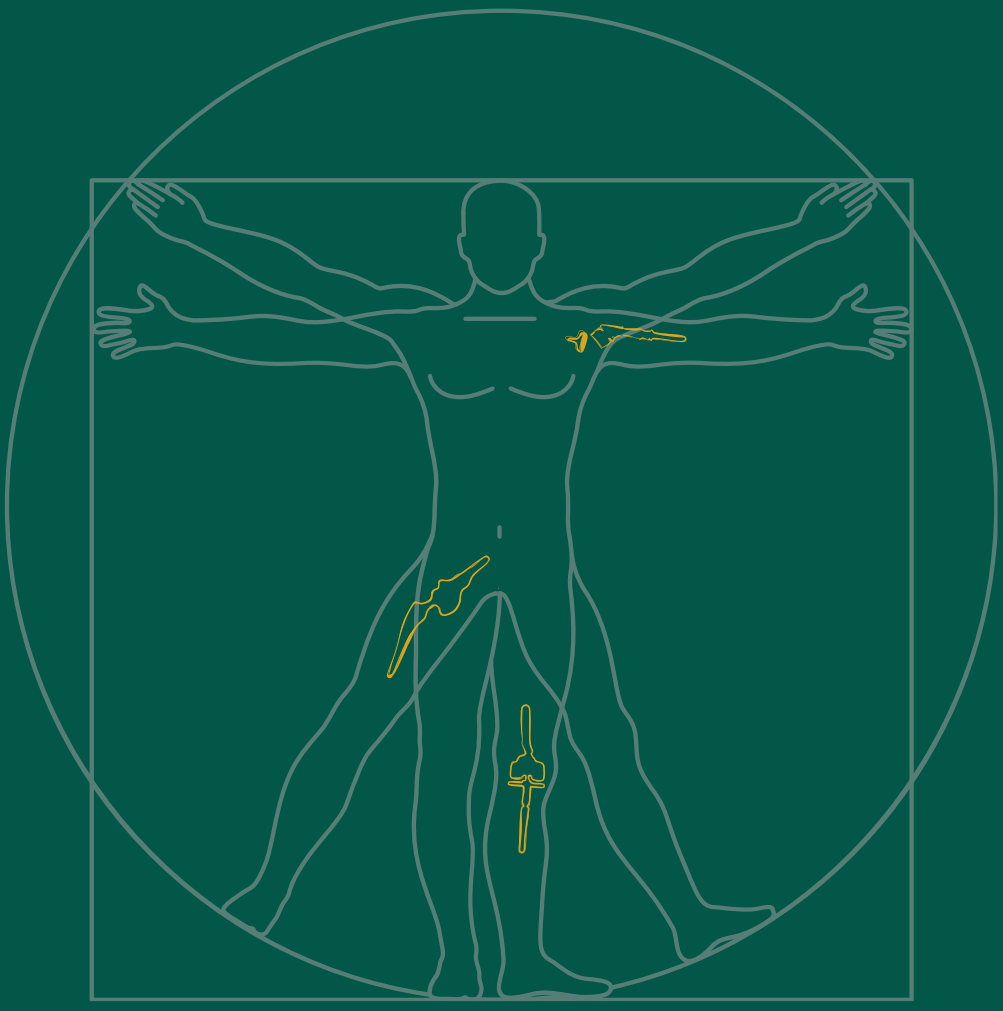
Advances in diagnosis, prognosis and reconstructive procedures in orthopaedic oncology



Richard Evenhuis

Advances in diagnosis, prognosis, and reconstructive procedures in orthopaedic oncology

PhD thesis, Leiden University, the Netherlands

Richard Eduard Evenhuis

Cover design and lay-out Lidewij Boogers and Richard Evenhuis
Printed by Proefschriftmaken.nl

The research projects in this thesis were supported by an unconditional research grant from Implantcast GmbH, Buxtehude, Germany.

Publication and printing of this thesis was kindly supported by: Implantcast GmbH, Nederlandse Orthopaedische Vereniging (NOV), Universiteit Leiden, Anna Fonds|NOREF, Vakgroep Orthopaedie Alrijne, Regelzorg, ABN AMRO, ChipSoft.

Advances in diagnosis, prognosis, and reconstructive procedures in orthopaedic oncology

Proefschrift

ter verkrijging van

de graad van doctor aan de Universiteit Leiden,

op gezag van rector magnificus prof.dr.ir. H. Bijl,

volgens besluit van het college voor promoties

te verdedigen op woensdag 14 mei 2025

klokke 16:00 uur

door

Richard Eduard Evenhuis

geboren te Glane

in 1995

Promotores

Prof. dr. M.A.J. van de Sande

Prof. dr. M. Fiocco

Copromotor

Dr. M.P.A. Bus

Leden promotiecommissie

Prof. dr. R.G.H.H. Nelissen

Dr. K. van Langevelde

Prof. dr. A.J. Gelderblom

Dr. R.J.P. van der Wal

Prof. dr. H.W.B. Schreuder, Radboud UMC

Prof. dr. J.A.M. Bramer, Amsterdam UMC

Table of contents

Chapter 1	General introduction and thesis outline	7
Part I	**Advances in the evaluation of diagnosis and prognosis in patients with bone tumors**	19
Chapter 2	Diagnosis of chondrosarcoma in a non-invasive way using volatile organic compounds in exhaled breath: a pilot study	21
Chapter 3	Survival analysis of 3 different age groups and prognostic factors among 402 patients with skeletal high-grade osteosarcoma. Real world data from a single tertiary sarcoma center	41
Chapter 4	Relative wash-in rate on dynamic contrast-enhanced MRI as a new prognostic biomarker on event-free-survival in 82 patients with osteosarcoma; a multicenter study	67
Part II	**MUTARS reconstructions in patients with extensive bone defects following orthopaedic oncological resections**	89
Chapter 5	LUMiC endoprosthetic reconstruction of periacetabular tumor defects: a multicenter follow-up study	91
Chapter 6	Evaluating polyethylene, polyether-ether-ketone, and metal-on-metal locking mechanism survival in Modular Universal Tumour and Revision System knee reconstructions for oncological indications: insights from the MUTARS Orthopedic Registry Europe	113
Chapter 7	Proximal humeral endoprosthetic reconstruction for tumor defects: clinical outcomes of 165 patients from the MUTARS Orthopaedic Registry Europe (MORE)	133
Chapter 8	General summary, discussion, and future perspectives	155
Chapter 9	Summary in Dutch (Nederlandse samenvatting)	175
Appendices	List of publications, acknowledgements, curriculum vitae	183

Chapter 1

General introduction and thesis outline

Background and epidemiology of bone tumors

Bone tumors, which encompass a diverse spectrum of neoplastic conditions, pose unique challenges in diagnosis, prognosis and treatment. They can either be benign and less invasive, or malignant and highly aggressive. Although bone tumors are rare, they remain one of the most common malignancies in patients from childhood through young adulthood(1). Sarcomas specifically, are a complex group of mesenchymal tumors that originate in bones and soft tissues(2). Osteosarcoma is the most common primary bone malignancy, with an incidence of 4 cases per million people per year(3). Chondrosarcoma is the second most common primary malignant bone tumor with an incidence of 2-4 cases per million people per year(4, 5).

Background of chondrosarcoma

Chondrosarcoma is a rare type of cancer originating from cartilaginous cells, and typically occurs in the pelvis, femur, and humerus(4). It was initially described in the mid-1800s by Sir James Paget, a notable British surgeon and pathologist(6). In the early 20th century, pathologists and other medical professionals began to recognize chondrosarcoma as a distinct type of bone tumor. Advancements in pathology allowed for better differentiation between cartilage and bone tumors and even the identification of various subtypes of chondrosarcoma(7). Historically, treatment of chondrosarcomas primarily involved wide tumor resection, often necessitating extensive resections or even limb amputation(8). The tumor's relative resistance to chemo- and radiotherapy is believed to be caused by poor vascularization, a dense extracellular matrix, and low mitotic activity(9, 10). Therefore, surgical intervention remains the cornerstone of treatment, with limb-salvaging tumor resection as the gold standard during recent decades(10).

Recent diagnostic and prognostic advances in chondrosarcoma

Over the past decades, researchers endeavored to gain a deeper understanding of the different types of chondrosarcoma. It has been recognized that low-grade chondrosarcomas rarely metastasize and typically have a favorable prognosis following surgical resection(10). This led to a reclassification of chondrosarcoma by the World Health Organization in 2013(11). Chondrosarcoma grade I was reclassified to Atypical Cartilaginous Tumor (ACT). In contrast, chondrosarcoma grades II and III are considered high-grade tumors, associated with the risk of metastasis, local recurrence, and less favorable outcomes(12). Advancements in diagnostic techniques, particularly high-quality magnetic resonance imaging (MRI), have significantly enhanced the ability to differentiate between low- and high-grade chondrosarcomas. Despite these imaging advancements, accurately distinguishing between different cartilage tumor types, specifically between ACTs and higher grade chondrosarcomas, remains challenging(7). Furthermore, the increased use of diagnostic imaging and an aging population have led to a significant rise in the incidence of cartilage tumors in recent years(4). Consequently, differentiating between benign cartilaginous tumors or ACTs and high-grade chondrosarcomas is becoming increasingly relevant. The management of cartilaginous tumors have evolved, with low-grade or benign cartilaginous tumors now being treated with less aggressive approaches, such as curettage or observation, while high-grade chondrosarcomas typically require extensive surgical resection and often necessitate limb reconstruction(10, 13, 14). Recent literature also supports active surveillance and MRI follow-up as safe for benign or low-grade cartilaginous tumors, with no significant advantage shown for intralesional curettage over conservative clinical and radiological monitoring(15, 16).

Background of osteosarcoma

Osteosarcoma is a primary malignant bone producing tumor first described by Boyer et al. in 1805(17). However, a recent discovery by a team of South-African scientists revealed a likely case of osteosarcoma in a 1.7 million year old metatarsal bone of a human ancestor, representing the earliest known instance of bone cancer(18) (Figure 1). This indicates that this disease has been a longstanding issue for humanity. Historically, bone tumors,

particularly osteosarcoma, were treated with amputation, often resulting in a quick death due to distant metastases(1, 19). This approach led to unsatisfactory cosmetic results, loss of physical function, and a poor 5-year survival rate of approximately 20%(19, 20). However, advances in diagnostic imaging, adjuvant chemotherapy, and surgery significantly improved 5-year survival rates to approximately 65%, shifting the treatment of primary malignant bone tumors from amputation to limb-salvaging surgery(21, 22).

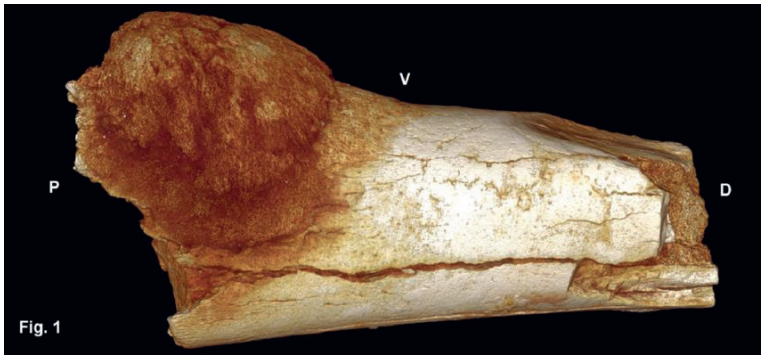


Figure 1. A hominin 5th metatarsal, exhibits a hemi-spherical bony mass located on the proximo-ventral aspect of the shaft, abutting the cortical bone surface.

Recent diagnostic and prognostic advances in osteosarcoma

Dr. Norman Jaffe was one of the pioneers in the use of chemotherapy and significantly changed the treatment landscape for osteosarcoma patients(23, 24). In 1982, Link et al. performed a multi-institutional randomized study on patients with non-metastatic extremity osteosarcoma. They compared survival outcomes after treatment with Methotrexate, Adriamycin, and Cisplatin (MAP) versus observation after surgical resection. They found that the 2-year relapse-free survival, including both local relapse and distant metastases, was 66% with (neo-)adjuvant chemotherapy, compared to 17% in the observation group(19). Since then, the combination of chemotherapy and surgical resection has remained the gold standard treatment for osteosarcoma patients(25-27). Accompanied with a massive improvement of patient survival, the need for limb salvaging surgery came up. Additionally, Professor Andrew Huvos, a distinguished professor in

pathology, introduced a classification that was named after him to assess histological response to neo-adjuvant chemotherapy (NAC)(28-30). According to this classification, a favorable response to NAC is characterized by <10% viable tumor cells in the resection specimen, whereas >10% viable tumor cells indicate poor response(29, 30). Despite limitations such as examining only one slab of tumor tissue, inter-observer variability, and the inability to assess response pre-resection, this classification remains widely regarded as the gold standard for assessing response to NAC.

The evolution of massive bone defect reconstruction

As described previously, the gold standard for treating primary malignant bone tumors has shifted from amputation to limb-salvaging tumor resection during the past century, aiming to preserve both limb function and appearance. Advances in chemotherapy, radiotherapy, and surgical techniques have further enhanced treatment effectiveness, making limb-salvaging surgery a less invasive and more viable option.

One of the forerunners of reconstructive surgery was the rotationplasty, an ablative but limb-salvaging procedure first described by Borggreve et al. in the 1930s. Initially used for patients with congenital femoral deficiencies, this procedure is most often performed in pediatric patients, and involves rotating the lower limb 180 degrees and reattaching it after resection of the distal femur or proximal tibia, including the knee joint(31). The ankle joint then functions as a knee joint. Rotationplasty offers a durable and functional alternative to above-knee amputation, and is still used today for reconstruction after tumor resection(32).

Dr. William Enneking was a pioneer in limb-salvage surgery, driven by the need for durable and functional reconstructions of large bone defects following tumor resection, and described his experiences in his book “Musculoskeletal Tumor Surgery” in 1983(33). Since then, various reconstructive procedures have been developed, including allograft reconstructions using donor bone tissue, autograft reconstructions involving patient’s own bone tissue (often a harvested fibula), and allograft-prosthetic composites (APCs) that

combine allograft with prosthetic components(33-39). Additionally, custom-made prostheses tailored to the patients' specific anatomy and defects, as well as mega prostheses for the reconstruction of large bone defects have been described(37, 40, 41). Each technique has its own indications, advantages, and disadvantages. Despite relative high complication rates in orthopaedic oncology, these procedures are widely used.

In this thesis, we will focus specifically on endoprosthetic reconstructions for tumor defects (i.e., megaprostheses). The early designs of the endoprosthetic reconstructions, laid the groundwork for the development of the different modular systems which could be adjusted depending on the patient's specific extent of the tumor. The KOTZ Modular Femur and Tibia Reconstruction (KMFTR) system, developed by Dr. Kotz and colleagues in Vienna, Austria, from the late 1970s to 1980s, was among the first modular prosthetic systems(38). The system allowed for intra-operative adjustments and adaptation to various bone defects. Subsequently, other systems were brought to the market, such as the Howmedica Modular Resection System (HMRS), the Global Modular Replacement System (GMRS), Stanmore, the Orthopaedic Salvage System (OSS), and others(42-44). In 1992, Implantcast GmbH (Buxtehude, Germany) introduced the Modular Universal Tumor And Revision System (MUTARS). MUTARS has since become widely adopted for reconstructions in various locations including the upper extremity, pelvis, and lower extremity(39, 45, 46).

Aim and outline of this thesis

Bone tumors, including osteosarcoma and chondrosarcoma, present significant challenges in diagnosis, prognosis prediction, and treatment. Since the 1970s, the treatment paradigms for these tumors have evolved, yet many aspects remain static or minimally changed. For instance, osteosarcoma treatment has largely adhered to established protocols, while treatment for low-grade chondrosarcoma has gradually shifted towards less aggressive approaches.

Improving diagnostic accuracy in chondrosarcoma can prevent both under- and overtreatment, thereby reducing complications and mortality, which is essential for improving patient care.

One of the current challenges in osteosarcoma treatment is to identify patients with a high-risk of poor prognosis. Although there are no evidence-based alternative therapies available at this moment, these high-risk patients could be potential subjects for future trials exploring novel treatment regimens. A potential tool for pre-operative identification of high-risk osteosarcoma patients is the use of use of dynamic contrast enhanced MRI to evaluate the response to neoadjuvant chemotherapy.

Challenges in the reconstructive treatment of patients with bone tumors remain. Bone tumors' rarity, the diversity among study populations, and the wide array of reconstructive systems globally have resulted in a scarcity of large-scale, high-quality studies on endoprosthetic reconstruction outcomes. The challenge now lies in consolidating data through multicenter collaborations within a scientific landscape governed by varying rules and agreements across countries and continents. For the reconstructive treatment, we tried to achieve this by setting up the MUTARS Orthopaedic Registry Europe (MORE), a multicenter global initiative, aiming to register as much as possible MUTARS cases, regardless of the indication or location of the reconstruction. This collective effort aims to enhance our understanding on the occurrence of complications, identify associated risk factors, and ultimately to improve patient outcomes in musculoskeletal surgery.

Part I of this thesis focuses on a potential novel diagnostic tool for chondrosarcoma, prognostic factors for survival and advances in the diagnostic process for osteosarcoma patients.

Chapter 2 features the outcomes from a single center explorative pilot study. This study evaluates the eNose's ability to differentiate between healthy individuals and patients with chondrosarcoma by analyzing their volatile organic compound (VOC) profiles in exhaled breath. In **chapter 3**, we assessed the oncological outcomes for osteosarcoma in three different age groups (children, adolescents and young adults [AYAs], and adults), and described risk factors for event-free and overall survival in different age groups. In **chapter 4,** we present a multicenter study aiming to explore the potential of response prediction to neoadjuvant chemotherapy (NAC) by the relative wash-in rate (rWIR), as a prognostic factor for clinical outcome and determine its added value to known prognostic factors in osteosarcoma patients.

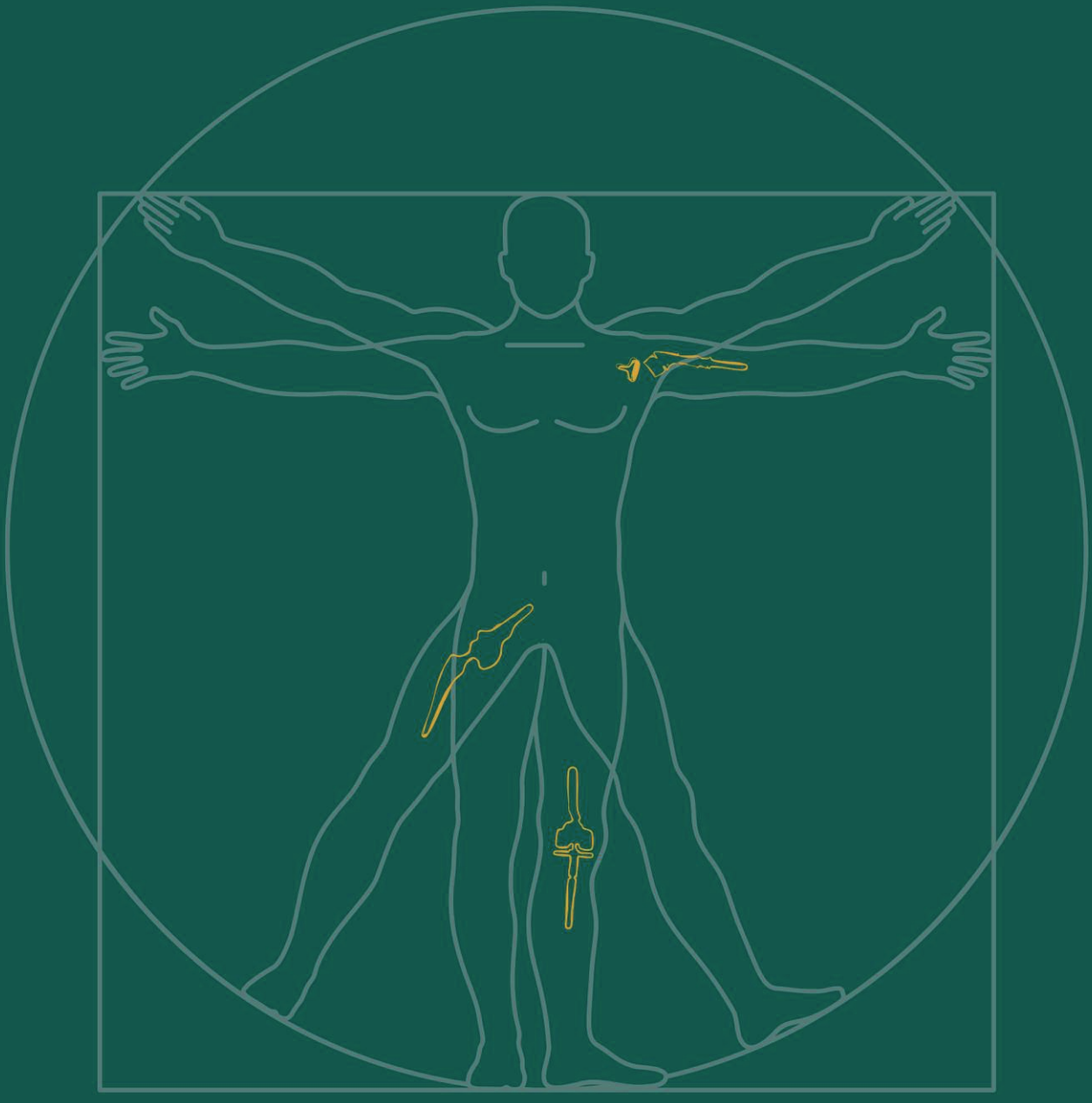
Part II of this thesis focuses on the evaluation of clinical outcomes of patients reconstructed with various types of MUTARS endoprosthetic reconstructions following orthopaedic oncological resections, utilizing the MUTARS Orthopaedic Registry Europe. **Chapter 5** evaluates the mid-term clinical outcomes of patients who underwent periacetabular tumor resection followed by reconstruction with the LUMiC prosthesis. The chapter evaluates complication rates, identifies associated risk factors, and estimates cumulative incidences of implant revision (i.e. the probability of revision at any time during the follow-up). **Chapter 6** estimates the cumulative incidences of implant revision for three different locking-mechanisms used in MUTARS distal femur and proximal tibia reconstructions. **Chapter 7** outlines the clinical outcomes of patients reconstructed with three different MUTARS proximal humerus endoprostheses. The study investigates complication rates, associated risk factors, cumulative incidences of implant revision, and functional outcomes for hemiarthroplasty, reverse shoulder arthroplasty, and total shoulder arthroplasty.

References

1. Ferguson JL, Turner SP. Bone Cancer: Diagnosis and Treatment Principles. Am Fam Physician. 2018;98(4):205-13.
2. Ferrari A, Dirksen U, Bielack S. Sarcomas of Soft Tissue and Bone. Prog Tumor Res. 2016;43:128-41.
3. Ottaviani G, Jaffe N. The epidemiology of osteosarcoma. Cancer Treat Res. 2009;152:3-13.
4. van Praag Veroniek VM, Rueten-Budde AJ, Ho V, Dijkstra PDS, Fiocco M, van de Sande MAJ. Incidence, outcomes and prognostic factors during 25 years of treatment of chondrosarcomas. Surg Oncol. 2018;27(3):402-8.
5. Thorkildsen J, Myklebust TÅ. The national incidence of chondrosarcoma of bone; a review. Acta Oncologica. 2023;62(2):110-7.
6. Paget J. Lectures on surgical pathology. London: Longman, Brown, Green, and Longmans. 1853;1.
7. Zając AE, Kopeć S, Szostakowski B, Spałek MJ, Fiedorowicz M, Bylina E, et al. Chondrosarcoma-from Molecular Pathology to Novel Therapies. Cancers (Basel). 2021;13(10).
8. Gazendam A, Popovic S, Parasu N, Ghert M. Chondrosarcoma: A Clinical Review. J Clin Med. 2023;12(7).
9. Gilbert A, Tudor M, Montanari J, Commenchail K, Savu DI, Lesueur P, et al. Chondrosarcoma Resistance to Radiation Therapy: Origins and Potential Therapeutic Solutions. Cancers (Basel). 2023;15(7).
10. Gelderblom H, Hogendoorn PC, Dijkstra SD, van Rijswijk CS, Krol AD, Taminiau AH, et al. The clinical approach towards chondrosarcoma. Oncologist. 2008;13(3):320-9.
11. Fletcher C, Bridge JA, Hogendoorn PCW, Mertens F. WHO classification of tumours of soft tissue and bone: WHO classification of tumours, vol. 5: World Health Organization; 2013.
12. Fromm J, Klein A, Baur-Melnyk A, Knösel T, Lindner L, Birkenmaier C, et al. Survival and prognostic factors in conventional central chondrosarcoma. BMC Cancer. 2018;18(1):849-.
13. Dierselhuis EF, Goulding KA, Stevens M, Jutte PC. Intralesional treatment versus wide resection for central low-grade chondrosarcoma of the long bones. Cochrane Database Syst Rev. 2019;3(3):Cd010778.
14. Deckers C, de Leijer EM, Flucke U, de Rooy JWJ, Schreuder HWB, Dierselhuis EF, et al. Curettage and cryosurgery for enchondroma and atypical cartilaginous tumors of the long bones: Oncological results of a large series. J Surg Oncol. 2021;123(8):1821-7.
15. Omlor GW, Lohnherr V, Lange J, Gantz S, Mechtersheimer G, Merle C, et al. Outcome of conservative and surgical treatment of enchondromas and atypical cartilaginous tumors of the long bones: retrospective analysis of 228 patients. BMC Musculoskelet Disord. 2019;20(1):134.
16. Scholte CHJ, Dorleijn DMJ, Krijvenaar DT, van de Sande MAJ, van Langevelde K. Wait-and-scan: an alternative for curettage in atypical cartilaginous tumours of the long bones. Bone Joint J. 2024;106-b(1):86-92.
17. Boyer A, Richerand A. The lectures of Boyer upon diseases of the bones: J. Humphreys; 1805.
18. Odes EJ, Randolph-Quinney PS, Steyn M, Throckmorton Z, Smilg JS, Zipfel B, et al. Earliest hominin cancer: 1.7-million-year-old osteosarcoma from Swartkrans Cave, South Africa. South African Journal of Science. 2016;112(7/8):5.
19. Link MP, Goorin AM, Miser AW, Green AA, Pratt CB, Belasco JB, et al. The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. N Engl J Med. 1986;314(25):1600-6.
20. Ottaviani G, Robert RS, Huh WW, Jaffe N. Functional, psychosocial and professional outcomes in long-term survivors of lower-extremity osteosarcomas: amputation versus limb salvage. Cancer Treat Res. 2009;152:421-36.

