequently occurring neoplasm of the foot's soft tissues. (Angelini et al., 2023; Bos GD et al, 2002) The majority of patients are young adults, with the highest frequency of presentation occurring in the 40s. Females suffer more significantly compared to males, and this form of cancer poses a specific hazard for young females. The plantar surface

and subungual areas are the most frequent sites of the tumor presentation (DeGroot, 2008, p. 174). There are some risk factors that cause the tumor. For exposed areas, chronic or intermittent sun exposure associated with sunburn are the main factors implicated in the genesis of the disease. While for unexposed areas, pre-existing plantar lesions contribute most in the progress. (Angelini et al., 2023) The 5-year overall survival rate ranges from 52% to 63%, whereas the 10-year overall survival rate is 51% (DeGroot, 2008, p. 174).

3. Diagnosis

Currently, the diagnosis of foot tumors is often delayed due to clinicians' lack of experience and the rarity of these malignancies (Young et al., 2013).

3.1 X-rays & CT & MRI

CT imaging offers outstanding clarity in visualizing bone structures, while MRI imaging excels in providing detailed imaging of soft tissues (Bos GD et al., 2002). In comparison to the previous diagnostic methods, X-rays—also called plain radiographs—provide a more extensive analysis. When examining bone tumors, X-rays can reveal the exact location of the lesion, its aspect, the pattern of bone destruction, the presence of calcifications, thinning or destruction of the outer layer of bone (cortex), periosteal reaction, and the likelihood of pathological fractures. In the case of soft tissue tumors, X-rays specifically emphasize the detection of calcifications within the soft tissues. (Angelini et al, 2023) Take the diagnosis of OS and SS, the most common bone tumor and soft tissue tumor in foot, as an example. Plain radiographs of OS demonstrate cloudlike bone formation in the intramedullary space. Meanwhile, the SS scan reveals the presence of a soft-tissue mass that has calcification along its edges, which is not specific. On MRI, SS appears as a diverse and nonspecific mass, with most cases showing many compartments, internal partitions, and clearly defined edges. (Morley & Paintal et al., 2019)

3.2 Biopsy

Biopsy is a crucial component of the staging process; however it may not always be the final step. Conducting a biopsy prior to finishing the staging process helps prevent the need for additional systemic imaging tests in non-cancerous tumors. A biopsy that is sufficient ensures that the tissue collected is both representative and viable, allowing for an accurate diagnosis.

The choice of biopsy procedure is contingent upon the specific clinical circumstances (Angelini et al., 2023).

(1) Core needle biopsy: It is a standard for sampling that preserves tissue structure, with a low contamination rate and a minimally intrusive method (Angelini et al., 2023).

(2) Closed biopsy: It is suitable for most tumors and is most effective when the mass is greater than 2 cm in diameter. The treatment can be conducted without the use of imaging for visible masses, or with the assistance of CT guidance for masses located deep within the body. Nevertheless, the operation carries a higher possibility of infection, requiring patients to discontinue antibiotic usage for the entire treatment (Bos GD et al, 2002).

(3) Open biopsy: This method is suitable for the majority of bone tumors and achieves the best results when the size of the mass is larger than 2 cm in diameter. But it is seldom used due to its greater complication rate compared to alternative treatments (Bos GD et al., 2002).

(4) Incisional biopsy: It is frequently used in the treatment of soft tissue tumors. Biopsies of soft-tissue lesions should be performed by making an incision immediately over the lesion to reduce the risk of contaminating unaffected tissue areas. Besides, to facilitate future resection, it is preferable to make a longitudinal incision (Bos GD et al, 2002).

(5) Excisional biopsy: This is an open surgical procedure in which a tumor is removed, and it is surrounded by healthy tissue (Angelini et al., 2023).

4. Treatments

For the foot tumor, main treatment methods include radiotherapy, chemotherapy, cryosurgery, surgery and immunotherapy.