21. Yang Y, Han L, He Z, Li X, Yang S, Yang J, et al. Advances in limb salvage treatment of osteosarcoma. J Bone Oncol. 2018;10:36-40.
22. Huvos AG. Bone tumors: Diagnosis, treatment and prognosis Second edition. United States: WB Saunders CBS Educ and Professional Publ; 1987.
23. Jaffe N, Puri A, Gelderblom H. Osteosarcoma: evolution of treatment paradigms. Sarcoma. 2013;2013:203531.
24. Jaffe N, Patel SR, Benjamin RS. Chemotherapy in Osteosarcoma: Basis for Application and Antagonism to Implementation; Early Controversies Surrounding its Implementation. Hematology/Oncology Clinics of North America. 1995;9(4):825-40.
25. Bone sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Annals of Oncology. 2014;25:iii113-iii23.
26. Ingley KM, Maleddu A, Grange FL, Gerrand C, Bleyer A, Yasmin E, et al. Current approaches to management of bone sarcoma in adolescent and young adult patients. Pediatr Blood Cancer. 2022;69(2):e29442.
27. Jafari F, Javdansirat S, Sanaie S, Naseri A, Shamekh A, Rostamzadeh D, et al. Osteosarcoma: A comprehensive review of management and treatment strategies. Ann Diagn Pathol. 2020;49:151654.
28. Carlson DL. Dr. Andrew Huvos (1934-2006) retrospective: a tribute to the pathologist and the man. Head Neck Pathol. 2013;7(1):1-4.
29. Rosen G, Caparros B, Huvos AG, Kosloff C, Nirenberg A, Cacavio A, et al. Preoperative chemotherapy for osteogenic sarcoma: selection of postoperative adjuvant chemotherapy based on the response of the primary tumor to preoperative chemotherapy. Cancer. 1982;49(6):1221-30.
30. Huvos AG, Rosen G, Marcove RC. Primary osteogenic sarcoma: pathologic aspects in 20 patients after treatment with chemotherapy en bloc resection, and prosthetic bone replacement. Arch Pathol Lab Med. 1977;101(1):14-8.
31. Borggreve. Kniegelenksersatz durch das in der Beinlängsachse um 180 gedrehte Fussgelenk. Archiv für orthopädische und Unfall-Chirurgie, mit besonderer Berücksichtigung der Frakturenlehre und der orthopädisch-chirurgischen Technik. 1930;28(1):175-8.
32. Hardes J, Gebert C, Hillmann A, Winkelmann W, Gosheger G. [Rotationplasty in the surgical treatment plan of primary malignant bone tumors. Possibilities and limits]. Der Orthopade. 2003;32(11):965-70.
33. Enneking WF. Musculoskeletal Tumor Surgery: Churchill Livingstone; 1983.
34. Muscolo DL, Ayerza MA, Aponte-Tinao LA. Massive allograft use in orthopedic oncology. Orthop Clin North Am. 2006;37(1):65-74.
35. Chiarello E, Cadossi M, Tedesco G, Capra P, Calamelli C, Shehu A, et al. Autograft, allograft and bone substitutes in reconstructive orthopedic surgery. Aging Clin Exp Res. 2013;25 Suppl 1:S101-3.
36. Donati D, Colangeli M, Colangeli S, Di Bella C, Mercuri M. Allograft-prosthetic composite in the proximal tibia after bone tumor resection. Clin Orthop Relat Res. 2008;466(2):459-65.
37. Kotrych D, Angelini A, Bohatyrewicz A, Ruggieri P. 3D printing for patient-specific implants in musculoskeletal oncology. EFORT Open Rev. 2023;8(5):331-9.
38. Kotz R. The History of Bone Tumour Treatment and the State of the Art in Vienna. Pril (Makedon Akad Nauk Umet Odd Med Nauki). 2017;38(3):31-8.
39. Bus MPA, Szafranski A, Sellevold S, Goryn T, Jutte PC, Bramer JAM, et al. LUMiC(®) Endoprosthetic Reconstruction After Periacetabular Tumor Resection: Short-term Results. Clin Orthop Relat Res. 2017;475(3):686-95.
40. Bus MPA, van de Sande MAJ, Fiocco M, Schaap GR, Bramer JAM, Dijkstra PDS. What Are the Long-term Results of MUTARS(®) Modular Endoprostheses for Reconstruction of Tumor Resection of the Distal Femur and Proximal Tibia? Clin Orthop Relat Res. 2017;475(3):708-18.

41. Jeys LM, Kulkarni A, Grimer RJ, Carter SR, Tillman RM, Abudu A. Endoprosthetic reconstruction for the treatment of musculoskeletal tumors of the appendicular skeleton and pelvis. J Bone Joint Surg Am. 2008;90(6):1265-71.
42. Kotz R. [Megaprostheses: KMFTR to GMRS]. Orthopade. 2010;39(10):922-30.
43. Smolle MA, Andreou D, Tunn PU, Leithner A. Advances in tumour endoprostheses: a systematic review. EFORT Open Rev. 2019;4(7):445-59.
44. Schindler OS, Cannon SR, Briggs TW, Blunn GW. Stanmore custom-made extendible distal femoral replacements. Clinical experience in children with primary malignant bone tumours. J Bone Joint Surg Br. 1997;79(6):927-37.
45. Streitbuerger A, Henrichs M, Gosheger G, Ahrens H, Nottrott M, Guder W, et al. Improvement of the shoulder function after large segment resection of the proximal humerus with the use of an inverse tumour prosthesis. Int Orthop. 2015;39(2):355-61.
46. Schmolders J, Koob S, Schepers P, Gravius S, Wirtz DC, Burger C, et al. [The Role of a Modular Universal Tumour and Revision System (MUTARS®) in Lower Limb Endoprosthetic Revision Surgery - Outcome Analysis of 25 Patients]. Z Orthop Unfall. 2017;155(1):61-6.



PART I

Advances in the evaluation of diagnosis and prognosis in patients with bone tumors

Chapter 2

Diagnosis of chondrosarcoma in a noninvasive way using volatile organic compounds in exhaled breath: a pilot study

R.E. Evenhuis[1], I. Acem[1], V.M. van Praag[1], R.J.P. van der Wal[1], M.P.A. Bus[1], M.A.J. van de Sande[1]

1. Department of Orthopaedic Surgery, Leiden University Medical Center, 2300RC Leiden, the Netherlands

Journal of Future Oncology, June 2024

Abstract

Aim: Aim of this explorative pilot study was to evaluate the capability of an electronic nose (aeoNose, the eNose Company) to classify healthy individuals and patients with chondrosarcoma, based on their volatile organic compound profiles in exhaled breath. Materials & methods: Fifty-seven patients (25 healthy controls, 24 chondrosarcoma and 8 different benign lesions) were included in the study from 2018 to 2023. An artificial neural network was used as classifier. Results: The developed model had a sensitivity of 75%, and a specificity of 65% with an AUC of 0.66. Conclusion: Results show that there is not enough evidence to include the aeoNose as diagnostic biomarker for chondrosarcoma in daily practice. However, the aeoNose might play an additional role alongside MRI, in questionable chondrosarcoma cases.

Background

Chondrosarcoma is a rare malignant neoplasm, originating from cartilaginous tissue and accounts for approximately 20% of all primary malignant bone tumors(1). The prognosis and outcomes depend on chondrosarcoma subtype, grade, tumor location, timely and accurate identification and surgical treatment(2, 3). Most patients with high-grade chondrosarcoma present with pain at night and local swelling, while benign or atypical cartilaginous tumors are most often coincidental findings(2, 4, 5). The diagnostic pathway for chondrosarcoma consists of plain radiography, followed by magnetic resonance imaging (MRI). In some cases, or based on center preferences, a biopsy may be performed, although biopsies of cartilaginous lesions are notoriously unreliable because of a substantial risk of sampling error and has the potential risk of seeding along the biopsy tract. Moreover, pathological assessment has considerable interobserver variability(2, 6, 7). The diagnostic accuracy of MRI for the differentiation between a benign cartilaginous lesion and a high-grade chondrosarcoma is approximately 90%(8). However, there are still cases in which the diagnosis remains debatable(9). The importance of an accurate preoperative diagnosis lies in the potential consequences of the treatment. High-grade chondrosarcomas require resection with clear surgical margins and often subsequent reconstruction, carrying a substantial risk of complications and considerable morbidity. On the other hand, benign cartilaginous lesions may be followed with MRI, or treated with less aggressive surgery, in other words, intralesional curettage(3, 10-13). Therefore, there is a need for an additional diagnostic tool to differentiate between the two entities. Promising results have been reported for using an electronic nose (eNose) in detecting various tumor types, including head and neck cancer, lung cancer, colorectal cancer and soft tissue sarcoma(14-17). eNoses analyze volatile organic compounds (VOCs) in exhaled breath(16, 18). VOCs are degradation products of biochemical processes in the human body. Their composition can be influenced by the presence of specific pathological processes within the body and can be detected in body fluids such as urine, feces, saliva or blood(14, 16, 19). To date, there is no literature on the detection of chondrosarcoma using VOC profiles. Therefore, the objective of this explorative study is to evaluate if the

aeoNose can be used to distinguish healthy individuals from patients with chondrosarcoma, based on their VOC profiles in exhaled breath.

Materials & methods

Design, setting & participants

Materials and methods were previously described in a similar study, employing the aeoNose (aeoNose, the eNose Company, Zutphen, The Netherlands) to detect soft-tissue sarcoma, during the same period(15). This single-center prospective pilot study was conducted at the Leiden University Medical Center, The Netherlands (LUMC), a tertiary referral center for bone tumors. Patients were included between 2018 and 2023. At our outpatient clinic, we asked all patients who were suspected of having a high-grade chondrosarcoma to participate in this study. Patients were enrolled between 2018 and 2023. Minimum age was 18 years. Patients with any history of cancer, chronic respiratory disease and chemo- or radiotherapy were excluded. Furthermore, we excluded patients in whom metastases were found within 3 months following primary surgery, as we theorized that these were easier to identify. The goal was to identify patients with localized disease who could be considered for curative treatment. The breath test was performed in parallel with the regular diagnostic work up. As a control group, we invited people who visited the outpatient clinic for other (non-oncological) conditions, people who accompanied a patient to our outpatient clinic, and department employees. The control group underwent an eligibility check through an interview on their medical history, without additional diagnostic tests such as radiography. Suspected chondrosarcoma cases that turned out to be benign were excluded from the primary analysis (model 1) but were included in the secondary analysis as controls (model 2), to increase the number of patients. The control group was matched to our chondrosarcoma population based on age and sex in a 1:1 ratio. Both controls and chondrosarcoma cases adhered to the same in- and exclusion criteria. The patient records were reviewed by the investigator to obtain baseline characteristics, medical history and tumor characteristics. In total, 57 patients were included (35 males,

61%). The median age for the entire cohort was 51 years (interquartile range [IQR] 48–70; Table 1). Among them, 24 patients (42%) had a histologically proven high-grade chondrosarcoma (grade 2, 3 or dedifferentiated), while eight (14%) had a benign bone tumor (atypical cartilaginous tumor [n = 3, one distal femur, two of the hand], chordoma [n = 2], fibrous dysplasia [n = 1], hemangioendothelioma [n = 1], or Langerhans cell histiocytosis [n = 1]). There were 25 (44%) healthy controls (Table 2).

Materials & procedure

The eNose used in this study is a portable, battery -powered device designed to analyze VOCs. The study participants were instructed to abstain from food, drinks (except for water), and smoking at least 3h prior to the breath test. They were instructed to breathe through a disposable connecting mouthpiece, which included a carbon filter equipped with high-efficiency particulate air filters and one-way valves to prevent viral or bacterial contamination of the device, for 5 min. Furthermore, a nose clip was applied to prevent the entry of unfiltered air during measurements, minimizing external influences on VOCs (see appendix for setup, Figure 1). The breathing test consisted of 5 min of breathing followed by 10 min of aeoNose regeneration, thus a total of 15 min. The initial 2 min were used to clean the lungs with filtered air, to eliminate external VOCs. During the subsequent 3 min, exhaled breath interacts with three hotplate metal-oxide sensors with distinct material properties. These sensors are periodically heated between 260 and 340◦C, simulating multiple identical sensors, functioning at various temperatures. This triggers a redox reaction at the surface, resulting in changes in conductivity over time. The alterations in conductivity form a distinctive VOC profile, or breath print for each patient. Detailed information on the aeNose technology was previously published elsewhere(20).

Statistical analysis

Descriptive statistics were used to report baseline characteristics. Categorical data are presented as contingency tables (frequencies and percentages). Medians including interquartile range (IQR) were reported for continuous data. To assess differences in baseline characteristics between patients and the control group, the Mann–Whitney U

test, or the Chi-square test was performed for continuous and categorical variables, respectively. No formal sample size calculation was performed, since this is a pilot study with 25 chondrosarcoma patients. Data analysis was performed using SPSS version 25.0. (IBM Corp., NY, USA). The level of significance was set at a p-value < 0.05. The breath test resulted in an aeoNose measurement, or breath print, with a unique time-series of conductivity values for every sensor. Developing an algorithm for distinguishing exhaled-breath patterns involved training an artificial neural network (ANN), with data analysis carried out using the proprietary software called 'Aethena' (The eNose Company, Zuthpen, The Netherlands). Data compression was performed using a TUCKER3-like solution, as Waltman et al. described previously(21). Subsequently, the ANN served as a classifier for the created models, ranked by the area under the curve (AUC) through the leave-10%-out cross validation method (LOCV). The LOCV method divides data into subsets, each containing 10% of patients, allowing classifications based on 10 separate models. The validation technique assesses how results of a predictive model will be generalized to an independent dataset. Thus, participants were classified in 10 steps based on 10 separate models, resulting in an ROC based on unseen training data. Optimal AUC results, along with the corresponding sensitivity and specificity (including 95% CI), were reported for each analysis. The predicted response values for healthy controls and chondrosarcoma patients were presented in a scatterplot. A detailed description of the statistical method used by aeoNose, can be found in the article of Kort et al.(22).

Study ethics

This study was approved by our institutional review board (P19.046). All study participants signed an informed consent form, prior to participation.

Table 1. Study population.

	Model 1			**Model 2**		
	Chondrosarcoma (n=24)	**Controls** (n=25)	**p-value**	**Chondrosarcoma** (n=24)	**Controls** (n=33)	**p-value**
Age, Median (IQR)	51 (40-58)	54 (41-61)	0.99	51 (40-58)	54 (45-61)	0.82
Sex, male	16 (67%)	15 (60%)	0.63	16 (67%)	19 (58%)	0.49

IQR = interquartile range

Table 2. Tumor details.

Diagnosis	**Model 1**	**Model 2**
Chondrosarcoma (n=24)		
Chondrosarcoma grade 2	12 (50%)	12 (50%)
Chondrosarcoma grade 3	6 (25%)	6 (25%)
Periosteal chondrosarcoma	5 (21%)	5 (21%)
Dedifferentiated chondrosarcoma	1 (4%)	1 (4%)
Benign lesions (n=8)		
Atypical cartilaginous tumor	-	3 (38%)
Chordoma	-	2 (25%)
Fibrous dysplasia	-	1 (13%)
Hemangioendothelioma	-	1 (13%)
Langerhans cell histiocytosis	-	1 (13%)
Tumor location		
Axial skeleton (including head)	16 (67%)	2 (25%)
Upper extremity	2 (8%)	3 (38%)
Lower extremity	6 (25%)	3 (38%)

Results

Model 1

The primary analysis consisted of 24 patients with a chondrosarcoma, and 25 healthy controls. This model predicted the correct diagnosis in 34/49 patients, yielding an accuracy of 70%. A threshold of -0.22 was used, to maximize sensitivity and specificity; 18 out of 24 chondrosarcoma patients were correctly identified by the aeoNose, and six false negative results were observed. Sixteen out of 25 healthy controls were correctly identified, and nine false positive results were observed. This resulted in a sensitivity of 75% (95% CI: 53–89%), and a specificity of 64% (95% CI: 43–81%). The corresponding ROC curve for the best fit of model 1 comprised of an area under the curve (AUC) of 0.66 (Figure 2A). The scatterplot shows the predicted value of each measurement (Figure 2B).

Model 2

The second analysis was performed using an expanded study population. The same 24 chondrosarcoma and 25 control patients were included. However, eight patients who were initially suspected of having a chondrosarcoma (but turned out to have a benign bone tumor), were added to the control-group. This model predicted the diagnosis correctly in 39/57 patients, yielding an accuracy of 68%. Eighteen out of 24 chondrosarcoma patients were correctly identified by the aeoNose, and six false negative results were observed. Twenty-one out of 33 controls were correctly identified, and 12 false positive results were observed. This resulted in a sensitivity of 75% (95%CI: 53–89%), and a specificity of 64% (95% CI: 45–79). The corresponding ROC curve for the best fit of model 2 comprised of an AUC of 0.69, with a threshold of -0.22 (Figure 3A). The scatterplot shows the predicted value of each measurement (Figure 3B).

Figure 1. Model 1: (A) ROC curve (AUC: 0.66). (B) Scatter plot of individual predicted values based on the cross-validated model 1. The red squares represent patients with chondrosarcoma, the green circles represent healthy controls. AUC: Area under the curve; ROC: Receiver operating characteristic.

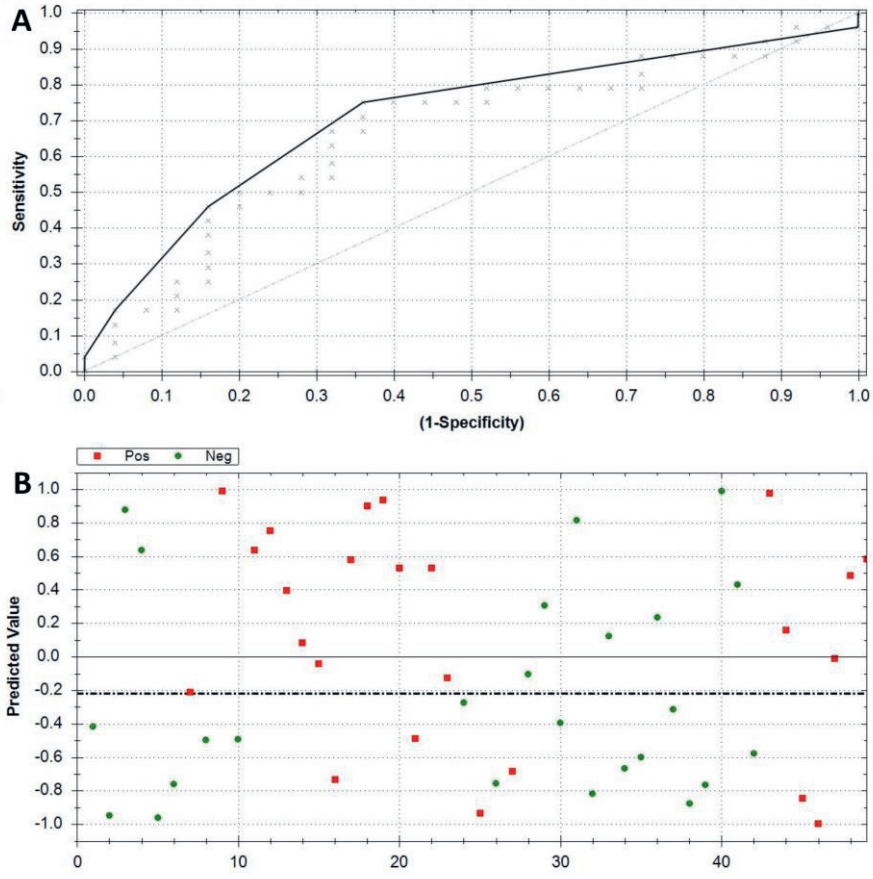


Figure 2. Model 2: (A) ROC curve (AUC: 0.69) (B) Scatter plot of individual predicted values based on the cross-validated model 2. The red squares represent patients with chondrosarcoma, the green circles represent healthy controls. AUC: Area under the curve; ROC: Receiver operating characteristic.

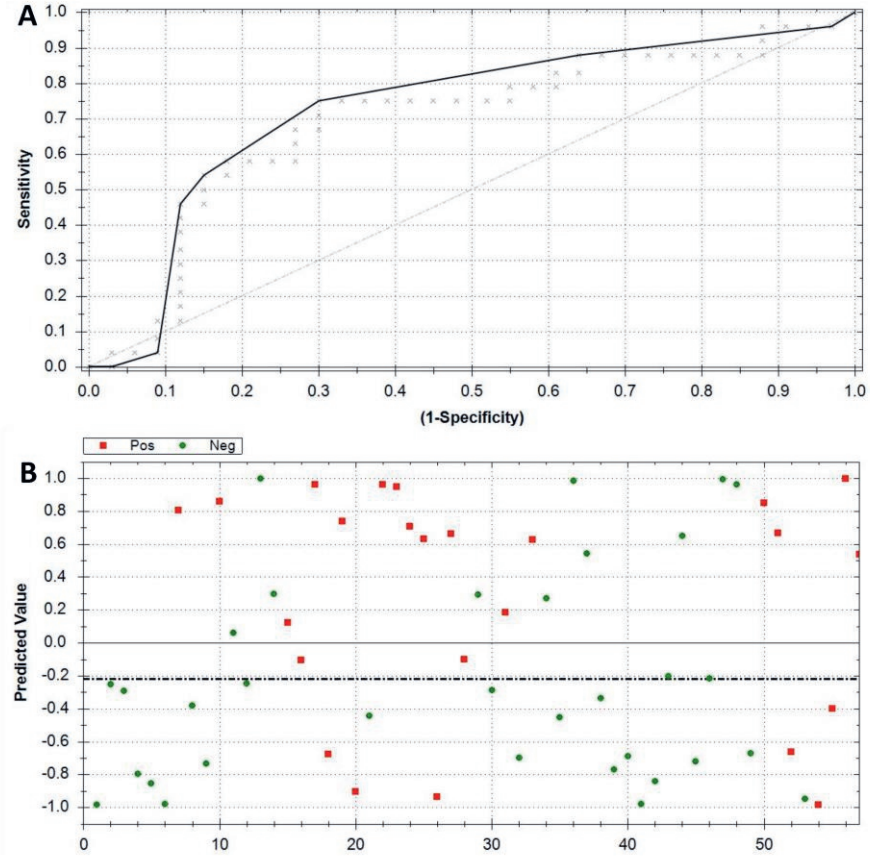


Figure 3. Setup aeoNose.

Discussion

Electronic noses potentially offer a noninvasive, easy-to-use method for the diagnosis of various cancer types by analyzing volatile organic compounds in exhaled air. This is the first pilot study exploring the potential of electronic noses in the diagnostic process of chondrosarcoma of bone. Our model shows an AUC of 0.66 with a 75% sensitivity and a 64% specificity. Oxidative stress, inflammation and cell death can change VOC profiles. An electronic nose, as well as gas chromatography-mass spectrometry (GC-MS), can detect changes in these VOC profiles. Metabolic VOC profiling could therefore be a potential tool for diagnostic purposes, since it reflects the metabolic state of cells or even organisms(23). GC-MS is a standardized method which is suitable for the detection of individual VOC profiles based on molecular weight. However, this method is expensive and requires trained personnel(24). The aeoNose uses VOC profile pattern recognition and needs to be trained by a training dataset. Accuracy of the diagnostic tool depends among other things on the size of the training dataset, and the representativeness of the sample population(25). Moreover, this instrument is user-friendly, inexpensive, and, once trained

and validated, capable of real-time analysis for chondrosarcoma detection. This technique holds potential as a screening method to achieve a higher pretest probability, upon validation and availability of other models.