4.1 Radiotherapy

With the right planning, radiation therapy can be used along with surgery to treat problems in the foot and ankle. To get good results with radiation on the foot, use of low-dose brachytherapy and special training are needed. Radiation side effects, like fibrosis and abnormal fracture, can make the foot hurt and make it impossible to use. (Bos GD et al, 2002)

4.2 Cryosurgery

Cryosurgery is the therapeutic application of colds, liquid nitrogen, intended for ablation to cause tissue necrosis. (Bickels, J et al., 1999)

It has some clear benefits over other adjuvant methods. Above all, the dosage may be regulated so that the operation can be designed for the particular type of bone tumor and location, ensuring the accuracy and efficiency, and it is an aggressive local adjuvant with no systemic side-effects, non-toxic to the patient and those working with it (Schreuder, 2001). However, it still has certain restrictions with big, high-grade malignant bone tumors including soft tissue structures. (Chen C. et al., 2017)

4.3 Surgery

4.3.1 Forefoot

The appropriate treatment for the tumor in the toes would be a partial amputation, determined on the extent of tumor spread. For significant tumors in the metatarsals, it is recommended to undergo a mid-foot amputation, although lesser tumors can be treated with an intercalary excision. (Mascard. et al., 2017)

4.3.2 Midfoot

For malignant bone tumors that are contained within the bone or have limited local spread, it is recommended to use conservative therapy due to the difficulty of establishing the requisite broad margins. (Mascard et al., 2017)

4.3.3 Hindfoot

Surgically removing a tumor in the calcaneus bone is a complex procedure that can only be done in circumstances where the tumor is cancerous and located within the bone. The surgeon should be aware of the potential for attaining narrow resection margins. Two surgical approaches may be required. Additionally, a posterior method can be employed when doing an Achilles tendon segment. (Mascard et al., 2017)

4.4 Immunotherapy

To break through the limitations of these conventional treatments, and improve efficiency and safety for patients, immunotherapies for sarcomas are promoted currently. Compared to conventional therapy, the treatment induces the natural defenses of the host immune system to attack tumor cells rather than destroying the cancer cells directly. (Panagi M et al., 2022)

4.4.1 Adoptive Cell Therapy (ACT)

The therapy entails the intravenous infusion of either immune cells existing in the tumor or immune cells taken from blood that have been genetically modified. This is done to enhance the immune responses against the tumor. It generally involves two types of treatment —CAR-T & tumor-infiltrating lymphocytes (TIL) (Panagi M et al., 2022). For CAR-T therapy, it must meet two basic criteria. To avoid toxicity and harm in normal tissues, CAR-T cells should first target sarcoma-specific epitopes. Second, the target should be broadly expressed in sarcoma metastases (Li X et al., 2020). While for TIL, it is only proved to have a reliable effect on melanoma, evidently because the synthesis and reactivity of TILs from other various kinds of solid tumors have resulted in inconsistent antitumor responses (Panagi M et al., 2022).

4.4.2 Cancer Vaccines

Cancer vaccines involve the external delivery of certain tumor-associated antigens (TAA) and adjuvants. Antigens have typically been delivered in the form of DNA, RNA, and peptides, as well as by autologous dendritic cells (DC) (Panagi M et al., 2022). While DC vaccines are the most frequent type of immunization for the sarcoma, and they can be loaded with particles that have been treated with immune-adjuvants outside of the body before being injected back into patients (Li X et al, 2020). The primary objective of this therapy is to stimulate a T cell response that is capable of eliminating any remaining tumor and creating a long-lasting memory against cancer, without causing any side effects or non-specific reactions. (Panagi M et al., 2022)

4.4.3 In Situ Vaccines (iSVs)

iSVs utilize antigens derived from deceased or deteriorating tumor cells to produce a vaccine within the tumor microenvironment, stimulating the development of internal anticancer responses. The primary mechanisms by which iSVs exert their effects involve the activation of innate immune pattern recognition receptors and the stimulation of interferon genes protein (Saxena M, et al., 2021). One more group of new iSV agents is called oncolytic viruses. Oncolytic viruses that have been genetically or chemically modified to produce immuno-modulators specifically infect and replicate within cancer cells, killing them and releasing TAA and neoantigens as a result. (Panagi M et al., 2022)

4.4.4 Checkpoint Inhibitor (ICI)

Tumor cells govern the response of immunotherapy through immunological checkpoints. The PD-1/PD-L1 pathway and the combination of CTLA-4 and CD28 prevent T cell activation. PD-1 is a surface protein found on T cells, particularly on T cells that have been active for a long time. PD-L1, the ligand of PD-1, is mainly found on antigen-presenting cells such DCs, macrophages, and TILs, but it can also be present on tumor cells. Therefore, PD-1 binding to PD-L1 hinders the activation and release of cytotoxic agents by T cells in tumors, resulting in a weakened immune response against the tumor. Meanwhile, CTLA-4 &CD28 are also the immune checkpoint molecules. They are increased in expression when T cells are activated in order to bind to CD80/86 molecules on dendritic cells (DCs). They also engage in competition with one another. Due to its higher affinity for CD80/86 compared to CD28, CTLA-4 functions as an inhibitory signal, resulting in T-cell anergy and death. As a result, administering antibodies that target PD-1, PD-L1, and CTLA-4 inhibits immune suppression and thereby boosts the destruction of tumors (Li X et al., 2020). In addition to CTLA-4 and PD-1, numerous additional molecules present on cell surfaces may disrupt the immune system's capacity to combat tumors, Such as Tim-3, IDO, LAG-3, VISTA, and KIRs (Dempke WCM et al., 2017). In the future, these targets could potentially be utilized in sarcoma immunotherapy to enhance the functionality of the immune system.

4.4.5 Immunotherapy and Tumor Types

The therapeutic effect of immunotherapy can be significantly influenced by the tumor microenvironment, which can impede the administration of immunotherapeutic drugs and induce immunosuppression. It entails restrictions on the range of cancer types. Through the research, it is found that among all the foot tumor mentioned previously, only synovial sarcoma, Osteosarcoma, Ewing sarcoma, and melanoma can process reliable immunotherapy (Panagi M et al., 2022).

(1) Synovial sarcoma: The utilization of ICI in the treatment of SS as a component of clinical trials has yielded unsatisfactory results (Panagi M et al., 2022). While the method of iSV is considered to be useful, as ZD10 is a suitable target for iSV, which is highly expressed in SS and acts as a potential receptor for Wnt signaling (Li HK, et al., 2018).

(2) Osteosarcoma: Both ICI and cancer vaccines are useful. At the moment, ICI is the most popular immune treatment for OS that is used in real life (Panagi M et al., 2022). When it comes to cancer vaccines, CTLA-4 blockade worked well with a cryo-treated tumor lysate-pulsed DC vaccine to stop the spread of lung metastasis by lowering Treg levels and increasing the number of cytotoxic CD8+ cells that entered the metastatic tumor (Kawano M. et al., 2013).

(3) Ewing sarcoma: ACT can be used as an individual therapy or in combination with iSVs (Panagi M et al., 2022).

(4) Melanoma: Both iSVs and ACT therapy are available. For example, the T-vec is a genetically engineered herpes simplex virus that expresses GM-CSF. It is the only form of oncolytic immunotherapy authorized by the FDA for treating metastatic melanoma. (Andtbacka RH. et al., 2015; Panagi M et al., 2022)

5. Reconstruction Methods

5.1 Structural Allograft Reconstruction

Structural allografts are utilized for the purpose of correcting deformities or filling bone defects that occur as a result of tumor removal, trauma, osteochondral lesions, or intercalary arthrodesis. The scientific findings indicate that the use of structural allograft reconstruction in the foot and ankle following tumor removal can result in long-lasting outcomes, with a survival rate of 79% at both the 5-year and 10-year marks. Hence, it demonstrates its efficacy and accessibility in the regeneration of foot bone tumors. (Ayerza, M.A et al., 2016)

5.2 Plastic Surgical Reconstruction

The objective of the reconstruction method is to decrease functional disability and cover the damage to soft tissues, especially in situations when there is a large tumor, or it is located near important anatomical structures. This leads to an enhancement in the quality of life for these patients. To reach the aim, local flaps and free flaps can be used in the plastic surgery during the process depending on different conditions.