Although Alhumaid et al. demonstrated an adequate efficacy of MRI in differentiating between ACTs and high-grade chondrosarcoma, the SLICED study group found a relatively low reliability in grading cartilaginous neoplasms (benign, low-grade malignant or high-grade malignant) in the long bones. The interobserver reliability for pathologists was 0.443, and for radiologists, it was 0.345, judging the reliability as fair to moderate reliability in differentiating between benign and malignant cartilaginous lesions(8, 26). Again, this emphasizes the need for an additional diagnostic test to enhance the diagnostic workup and prevent unnecessary overtreatment or undertreatment. While the diagnostic accuracy of the aeoNose, as observed in this explorative study, is currently insufficient for a reliable diagnosis or exclusion of chondrosarcoma of bone, it could potentially serve as an additional diagnostic tool in addition to MRI, particularly in cases involving uncertain high-grade chondrosarcoma. However, the question remains whether the accuracy of the aeoNose can be improved in the future with a larger study population. To date, there are no studies on the use of VOC profiles in exhaled breath for the diagnosis of high-grade chondrosarcoma. Previous studies have shown that eNoses are capable to differentiate between healthy controls and conditions such as; head and neck cancer, lung cancer, breast cancer, gastric cancer, colorectal cancer, prostate cancer and soft tissue sarcoma with an AUC ranging from 79 to 90%(15, 17, 21, 27-31). The lower AUC observed in our study, might be attributed to the heterogeneity of chondrosarcoma, which includes various subtypes such as periosteal chondrosarcoma, chondrosarcoma grade 2 and 3 and dedifferentiated chondrosarcoma, each distinguished by unique characteristics(32). The development of a model that encompasses VOCs from all these diverse chondrosarcoma subtypes might potentially lead to reduced diagnostic accuracy.

Limitations

This study has a number of limitations. First, our model may have been affected by artifacts unrelated to chondrosarcoma, resulting from exogenous VOCs, primarily due to

the limited sample size. We attempted to over- come this limitation by employing a mouth-piece with carbon filters to eliminate exogeneous VOCs, and by performing all measurements in the same room. Future larger study populations are needed to explore the true differences in VOC profiles. Second, the population of chondrosarcoma patients is heterogenous with regard to gender, age, BMI, diet, smoking behavior and medical history, while these factors may influence VOC profiles(21, 33, 34). We tried to overcome this limitation by matching our control group to the chondrosarcoma group by age and gender. However, the limited sample sizes hampered us from matching for the other potential influencing factors. Furthermore, we instructed participants to abstain from food, drinks and smoking 3h prior to testing and only included patients without a history of chemo- and radiotherapy, which causes oxidative stress. Third, our model was internally cross-validated, limiting its reliability and generalizability to a broader study population in diverse clinical settings. Acknowledging the necessity for future larger, externally validated studies to enhance the reliability and accuracy of the model, this explorative pilot study might offer direction for future more comprehensive research on this topic. Furthermore, it would be of particular interest to study whether the diagnostic accuracy can be improved by combining information from the aeoNose and MRI in debatable cases.

Conclusion

This pilot study contributes to the growing body of research investigating noninvasive diagnostic methods for chondrosarcoma. While the relatively low observed accuracy is currently insufficient to introduce VOC analysis as a diagnostic biomarker in daily practice, it might play a future role as an additional diagnostic tool in combination with MRI features to guide in questionable high-grade chondrosarcoma cases. Future research based on larger cohorts, with external validation is warranted before the aeoNose can be considered a reliable diagnostic tool for chondrosarcoma of bone.

Article highlights

• It is important to differentiate between high-grade chondrosarcoma and benign cartilaginous lesions, due to the potential consequences of the treatment.

• Diagnostic accuracy on high-grade chondrosarcoma can be challenging.

• This explorative study aimed to assess the feasibility of the aeoNose to differentiate between high-grade chondrosarcoma, and healthy controls.

• 24 high-grade chondrosarcoma patients, 25 controls and 8 benign cartilaginous lesions were included for breath analysis, and were matched on age and gender.

• The aeoNose uses volatile organic compound profile pattern recognition, and an artificial neural network appeared to be the most optimal classifier.

• This pilot study contributes to the growing body of research investigating noninvasive diagnostic methods for high-grade chondrosarcoma.

• The current accuracy is not sufficient to include the aeoNose as diagnostic biomarker for high-grade chondrosarcoma in daily practice, although the aeoNose might play an additional role in questionable high-grade chondrosarcoma cases.

• Future larger externally validated studies are warranted to improve the reliability, accuracy and to determine the role of the aeoNose in high-grade chondrosarcoma patients.

Acknowledgments

The eNose Company, Zutphen, The Netherlands, provided the eNose and corresponding software.

Author contributions

Conceptualization: VM van Praag, MAJ van de Sande, methodology: RE Evenhuis, I Acem, VM van Praag, MPA Bus, investigation: RE Evenhuis, I Acem, MPA Bus, data curation: RE Evenhuis, I Acem, writing (review and editing) RE Evenhuis, I Acem, MPA Bus, MAJ van de Sande, visualization: RE Evenhuis, I Acem, MPA Bus, RJP van der Wal , MAJ van de Sande, supervision: MPA Bus, RJP van der Wal, MAJ van de Sande.

Financial disclosure

The authors have no financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Competing interests disclosure

The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Writing disclosure

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval (Medical Ethical Committee of the Leiden University Medical Center (P19.046)) or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Data sharing statement

The study protocol can be request ed at the corresponding author (RE Evenhuis). Anonymized data is available on request.

References

1. Thorkildsen J, Taksdal I, Bjerkehagen B, Haugland HK, Børge Johannesen T, Viset T, et al. Chondrosarcoma in Norway 1990-2013; an epidemiological and prognostic observational study of a complete national cohort. Acta Oncol. 2019;58(3):273-82.
2. Gazendam A, Popovic S, Parasu N, Ghert M. Chondrosarcoma: A Clinical Review. J Clin Med. 2023;12(7).
3. van Praag Veroniek VM, Rueten-Budde AJ, Ho V, Dijkstra PDS, Fiocco M, van de Sande MAJ. Incidence, outcomes and prognostic factors during 25 years of treatment of chondrosarcomas. Surg Oncol. 2018;27(3):402-8.
4. Limaiem F, Davis DD, Sticco KL. Chondrosarcoma. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC.; 2023.
5. Unni KK. Cartilaginous lesions of bone. J Orthop Sci. 2001;6(5):457-72.
6. Jennings R, Riley N, Rose B, Rossi R, Skinner JA, Cannon SR, et al. An evaluation of the diagnostic accuracy of the grade of preoperative biopsy compared to surgical excision in chondrosarcoma of the long bones. Int J Surg Oncol. 2010;2010:270195.
7. Logie CI, Walker EA, Forsberg JA, Potter BK, Murphey MD. Chondrosarcoma: A Diagnostic Imager's Guide to Decision Making and Patient Management. Semin Musculoskelet Radiol. 2013;17(2):101-15.
8. Alhumaid SM, Alharbi At, Aljubair H. Magnetic Resonance Imaging Role in the Differentiation Between Atypical Cartilaginous Tumors and High-Grade Chondrosarcoma: An Updated Systematic Review. Cureus. 2020;12(10):e11237.
9. Jo I, Gould D, Schlicht S, Taubman K, Choong P. Diagnostic accuracy of functional imaging modalities for chondrosarcoma: A systematic review and meta-analysis. J Bone Oncol. 2019;19:100262.
10. Dierselhuis EF, Goulding KA, Stevens M, Jutte PC. Intralesional treatment versus wide resection for central low-grade chondrosarcoma of the long bones. Cochrane Database Syst Rev. 2019;3(3):Cd010778.
11. Deckers C, de Leijer EM, Flucke U, de Rooy JWJ, Schreuder HWB, Dierselhuis EF, et al. Curettage and cryosurgery for enchondroma and atypical cartilaginous tumors of the long bones: Oncological results of a large series. J Surg Oncol. 2021;123(8):1821-7.
12. Gelderblom H, Hogendoorn PC, Dijkstra SD, van Rijswijk CS, Krol AD, Taminiau AH, et al. The clinical approach towards chondrosarcoma. Oncologist. 2008;13(3):320-9.
13. Fromm J, Klein A, Baur-Melnyk A, Knösel T, Lindner L, Birkenmaier C, et al. Survival and prognostic factors in conventional central chondrosarcoma. BMC Cancer. 2018;18(1):849-.
14. Farraia MV, Cavaleiro Rufo J, Paciência I, Mendes F, Delgado L, Moreira A. The electronic nose technology in clinical diagnosis: A systematic review. Porto Biomed J. 2019;4(4):e42.
15. Acem I, van Praag VM, Mostert CQ, van der Wal RJ, Neijenhuis RM, Verhoef C, et al. Noninvasive detection of soft tissue sarcoma using volatile organic compounds in exhaled breath: a pilot study. Future Oncol. 2023;19(10):697-704.
16. Scheepers M, Al-Difaie Z, Brandts L, Peeters A, van Grinsven B, Bouvy ND. Diagnostic Performance of Electronic Noses in Cancer Diagnoses Using Exhaled Breath: A Systematic Review and Meta-analysis. JAMA Netw Open. 2022;5(6):e2219372.
17. Anzivino R, Sciancalepore PI, Dragonieri S, Quaranta VN, Petrone P, Petrone D, et al. The Role of a Polymer-Based E-Nose in the Detection of Head and Neck Cancer from Exhaled Breath. Sensors (Basel). 2022;22(17).
18. Gardner JW, Bartlett PN. A brief history of electronic noses. Sensors and Actuators B: Chemical. 1994;18(1):210-1.
19. Nakhleh MK, Amal H, Jeries R, Broza YY, Aboud M, Gharra A, et al. Diagnosis and Classification of 17 Diseases from 1404 Subjects via Pattern Analysis of Exhaled Molecules. ACS

Nano. 2017;11(1):112-25.
20. Bruins M, Gerritsen JW, van de Sande WWJ, van Belkum A, Bos A. Enabling a transferable calibration model for metal-oxide type electronic noses. Sensors and Actuators B: Chemical. 2013;188:1187-95.
21. Waltman CG, Marcelissen TAT, van Roermund JGH. Exhaled-breath Testing for Prostate Cancer Based on Volatile Organic Compound Profiling Using an Electronic Nose Device (Aeonose™): A Preliminary Report. European Urology Focus. 2020;6(6):1220-5.
22. Kort S, Brusse-Keizer M, Gerritsen JW, van der Palen J. Data analysis of electronic nose technology in lung cancer: generating prediction models by means of Aethena. J Breath Res. 2017;11(2):026006.
23. Janfaza S, Khorsand B, Nikkhah M, Zahiri J. Digging deeper into volatile organic compounds associated with cancer. Biol Methods Protoc. 2019;4(1):bpz014.
24. van de Goor RMGE, van Hooren MRA, Henatsch D, Kremer B, Kross KW. Detecting head and neck squamous carcinoma using a portable handheld electronic nose. Head & Neck. 2020;42(9):2555-9.
25. van de Goor R, van Hooren M, Dingemans A-M, Kremer B, Kross K. Training and Validating a Portable Electronic Nose for Lung Cancer Screening. Journal of Thoracic Oncology. 2018;13(5):676-81.
26. Reliability of histopathologic and radiologic grading of cartilaginous neoplasms in long bones. J Bone Joint Surg Am. 2007;89(10):2113-23.
27. Schuermans VNE, Li Z, Jongen A, Wu Z, Shi J, Ji J, et al. Pilot Study: Detection of Gastric Cancer From Exhaled Air Analyzed With an Electronic Nose in Chinese Patients. Surg Innov. 2018;25(5):429-34.
28. van Keulen KE, Jansen ME, Schrauwen RWM, Kolkman JJ, Siersema PD. Volatile organic compounds in breath can serve as a non-invasive diagnostic biomarker for the detection of advanced adenomas and colorectal cancer. Aliment Pharmacol Ther. 2020;51(3):334-46.
29. van de Goor RMGE, Leunis N, van Hooren MRA, Francisca E, Masclee A, Kremer B, et al. Feasibility of electronic nose technology for discriminating between head and neck, bladder, and colon carcinomas. European Archives of Oto-Rhino-Laryngology. 2017;274(2):1053-60.
30. Chen K, Liu L, Nie B, Lu B, Fu L, He Z, et al. Recognizing lung cancer and stages using a self-developed electronic nose system. Computers in Biology and Medicine. 2021;131:104294.
31. Herman-Saffar O, Boger Z, Libson S, Lieberman D, Gonen R, Zeiri Y. Early non invasive detection of breast cancer using exhaled breath and urine analysis. Computers in Biology and Medicine. 2018;96:227-32.
32. Kim JH, Lee SK. Classification of Chondrosarcoma: From Characteristic to Challenging Imaging Findings. Cancers (Basel). 2023;15(6).
33. Zając A, Król SK, Rutkowski P, Czarnecka AM. Biological Heterogeneity of Chondrosarcoma: From (Epi) Genetics through Stemness and Deregulated Signaling to Immunophenotype. Cancers (Basel). 2021;13(6).
34. Blanchet L, Smolinska A, Baranska A, Tigchelaar E, Swertz M, Zhernakova A, et al. Factors that influence the volatile organic compound content in human breath. J Breath Res. 2017;11(1):016013.

Chapter 3

Survival analysis of 3 different age groups and prognostic factors among 402 patients with skeletal high-grade osteosarcoma. Real world data from a single tertiary sarcoma center

R.E. Evenhuis[1], I. Acem[1,2], A.J. Rueten-Budde[3], D.S.A. Karis[1], M. Fiocco[3], D.M.J. Dorleijn[1,] F.M. Speetjens[4], J. Anninga[5], H. Gelderblom[4], and M.A.J. van de Sande[1,5]

1. Department of Orthopaedic Surgery, Leiden University Medical Center, 2300RC Leiden, The Netherlands
2. Department of Surgical Oncology and Gastrointestinal Surgery, Erasmus MC Cancer Institute, 3000CB Rotterdam, The Netherlands
3. Department of Biomedical Data Science, Section Medical Statistics and Bioinformatics, Mathematical Institute Leiden University, 2300RC Leiden, The Netherlands
4. Department of Medical Oncology, Leiden University Medical Center, 2300RC Leiden, The Netherlands
5. Princess Máxima Center for Pediatric Oncology, 3720AC Utrecht, The Netherlands

Cancers, February 2021

Simple Summary

Age is one of many prognostic factors for overall survival in patients with skeletal osteosarcoma. This retrospective study provides an overview of survival in patients with high-grade osteosarcoma in different age groups. It shows prognostic variables for survival and local control among the overall cohort. In this study, in which 402 patients with skeletal high-grade osteosarcoma were included, poor survival was associated with increasing age. Age groups, tumor size, poor histopathological response, distant metastasis at presentation, and local recurrence were independent prognostic factors associated to overall survival and event-free survival. Differences in outcome among different age groups can be partially explained by patient characteristics and treatment characteristics.

Abstract

Age is a known prognostic factor for many sarcoma subtypes, however in the literature there are limited data on the different risk profiles of different age groups for osteosarcoma survival. This study aims to provide an overview of survival in patients with high-grade osteosarcoma in different age groups and prognostic variables for survival and local control among the entire cohort. In this single center retrospective cohort study, 402 patients with skeletal high-grade osteosarcoma were diagnosed and treated with curative intent between 1978 and 2017 at the Leiden University Medical Center (LUMC). Prognostic factors for survival were analyzed using a Cox proportional hazard model. In this study poor overall survival (OS) and event-free survival (EFS) were associated with increasing age. Age groups, tumor size, poor histopathological response, distant metastasis (DM) at presentation and local recurrence (LR) were important independent prognostic factors influencing OS and EFS. Differences in outcome among different age groups can be partially explained by patient and treatment characteristics.

Keywords: osteosarcoma; survival; prognosis; age groups; chemotherapy; metastasis; local recurrence

Introduction

High-grade conventional osteosarcoma is a primary malignant bone tumor that has a bimodal distribution curve. The first peak is at the age of puberty and adolescence, the second curve arises after the age of 40(1, 2). Despite being a rare disease (prevalence of 3–4 cases per million per year(3, 4)), osteosarcoma is the most common primary malignant bone tumor. It continues to be a high risk malignancy and has one of the highest mortality rates of any type of cancer diagnosed around puberty(5). Before the introduction of chemotherapy in the 1980's, survival for patients with high-grade osteosarcoma was poor with survival probabilities as low as less than 20%(3). After the introduction of chemotherapy, the overall survival (OS) increased to an average of 60%(3, 6, 7).

Multiple studies conclude more favorable survival probabilities in pediatric patients compared with adolescent and young adults (AYA) or older adults(8-10). In contrast, some studies stated that no differences in survival were found between pediatric patients and older adults(11, 12). The variation in survival probabilities among age groups might be due to differences in tumor characteristics, chemotherapy regimens, pathohistological response, or different patient characteristics(9, 13-18).

The aim of this single center retrospective study is to provide an overview of survival outcome within three age groups (pediatric, AYA, adult) and for the total cohort. The second aim is to identify prognostic factors for OS and event-free survival (EFS) in patients with high-grade osteosarcoma.

Methods

Design, Setting, Data Source, Participants

This observational retrospective cohort study was performed at the Leiden University Medical Center (LUMC) in the Netherlands between 1978 and 2017. All consecutive patients diagnosed with histologically proven high-grade osteosarcoma treated with curative intent that met inclusion criteria were included. Patients with a skeletal high-

grade primary osteosarcoma, treated with curative intent using (neo)adjuvant chemotherapy and surgery, were eligible for this study. Patients were excluded if they were diagnosed with, a low grade (parosteal) or intermediate grade osteosarcoma (periosteal), had a secondary osteosarcoma (i.e., radiation-induced), received a treatment with palliative intent, if data about surgery or chemotherapy were missing, or when the tumor location was facial or extra-skeletal. Patients with metastasis at presentation were eligible when curative intent was set at start of the treatment including planned metastasectomy. High-grade osteosarcoma consists of conventional osteosarcoma (osteoblastic, chondroblastic and fibroblastic), small cell and telangiectatic osteosarcoma. Apart from these subgroups, the WHO distinguishes high-grade surface osteosarcoma and secondary osteosarcoma as other types of high-grade osteosarcoma. This study was approved by the medical ethical committee of the LUMC as no patients were approached and data were handled anonymously. The approval code is G18.065/SH/gk. The used data comprised real world data.

Variables

Baseline variables were age, sex, location and size of the tumor and distant metastasis (DM) at presentation. Treatment data include LR, surgical margin, type of resection and response to chemotherapy. Patients were categorized into one of three age groups (children 0–<16, AYA 16–<40, older adults ≥ 40). Location of the primary tumor was defined as extremity (upper or lower extremity) or axial (tumors of the chest including ribs, spine or pelvis). The size of the primary tumor was divided according to the American Joint Committee on Cancer (AJCC) into small (≤8 cm) or large (>8 cm)(19). Radical resection was defined as a wide radical resection with both macroscopic as microscopic surgical margins free of tumor and the entire dissection performed through healthy tissues. Marginal surgical margin was defined as a dissection that extended into or through the reactive zone that surrounds the tumor. Irradical or intralesional margin was defined as entering the tumor at any point during surgery(20).

The type of resection was divided into 3 subgroups; (1). reconstruction with an allo- or autograft, prosthesis or rotationplasty; (2). amputation of the affected limb or exarticulation of the joint without reconstruction; (3). resection that consisted of local resection, en-bloc resection or hemipelvectomy without reconstruction. The protocolized planned chemotherapy was either an intentional treatment with (Methotrexate, Doxorubicin, Cisplatin (MAP) or with Doxorubicin, Cisplatin (AP). Patients were treated with at least one cycle to a maximum of 6 cycles chemotherapy. Patients receiving preoperative chemotherapy were categorized in three groups (1 cycle MAP or 2 cycles AP preoperative, 2 cycles MAP or 3 cycles AP preoperative and >2 cycles MAP or >3 cycles AP preoperative). Generally, 2 cycles MAP or 3 cycles AP are used preoperatively. The other variants show patients receiving less or more cycles preoperative chemotherapy. Histopathological response on chemotherapy was obtained by a reference pathologist after histopathologic examination of the resected primary tumor. The percentage of tumor necrosis attributable to preoperative chemotherapy was defined by the Huvos grading. Huvos grading stage 1 and 2 is defined as ≤90% necrosis (bad responders). Huvos grading stage 3 and 4 defined is as >90% necrosis (good responders)(21).

Primary outcome was OS from surgery until death or until last date of follow-up. Secondary outcome was EFS; from resection to first event which consisted of LR, progression of metastasis, new metastasis, death or last date of follow-up. In patients with DM at presentation the next event was considered for EFS. LR was defined as a relapse of primary tumor situated at the same location of the primary tumor which was radically or marginally resected.

Follow-Up

Patients were followed at the outpatient clinic for local control, functional outcome and disease progression. Follow-up consisted of physical examination and radiographic control. Radiographic control comprised chest radiography and radiography of the affected bone. Follow-up visits were performed maximum 25 years after diagnosis with frequent visits in the first years after initial diagnosis and less frequent in later years according to the EURAMOS protocol(22).

Statistical Analysis

A Cox proportional hazards regression model with time fixed and time dependent covariates(23) was estimated to evaluate the association between OS, EFS and prognostic factors. Age group, location of the tumor, size of the tumor, the presence of DM at presentation, surgical margin, response to chemotherapy and local recurrence of disease were included in the Cox model. The effect of LR on survival outcomes was analyzed in two different ways, as a time-dependent covariate in the Cox model and by using the Landmark approach(24). A landmark model only uses information available at the landmark time (tLM). Only patients alive at tLM are included in the analysis. In our study tLM is chosen at 24 months after the date of surgery. At the landmark time patients were classified as having experienced LR before 24 months or not. Survival curves were estimated using the Kaplan–Meier (KM) methodology. Outcomes were statistically significant when the p-value was <0.05. Because of a low number of patients for some crosstabulations, the Fisher exact test was used instead of the Chi-square test when testing categorical variables. Median follow-up time was computed using the reversed KM estimator. Missing covariates were imputed using multiple imputation methods(25) for survival data with the event indicator and the Nelson–Aalen estimator of the cumulative hazard as variables in the imputation model(26). In total 20 data sets were imputed, Rubin's rule was applied to obtain the final estimates along with their standard error. The analysis was performed by using SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).

Results

Baseline Characteristics

The total LUMC-cohort contained 610 patients with osteosarcoma (Figure 1). Twenty patients were excluded due to secondary osteosarcoma, 88 patients due to low, intermediate or unknown grade osteosarcoma and 1 patient due to an inconclusive pathology report. Among 501 patients with high-grade osteosarcoma, 84 patients were

not treated with curative intent, for 2 patients the date of resection was unknown, and 13 patients were excluded because the primary tumor was located facially or extra-skeletally (soft-tissue). After applying the exclusion criteria, 402 patients were included in this study. The median age at diagnosis was 19.14 years (range 3–82 years). The three age groups comprised 114 children (28.7%) aged 0 to <16 years, 218 (54.2%) adolescents and young adults (AYA) aged 16–<40 and 70 (17.4%) older adults aged ≥40 years. Among all patients 60% of them had a poor histopathological response on chemotherapy and 40% had a good histopathological response on chemotherapy.

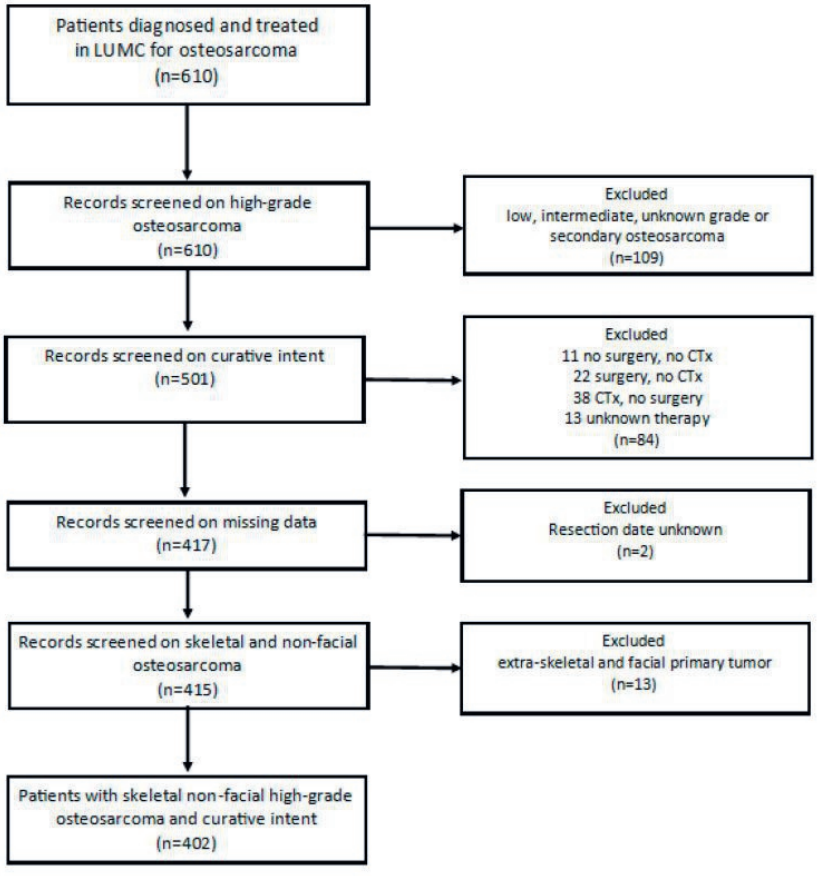


Figure 1. Flowchart patient selection.

Legend: LUMC = Leiden University Medical Center, CTx = Chemotherapy.

Differences in Presentation Among Age Groups

A significant difference at presentation was found among the age groups comparing tumor location ($p < 0.001$) (Table 1). Older adults more often presented with an axial tumor compared to children and AYA. A significant difference was found among age groups and patients presenting with pathological fractures ($p = 0.007$). Of all patients, 347 (89.4%) presented without a pathological fracture of whom 102 children (90.3%), 193 AYA (92.3%) and 52 older adults (78.8%). Children were diagnosed significantly more often with DM at presentation compared to AYA and older adults ($p = 0.037$). Children, AYA and older adults, respectively, presented with at least one pulmonary metastasis in 16.5%, 12% and 5.7% of patients. Of all patients, 55 children (51.9%) underwent a radical resection compared to 99 AYA (48.3%) and 29 (42.6%) older adults. A total of 50 patients (13.2%) had an irradical resection: 7 children (6.6%), 31 AYA (15.1%) and 12 older adults (17.6%). No significant differences were found among the age groups between different types of resection ($p = 0.070$). However, the 258 patients (66.7%) receiving resection and reconstruction comprised of 77 children (71.3%), 139 AYA (66.2%), and 42 older adults (60.9%). The 56 (14.5%) patients receiving resection comprised of 7 children only (6.5%) compared to 36 AYA (17.1%) and 13 older adults (18.8%). Older adults were significantly more often treated with AP chemotherapy ($p < 0.001$), where children were more often treated with MAP ($p < 0.001$). The amount of received pre-operative chemotherapy cycles did not differ significantly among age groups. The majority of the patients (77.7%) received two MAP cycles or three AP cycles pre-operative. Finally, the response on chemotherapy differed significantly among the age groups ($p = 0.005$). Children had a good histopathological response significantly more often on pre-operative chemotherapy compared with AYA and older adults.

Table 1. Characteristics of the overall cohort diagnosed with skeletal high-grade osteosarcoma.

Characteristic	N (%)	Children (0–<16 yrs)	AYA (16–<40 yrs)	Older Adults (≥40 yrs)	*p*-value
Gender	402	114 (28.7)	218 (54.2)	70 (17.4)	0.092
Male	228 (56.7)	64 (56.1)	132 (57.9)	32 (45.7)	
Female	174 (43.3)	50 (43.9)	86 (39.4)	38 (54.3)	
Location tumor	402	114 (28.4)	218 (54.2)	70 (17.4)	<0.001
Extremities	372 (92.5)	112 (98.2)	203 (93.1)	57 (81.4)	
Axial (pelvis, chest, spine)	30 (7.5)	2 (1.8)	15 (6.9)	13 (18.6)	
Tumor size	375	107 (28.5)	200 (53.3)	68 (18.1)	0.377
Small (≤8 cm)	154 (41.1)	43 (40.2)	78 (39)	33 (48.5)	
Large (≥8 cm)	221 (58.9)	64 (59.8)	122 (61)	35 (51.5)	
Pathologic fracture	388	113 (29.1)	209 (53.9)	66 (17)	0.007
No	347 (89.4)	102 (90.3)	193 (92.3)	52 (78.8)	
Yes	41 (10.6)	11 (9.7)	16 (7.7)	14 (21.2)	
Distant metastasis at presentation	391	111 (28.4)	210 (53.7)	70 (17.9)	0.037
No	325 (83.1)	87 (78.4)	173 (82.4)	65 (92.9)	
Yes	66 (16.9)	24 (21.6)	37 (17.6)	5 (7.1)	
***No. of lungmets at presentation**	388	109 (28.1)	209 (53.9)	70 (18)	0.389
None	341 (87.9)	91 (83.5)	184 (88)	66 (94.3)	
1	9 (2.3)	3 (2.8)	6 (2.9)	0 (0)	
2–5	30 (7.7)	11 (10.1)	16 (7.7)	3 (4.3)	
>5	8 (2.1)	4 (3.7)	3 (1.4)	1 (1.4)	

Characteristic	N (%)	Children (0–<16 yrs)	AYA (16–<40 yrs)	Older Adults (≥40 yrs)	*p*-value
Surgical margin	379	106 (28)	205 (54.1)	68 (17.9)	0.178
Radical	183 (48.3)	55 (51.9)	99 (48.3)	29 (42.6)	
Marginal	146 (38.5)	44 (41.5)	75 (36.6)	27 (39.7)	
Irradical	50 (13.2)	7 (6.6)	31 (15.1)	12 (17.6)	
Type of resection	387	108 (27.9)	210 (54.3)	69 (17.8)	0.070
Resection/reconstruction	258 (66.7)	77 (71.3)	139 (66.2)	42 (60.9)	
Amputation/exarticulation	73 (18.9)	24 (22.2)	35 (16.7)	14 (20.3)	
Resection only	56 (14.5)	7 (6.5)	36 (17.1)	13 (18.8)	
Chemotherapy treatment	359	98 (27.3)	198 (55.6)	63 (17.5)	<0.001
Intention AP	225 (62.7)	43 (43.9)	125 (63.1)	57 (90.5)	
Intention MAP	134 (37.3)	55 (56.1)	73 (36.9)	6 (9.5)	
***Pre-op CTx cycles**	309	89 (28.8)	176 (57)	44 (14.2)	0.256
1 MAP or 2 AP	41 (13.3)	12 (13.5)	22 (12.5)	7 (15.9)	
2 MAP or 3 AP	240 (77.7)	74 (83.1)	134 (76.1)	32 (72.7)	
>2 MAP or >3 AP	28 (9.1)	3 (3.4)	20 (11.4)	5 (11.4)	
***Response on chemotherapy**	337	105 (31.2)	184 (54.6)	48 (14.2)	0.005
Poor (Huvos 1,2)	202 (59.9)	51 (48.6)	115 (62.5)	36 (75)	
Good (Huvos 3,4)	135 (40.1)	54 (51.4)	69 (37.5)	12 (25)	
***/** Local recurrence**	391	106 (27.1)	215 (55)	70 (17.9)	
No	346 (88.5)	102 (96.2)	190 (88.4)	54 (77.1)	
Yes	45 (11.5)	4 (3.8)	25 (11.6)	16 (22.9)	

Legend: AYA = Adolescent and Young Adult, Lungmets = lung metastasis, AP = Adriamycine-CisPlatin, MAP = Methotrexate-Adriamycine-CisPlatin, CTx = Chemotherapy, pre-op = pre-operative, * Fisher exact test because number of patients <5, ** No p-value because of time dependent variable.

Overall Survival in Total Cohort

Median follow-up time for the overall cohort containing 402 patients, was 136 months (95%CI 116.4–155.6). Among these patients, 5-year OS was 59.1% (95%CI 54.2–64.0). The 5-year OS for 114 children, 218 AYA and 70 older adults was, respectively, 67.2% (95%CI 58.18–76.22), 56.5% (49.84–63.16), 54.3% (42.34–66.26) as can be seen in Figure 2 and Table 3. The 5-year OS for 325 patients (83.1%) without DM at presentation was 66.1% (95%CI 60.81–71.40). OS for 66 patients (16.9%) with DM at presentation was significantly lower ($p < 0.001$) with a 5-year OS of 30% (95%CI 18.63–41.37) (Table 2, Figure 3). Among patients presenting without DM, OS differed significantly between the three age groups ($p = 0.006$). Children, AYA and older adults had, respectively, a 5-year OS of 78.5% (95%CI 87.32–69.68), 63.8% (95%CI 56.35–71.25) and 55.4% (95%CI 43.05–67.75).

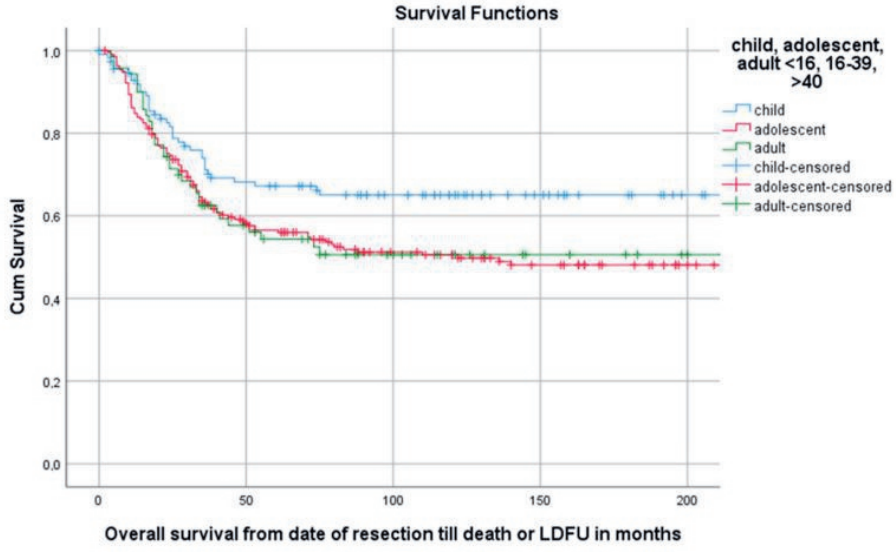


Figure 2. Kaplan–Meier (KM) estimation of OS in the total cohort divided by age group.
Legend: OS = overall survival, cum survival = cumulative survival, LDFU = last date of follow-up.

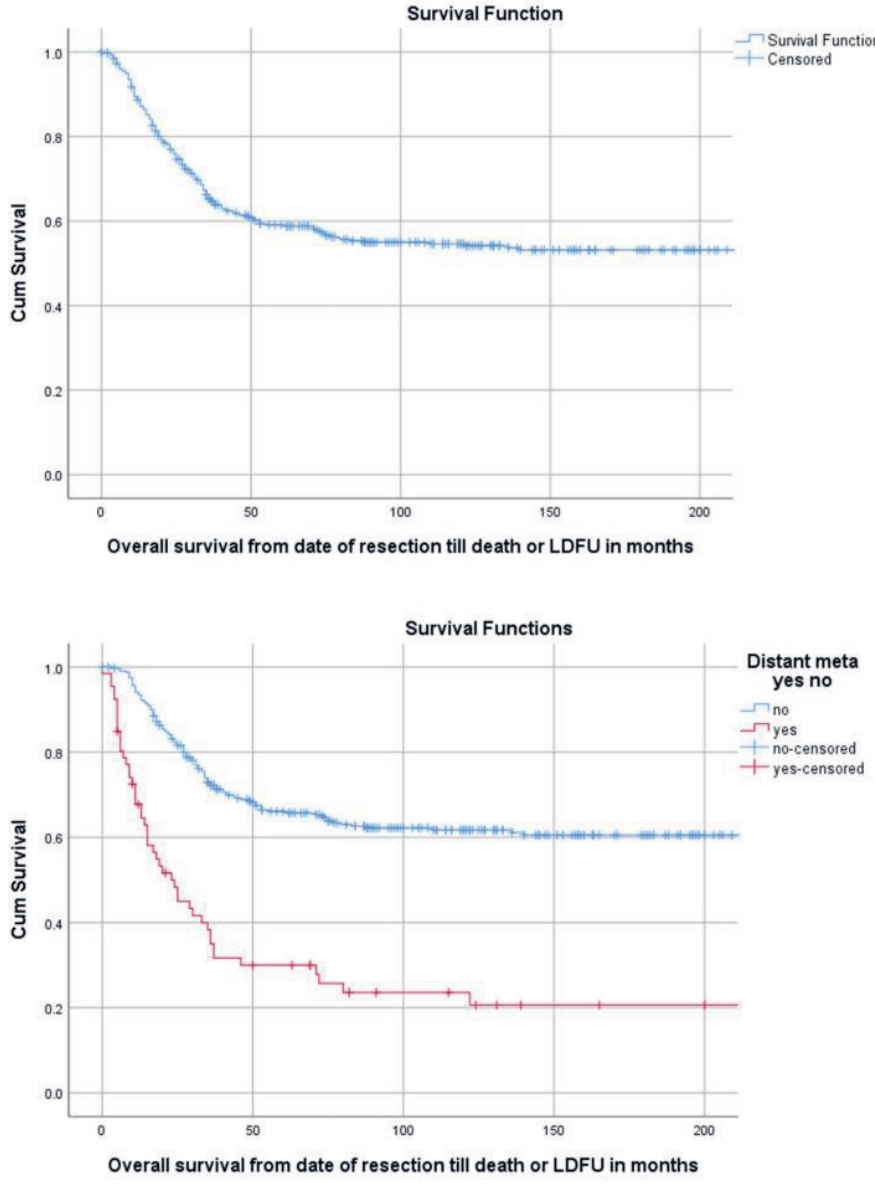


Figure 3. KM estimation of OS in the total cohort (upper panel) and of patients with and without distant metastasis (lower panel).

Legend: OS = overall survival, DM = distant metastasis at presentation, cum survival = cumulative survival, LDFU = last date of follow-up.

Table 2. Overall survival (OS) among different age groups with or without distant metastasis (DM) at presentation.

Factors	N (%)	5-yr OS among M0 (%)	*p*-value	N (%)	5-yr OS among M1 (%)	*p*-value
Overall group	325 (83.1)	66.1		66 (16.9)	30	
			0.006			0.971
Child (0–<16)	87 (26.8)	78.5		24 (36.4)	21.7	
AYA (16–<40)	173 (53.2)	63.8		37 (56.1)	32.4	
Older adults ≥40	65 (20)	55.4		5 (7.6)	40	

Legend: M0 = patients without metastasis at presentation, M1 = patients with metastasis at presentation.

Event Free Survival

Of all 402 patients, 55.5% (223/402) experienced an event defined as LR, progression of metastasis, diagnosis of new metastasis or death. The 5-year EFS for 114 children, 218 AYA and 70 older adults was, respectively, 58.5% (95%CI 49.29–67.71), 40.6% (95%CI 33.94–47.26), 38.9% (95%CI 27.34–50.46) as can be seen in Table 3 and Figure 4. A total of 1, 3 and 5 years after surgery the event-free survival was, respectively, 71.6% (95%CI 67.1–76.1), 49.2% (95%CI 44.3–54.1) and 45.3% (95%CI 40.4–50.2) (Figure 5).

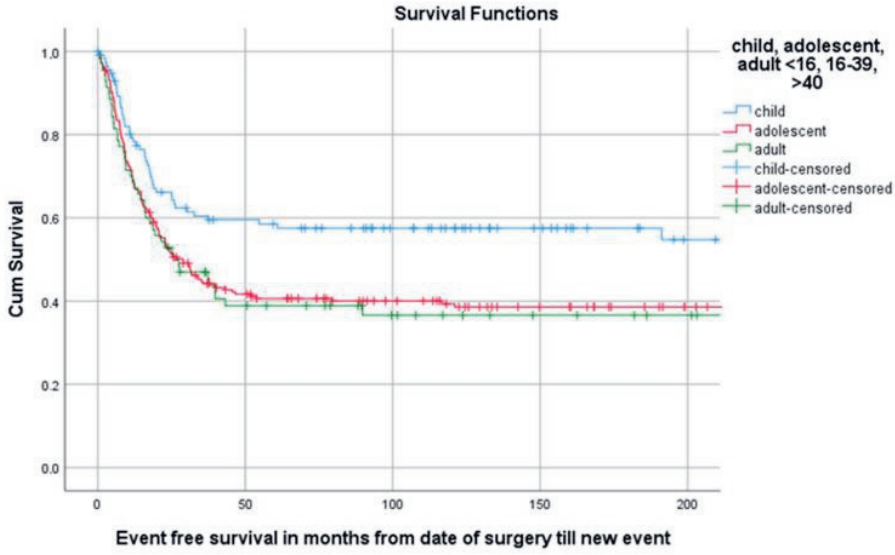


Figure 4. KM estimation of EFS in total cohort divided by age group.

Legend: EFS = event-free survival, cum survival = cumulative survival.

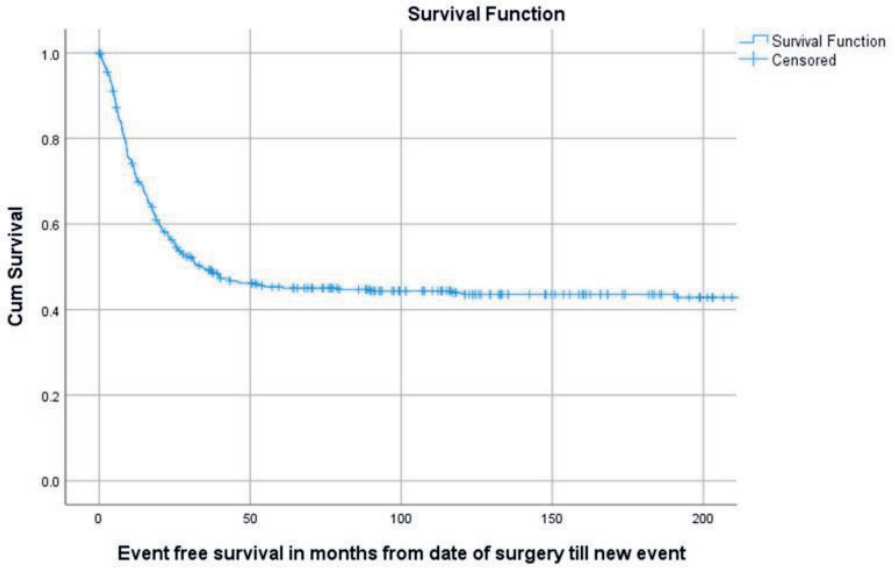


Figure 5. KM estimation of EFS of total cohort. Legend: EFS = Event-free survival, cum survival = cumulative survival.

Table 3. OS and EFS at 5 years along with 95% confidence interval (CI).

Factors	N (%)	5-Year OS (%) with 95%CI	*p*-value	N (%)	5-Year EFS (%) with 95%CI	*p*-value
Sex	402		0.126	402		0.033
Male	228 (56.7)	55.5 (48.8–62.16)		228 (56.7)	40.7 (34.23–47.17)	
Female	174 (43.3)	63.6 (56.35–70.85)		174 (43.3)	51.3 (43.85–58.75)	
Age group	402		0.044	402		0.007
Child (0–<16)	114 (28.4)	67.2 (58.18–76.22)		114 (28.4)	58.5 (49.29–67.71)	
AYA (16–<40)	218 (54.2)	56.5 (49.84–63.16)		218 (54.2)	40.6 (33.94–47.26)	
Older adults ≥40	70 (17.4)	54.3 (42.34–66.26)		70 (17.4)	38.9 (27.34–50.46)	
Location	402		0.960	402		0.361
Extremities	372 (92.5)	59.1 (54.0–64.2)		372 (92.5)	45.8 (40.70–50.90)	
Axial (chest, spine, pelvis)	30 (7.5)	60 (42.56–77.44)		30 (7.5)	40 (22.56–57.44)	
Tumor size	375		<0.001	375		<0.001
Small ≤8 cm	154 (41.1)	72.4 (65.15–79.65)		154 (41.1)	70.1 (52.26–67.94)	
Large ≥8 cm	221 (58.9)	50.2 (43.34–57.06)		221 (58.9)	34.5 (28.03–40.97)	
Surgical margin	379		0.037	379		0.030
Radical	183 (48.3)	60.7 (53.45–67.95)		183 (48.3)	48.2 (40.75–55.65)	
Marginal	146 (38.5)	62.3 (54.26–70.34)		146 (38.5)	47.5 (39.27–55.73)	
Irradical	50 (13.2)	45.4 (31.48–59.32)		50 (13.2)	29.9 (17.16–42.64)	
Type of resection	387		0.002	387		0.004
Resection/reconstruction	258 (66.7)	60.6 (54.52–66.68)		258 (66.7)	47.1 (40.83–53.37)	
Amputation/exarticulation	73 (18.9)	45.7 (34.14–57.26)		73 (18.9)	33.6 (22.62–44.58)	
Resection only	56 (14.5)	72.2 (60.24–84.16)		56 (14.5)	56.7 (43.57–69.83)	
Response on chemotherapy	337		<0.001	337		<0.001
Poor (Huvos 1,2)	202 (59.9)	46.6 (39.54–53.66)		202 (59.9)	31.2 (24.73–37.67)	
Good (Huvos 3,4)	135 (40.1)	74.5 (67.05–81.95)		135 (40.1)	66.9 (58.86–74.94)	
Distant metastasis at presentation	391		<0.001	391		<0.001
No	325 (83.1)	66.1 (60.81–71.39)		325 (83.1)	50.9 (45.41–56.39)	
Yes	66 (16.9)	30 (18.63–41.37)		66 (16.9)	20.9 (10.71–31.09)	

Legend: CTx = Chemotherapy.

Landmark Analysis

Survival from landmark time at 24 months post-surgery was estimated for patients with and without LR at tLM. In this analysis 304 patients were included; 20 patients (6.6%) had an LR within 24 months post-surgery. Patients with LR at tLM had a poor survival compared to patients without ($p < 0.001$) (Figure 6).

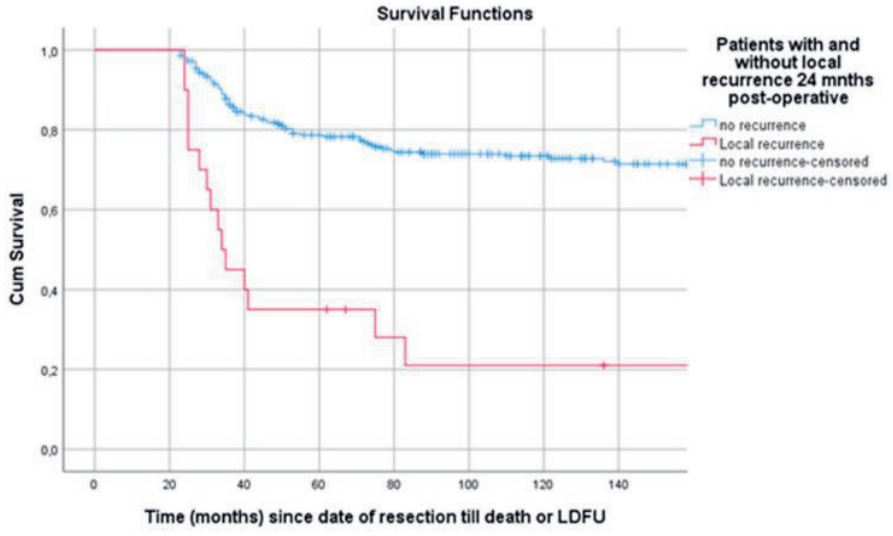


Figure 6. Landmark analysis of patients with and without LR 24 months post-surgery.
Legend: LR = local recurrence, cum survival = cumulative survival, LDFU = last date of follow-up.

Prognostic Factors

Size of the tumor (HR 1.711, 95%CI 1.193–2.455), the response to chemotherapy (HR 0.422, 95%CI 0.276–0.646), the presence of distant metastasis at presentation (HR 3.578, 95%CI 2.492–5.138) and local recurrence of disease (HR 4.456, 95%CI 2.911–6.682) were significantly associated with OS (Table 4). Age group (AYA vs. children, HR 1.499, 95%CI 1.067–2.108), (older adults vs. children, HR 1.708, 95%CI 1.094–2.666), size of the tumor (HR 1.836 95%CI 1.335–2.527), response on chemotherapy (HR 0.407, 95%CI 0.288–0.574) and distant metastasis at presentation (HR 2.575, 95%CI 1.859–3.565) were associated with EFS. Age group was found to be an independent prognostic factor of EFS but not for OS. An HR of 1.313 on OS was found comparing AYA and children (95%CI 0.891–1.935). An HR of 1.326 on OS was found comparing older adults and children (95%CI 0.802–2.193).