5.2.1 Local Flaps

The common local flaps used for soft tissue reconstruction on foot include simple cutaneous or myocutaneous V-Y flaps, sensible local flaps, distally based sural flap, and instep-island flap.

The choice of flaps is mainly determined by the size and location of the defect. Simple cutaneous or myocutaneous V-Y flaps are used to cover small defects at the non-weight-bearing sole; Sensible local flaps can reconstruct the defects at the weight-bearing hind foot and prevent the occurrence of ulcerations; The distally based sural flap is a suitable option for covering smaller defects at the hind foot and malleolar region. Since it has a dependable blood supply, appropriate size, and causes only a mild defect at the donor site; The instep-island flap is appropriate for minor defects, and the donor site typically requires a skin graft for transplantation (Ring A. et al., 2016). In brief, the local flaps are often used for small defects that are usually located at the region of hind foot or malleolar.

5.2.2 Free Flaps

For the defects that are not satisfied the qualification of local flaps, free microvascular myocutaneous or fasciocutaneous tissue transfer are widely used. Free microvascular myocutaneous mainly includes propeller perforator flaps. The procedure relies on the use of perforators originating from the anterior and posterior tibial arteries, as well as the peroneal artery. Free fasciocutaneous tissue transfer involves the application of parascapular flap, anterolateral thigh flap and latissimus dorsi flap: (1) The parascapular flap is a type of fasciocutaneous flap that is located on the posterior trunk. It receives its blood supply from the descending branch of the circumflex scapular artery, which originates from the triangle gap formed by the teres major, teres minor, and long head of the triceps brachii muscle. (2) The anterolateral thigh flap is a flexible fasciocutaneous flap situated on the anterolateral aspect of the thigh. The main component originates from the septocutaneous or myocutaneous perforators of the descending branch of the lateral circumflex femoral artery. (3) The latissimus dorsi muscle, which has a dependable blood supply through the thoracodorsal artery, can be obtained from the back either with or without a section of covering skin. Hence, the flap is very suitable for extensive soft tissue defects (Ring A. et al., 2016).

6. Discussion

The essay encompasses a range of subjects, but the most significant insights are related to the application of immunotherapy in treating foot tumors. Comparing mortality rates between location of foot tumors, a research in 2018 presented that malignant tumor shows no preference on the location of foot, but the benign tumors distribute more at hind foot, with a high rate of 40.25%, than other position (Toepfer et al., 2018). Thus, it is not unexpected to see that hindfoot foot tumors are more prone to develop aggressive and complex characteristics. (Toepfer et al., 2018) From the perspective of whole tumor treatment, the combination between different kinds of immunotherapy has made huge progress—based on encouraging preclinical data, checkpoint inhibitors have also been used together with vaccines and CAR-T therapy in phase I trials. Moreover, the use of immunotherapy also makes a strong contribution by combining with other types of treatments like chemotherapy, radiotherapy. (Li X et al., 2020) For the further advancement of immunotherapy, the exponential development of genomic information gathering, and the availability of targeted medications have offered a new paradigm for exploring sarcoma treatments. (Li X et al., 2020) MULTISARC (NCT03784014) is an ongoing clinical trial that is evaluating the feasibility of identifying actionable mutations in metastatic soft tissue sarcoma patients using next generation sequencing of the exome. The subsequent phase will involve the integration of the data from clinical cohorts and preclinical studies in sarcoma cell lines, patient-derived samples, and tumor models to enhance the prediction of therapy response. Investigating circulating tumor cells, cell-free circulating DNA, tumor-derived extracellular vesicles, and metabolomic profiles could supplement immunohistochemistry data and enhance therapy strategies that rely on genetics (Panagi M et al., 2022).