Table 4. Hazard ratio for prognostic factors on OS and EFS along with the 95% confidence interval estimated with the Cox proportional hazards regression model.

Factors	HR_{OS}	95% CI	*p*-value	HR_{EFS}	95% CI	*p*-value
Sex			0.490			0.097
Male						
Female	0.891	0.642–1.237		0.786	0.592–1.044	
Age group						
Child (0–<16)	*Reference group*			*Reference group*		
AYA (16–<40)	1.313	0.891–1.935	0.168	1.499	1.067–2.108	0.020
Older adults ≥40	1.326	0.802–2.193	0.272	1.708	1.094–2.666	0.018
Location			0.678			0.346
Extremities						
Axial (chest, spine, pelvis)	0.868	0.446–1.692		1.277	0.768–2.123	
Tumor size			0.004			<0.001
Small ≤8 cm						
Large ≥8 cm	1.711	1.193–2.455		1.836	1.335–2.527	
Surgical margin						
Radical	*Reference group*			*Reference group*		
Marginal	0.839	0.586–1.203	0.340	0.941	0.689–1.285	0.702
Irradical	1.248	0.783–1.988	0.351	1.141	0.769–1.693	0.513
Response on chemotherapy			<0.001			<0.001
Poor (Huvos 1,2)						
Good (Huvos 3,4)	0.422	0.276–0.646		0.407	0.288–0.574	
Distant metastasis at presentation			<0.001			<0.001
No						
Yes	3.578	2.492–5.138		2.575	1.859–3.565	
**** Local recurrence**			<0.001			
No						
Yes	4.456	2.911–6.682				

Legend: CTx = Chemotherapy, ** = time dependent variable, HR = Hazard Ratio

Discussion

This study shows significant differences in tumor characteristics, treatment characteristics and outcome survival outcomes as OS and EFS among children, AYA and older adult population in patients with high-grade osteosarcoma. Children and AYA had better OS and EFS compared to the older adults. These results are in line with previous studies(8, 11, 14, 15, 17, 18). Older adults present more often with an axial located tumor, pathological fracture and the protocolized treatment consists more often of AP instead of MAP. Furthermore, a good histopathological response on chemotherapy is less often seen in older adults.

In line with previous studies(3, 16) age group was found to be an independent prognostic factor for EFS, resulting in poor EFS among older patients. When comparing AYA vs. children and older adults vs. children, respectively, an HR of 1.499 (95%CI 1.067–2.108) and 1.708 (95%CI 1.094–2.666) was found. A possible explanation for a poor EFS in older patients is that older patients suffer more often of axial located tumors that are technically more difficult to operate on and could lead to a higher risk of incomplete surgical resection(3, 4, 14, 15, 17).

A higher frequency of AP chemotherapy among an older group was possibly due to the fact that the older adults tolerate a less intensive chemotherapy protocol. Dose limitations due to comorbidities, age-related organ dysfunction or chemotherapy related toxicity might be associated to poorer response to chemotherapy compared with younger patients(8, 17). Finally, osteosarcoma in older adults seems to have another biological behavior and tends to be more resistant to chemotherapy than that in younger patients(3, 8, 9). All these factors can (partly) lead to a decreased EFS in older patients.

DM at presentation is another important prognostic factor resulting in poor survival(11, 27). In this study children present more often with DM at presentation compared to AYA and older adults. Our findings are in contrast with the studies of Hagleitner et al. and Tsuda et al.(8, 9), both stating that metastasis presented less frequently in younger patients. However, Hagleitner et al. and Tsuda et al. both used a different distribution of

age groups (respectively, patients aged 0–14 yrs, 15–19 yrs, 20–40 yrs and patients aged <40 yrs, 41–64 yrs, >65 yrs). It is of methodological importance in which categorial variable age has been converted and therefore outcomes can vary fairly(10, 17). Another explanation could be the inclusion criteria of this study possibly resulting in a low number of older adults who are more likely to develop DM. As a result of the inclusion criteria, the number of excluded older adults with DM at presentation might be higher. Comorbidities in older adults could lead to restrictions in chemotherapy regimens and therefore have a higher risk of palliative therapy (15, 28). In the study of Tsuda et al. patients with palliative therapy were taken into account as well. In the study of Hagleitner et al. it is not clearly described if patients received palliative therapy. This led to the fact that care should be taken while comparing this study with the studies of Hagleitner et al. and Tsuda et al.

The factors associated with OS were tumor size, histopathological response to chemotherapy, DM at presentation and LR. The factors associated with an effect on EFS were age group, tumor size, histopathological response to chemotherapy and DM at presentation. These results are in line with previous studies (3, 9, 17, 18, 29, 30). Age groups were found to be an independent prognostic factor for EFS but not for OS. These results are not in line with the studies of Hagleitner et al. and Mankin et al. (8, 31). This could be explained by the fact that Hagleitner et al. performed a study with only 102 patients. Therefore, adjustment for all important variables in the multivariate analysis could not be done. Furthermore, both studies used different inclusion criteria, therefore a proper comparison could not be made. Finally, care should be taken when interpreting the effect of histopathological response on OS and EFS. In the multivariate analysis, both AP as MAP chemotherapy were taken into account while analyzing the effect on histopathological response. The histopathological response in patients receiving AP chemotherapy is evaluated earlier (after 6 weeks) in comparison to patients receiving MAP (after 10 weeks). In addition, MAP is a more intensive chemotherapy regimen compared to AP and therefore possibly influencing the effect on the primary outcome.

After 40 years of (neo)adjuvant chemotherapy for osteosarcoma, whose benefits in terms of survival are well established but have not improved, this paper clearly shows that it is time to change the approach and consider additional therapeutic options. In recent years

there have been no major results in phase 3 trials in the (neo)adjuvant treatment of patients with resectable osteosarcoma. Phase-2 trials so far have shown no effective trials for poor prognosis osteosarcoma(32-34). The international community of physicians involved in this disease awaits results of the investigation of the complete genomic landscape of osteosarcoma(35). Insights from pan-genomic studies could gain a better insight into the development and clonal evolution of this malignancy, that hopefully will lead to the development of more specific drugs for osteosarcoma(36).These results should guide the development of new (neo)adjuvant trials.

Strengths and Limitations

Our study is one of the largest single center studies investigating prognostic factors on survival. This cohort offers a long median follow-up time of 136 months. In addition, it is one of the few studies describing patient and treatment characteristics in three different age groups and therefore it could be directive to future studies. Other studies describe small study populations or present data from prospective or randomized controlled trials with different pre-empted endpoints and inclusion criteria(8, 9, 14-18).

Due to the retrospective nature of this study, several limitations were present. In this study we were unable to assess histopathological response per type of chemotherapy regimen. Although histopathological response is an important prognostic factor influencing OS and EFS, care should be taken be taken while interpreting these data. Furthermore, we were unable to assess the association of chemotherapy treatment with survival in the multivariate analysis. Finally, not all known pathological and biochemical features of osteosarcoma patients were taken into account in this paper. The retrospective nature of this study explains for the lack of some possibly important prognostic factors that could not be retrieved for most of the patients.

Conclusions

In this single center study, we found poor OS and EFS in older adults with high-grade osteosarcoma compared to AYA and children. Large tumor size, a poor histopathological response, DM at presentation and LR are important independent prognostic factors influencing OS negatively. Age group (older adults), large tumor size, a poor histopathological response and DM at presentation were found to be important independent prognostic factors influencing EFS negatively. DM and LR can make a significant difference in prognosis and is therefore key in the approach of patients suffering high-grade skeletal osteosarcoma. Differences in outcome among different age groups can be partially explained by patient and treatment characteristics.

References

1. Bone sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Annals of Oncology. 2014;25:iii113-iii23.
2. Ferrari S, Bertoni F, Mercuri M, Picci P, Giacomini S, Longhi A, et al. Predictive factors of disease-free survival for non-metastatic osteosarcoma of the extremity: An analysis of 300 patients treated at the Rizzoli Institute. Annals of Oncology. 2001;12(8):1145-50.
3. Smeland S, Bielack SS, Whelan J, Bernstein M, Hogendoorn P, Krailo MD, et al. Survival and prognosis with osteosarcoma: outcomes in more than 2000 patients in the EURAMOS-1 (European and American Osteosarcoma Study) cohort. Eur J Cancer. 2019;109:36-50.
4. Bielack SS, Kempf-Bielack B, Delling G, Exner GU, Flege S, Helmke K, et al. Prognostic Factors in High-Grade Osteosarcoma of the Extremities or Trunk: An Analysis of 1,702 Patients Treated on Neoadjuvant Cooperative Osteosarcoma Study Group Protocols. 2002;20(3):776-90.
5. Zhang C, Guo X, Xu Y, Han X, Cai J, Wang X, et al. Lung metastases at the initial diagnosis of high-grade osteosarcoma: prevalence, risk factors and prognostic factors. A large population-based cohort study %J Sao Paulo Medical Journal. 2019;137:423-9.
6. Mirabello L, Troisi RJ, Savage SA. Osteosarcoma incidence and survival rates from 1973 to 2004. 2009;115(7):1531-43.
7. Berner K, Johannesen TB, Berner A, Haugland HK, Bjerkehagen B, Bøhler PJ, et al. Time-trends on incidence and survival in a nationwide and unselected cohort of patients with skeletal osteosarcoma. Acta Oncologica. 2015;54(1):25-33.
8. Hagleitner MM, Hoogerbrugge PM, van der Graaf WTA, Flucke U, Schreuder HWB, te Loo DMWM. Age as prognostic factor in patients with osteosarcoma. Bone. 2011;49(6):1173-7.
9. Tsuda Y, Ogura K, Shinoda Y, Kobayashi H, Tanaka S, Kawai A. The outcomes and prognostic factors in patients with osteosarcoma according to age: a Japanese nationwide study with focusing on the age differences. BMC Cancer. 2018;18(1):614.
10. Harting MT, Lally KP, Andrassy RJ, Vaporciyan AA, Cox CS, Hayes-Jordan A, et al. Age as a prognostic factor for patients with osteosarcoma: an analysis of 438 patients. Journal of cancer research and clinical oncology. 2010;136:561-70.
11. Aljubran AH, Griffin A, Pintilie M, Blackstein M. Osteosarcoma in adolescents and adults: survival analysis with and without lung metastases. Annals of Oncology. 2009;20(6):1136-41.
12. Glasser DB, Lane JM, Huvos AG, Marcove RC, Rosen G. Survival, prognosis, and therapeutic response in osteogenic sarcoma. The Memorial Hospital experience. Cancer. 1992;69(3):698-708.
13. Hanafy E, Al Jabri A, Gadelkarim G, Dasaq A, Nazim F, Al Pakrah M. Tumor histopathological response to neoadjuvant chemotherapy in childhood solid malignancies: is it still impressive? Journal of Investigative Medicine. 2018;66(2):289-97.
14. Imura Y, Takenaka S, Kakunaga S, Nakai T, Wakamatsu T, Outani H, et al. Survival analysis of elderly patients with osteosarcoma. International Orthopaedics. 2019;43(7):1741-7.
15. Ferrari S, Bielack SS, Smeland S, Longhi A, Egerer G, Sundby Hall K, et al. EURO-BOSS: A European study on chemotherapy in bone-sarcoma patients aged over 40: Outcome in primary high-grade osteosarcoma. Tumori Journal. 2018;104(1):30-6.
16. Ali BA, Salman M, Ghanem KM, Boulos F, Haidar R, Saghieh S, et al. Clinical Prognostic Factors and Outcome in Pediatric Osteosarcoma: Effect of Delay in Local Control and Degree of Necrosis in a Multidisciplinary Setting in Lebanon. 2019(5):1-8.
17. Janeway KA, Barkauskas DA, Krailo MD, Meyers PA, Schwartz CL, Ebb DH, et al. Outcome for adolescent and young adult patients with osteosarcoma: a report from the Children's Oncology Group. Cancer. 2012;118(18):4597-605.
18. Nagano A, Ishimaru D, Nishimoto Y, Akiyama H, Kawai A. Primary bone sarcomas in patients over 40 years of age: A retrospective study using data from the Bone Tumor Registry of

Japan. Journal of orthopaedic science : official journal of the Japanese Orthopaedic Association. 2017;22(4):749-54.
19. Edge SB, American Joint Committee on Cancer ACS. AJCC cancer staging handbook: from the AJCC cancer staging manual: Springer; 2010.
20. Enneking WF, Spanier SS, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. Clinical Orthopaedics and Related Research (1976-2007). 1980;153:106-20.
21. Rosen G, Caparros B, Huvos AG, Kosloff C, Nirenberg A, Cacavio A, et al. Preoperative chemotherapy for osteogenic sarcoma: selection of postoperative adjuvant chemotherapy based on the response of the primary tumor to preoperative chemotherapy. Cancer. 1982;49(6):1221-30.
22. Whelan JS, Bielack SS, Marina N, Smeland S, Jovic G, Hook JM, et al. EURAMOS-1, an international randomised study for osteosarcoma: results from pre-randomisation treatment. Ann Oncol. 2015;26(2):407-14.
23. Barr L, Stotter A, A'Hern R. Influence of local recurrence on survival: a controversy reviewed from the perspective of soft tissue sarcoma. Journal of British Surgery. 1991;78(6):648-50.
24. Van Houwelingen HC. Dynamic prediction by landmarking in event history analysis. Scandinavian Journal of Statistics. 2007;34(1):70-85.
25. Rubin DB. Multiple imputation after 18+ years. Journal of the American statistical Association. 1996;91(434):473-89.
26. Li P, Stuart EA, Allison DB. Multiple Imputation: A Flexible Tool for Handling Missing Data. JAMA. 2015;314(18):1966-7.
27. Petrilli AS, de Camargo B, Filho VO, Bruniera P, Brunetto AL, Jesus-Garcia R, et al. Results of the Brazilian Osteosarcoma Treatment Group Studies III and IV: prognostic factors and impact on survival. J Clin Oncol. 2006;24(7):1161-8.
28. Aggerholm-Pedersen N, Maretty-Nielsen K, Keller J, Baerentzen S, Safwat A. Comorbidity in adult bone sarcoma patients: a population-based cohort study. Sarcoma. 2014;2014(1):690316.
29. Weeden S, Grimer RJ, Cannon SR, Taminiau AH, Uscinska BM. The effect of local recurrence on survival in resected osteosarcoma. European journal of cancer (Oxford, England : 1990). 2001;37(1):39-46.
30. Hauben E, Weeden S, Pringle J, Van Marck E, Hogendoorn P. Does the histological subtype of high-grade central osteosarcoma influence the response to treatment with chemotherapy and does it affect overall survival? A study on 570 patients of two consecutive trials of the European Osteosarcoma Intergroup. European Journal of Cancer. 2002;38(9):1218-25.
31. Mankin HJ, Hornicek FJ, Rosenberg AE, Harmon DC, Gebhardt MC. Survival Data for 648 Patients with Osteosarcoma Treated at One Institution. 2004;429:286-91.
32. van Maldegem AM, Bhosale A, Gelderblom HJ, Hogendoorn PC, Hassan AB. Comprehensive analysis of published phase I/II clinical trials between 1990-2010 in osteosarcoma and Ewing sarcoma confirms limited outcomes and need for translational investment. Clinical sarcoma research. 2012;2:1-15.
33. Lagmay JP, Krailo MD, Dang H, Kim A, Hawkins DS, Beaty III O, et al. Outcome of patients with recurrent osteosarcoma enrolled in seven phase II trials through Children's Cancer Group, Pediatric Oncology Group, and Children's Oncology Group: learning from the past to move forward. Journal of Clinical Oncology. 2016;34(25):3031-8.
34. Omer N, Le Deley M-C, Piperno-Neumann S, Marec-Berard P, Italiano A, Corradini N, et al. Phase-II trials in osteosarcoma recurrences: a systematic review of past experience. European Journal of Cancer. 2017;75:98-108.
35. Roberts RD, Lizardo MM, Reed DR, Hingorani P, Glover J, Allen-Rhoades W, et al. Provocative questions in osteosarcoma basic and translational biology: A report from the Children's Oncology Group. Cancer. 2019;125(20):3514-25.
36. Tirtei E, Cereda M, De Luna E, Quarello P, Asaftei SD, Fagioli F. Omic approaches to pediatric bone sarcomas. Pediatric Blood & Cancer. 2020;67(2):e28072.

Chapter 4

Relative wash-in rate in dynamic contrast-enhanced magnetic resonance imaging as a new prognostic biomarker for event-free survival in 82 patients with osteosarcoma: a multicenter study

G.M. Kalisvaart[1], R.E. Evenhuis[2], W. Grootjans[1], T. Van Den Berghe[3], M. Callens[3], J.V.M.G. Bovée[4], D. Creytens[5], H. Gelderblom[6], F.M. Speetjens[6], L. Lapeire[7], G. Sys[8], M. Fiocco[9,10,11], K.L. Verstraete[3], M.A.J. van de Sande[2,10], J.L. Bloem[1]

1. Department of Radiology, Leiden University Medical Center, 2333 Leiden, The Netherlands
2. Department of Orthopaedic Surgery, Leiden University Medical Center, Albinusdreef 2, 2333 Leiden, The Netherlands
3. Department of Radiology, Ghent University Hospital, 9000 Ghent, Belgium
4. Department of Pathology, Leiden University Medical Center, 2333 Leiden, The Netherlands
5. Department of Pathology, Ghent University Hospital, 9000 Ghent, Belgium
6. Department of Medical Oncology, Leiden University Medical Center, 2333 Leiden, The Netherlands
7. Department of Medical Oncology, Ghent University Hospital, 9000 Ghent, Belgium
8. Department of Orthopaedic Surgery and Traumatology, Ghent University Hospital, 9000 Ghent, Belgium
9. Department of Biomedical Science, Section Medical Statistics, Leiden University Medical Center, 2333 Leiden, The Netherlands
10. Center for Pediatric Oncology, Princess Maxima Center, 3584 Utrecht, The Netherlands
11. Mathematical Institute, Leiden University, 2300 Leiden, The Netherlands

Cancers, May 2024

Simple Summary

This study explores the potential of the relative wash-in rate (rWIR) in dynamic contrast-enhanced MRI as a prognostic factor for event-free survival (EFS) in osteosarcoma patients. Eighty-two patients were retrospectively included, and rWIR was determined based on preoperative imaging. Patients with rWIR < 2.3 were considered to have a poor radiological response, while those with rWIR ≥ 2.3 had a good response. This study identified that poor radiological response (rWIR < 2.3) was associated with shorter EFS, even when adjusted for traditional prognostic factors. The 2- and 5-year EFS rates for patients with rWIR ≥ 2.3 were 85% and 75%, compared to 55% and 50% for those with rWIR < 2.3. The findings suggest that the predicted poor chemo response with MRI is associated with shorter EFS and shows similar results to histological response evaluation. rWIR is a potential tool for future response-based individualized healthcare in osteosarcoma patients.

Abstract

Background: The decreased perfusion of osteosarcoma in dynamic contrast-enhanced (DCE) MRI, reflecting a good histological response to neoadjuvant chemotherapy, has been described. Purpose: In this study, we aim to explore the potential of the relative wash-in rate as a prognostic factor for event-free survival (EFS). Methods: Skeletal high-grade osteosarcoma patients, treated in two tertiary referral centers between 2005 and 2022, were retrospectively included. The relative wash-in rate (rWIR) was determined with DCE-MRI before, after, or during the second cycle of chemotherapy (pre-resection). A previously determined cut-off was used to categorize patients, where rWIR < 2.3 was considered poor and rWIR ≥ 2.3 a good radiological response. EFS was defined as the time from resection to the first event: local recurrence, new metastases, or tumor-related death. EFS was estimated using Kaplan–Meier's methodology. Multivariate Cox proportional hazard model was used to estimate the effect of histological response and rWIR on EFS, adjusted for traditional prognostic factors. Results: Eighty-two patients (median age: 17 years; IQR: 14–28) were included. The median follow-up duration was

11.8 years (95% CI: 11.0–12.7). During follow-up, 33 events occurred. Poor histological response was not significantly associated with EFS (HR: 1.8; 95% CI: 0.9–3.8), whereas a poor radiological response was associated with a worse EFS (HR: 2.4; 95% CI: 1.1–5.0). In a subpopulation without initial metastases, the binary assessment of rWIR approached statistical significance (HR: 2.3; 95% CI: 1.0–5.2), whereas its continuous evaluation demonstrated a significant association between higher rWIR and improved EFS (HR: 0.7; 95% CI: 0.5–0.9), underlining the effect of response to chemotherapy. The 2- and 5-year EFS for patients with a rWIR ≥ 2.3 were 85% and 75% versus 55% and 50% for patients with a rWIR < 2.3. Conclusion: The predicted poor chemo response with MRI (rWIR < 2.3) is associated with shorter EFS even when adjusted for known clinical covariates and shows similar results to histological response evaluation. rWIR is a potential tool for future response-based individualized healthcare in osteosarcoma patients before surgical resection.

Keywords: osteosarcoma, neoadjuvant chemotherapy, response monitoring, histological response, dynamic contrast-enhanced MRI, survival outcome

Introduction

Osteosarcoma is a malignant bone tumor that generally affects young patients, with a second peak at >40 years of age. Neoadjuvant chemotherapy (NAC) followed by tumor resection is key in curative treatment(1-3). The gold standard for evaluating response to NAC in osteosarcoma patients relies on the histological assessment according to the modified Huvos classification(4, 5). This method has limitations, including the examination of only one slab of tumor tissue, high inter-observer variability, the use of a binary cut-off (≥10% viable tumor cells indicate poor response), and the inability to assess response before resection. These limitations partially cause the lack of clinical implications of histological response assessment in current clinical guidelines as they only become apparent after surgical resection(6). Consequently, there is a need for a non-invasive prognostic biomarker able to accurately predict chemotherapy treatment response before surgery.

Dynamic contrast-enhanced (DCE-)MRI is an imaging sequence capable of visualizing and quantifying various tumor properties such as tissue perfusion and capillary permeability(7, 8). In a previous study, the relative wash-in rate (rWIR) was described to correlate with a histological response. The rWIR, derived from the baseline imaging's maximum slope of contrast enhancement (wash-in rate) divided by the post-NAC wash-in rate observed on DCE-MRI time-intensity curves, reflects alterations in tumor perfusion before and after NAC(9). Utilizing this technique, the response to NAC can be predicted before tumor resection. Association between response assessment before tumor resection and prognosis could thus potentially provide tools for treatment personalization.

Previous studies identified age, tumor size, the presence of metastases at presentation, histological response to chemotherapy, and local recurrence (LR) as risk factors for EFS in osteosarcoma patients treated with curative intent(10-14). The aim of this multicenter retrospective study is to explore the potential of the rWIR as a prognostic factor for clinical outcome and determine its added value to known prognostic factors.

Materials and Methods

Design, Setting, and Participants

This multicenter observational retrospective cohort study was conducted between 2005 and 2022 at the Leiden University Medical Center (LUMC) and the Ghent University Hospital (GUH). The study was approved by the ethical review board in both centers, and the need for informed consent was waived due to the retrospective nature of this study (protocol and approval codes: B19.050, BC-09111, and G18.065/SH/gk). Patients with histologically proven skeletal high-grade osteosarcoma and treated with curative intent consisting of chemotherapy and tumor resection were included. All participants underwent DCE-MRI both before and after NAC, using the same scan protocol. Exclusion criteria included patients with secondary osteosarcoma, craniofacial lesions, pre- and post-NAC MRI performed in different centers, a history of previous chemotherapy, and tumor resection or concomitant radiotherapy at the same site. Among 502 initially enrolled patients, 420 were excluded, resulting in a total study population of 82 patients (Figure 1). Of these, 53 were treated at the LUMC and 29 at the GUH. The entire study population of 82 patients was previously studied(9, 10). The first study provided an overview of survival and prognostic factors in 402 patients with skeletal high-grade osteosarcoma, including 53 patients from the current cohort(10). The second study described the development of the model, predicting the histological response to NAC in 85 osteosarcoma patients, incorporating 82 patients from the current cohort(9). In this study, we report the potential of the rWIR as a prognostic factor for clinical outcomes and determine its added value to known prognostic factors.

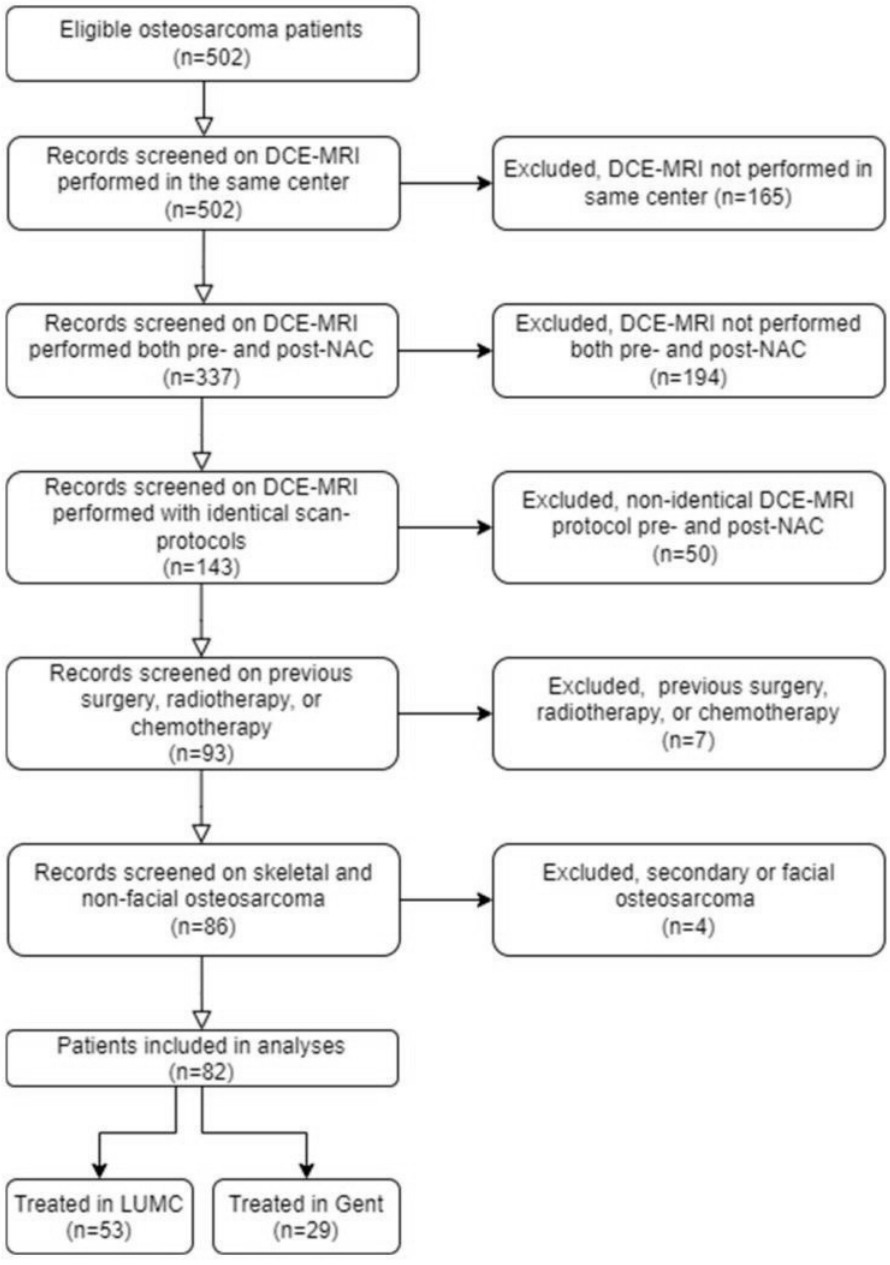


Figure 1. Flowchart of patient selection.

Legend: DCE-MRI = dynamic contrast-enhanced magnetic resonance imaging; NAC = neoadjuvant chemotherapy.

rWIR and Selection of Prognostic Variables

DCE-MRIs, and the corresponding rWIR, were processed in a blinded and independent manner by G.M.K. (4 years of experience) for LUMC patients and T.V.D.B. (4 years of experience) for GUH patients, and rWIR was determined for all included patients. Previous research reported an intraclass correlation coefficient of 0.81 for rWIR in neoadjuvant-treated osteosarcoma, suggesting good repeatability. The rWIR was calculated by dividing the maximum slope of contrast enhancement on the time–intensity curves (wash-in rate) from baseline imaging by the wash-in rate post-NAC. Details can be found in a previous study by Kalisvaart and Van Den Berghe et al.(9). A prior study by Evenhuis et al.(10) identified prognostic factors for survival in 402 patients treated for a skeletal high-grade osteosarcoma at the LUMC between 1978 and 2017. Age groups, tumor sizes, poor histopathological responses, and metastases at presentation were found to be independent prognostic factors influencing EFS in a multivariate Cox proportional hazard model and were also used in the current analysis(10). For the current study, patient records were reviewed by the local investigator to obtain demographics, treatment details, and clinical outcomes. Baseline variables included sex, age group (children: 0–<16 years; adolescents and young adults [AYA]: 16–<40 years; older adults: ≥40 years), tumor location, tumor size (≤8 cm or >8 cm), metastases at presentation, histological response according to the Huvos classification (poor response: ≥10% viable tumor cells; good response: <10% viable tumor cells and >90% response) and rWIR(4, 9). The rWIR was analyzed both as a dichotomous variable (rWIR < 2.3 indicated a poor radiological response, and rWIR ≥ 2.3 indicated a good radiological response) and as a continuous variable to evaluate the potential of rWIR to overcome the limitation of the arbitrary threshold for poor response originating from the 10% viable cells threshold in the Huvos classification. EFS was defined as the time from resection to the first event that consisted of LR, new metastases, or tumor-related death. In patients with metastatic disease at presentation, the next consecutive event was considered for EFS.

Follow-Up

Patients were monitored at the outpatient clinic for local control and disease progression. Follow-up protocols varied by center but generally included physical examinations and imaging modalities including computerized tomography (CT), MRI, and radiography.

Statistical Analysis

A multivariate Cox proportional hazard regression model was estimated to study the effect of risk factors on EFS. The model included age group, histological response to chemotherapy, tumor size, and metastases at presentation. A second model included the same prognostic factors but replaced histological response with rWIR. The rWIR was used as a categorical parameter (rWIR < 2.3 indicated a poor radiological response) and afterwards as a continuous parameter. The proportional hazard assumption was tested by using the weighted residuals(15). This analysis was also conducted on a subpopulation that excluded patients with baseline metastases. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were reported. To evaluate the additional value of rWIR, a comparison between two nested Cox models on the same data set with and without rWIR were compared using a likelihood ratio test(16). EFS was estimated by employing the Kaplan–Meier (KM) methodology. The median follow-up time was computed using the reversed Kaplan–Meier methodology(17). The combining batches (ComBat) harmonization method was used to reduce center-specific effects for the rWIR in the previous rWIR study(9). In the current study, analysis was performed with rWIR after ComBat harmonization and repeated with data without harmonization. Statistical analyses were performed using the SPSS version 25.0 (IBM Corp., Armonk, NY, USA) and R-studio software version 4.2.1. The level of significance was set at a p-value of < 0.05.

Results

Participants and Baseline Characteristics

The cohort consisted of 50 males (61%) and 32 females (39%), with a median age of 17.4 years (interquartile range [IQR]: 13.7–27.7). Respectively, 7/43 patients (16%) with a poor and 5/39 patients (13%) with a good histological response had metastases at presentation (Table 1). The median follow-up time was 11.8 years (95% CI: 11.0–12.7), and there were no dropouts. A total of 33 events were observed during the follow-up. The histological and radiological responses were classified as poor in 43 (52%) and 41 (50%) patients, respectively. In 18 patients (22%), histological and radiological response classifications were discordant. LR was observed in nine patients (11%). All patients with LR underwent re-resection, without additional chemo- or radiotherapy. The development of metastases during follow-up was observed in 31 patients (38%) that were treated with metastasectomy alone (n = 16, 52%), metastasectomy and chemotherapy (n = 5, 17%), metastasectomy and radiotherapy (n = 3, 10%), chemotherapy (n = 3, 10%), and metastasectomy, chemotherapy, and radiotherapy (n = 1, 3%), and 3 patients (10%) were not treated due to poor prognosis.

Table 1. Characteristics of the overall cohort.

Characteristics	N Total (%)	LUMC	GUH	*p*-value
Total	82	53 (65)	29 (35)	
Sex				0.20
Male	50 (61)	35 (66)	15 (52)	
Female	32 (39)	18 (34)	14 (48)	
Age group				0.16
Children (0–<16 yrs)	35 (43)	19 (36)	16 (55)	
AYA (16–<40 yrs)	35 (43)	24 (45)	11 (38)	
Older adults (≥40 yrs)	12 (15)	10 (19)	2 (7)	
Location tumor	86			0.10
Lower extremity	68 (83)	41 (77)	27 (93)	
Upper extremity	7 (9)	5 (9)	2 (7)	
Axial skeleton	7 (9)	7 (13)	0	
Tumor size				0.92
Small (≤8 cm)	39 (48)	25 (47)	14 (48)	
Large (>8 cm)	43 (52)	28 (53)	15 (52)	
Metastases at presentation				0.98
No	70 (85)	46 (87)	24 (83)	
Yes	12 (12)	7 (13)	5 (17)	

Legend: AYA = adolescents and young adults; yrs = years; MAP = Methotrexate, Adriamycin, and Cisplatin; AP = Adriamycin and Cisplatin; CTx = chemotherapy; and rWIR = relative wash-in rate.

Characteristics	N Total (%)	LUMC	GUH	*p*-value
Preoperative CTx treatment	81	52	29	0.17
1 MAP or 2 AP completed	4 (5)	4 (8)	0 (0)	
2 MAP or 3 AP completed	71 (87)	43 (83)	28 (97)	
>2 MAP or >3 AP completed	6 (7)	5 (10)	1 (3)	
Histological response to CTx				0.20
Poor (≥10% viable tumor cells)	43 (52)	25 (47)	18 (62)	
Good (<10% viable tumor cells)	39 (39)	28 (53)	11 (38)	
Radiological response to CTx				0.49
Poor response (rWIR < 2.3)	41 (50)	28 (53)	13 (45)	
Good response (rWIR ≥ 2.3)	41 (50)	25 (47)	16 (55)	
Local recurrence				0.38
No	73 (89)	46 (78)	27 (93)	
Yes	9 (11)	7 (13)	2 (7)	
Metastases during follow-up				0.06
No	51 (62)	29 (55)	22 (76)	
Yes	31 (38)	24 (45)	7 (24)	

Legend: AYA = adolescents and young adults; yrs = years; MAP = Methotrexate, Adriamycin, and Cisplatin; AP = Adriamycin and Cisplatin; CTx = chemotherapy; and rWIR = relative wash-in rate.

Prognostic Factors' Effect on EFS

In the first model (histological response included), none of the variables were significantly associated with EFS. Histological response (HR: 1.8; 95% CI: 0.9–3.8; reference category: good responder) and metastases at presentation (HR: 2.3; 95% CI: 0.9–5.8; reference category: no metastases) were the most influential factors, though not significant (Table 2). In the second model, the rWIR was used instead of the histological response to chemotherapy. The rWIR < 2.3 was significantly associated with worse EFS (HR: 2.4; 95% CI: 1.1–5.0; reference category: rWIR > 2.3), but metastases at presentation (HR: 2.3; 95% CI: 0.9–5.9) was not. Repeating the analysis in the none ComBat harmonization cohort showed that rWIR < 2.3 was still associated with EFS (HR: 2.8; 95% CI: 1.3–5.9). In the third model, the rWIR as a continuous variable was incorporated. None of the included variables were significantly associated with EFS, although the rWIR as a continuous variable (HR 0.8, 95% CI 0.6–1.0) and metastases at presentation (HR 1.9, 95% CI 0.7–4.9) were the most influential variables. A further subpopulation analysis, including 70 patients (85%) without metastases at presentation, revealed that rWIR as a binary variable nearly approached significance, suggesting an association with EFS (HR: 2.3; 95% CI: 1.0–5.2) (Table 3). rWIR as a continuous variable was significantly associated with EFS (HR: 0.7; 95% CI: 0.5–0.9). Thus, an increase in the continuous rWIR (and a decrease in wash-in rate during NAC) resulted in an increased EFS. The proportional hazard assumption for each covariate was not violated. Analysis of deviance suggests that adding rWIR to the multivariate Cox model leads to an improved fit over the model ($p = 0.07$), although further research is necessary to obtain more robust results.

Table 2. Hazard ratios (HRs) along with the 95% confidence intervals using multivariate Cox regression models for EFS in a study population (n = 82), with prognostic factors including histological response (left), rWIR as a binary variable (middle), and rWIR as a continuous variable (right) as the prognostic factors.

Factors	**HR**	**95% CI**	**Factors**	**HR**	**95% CI**	**Factors**	**HR**	**95% CI**
Age Group			**Age group**			**Age Group**		
Children	Ref		Children	Ref		Children	Ref	
AYA	1.36	0.61–3.03	AYA	1.43	0.64–3.22	AYA	1.32	0.59–2.98
Older adults	1.26	0.45–3.55	Older adults	1.55	0.55–4.41	Older adults	1.41	0.50–3.97
Tumor size			**Tumor size**			**Tumor size**		
Small ≤ 8 cm			Small ≤ 8 cm			Small ≤ 8 cm		
Large ≥ 8 cm	0.90	0.46–2.00	Large ≥ 8 cm	0.97	0.47–2.00	Large ≥ 8 cm	0.96	0.46–2.01
Histological response to CTx			**DCE-MRI response (binary) to CTx**			**DCE-MRI response (continuous) to CTx**	0.78	0.60–1.01
Good responder (<10% viable tumor cells)			Good responder (rWIR < 2.3)					
Poor responder (≥10% viable tumor cells)	1.82	0.86–3.84	Poor responder (rWIR ≥ 2.3)	2.39	1.14–5.01			
Metastases at presentation			**Metastases at presentation**			**Metastases at presentation**		
No			No			No		
Yes	2.29	0.90–5.83	Yes	2.31	0.90–5.92	Yes	1.85	0.70–4.94

Legend: HR = hazard ratio; ref = reference category; 95% CI = 95% confidence interval; CTx = chemotherapy; DCE-MRI = dynamic contrast-enhanced magnetic resonance imaging; AYA = adolescents and young adults; and rWIR = relative wash-in rate

Table 3. Hazard ratios (HRs) along with the 95% confidence intervals using multivariate Cox regression models for EFS with prognostic factors including histological response (left), rWIR as a binary variable (middle), and rWIR as a continuous variable (right) as the prognostic factors in a subpopulation of 70 patients without metastases at presentation.

Factors	HR	95% CI	Factors	HR	95% CI	Factors	HR	95% CI
Age group			**Age group**			**Age group**		
Children	Ref		Children	Ref		Children	Ref	
AYA	1.43	0.59–3.46	AYA	1.46	0.61–3.53	AYA	1.28	0.53–3.13
Older adults	2.11	0.66–6.79	Older adults	2.30	0.74–7.21	Older adults	2.02	0.63–6.50
Tumor size			**Tumor size**			**Tumor size**		
Small ≤ 8 cm			Small ≤ 8 cm			Small ≤ 8 cm		
Large ≥ 8 cm	1.26	0.55–2.92	Large ≥ 8 cm	1.33	0.60–2.97	Large ≥ 8 cm	1.23	0.54–2.80
Histological response to CTx			**DCE-MRI response (binary) to CTx**			**DCE-MRI response (continuous) to CTx**	0.69	0.50–0.94
Good responder (<10% viable tumor cells)			Good responder (rWIR < 2.3)					
Poor responder (≥10% viable tumor cells)	1.98	0.84–4.67	Poor responder (rWIR ≥ 2.3)	2.28	1.00–5.19			

Legend: HR = hazard ratio; ref = reference category; 95% CI = 95% confidence interval; CTx = chemotherapy; DCE-MRI = dynamic contrast-enhanced magnetic resonance imaging; AYA = adolescents and young adults; and rWIR = relative wash-in rate

Event-Free Survival

The 2- and 5-year EFS for patients with a rWIR of ≥2.3 (a good response) were 85% (95% CI: 74–96) and 75% (95% CI: 62–89) versus 55% (95% CI: 40–70) and 50% (95% CI: 35–66) for patients with a rWIR of <2.3 (a poor response) (Figure 2).

Among 70 patients without metastases at presentation, 24 (35%) experienced an event. The 2- and 5-year EFS for patients with a rWIR of ≥ 2.3 (a good response) were 89% (95% CI: 79–99) and 77% (95% CI: 63–91) versus 61% (95% CI: 44–78) and 55% (95% CI: 38–72) for patients with a rWIR of <2.3 (a poor response) (Figure 3). The 2- and 5-year recurrence-free survival for patients with a rWIR of ≥2.3 were 98% (95% CI: 93–100) and 98% (95% CI: 93–100) versus 87% (95% CI: 77–97) and 82% (95% CI: 69–94) for patients with a rWIR of <2.3. The 2- and 5-year metastasis-free survival for patients with a rWIR ≥ of 2.3 were 85% (95% CI: 75–96) and 75% (95% CI: 61–88) versus 57% (95% CI: 41–72) and 52% (95% CI: 36–67) for patients with a rWIR of <2.3.

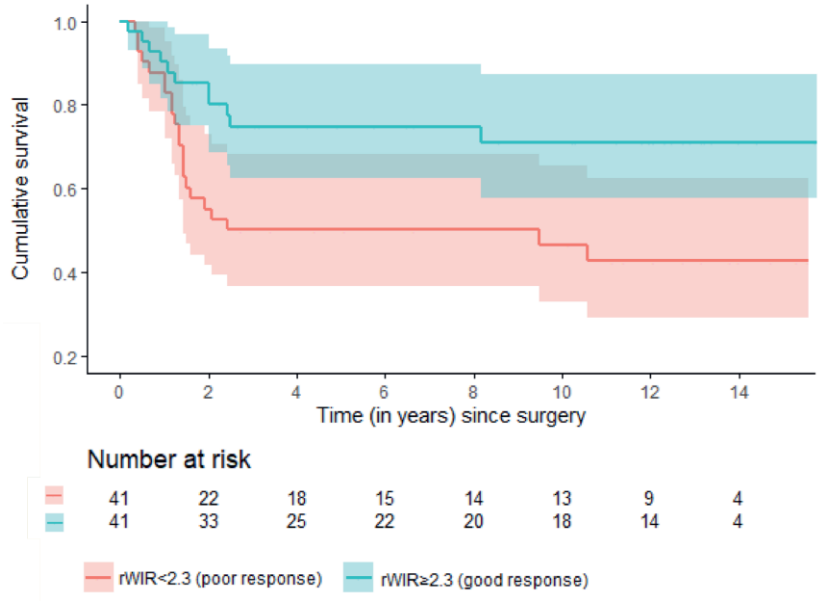


Figure 2. Estimated event-free survival among good and poor responders based on the rWIR with a cut-off of 2.3.

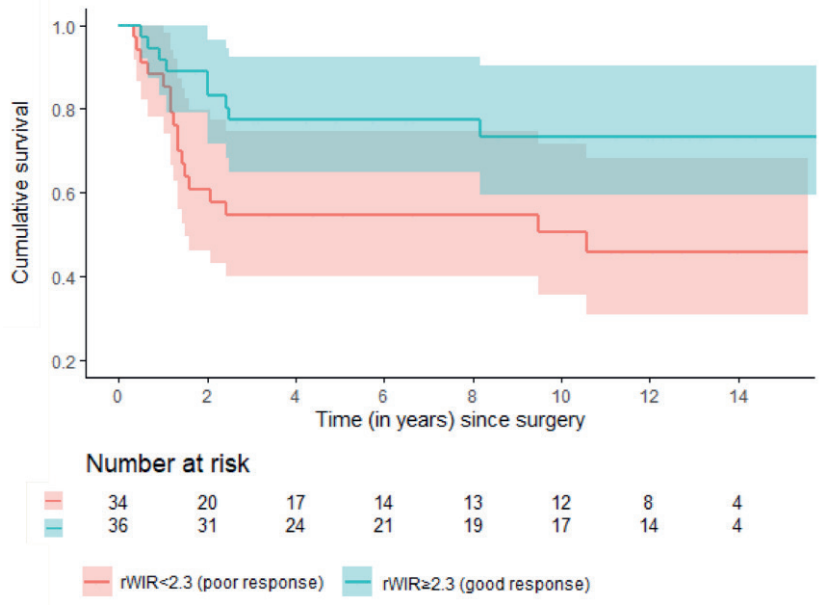


Figure 3. Estimated event-free survival among good and poor responders based on the rWIR with a cut-off of 2.3 in a subpopulation of 70 patients without metastases at presentation.

Discussion

In this multicenter study, rWIR, as determined using pre- and post-NAC DCE-MRI, was found to be associated with EFS in patients with osteosarcoma. To the best of our knowledge, this is the first study to date on the prognostic value of rWIR for EFS. Results show that a previously determined cut-off of rWIR < 2.3 is associated with poor EFS when adjusted for age group, tumor size, and metastases at presentation. Furthermore, the continuous rWIR was significantly associated with EFS in a subpopulation without metastases at presentation. Our findings suggest rWIR might have value for response stratification in patients without metastases at diagnosis, as rWIR can be determined before resection and used as a continuous variable in survival prediction. This contrasts with the traditionally used histological response, and in our population, it was not significantly associated with EFS.

The link between DCE-MRI-based perfusion characteristics and histological responses has been described extensively in the literature(7, 18). Guo et al. and Hao et al. found that several features, describing tissue permeability and perfusion, were correlated with histologic responses(7, 19). In a previous rWIR study, standardized optimal methods to use perfusion characteristics, specifically the derived time–intensity curve, for histological response prediction were identified(9). This determination of the association with biological changes in tumor tissues allows a more explainable association of this imaging characteristic with survival outcomes in the current study.

Although in this study the use of pre- and post-NAC DCE-MRI was investigated to predict clinical outcome of osteosarcoma patients, there are other functional imaging techniques such as PET-CT and DWI that have been described for predicting the response to chemotherapy(7, 20, 21). These studies typically predict the histological response instead of survival. Studies evaluating quantitative, texture-based imaging features (radiomics) for predicting treatment response and survival have not yet resulted in widely accepted and implemented prognostic imaging biomarkers(22-26). Interpretation of results in radiomics studies is often complicated by a lack of correcting methods for other prognostic factors,

such as the presence of metastases or age and complexity of radiomics models. Furthermore, implementation is challenging, since specific software, quality control, and adherence to standardized study protocols are needed to assure reliable results and reproducibility of the results(27, 28). In this regard, the rWIR is a practical and explainable biomarker that is associated with clinical outcome when adjusted for most important covariates. Moreover, it facilitates a deeper understanding of tumor behavior during treatment, providing radiologists and oncologists with a comprehensive tool for analysis and interpretation.

A limitation of this study is that it included patients previously described in the study deciphering the association between rWIR and histological response. Ideally, new patients should have been included. However, the model, which was used to identify rWIR, was not trained using survival data, causing the current study to provide valuable added information on patient stratification. Additionally, T1-mapping was not available in this study, preventing the use of Tofts features from the analyses(29). DCE-MRI features based on the Tofts-model, such as differences in relative extravascular extracellular space and influx volume transfer constant, have been shown to be prognostic factors for EFS and overall survival (OS)(7, 19). However, limited cohort sizes, arbitrary cut-offs for radiological response classification, and a lack of correction for other prognostic factors limit the interpretability of these results described in the literature. Nevertheless, future studies should determine if Tofts modeling strengthens the prognostic value of DCE-MRI characteristics for patient stratification.

The rWIR holds potential for the early evaluation of NAC treatment response and EFS prediction in a non-invasive way before tumor resection. Moreover, patients with a poor radiological response to NAC experienced recurrences more often and seemed to have a shorter recurrence-free survival. Once further investigated and validated in larger sample sizes, this method could allow for standardized response monitoring in studies on neoadjuvant therapies, for example, in the development of new chemotherapy regimens. This, in turn, might contribute to individualized therapies and decision making. It involves the potential to either avoid or intensify ineffective chemotherapy cycles. Additionally, it

might justify a more invasive surgical or adjuvant radiotherapy treatment in patients with predicted poor prognosis, aiming to prevent local recurrences and improve survival outcomes.

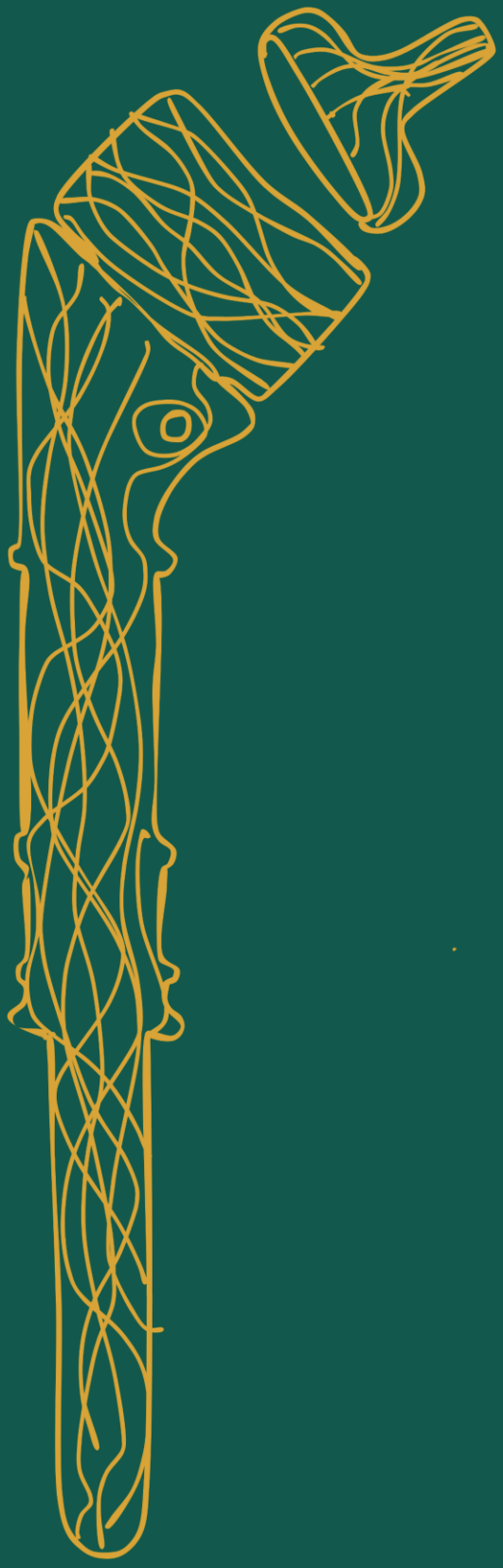
Conclusions

The rWIR is associated with EFS and is a valuable addition to other clinical parameters. Future prospective studies on response monitoring and EFS prediction should be compared to the performance of rWIR.