7. Conclusion

The essay summarizes the various factors of foot tumors, encompassing the pathology, causes, treatment, reconstruction, especially the development of immunotherapy, sin order to address the previously existing vacancy in this area. Thus, it can also bring advantages for forthcoming investigations. However, the review also has certain shortcomings. The text is deficient in recent and up-to-date research, leading to the inclusion of outdated references that may have limitations and delays for the times. Furthermore, the evaluation does not include specific information on the many types

of reconstructive methods used for different foot tumors, as there are only a limited number of research instances that demonstrate high universality.

References

Angelini, A., Biz, C., Cerchiaro, M., Longhi, V., & Ruggieri, P. (2023). Malignant bone and soft tissue lesions of the foot. *Journal of Clinical Medicine, 12*(8), 3038. https://doi.org/10.3390/jcm12083038

Andtbacka, R. H. I., Kaufman, H. L., Collichio, F. et al. (2015). Talimogene Laherparepvec improves durable response rate in patients with advanced melanoma. *Journal of Clinical Oncology, 33*(25), 2780-2788. https://doi.org/10.1200/jco.2014.58.3377

Ayerza, M. A., Piuzzi, N. S., Aponte-Tinao, L. A., Farfalli, G. L., & Muscolo, D. L. (2016). Structural allograft reconstruction of the foot and ankle after tumor resections. *Musculoskeletal Surgery, 100*(2), 149-156. https://doi.org/10.1007/s12306-016-0413-4

Bickels, J., Robert, C. K., Eller, I., & Malawer, M. M. (1999). Cryosurgery in the treatment of bone tumors. *Operative Techniques in Orthopaedics, 9*(2), 79-83. https://doi.org/10.1016/s1048-6666(99)80025-1

Bone cancer: Symptoms, signs, treatment, causes & stages. Cleveland Clinic. (2021). https://my.clevelandclinic.org/health/diseases/17745-bone-cancer

Bos, G. D., Esther, R. J., & Woll, S. T. (2002). Foot tumors: Diagnosis and treatment. *Journal of the American Academy of Orthopaedic Surgeons, 10*(4), 259-270. https://doi.org/10.5435/00124635-200207000-00004

Bourcier, K. et al. (2019). Basic knowledge in soft tissue sarcoma. *Cardio Vascular and Interventional Radiology, 42*(9), 1255-1261. doi:10.1007/s00270-019-02259-w

Chen, C., Garlich, J., Vincent, K., & Brien, E. (2017). Postoperative complications with cryotherapy in bone tumors. *Journal of Bone Oncology, 7*, 13-17. https://doi.org/10.1016/j.jbo.2017.04.002

DeGroot, H. (2008). Approach to the management of soft tissue tumors of the foot and ankle. *Foot & Ankle Specialist, 1*(3), 168-176. https://doi.org/10.1177/1938640008318511

Dempke, W. C. M., Fenchel, K., Uciechowski, P., & Dale, S. P. (2017). Second- and third-generation drugs for immuno-oncology treatment—the more the better? *European Journal of Cancer, 74*, 55-72. https://doi.org/10.1016/j.ejca.2017.01.001

Frazier, M., & Fuqua, T. (2021). Chapter 7: Diseases and conditions of the musculoskeletal system. In *Essentials of Human Diseases and Conditions* (p. 336-338). St. Louis, MO: Elsevier.