References

1. Bone sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Annals of Oncology. 2014;25:iii113-iii23.
2. Ingley KM, Maleddu A, Grange FL, Gerrand C, Bleyer A, Yasmin E, et al. Current approaches to management of bone sarcoma in adolescent and young adult patients. Pediatr Blood Cancer. 2022;69(2):e29442.
3. Jafari F, Javdansirat S, Sanaie S, Naseri A, Shamekh A, Rostamzadeh D, et al. Osteosarcoma: A comprehensive review of management and treatment strategies. Ann Diagn Pathol. 2020;49:151654.
4. Huvos AG, Rosen G, Marcove RC. Primary osteogenic sarcoma: pathologic aspects in 20 patients after treatment with chemotherapy en bloc resection, and prosthetic bone replacement. Arch Pathol Lab Med. 1977;101(1):14-8.
5. Rosen G, Caparros B, Huvos AG, Kosloff C, Nirenberg A, Cacavio A, et al. Preoperative chemotherapy for osteogenic sarcoma: selection of postoperative adjuvant chemotherapy based on the response of the primary tumor to preoperative chemotherapy. Cancer. 1982;49(6):1221-30.
6. Strauss SJ, Frezza AM, Abecassis N, Bajpai J, Bauer S, Biagini R, et al. Bone sarcomas: ESMO-EURACAN-GENTURIS-ERN PaedCan Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2021;32(12):1520-36.
7. Guo J, Reddick WE, Glass JO, Ji Q, Billups CA, Wu J, et al. Dynamic contrast-enhanced magnetic resonance imaging as a prognostic factor in predicting event-free and overall survival in pediatric patients with osteosarcoma. Cancer. 2012;118(15):3776-85.
8. Tofts PS, Brix G, Buckley DL, Evelhoch JL, Henderson E, Knopp MV, et al. Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusable tracer: standardized quantities and symbols. J Magn Reson Imaging. 1999;10(3):223-32.
9. Kalisvaart GM, Van Den Berghe T, Grootjans W, Lejoly M, Huysse WCJ, Bovée J, et al. Evaluation of response to neoadjuvant chemotherapy in osteosarcoma using dynamic contrast-enhanced MRI: development and external validation of a model. Skeletal Radiol. 2023.
10. Evenhuis RE, Acem I, Rueten-Budde AJ, Karis DSA, Fiocco M, Dorleijn DMJ, et al. Survival Analysis of 3 Different Age Groups and Prognostic Factors among 402 Patients with Skeletal High-Grade Osteosarcoma. Real World Data from a Single Tertiary Sarcoma Center. Cancers (Basel). 2021;13(3).
11. Smeland S, Bielack SS, Whelan J, Bernstein M, Hogendoorn P, Krailo MD, et al. Survival and prognosis with osteosarcoma: outcomes in more than 2000 patients in the EURAMOS-1 (European and American Osteosarcoma Study) cohort. Eur J Cancer. 2019;109:36-50.
12. Petrilli AS, de Camargo B, Filho VO, Bruniera P, Brunetto AL, Jesus-Garcia R, et al. Results of the Brazilian Osteosarcoma Treatment Group Studies III and IV: prognostic factors and impact on survival. J Clin Oncol. 2006;24(7):1161-8.
13. Weeden S, Grimer RJ, Cannon SR, Taminiau AHM, Uscinska BM. The effect of local recurrence on survival in resected osteosarcoma. European Journal of Cancer. 2001;37(1):39-46.
14. Testa S, Hu BD, Saadeh NL, Pribnow A, Spunt SL, Charville GW, et al. A Retrospective Comparative Analysis of Outcomes and Prognostic Factors in Adult and Pediatric Patients with Osteosarcoma. Curr Oncol. 2021;28(6):5304-17.
15. GRAMBSCH PM, THERNEAU TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika. 1994;81(3):515-26.
16. Lee KL, Harrell FE, Jr., Tolley HD, Rosati RA. A comparison of test statistics for assessing the effects of concomitant variables in survival analysis. Biometrics. 1983;39(2):341-50.
17. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Controlled Clinical Trials. 1996;17(4):343-6.

18. Xia X, Wen L, Zhou F, Li J, Lu Q, Liu J, et al. Predictive value of DCE-MRI and IVIM-DWI in osteosarcoma patients with neoadjuvant chemotherapy. Front Oncol. 2022;12:967450.
19. Hao Y, An R, Xue Y, Li F, Wang H, Zheng J, et al. Prognostic value of tumoral and peritumoral magnetic resonance parameters in osteosarcoma patients for monitoring chemotherapy response. Eur Radiol. 2021;31(5):3518-29.
20. Bajpai J, Kumar R, Sreenivas V, Sharma MC, Khan SA, Rastogi S, et al. Prediction of chemotherapy response by PET-CT in osteosarcoma: correlation with histologic necrosis. J Pediatr Hematol Oncol. 2011;33(7):e271-8.
21. Byun BH, Kong CB, Lim I, Choi CW, Song WS, Cho WH, et al. Combination of 18F-FDG PET/CT and diffusion-weighted MR imaging as a predictor of histologic response to neoadjuvant chemotherapy: preliminary results in osteosarcoma. J Nucl Med. 2013;54(7):1053-9.
22. Spraker MB, Wootton LS, Hippe DS, Ball KC, Peeken JC, Macomber MW, et al. MRI Radiomic Features Are Independently Associated With Overall Survival in Soft Tissue Sarcoma. Adv Radiat Oncol. 2019;4(2):413-21.
23. Zhao S, Su Y, Duan J, Qiu Q, Ge X, Wang A, et al. Radiomics signature extracted from diffusion-weighted magnetic resonance imaging predicts outcomes in osteosarcoma. J Bone Oncol. 2019;19:100263.
24. Zhang L, Ge Y, Gao Q, Zhao F, Cheng T, Li H, et al. Machine Learning-Based Radiomics Nomogram With Dynamic Contrast-Enhanced MRI of the Osteosarcoma for Evaluation of Efficacy of Neoadjuvant Chemotherapy. Front Oncol. 2021;11:758921.
25. Chen H, Zhang X, Wang X, Quan X, Deng Y, Lu M, et al. MRI-based radiomics signature for pretreatment prediction of pathological response to neoadjuvant chemotherapy in osteosarcoma: a multicenter study. Eur Radiol. 2021;31(10):7913-24.
26. Shapeero LG, Vanel D. Imaging evaluation of the response of high-grade osteosarcoma and Ewing sarcoma to chemotherapy with emphasis on dynamic contrast-enhanced magnetic resonance imaging. Semin Musculoskelet Radiol. 2000;4(1):137-46.
27. Crombé A, Fadli D, Italiano A, Saut O, Buy X, Kind M. Systematic review of sarcomas radiomics studies: Bridging the gap between concepts and clinical applications? Eur J Radiol. 2020;132:109283.
28. Fanciullo C, Gitto S, Carlicchi E, Albano D, Messina C, Sconfienza LM. Radiomics of Musculoskeletal Sarcomas: A Narrative Review. J Imaging. 2022;8(2).
29. Sourbron SP, Buckley DL. On the scope and interpretation of the Tofts models for DCE-MRI. Magn Reson Med. 2011;66(3):735-45.



PART II

MUTARS reconstructions in patients with extensive bone defects following orthopaedic oncological resections

Chapter 5

LUMiC endoprosthetic reconstruction of periacetabular tumor defects: a multicenter follow-up study

R.E. Evenhuis[1], M.A.J. van de Sande[1,2], M. Fiocco[2,3,4], E.F. Dierselhuis[5], D. Broekhuis[1], M.P.A. Bus[1], and the LUMiC® Study Group*

1. Department of Orthopaedic Surgery, Leiden University Medical Center, Albinusdreef 2, 2333 Leiden, The Netherlands
2. Center for Pediatric Oncology, Princess Maxima Center, 3584 Utrecht, The Netherlands
3. Mathematical Institute, Leiden University, 2300 Leiden, The Netherlands
4. Medical Statistics, Department of Biomedical Science, Leiden University Medical Center, Leiden, The Netherlands
5. Department of Orthopaedic Surgery, Radboudumc, Nijmegen, The Netherlands

Journal of Bone and Joint Surgery, May 2024

Abstract

Background: We previously reported promising early results for periacetabular tumor reconstructions using the LUMiC prosthesis. The current study evaluates mid-term complications, revision rates, cumulative incidence of implant revision, and risk factors for complications in a multicenter cohort. Methods: We assessed patients in whom a tumor defect after type P1b+2, P2, P2+3, or P1b+2+3 internal hemipelvectomy was reconstructed with a LUMiC prosthesis during the period of 2008 to 2022. Complications were reported according to the Henderson classification. Competing risks models were used to estimate the cumulative incidence of implant revision for mechanical and nonmechanical reasons, and reoperations for any complication. Cox models were used to study the effect of risk factors on dislocation and infection. Results: One hundred and sixty-six patients (median follow-up, 4.2 years [interquartile range, 2.6 to 7.6 years]) were included. A total of 114 (69%) were treated for a primary malignant tumor, 46 (28%) for metastatic carcinoma, 5 (3%) for a benign aggressive lesion, and 1 (1%) for another reason. One hundred and sixty-five reoperations were performed in 82 (49%) of the patients; 104 (63%) of the reoperations were within 6 months. Thirty-two (19%) of 166 implants were revised: 13 (8%) for mechanical reasons, mainly dislocation (n = 5, 3%), and 19 (11%) for nonmechanical reasons, mainly periprosthetic joint infection (PJI) (n = 15, 9%). The cumulative incidences of revision for mechanical reasons and PJI (Henderson 1 to 4) at 2, 5, and 10 years were 11% (95% confidence interval [CI], 7% to 17%), 18% (12% to 25%), and 24% (16% to 33%), respectively. Previous surgery at the same site was associated with an increased dislocation risk (cause-specific hazard ratio [HRCS], 3.0 [95% CI, 1.5 to 6.4]; $p < 0.01$), and resections involving the P3 region were associated with an increased infection risk (HRCS, 2.5 [95% CI, 1.4 to 4.7]; $p < 0.01$). Conclusions: Despite a substantial reoperation risk, the LUMiC prosthesis demonstrated its durability in the mid-term, with a low mechanical revision rate and most patients retaining their primary implant. Most complications occur in the first postoperative months. Patients with previous surgery at the same site had an increased dislocation risk and might benefit from more conservative rehabilitation and aftercare. Measures should be aimed at reducing the PJI risk, especially

in resections involving the P3 region. Level of Evidence: Therapeutic Level IV. See Instructions for Authors for a complete description of levels of evidence.

Introduction

Over the past decades, nonmodular stemmed acetabular cups have gained popularity for the reconstruction of periacetabular tumor defects because of their wide availability, intraoperative flexibility, relatively fast and easy implantation, and the possibility of allowing early weight-bearing and rapid postoperative mobilization(1, 2). Nevertheless, as with any periacetabular reconstruction technique, the risks of dislocation (3% to 31%), aseptic loosening (0% to 16%), and periprosthetic joint infection (PJI) (10% to 50%) remain substantial. These complications commonly necessitate revision surgery, resulting in an even higher risk of complications and morbidity(1-11).

The LUMiC prosthesis (Implantcast) was introduced in 2008 for the reconstruction of extensive periacetabular defects. This modular device consists of a stem that sits in the remaining ilium, in line with the weight-bearing axis of the pelvis, and an acetabular cup that is connected to the stem(12). The stem and cup are equipped with a sawtooth junction allowing for rotational adjustment of the cup. In a previous study(2), we reported promising short-term complication and implant survival rates compared with other techniques(1, 4, 13-15).

In the current study, we aimed to assess the mid-term results of this implant, in a larger multicenter cohort. Therefore, we evaluated (1) the complications and associated risk factors, (2) the reasons for implant revision, and (3) the cumulative incidence of implant revision at 2, 5, and 10 years.

Materials and Methods

Approval for conducting this study was obtained from the scientific committee of the Leiden University Medical Center (LUMC). The committee waived patients' informed consent (W.22.002/2022-029). Participating centers obtained approval by their local ethical review board.

Study Design, Setting, Participants

In this international, multicenter, observational retrospective study, we assessed all patients in whom an internal hemipelvectomy was performed for a bone tumor and in whom the LUMiC prosthesis was used for reconstruction of the defect during the period of 2008 to 2022. The minimum potential follow-up was 24 months; patients who died within 24 months after implantation were included. Fourteen tertiary referral centers participated. All patients had a periacetabular tumor defect (including P2 according to the modified Enneking classification(16)) in which the medial ilium was preserved as described in our previous work(2, 4). One hundred and sixty-six patients (87 female, 52%) with a median age of 57 years (range, 10 to 81 years) were included. The median follow-up for censored patients was 4.2 years (interquartile range [IQR], 2.6 to 7.6 years). The indication for reconstruction in 114 (69%) of the patients was resection of a primary malignant bone tumor, while 46 (28%) had been treated for metastatic carcinoma (Table 1). Twenty-six (16%) of the patients had ≥1 previous surgeries at the same site (Table 1). All patients received prophylactic antibiotics according to the local protocol: either as a single dose (n = 25, 15%) or over 24 hours (n = 55, 34%), 3 to 5 days (n = 53, 33%), or >5 days (n = 29, 18% [of 162 with data on antibiotic duration]) (Table 3). According to the modified Enneking classification, 17 (11%) of the patients underwent type P1b+2 resection; 83 (52%), type P2 resection; 50 (31%), type P2+3 resection; and 11 (7%), type P1b+2+3 resection(4, 16). In 60 (41%) of patients (146 with data), an extra-articular resection of the hip joint was performed.

Table 1. Study Population (N = 166)[*].

Variable	Values
Sex	166
Male	79 (48%)
Female	87 (52%)
BMI[†] *(kg/m²)*	25 [22-28]
ASA score	165
1	40 (24%)
2	81 (49%)
3	44 (27%)
Smoking	139
Yes, currently	20 (14%)
Yes, formerly (stopped >6 mo.)	17 (12%)
Diabetes	12/152 (8%)
Indication for reconstruction	166
Primary malignant tumors	114 (69%)
Chondrosarcoma	67 (40%)
Osteosarcoma	18 (11%)
Ewing sarcoma	11 (7%)
Soft-tissue sarcoma	9 (5%)
Multiple myeloma	4 (2%)
Other	5 (3%)
Metastatic carcinoma	46 (28%)
Benign aggressive lesions	5 (3%)
GCTB	2 (1%)
Chondroblastoma	1 (1%)
Chondromyxoid fibroma	1 (1%)
Yeast infection[‡]	1 (1%)
Other	1 (1%)
Previous surgery at same site	26 (16%)
Internal hemipelvectomy or partial pelvic tumor resection	9 (35%)
Total hip arthroplasty	13 (50%)
Curettage (GCTB/osteoblastoma)	4 (15%)
Soft-tissue involvement	91/158 (55%)
Pathological fracture at diagnosis	30/162 (19%)
Neoadjuvant chemotherapy	55/163 (34%)
Neoadjuvant radiation therapy	28/163 (17%)
Adjuvant chemotherapy	52/162 (32%)
Adjuvant radiation therapy	30/159 (19%)

*Legend: *The values are given as the number, with the percentage in parentheses, except where otherwise noted. BMI = body mass index, ASA = American Society of Anesthesiologists physical status, and GCTB = giant cell tumor of bone. †BMI values are given as the median, with the interquartile range (IQR) in square brackets. ‡Suspicious lesion in a patient with known multiple myeloma. Histology identified no tumor localization but a yeast infection.*

Table 2. Prosthesis and Surgical Details.

Variable	No. (%)*
Antibiotic administration	161
Cephalosporins	100 (62%)
Beta-lactam	13 (8%)
Cephalosporins + clindamycin	12 (8%)
Cephalosporins + metronidazole	8 (5%)
Glycopeptides	10 (6%)
Cephalosporins + aminoglycosides	6 (4%)
Glycopeptides + β-lactam	6 (4%)
Other	6 (4%)
Modified Enneking resection type	161
P1b+2	17 (11%)
P2	83 (52%)
P2+3	50 (31%)
P1b+2+3	11 (7%)
Use of computer-assisted surgery	49/166 (30%)
Concomitant proximal femoral reconstruction	56/165 (34%)
Silver-coated proximal femur	40/56 (71%)
Cemented LUMiC stem	30/165 (18%)
Cup size	163
50 mm	62 (38%)
54 mm	49 (30%)
60 mm	52 (32%)
Dual-mobility cup	107/164 (65%)
Silver-coated cup	36/166 (22%)
Cemented femoral component	62/164 (38%)
Use of Trevira tube	48/163 (29%)

*Total cohort, n = 166.

Preoperative Planning, Surgical Details, Procedure

The general surgical and procedural details were previously described(12). Although not available in all participating centers, the leading center prefers the use of intraoperative navigation to optimize stem placement. Press-fit fixation of an uncemented stem was preferred unless adequate press-fit fixation of the stem was not obtained, or if bone quality was inadequate. Conventional and dual-mobility cup articulations were available and were used at the surgeon's discretion, although the dual-mobility cup was preferred

on the basis of previous results(2). Depending on the surgeon's preferences, a Trevira attachment tube (Implantcast) was used to reattach soft tissues. Usually, early partial weight-bearing (with use of 2 crutches) was allowed under supervision of a physiotherapist. At 6 to 12 weeks, this was gradually increased to full weight-bearing. Combined flexion and external rotation was avoided. In some centers, orthoses were used.

Generally, patients with a suspected PJI underwent a DAIR (debridement, antibiotics, and implant retention) procedure, including intraoperative culturing and a thorough debridement, followed by at least 2 weeks of intravenous antibiotics. The standard antibiotic treatment regimen spanned a minimum of 12 weeks, depending on the isolated microorganism(s) and the susceptibility pattern. In some cases, eradication of the PJI was not achieved, resulting in chronic antibiotic suppression or a draining fistula, as described in our previous paper(11).

Variables

Patient records were reviewed to obtain demographics, surgical details, reconstruction details, complications, and functional outcomes at the last date of follow-up. Incision types were divided into 2 groups: a single iliofemoral ("question mark") incision or a star-shaped incision. Pelvic resection types were divided into 2 groups: P1b+2 and P2 or P1b+2+3 and P2+3. Revision was defined as any surgical procedure in which (part of) the implant was removed or replaced. Complications and the reason for implant revision were categorized according to the Henderson classification(17).

Statistical Analysis

Competing risks models(18) were used to estimate the cumulative incidences of implant revision and reoperations. A competing risks model with 3 competing events was used to estimate the cumulative incidences of mechanical failure and infection, with death and local recurrence as competing events. A second competing risks model with 2 competing events was employed to estimate the cumulative incidence of any complication, with death as a competing event.

Cause-specific Cox hazard regression models were estimated to study the effect of prognostic risk factors on time to dislocation and time to PJI. Cause-specific hazard ratios and 95% confidence intervals are reported. The proportion of complications was compared among different subgroups using chi-square analysis. Analyses of data were performed using SPSS version 25.0 (IBM) and RStudio version 4.2.1(19). The R Studio package "cmprsk" was used to estimate the cumulative incidence of implant revision and reoperations. The level of significance was set at $p < 0.05$.

Results

Complications, Implant Revision, Risk Factors

During the study period, 82 (49%) of the patients underwent ≥1 reoperation (Table 3). In total, 165 reoperations were performed, of which 104 (63%) were within 6 months.

Dislocations (Henderson 1A) occurred in 31 (19%) of the patients; 21 (13%) had a single dislocation and underwent closed or open reduction, and 10 (6%) had recurrent dislocations. The first dislocation occurred within 1 month in 2 (6%) of the 31 patients, between 1 and 6 months in 4 (13%), and later in 5 (16%). Patients who had previous surgery at the same site had a higher dislocation risk than those without previous surgery at the same site (cause-specific hazard ratio [HRCS], 3.0 [95% confidence interval (CI), 1.5 to 6.4]; $p < 0.01$) (Table 4). Utilization of the dual-mobility cup (HRCS, 0.6 [95% CI, 0.3 to 1.2]; $p = 0.17$) or the Trevira tube (HRCS, 0.7 [95% CI, 0.3 to 1.6]; $p = 0.38$) was not significantly associated with dislocation. Dislocations occurred in 15 (26%) of 57 patients with conventional cups compared with 16 (15%) of 107 with dual-mobility cups ($p = 0.08$). Dislocations occurred in 7 (15%) of 48 patients with reconstruction with a Trevira tube versus 24 (21%) of 115 without ($p = 0.35$). Dislocations occurred in 3 (10%) of 29 patients with reconstruction with a Trevira tube and dual-mobility cup versus 11 (30%) of 37 who had neither ($p = 0.06$). Five implants (3% of patients) were revised for instability. Four conventional cups (2%) were exchanged for a dual-mobility cup, and 1 (1%) resection arthroplasty was performed because of recurrent instability and poor oncological prognosis.

Table 3. Complication and Revision Rates, Time to Revision, and Reconstruction Status Among Revised Cases

Complication*	No. (%)		Time to Revision After Implantation *(mo)*	Reconstruction Status at Latest Follow-up (No.)
	Patients	Revisions		
Total	82/166 (49%)	32/166 (19%)	0-99	
H1A (dislocation)	31 (19%)	5 (3%)	0-45	Revision LUMiC (3), resection arthroplasty (1), hindquarter amputation (1)†
H1B (aseptic wound dehiscence)	7 (4%)	0 (0%)		
H2A (aseptic loosening <2 yr after implantation)	1 (1%)	1 (1%)	12	Resection arthroplasty (1)
H2B (aseptic loosening ≥2 yr after implantation)	4 (2%)	4 (2%)	53-77	Custom-made implant (4)
H3A (implant breakage or wear)	1 (1%)	1 (1%)	32	Revision LUMiC (1)
H3B (periprosthetic osseous fracture)	2 (1%)	2 (1%)	0, 9	Revision LUMiC (1), resection arthroplasty (1)
H4A (PJI <2 yr after implantation)	36 (22%)	11 (7%)	0-20	Revision LUMiC (2), resection arthroplasty (6), custom-made implant (1), hindquarter amputation (1), spacer (1)
H4B (PJI ≥2 yr after implantation)	5 (3%)	4 (2%)	35-65	Revision LUMiC (1), resection arthroplasty (2), rotationplasty (1)
H5A (soft-tissue progression of tumor)	2 (1%)	0 (0%)		
H5B (osseous progression of tumor)	13 (8%)	4 (2%)	0-99	Hindquarter amputation (3), resection arthroplasty (1)
Other	12 (7%)	0 (0%)		

*Legend: *H = Henderson classification, and PJI = periprosthetic joint infection. †One patient had revision LUMiC for dislocation but later underwent amputation due to osseous progression of tumor*

Table 4. Univariate Cause-Specific Cox Proportional Hazards Regression Model for Prognostic Factors for the Occurrence of Dislocation and PJI*.