Giannoudis, P. V., Faour, O., Goff, T., Kanakaris, N., & Dimitriou, R. (2011). Masquelet technique for the treatment of bone defects: Tips-tricks and future directions. *Injury, 42*(6), 591-598. https://doi.org/10.1016/j.injury.2011.03.036

KAWANO, M., ITONAGA, I., IWASAKI, T., & TSUMURA, H. (2013). Enhancement of antitumor immunity by combining anti-cytotoxic T lymphocyte antigen-4 antibodies and cryo-treated tumor lysate-pulsed dendritic cells in murine osteosarcoma. *Oncology Reports, 29*(3), 1001-1006. https://doi.org/10.3892/or.2013.2224

Kurvin, L. A., Volkering, C., & Keßler, S. B. (2008). Calcaneus replacement after total calcanectomy via vascularized pelvis bone. *Foot and Ankle Surgery, 14*(4), 221-224. https://doi.org/10.1016/j.fas.2008.03.004

Li, H. K., Sugyo, A., Tsuji, A. B., Morokoshi, Y. et al. (2018). A-particle therapy for synovial sarcoma in the mouse using an astatine-211-labeled antibody against Frizzled homolog 10. *Cancer Science, 109*(7), 2302-2309. https://doi.org/10.1111/cas.13636

Li, X., Wang, G., Cai, Z., & Sun, W. (2020). Immunotherapeutic strategies for sarcoma: Current perspectives. *American Journal of Translational Research*. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7791481/

Mascard, E., Gaspar, N., Brugières, L., Glorion, C., Pannier, S., & Gomez-Brouchet, A. (2017). Malignant tumors of the foot and ankle. *EFORT Open Reviews, 2*(5). https://doi.org/10.1302/2058-5241.2.160078

Morley, N., & Paintal, A. S. (2019). *Bone and soft tissue tumors*. In Springer eBooks (pp. 209–223).

https://doi.org/10.1007/978-3-030-24756-0_10

Panagi, M., Pilavaki, P., Constantinidou, A., & Stylianopoulos, T. (2022). Immunotherapy in soft tissue and bone sarcoma: Unraveling the barriers to effectiveness. *Theranostics, 12*(14), 6106-6129. https://doi.org/10.7150/thno.72800

Popovich, J. R., Kashyap, S., Gasalberti, D. P., & Cassaro, S. (2023). *Sarcoma. StatPearls* — NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK519533

Pullan, J. E. (2024). *Primary bone cancer.* Stat Pearls. https://www.ncbi.nlm.nih.gov/books/NBK560830/

Rickel, K., Fang, F., & Tao, J. (2017). Molecular genetics of osteosarcoma. Bone. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5393957/

Ring, A., Kirchhoff, P., Goertz, O., Behr, B., Daigeler, A., Lehnhardt, M., & Harati, K. (2016). Reconstruction of soft-tissue defects at the foot and ankle after oncological resection. *Frontiers in Surgery, 3*. https://doi.org/10.3389/fsurg.2016.00015

Saxena, M., van der Burg, S. H., Melief, C. J., & Bhardwaj, N. (2021). Therapeutic cancer vaccines. *Nature Reviews Cancer, 21*(6), 360-378. https://doi.org/10.1038/s41568-021-00346-0

Schreuder, H. W. (2001). Cryosurgery for bone tumors. In *Basics of Cryosurgery* (p. 231-251). https://doi.org/10.1007/978-3-7091-6225-5_14

Toma, C. D., Dominkus, M., Pfeiffer, M., Giovanoli, P., Assadian, O., & Kotz, R. (2007). Metatarsal reconstruction with use of free vascularized osteomyocutaneous fibular grafts following resection of malignant tumors of the midfoot. *The Journal of Bone & Joint Surgery, 89*(7), 1553-1564. https://doi.org/10.2106/jbjs.f.00659

Toepfer, A. *et al.* (2018). Distribution patterns of foot and ankle tumors: A university tumor institute experience. *BMC Cancer, 18*(1). doi:10.1186/s12885-018-4648-3.

Young, P. S., Bell, S. W., MacDuff, E. M., & Mahendra, A. (2013). Primary osseous tumors of the hindfoot: Why the delay in diagnosis and should we be concerned? *Clinical Orthopaedics & Related Research, 471*(3), 871-877. https://doi.org/10.1007/s11999-012-2570-6