Possible Risk Factors	Dislocation HR_{CS} (95% CI)	p-value	PJI HR_{CS} (95% CI)	p-value
Sex				
Female†				
Male	1.8 (0.89-3.77)	0.10	1.2 (0.66-2.21)	0.54
Age	1.0 (0.99-1.05)	0.07	1.0 (1.00-1.04)	0.05
BMI	1.0 (0.96-1.10)	0.49	1.0 (0.98-1.10)	0.21
ASA classification				
I†				
II	1.3 (0.56-3.20)	0.52	1.2 (0.57-2.73)	0.59
III	0.8 (0.28-2.51)	0.76	1.5 (0.62-3.49)	0.39
Smoking	NA			
No†				
Yes			0.5 (0.16-1.68)	0.27
Diabetes	NA			
No†				
Yes			1.9 (0.69-5.63)	0.20
Previous surgery at same site				
No†				
Yes	3.0 (1.47-6.41)	0.003	0.8 (0.34-1.89)	0.61
Incision type	NA			
Single incision†				
Star-shaped incision			1.3 (0.69-2.57)	0.39
Proximal femoral resection				
No†				
Yes	0.8 (0.35-1.64)	0.48	1.2 (0.66-2.26)	0.53
Type of pelvic resection				
P1b+2 and P2†				
P2+3 and P1b+2+3	1.4 (0.70-2.95)	0.32	2.5 (1.35-4.72)	0.004
Surgical duration *(hr)*	NA		1.1 (0.98-1.29)	0.09
Blood loss *(L)*	NA		1.1 (0.84-1.32)	0.67
Dual-mobility cup				
No†				
Yes	0.6 (0.29-1.23)	0.17	NA	
Use of silver-coated cup	NA			
No†				
Yes			2.1 (1.11-4.04)	0.02
Use of silver-coated proximal femur	NA			
No†				
Yes			0.2 (0.07-0.49)	<0.001
Use of computer-assisted surgery				
No†				
Yes	0.7 (0.38-1.92)	0.71	0.8 (0.37-1.54)	0.44
Use of Trevira tube				
No†				
Yes	0.7 (0.30-1.59)	0.38	1.6 (0.87-3.05)	0.13

*Legend: *PJI = periprosthetic joint infection, HRCS = cause-specific hazard ratio, 95% CI = 95% confidence interval, BMI = body mass index, ASA = American Society of Anesthesiologists physical status, and NA = not applicable.*
†Reference category.

Early aseptic loosening (Henderson 2A) of the stem occurred in 1 patient (1%), who previously had reconstruction with use of an allograft and total hip replacement that had failed as a result of PJI. After 5 years without further reconstruction, a cemented LUMiC prosthesis was implanted; it was removed 12 months later because of aseptic loosening.

Late aseptic loosening (Henderson 2B) occurred in 4 (2%) of the patients, 3 with an uncemented implant and 1 with a cemented implant. All underwent revision with use of a custom-made implant, 4.4 to 6.4 years after implantation. No complications preceded the aseptic loosening, and none of these patients had undergone reconstruction previously.

Intraprosthetic dissociation (Henderson 3A) occurred in 1 patient (1%), who had persistent subluxation. During revision surgery 32 months after implantation, the LUMiC dual-mobility liner appeared to have dissociated. The stem was well fixed and was left in place, and the liner and cup were revised.

Periprosthetic fracture at implantation (Henderson 3B) occurred in 2 (1%) of the patients; the fractures consisted of a periprosthetic fracture of the ilium around the uncemented stem. One patient underwent successful revision to an uncemented LUMiC stem, implanted slightly more dorsal and lateral in the remaining ilium, utilizing fresh bone stock. One was treated conservatively, but the fracture did not consolidate, resulting in revision to a custom-made prosthesis at 9 months. As a result of dislocation, revision surgery was performed to increase the offset. However, during the procedure, it turned out that the custom-made prosthesis had loosened because of poor bone quality, leading to implant removal and resection arthroplasty.

PJI (Henderson 4) occurred in 41 (25%) of the patients. In 22 (54%) of the patients, PJI occurred within 6 weeks; in 4 (10%), between 6 and 12 weeks; in 2 (5%), between 12 and 24 weeks; and in 13 (32%), at >24 weeks postoperatively. The success rate of ≥1 DAIR procedures was 50% (11 of 22) for patients with an early PJI between 0 and 6 weeks, 75% (3 of 4) with PJI between 6 and 12 weeks, 100% (2 of 2) with PJI between 12 and 24 weeks, and 69% (9 of 13) with PJI at >24 weeks postoperatively. Of the patients with infection

following reconstruction, 17 (71%) of 24 without a Trevira tube were successfully managed with DAIR procedures versus 8 (50%) of 16 with a Trevira tube (p = 0.18).

The median duration of the index surgery was 5.5 hours (IQR, 4.3 to 6.5 hours) in patients who developed PJI and 4.8 hours (IQR, 3.6 to 6.5 hours) in those who did not develop PJI (p = 0.13). Surgical duration was not associated with PJI risk (Table 4). The PJI risk was lower for patients with a concomitant proximal femoral reconstruction with silver coating compared with those without silver coating (HRCS, 0.2 [95% CI, 0.07 to 0.5]; p < 0.01). Nine (23%) of 40 with silver coating developed PJI compared with 8 (80%) of 10 without silver coating (p < 0.01) (data on silver coating available for 50 of 56 patients with proximal femoral reconstruction). Resections that included the P3 region had an increased PJI risk (HRCS, 2.5 [95% CI, 1.4 to 4.7]; p < 0.01). Median blood loss did not differ between patients with PJI (1.9 L [IQR, 1.0 to 2.5 L]) and those without (1.5 L [IQR, 1.0 to 2.3 L]) (p = 0.90). Ultimately, 15 (9%) of the patients underwent revision because of PJI. One had a previous reconstruction (pedestal-cup prosthesis) that had failed because of PJI, and the others did not have previous reconstructions. Four underwent a new reconstruction (3 were revised to a new LUMiC prosthesis during 1-stage [n = 2] or 2-stage [n = 1] revision, and 1 received a custom-made implant). Others underwent resection arthroplasty (n = 8), implant removal and spacer implantation (n = 1), hindquarter amputation (n = 1), or rotationplasty (n = 1) (Table 3).

Local recurrence (Henderson 5B) occurred in 13 (8%) of the patients, leading to implant removal in 4 (2%) of the cases (3 hindquarter amputations, 1 resection arthroplasty).

Cumulative Incidence of Implant Revision, Reconstruction Status, and Functional and Survival Outcomes

The cumulative incidence of implant revision for mechanical reasons (Henderson 1 to 3) at 2, 5, and 10 years was 4% (95% CI, 2% to 8%), 9% (95% CI, 4% to 15%), and 12% (95% CI, 6% to 20%). For PJI (Henderson 4), the rates were 7% (95% CI, 4% to 11%), 10% (95% CI, 5% to 16%), and 11% (95% CI, 6% to 18%) (Figure 1). For mechanical reasons and PJI (Henderson 1 to 4), the rates were 11% (95% CI, 7% to 17%), 18% (95% CI, 12% to 25%), and 24% (95% CI, 16% to 33%), respectively.

The cumulative incidence of reoperation for any complication at 2, 5, and 10 years was 44% (95% CI, 36% to 51%), 52% (95% CI, 43% to 60%), and 58% (95% CI, 47% to 67%) (Figure 2).

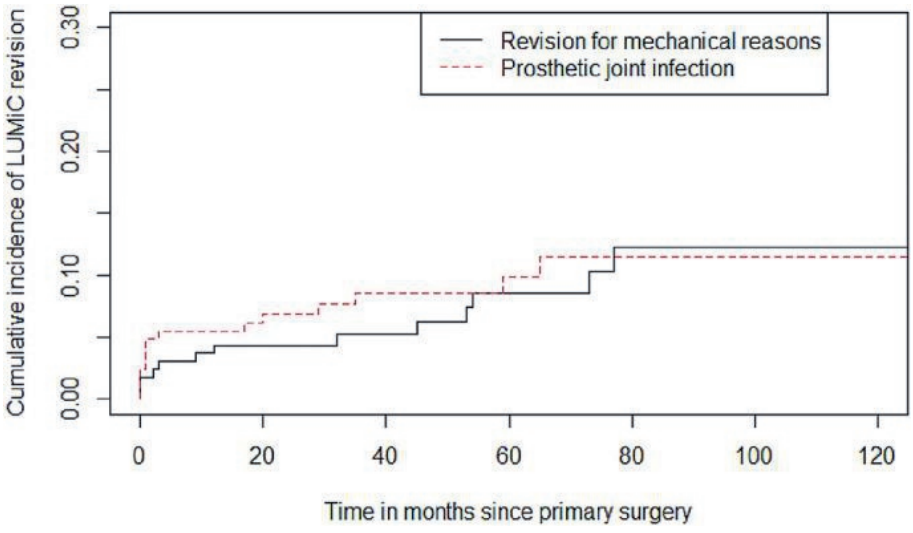


Figure 1. Cumulative incidence of LUMiC revision for mechanical complications (Henderson 1 to 3) and PJI (Henderson 4), using a competing risks model.

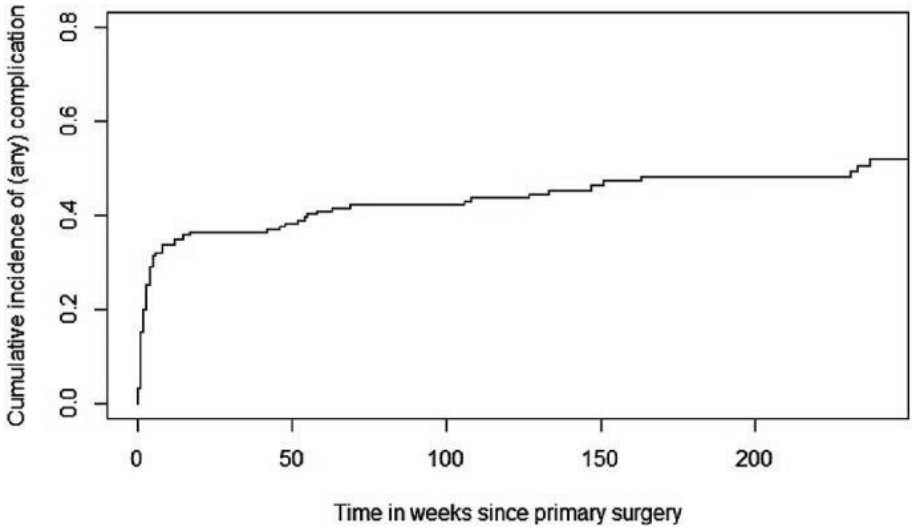


Figure 2. Cumulative incidence of reoperations for any complication, using a competing risks model.

During the study period, 24 LUMiC reconstructions (14% of the 166 patients) were removed. Four (2%) were removed for tumor progression via hindquarter amputation (n = 3) and resection arthroplasty (n = 1). One additional patient underwent revision for dislocation, but later underwent hindquarter amputation due to tumor progression. Nineteen reconstructions (11%) failed; 11 patients (7%) underwent resection arthroplasty, 5 (3%) were revised to a custom-made prosthesis, 1 (1%) underwent hindquarter amputation, 1 (1%) received a cement spacer, and 1 (1%) underwent rotationplasty (Table 3). In 160 (96%) of the patients, limb salvage was achieved. Fifty (30%) were able to walk without mobility aids, 47 (28%) used 1 crutch, 41 (25%) used 2 crutches, and 11 (7%) were not able to walk with crutches (149 with available data).

At the time of the most recent follow-up, 86 (52%) of the patients were alive without disease, 31 (19%) were alive with disease, 41 (25%) had died of disease, and 8 (5%) had died of other causes. The 5-year overall survival was 67% (95% CI, 58.6% to 75.4%).

Discussion

In the current study, we assessed the mid-term clinical outcomes of patients who underwent reconstruction for periacetabular tumor defects with use of the LUMiC prosthesis. To our knowledge, this is the largest oncological pelvic reconstruction series to date, and we found a substantial reoperation risk but a relatively low revision risk for mechanical complications. Dislocation and PJI remain the major concerns in the early postoperative period.

The dislocation rate (19%) in our cohort is comparable with that found for other stemmed acetabular implants, such as the pedestal-cup and the ice-cream cone prostheses (15% to 26%)(1, 4, 8, 20, 21). Previous surgery at the same site was associated with a higher dislocation risk. This is in line with conventional total hip arthroplasty and might be attributable to the compromised supporting soft tissues(22, 23). We found no association between dislocation risk and the use of a Trevira tube, although use of the Trevira tube might enhance the stability of the construct(12). The dislocation rate for dual-mobility cups (15%) was substantially higher than the 4% we previously found among 24 dual-mobility cups, which might be attributable to the longer follow-up of the dual-mobility articulations(2). Although the dislocation risk was not significantly higher for conventional cups (26%), we believe that it is reasonable to continue utilizing the dual-mobility cup. First, previous studies on re-revisions for dislocation in hip-revision surgery have shown promising results for dual-mobility articulations(24-26). Second, with the exception of a single intraprosthetic dissociation, no cup-specific complications were observed. Caution should be taken when comparing dislocation rates in the literature, since it is unclear if all dislocations (including those managed with closed reduction) are being reported or only those that require revision surgery(21). Furthermore, most prior studies did not include patients with failed previous reconstructions, while these had a higher dislocation risk in our study (36% versus 11%)(5-7, 20, 21). To reduce the dislocation rate, a postoperative abduction orthosis could be of value; Erol et al. found a 10% dislocation risk among 21 patients with LUMiC prostheses, all treated with a hip abduction orthosis for 6 to 12 weeks(7). Another factor that may contribute to the dislocation risk is the restoration of

the center of rotation. Although our study did not assess this aspect, other studies identified it as a risk factor(27, 28). A disadvantage of the LUMiC prosthesis in contrast to custom-made implants is that the vertical shift of the center of rotation is determined by the extent of iliac resection and cannot be adjusted by the length of the stem. A lateral shift of the center of rotation also depends on the cup orientation. On the femoral side, the surgeon may adjust the length and offset of the proximal femoral components to create a more stable situation, although this will not influence the center of rotation.

Stem loosening (Henderson 2) occurred in 3%, comparable with previous results on LUMiC reconstructions (0% to 6%)(2, 6, 7) and comparing favorably to those of other techniques, such as the stemmed pedestal-cup prosthesis (6% to 16%) and ice-cream cone prosthesis (8% to 15%)(1, 4, 8, 20, 21). The press-fit fixation of an uncemented hydroxyapatite (HA)-coated stem seems to provide durable fixation.

PJI (Henderson 4A) was the most common complication (25%), leading to implant revision in 9%. Our PJI rate is in line with previously reported results on pelvic reconstructions, which varied between 28% and 33%(2, 5, 8). In previous studies, surgical duration was found to be associated with the risk of PJI(23, 29). With the numbers we had, no significant association was identified. Resections including the pubis (P3) had a higher PJI risk. This might be explained by the proximity of the inguinal crease and the creation of a larger wound bed and cavity due to a medial osteotomy. Previous studies did not identify risk factors for PJI, probably because of small sample sizes and the multifactorial etiology. The extent of the resection and the resulting dead spaces, as well as the amount of blood loss, could contribute to development of PJI. Fisher et al. (9%) and Fujiwara et al. (11%) found a relatively low PJI rate in reconstructions with the cemented ice-cream cone prosthesis(1, 30). They believed that this was because of the utilization of antibiotic-laden cement around the cone.

Limitations

Our study had several limitations. First, the multicenter nature of the study resulted in variations in perioperative treatment protocols, possibly influencing outcomes. Additionally, the inclusion of patients over a 15-year period could present a confounding factor, as there was no accounting for potential secular trends. However, multicenter initiatives over time are needed to obtain sufficient numbers with these lower-incidence oncological conditions, and we present the largest series on pelvic reconstructions to date. Second, the limited number of events per complication did not allow for reliable multivariable analyses. The identification of risk factors remains challenging because of the multifactorial etiology of each complication. Third, there were data lacking concerning the functional outcome scores. Consequently, we added a straightforward question regarding the mobilization status of the patient at the time of the most recent follow-up.

Conclusions

As with any reconstruction technique for periacetabular tumor defects, we found a substantial reoperation risk. Apart from the reconstruction method used, this seems to be related to the extent of the surgical procedure itself. Nevertheless, efforts should be made to reduce the risk of complications, as these may interfere with the start of adjuvant cancer treatment in some patients. The initial 6 months are critical, as the majority of complications were observed in this period. We found a relatively low risk of mechanical failure in the mid-term, and the majority of patients had their primary implant in situ at the time of the most recent follow-up. On the basis of our findings, patients with previous surgery at the same site have an increased dislocation risk and might benefit from more conservative aftercare. Furthermore, resections involving the P3 region are associated with an increased PJI risk. Future research should focus on the identification of measures to reduce complication rates and enhance implant survival.

Acknowledgement

The authors thank emeritus Professor P.D.S. Dijkstra for the design and development of the LUMiC prosthesis and his active involvement in the current study.

Members of the LUMiC® study group

Prof. Daniel Kotrych, MD, PhD, Prof. Andrzej Bohatyrewicz, MD, PhD, Dr. Jakub Pawlik, MD, Ioannis G. Trikoupis, MD, Prof. Panayiotis J. Papagelopoulos, MD, PhD, Prof. Vasileios Kontogeorgakos, MD, PhD, Simen Sellevold, MD, PhD, Gilber Kask, MD, PhD, Minna K. Laitinen, MD, PhD, Silvan Wittenberg, MD, Daniel Rau, MD, PhD, Prof. Sven Maerdian, MD, PhD, Marko Bergovec, MD, PhD, Prof. Andreas Leithner, MD, PhD, Schalk Klopper, MD, Thomas Hilton, MD, Sebastian G. Walter, MD, Prof. Paul Jutte, MD, PhD, Prof. Jendrik Hardes, MD, PhD, Prof. Arne Streitbürger, MD, PhD, Prof. Thomas Schubert, MD, PhD, Maurizio Scorianz, MD, PhD, and Prof. Domenico A. Campanacci, MD, PhD.

References

1. Fisher NE, Patton JT, Grimer RJ, Porter D, Jeys L, Tillman RM, et al. Ice-cream cone reconstruction of the pelvis: a new type of pelvic replacement: early results. J Bone Joint Surg Br. 2011;93(5):684-8.
2. Bus MPA, Szafranski A, Sellevold S, Goryn T, Jutte PC, Bramer JAM, et al. LUMiC(®) Endoprosthetic Reconstruction After Periacetabular Tumor Resection: Short-term Results. Clin Orthop Relat Res. 2017;475(3):686-95.
3. Guo W, Li D, Tang X, Yang Y, Ji T. Reconstruction with modular hemipelvic prostheses for periacetabular tumor. Clin Orthop Relat Res. 2007;461:180-8.
4. Bus MP, Boerhout EJ, Bramer JA, Dijkstra PD. Clinical outcome of pedestal cup endoprosthetic reconstruction after resection of a peri-acetabular tumour. Bone Joint J. 2014;96-b(12):1706-12.
5. Witte D, Bernd L, Bruns J, Gosheger G, Hardes J, Hartwig E, et al. Limb-salvage reconstruction with MUTARS® hemipelvic endoprosthesis: A prospective multicenter study. European Journal of Surgical Oncology (EJSO). 2009;35(12):1318-25.
6. Rizkallah M, Ferguson PC, Basile G, Kim P, Werier J, Wilson D, et al. LUMiC® endoprosthesis for pelvic reconstruction: A Canadian experience. J Surg Oncol. 2023;127(4):727-33.
7. Erol B, Sofulu O, Sirin E, Saglam F, Buyuktopcu O. Reconstruction after periacetabular tumor resection with Lumic® endoprosthesis: What are the midterm results? J Surg Oncol. 2021;123(2):532-43.
8. Issa SP, Biau D, Babinet A, Dumaine V, Le Hanneur M, Anract P. Pelvic reconstructions following peri-acetabular bone tumour resections using a cementless ice-cream cone prosthesis with dual mobility cup. Int Orthop. 2018;42(8):1987-97.
9. Broekhuis D, Boyle R, Karunaratne S, Chua A, Stalley P. Custom designed and 3D-printed titanium pelvic implants for acetabular reconstruction after tumour resection. HIP International. 2022:11207000221135068.
10. Eisler T, Svensson O, Muren C, Elmstedt E. Early loosening of the stemmed McMinn cup. J Arthroplasty. 2001;16(7):871-6.
11. Sanders PTJ, Bus MPA, Scheper H, van der Wal RJP, van de Sande MAJ, Bramer JAM, et al. Multiflora and Gram-Negative Microorganisms Predominate in Infections Affecting Pelvic Endoprostheses Following Tumor Resection. JBJS. 2019;101(9).
12. Bus MPA, van de Sande MAJ. Implant Reconstruction of the Pelvis: II: Modular Pedestal Cup Prosthesis. In: Özger H, Sim FH, Puri A, Eralp L, editors. Orthopaedic Surgical Oncology For Bone Tumors : A Case Study Atlas. Cham: Springer International Publishing; 2022. p. 105-9.
13. Jaiswal PK, Aston WJ, Grimer RJ, Abudu A, Carter S, Blunn G, et al. Peri-acetabular resection and endoprosthetic reconstruction for tumours of the acetabulum. J Bone Joint Surg Br. 2008;90(9):1222-7.
14. Guo Z, Li J, Pei G-X, Li X-D, Wang Z. Pelvic reconstruction with a combined hemipelvic prostheses after resection of primary malignant tumor. Surgical Oncology. 2010;19(2):95-105.
15. Cottias P, Jeanrot C, Vinh TS, Tomeno B, Anract P. Complications and functional evaluation of 17 saddle prostheses for resection of periacetabular tumors. J Surg Oncol. 2001;78(2):90-100.
16. Enneking WF, Dunham WK. Resection and reconstruction for primary neoplasms involving the innominate bone. J Bone Joint Surg Am. 1978;60(6):731-46.
17. Henderson ER, O'Connor MI, Ruggieri P, Windhager R, Funovics PT, Gibbons CL, et al. Classification of failure of limb salvage after reconstructive surgery for bone tumours : a modified system Including biological and expandable reconstructions. Bone Joint J. 2014;96-b(11):1436-40.
18. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med. 2007;26(11):2389-430.

19. R Core team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2021 [Available from: https://www.R-project.org/.
20. Hipfl C, Stihsen C, Puchner SE, Kaider A, Dominkus M, Funovics PT, et al. Pelvic reconstruction following resection of malignant bone tumours using a stemmed acetabular pedestal cup. Bone Joint J. 2017;99-b(6):841-8.
21. Fujiwara T, Stevenson J, Parry M, Le Nail LR, Tsuda Y, Grimer R, et al. Pelvic reconstruction using an ice-cream cone prosthesis: correlation between the inserted length of the coned stem and surgical outcome. Int J Clin Oncol. 2021;26(6):1139-46.
22. Lu Y, Xiao H, Xue F. Causes of and treatment options for dislocation following total hip arthroplasty. Exp Ther Med. 2019;18(3):1715-22.
23. Gradl G, Bas de Witte P, Evans BT, Hornicek F, Raskin K, Ring D. Surgical Site Infection in Orthopaedic Oncology. JBJS. 2014;96(3):223-30.
24. Stucinskas J, Kalvaitis T, Smailys A, Robertsson O, Tarasevicius S. Comparison of dual mobility cup and other surgical construts used for three hundred and sixty two first time hip revisions due to recurrent dislocations: five year results from Lithuanian arthroplasty register. Int Orthop. 2018;42(5):1015-20.
25. Hailer NP, Weiss RJ, Stark A, Kärrholm J. Dual-mobility cups for revision due to instability are associated with a low rate of re-revisions due to dislocation: 228 patients from the Swedish Hip Arthroplasty Register. Acta Orthop. 2012;83(6):566-71.
26. Unter Ecker N, Kocaoğlu H, Zahar A, Haasper C, Gehrke T, Citak M. What Is the Dislocation and Revision Rate of Dual-mobility Cups Used in Complex Revision THAs? Clin Orthop Relat Res. 2021;479(2):280-5.
27. Qu H, Mou H, Wang K, Tao H, Huang X, Yan X, et al. Risk factor investigation for hip dislocation after periacetabular tumour resection and endoprosthetic reconstruction via thin-slice CT-based 3D model. Bone Joint J. 2022;104-b(10):1180-8.
28. Wang H, Tang X, Ji T, Yan T, Yang R, Guo W. Risk factors for early dislocation of the hip after periacetabular tumour resection and endoprosthetic reconstruction of the hemipelvis. Bone Joint J. 2021;103-b(2):382-90.
29. Kong L, Cao J, Zhang Y, Ding W, Shen Y. Risk factors for periprosthetic joint infection following primary total hip or knee arthroplasty: a meta-analysis. Int Wound J. 2017;14(3):529-36.
30. Fujiwara T, Sree DV, Stevenson J, Kaneuchi Y, Parry M, Tsuda Y, et al. Acetabular reconstruction with an ice-cream cone prosthesis following resection of pelvic tumors: Does computer navigation improve surgical outcome? Journal of Surgical Oncology. 2020;121(7):1104-14.

Chapter 6

Evaluating polyethylene, polyether-ether-ketone, and metal-on-metal locking mechanism survival in Modular Universal Tumour and Revision System knee reconstructions for oncological indications : insights from the MUTARS Orthopedic Registry Europe

R.E. Evenhuis[1], M.P.A. Bus[1], J. van Nes[1], S.G. Walter[2], J. Cabrolier[3], M. Fiocco[4,5,6], R.J.P. van der Wal[1], D. Broekhuis[1], S. Sellevold[7], M.A.J. van de Sande[1,4].

1. Department of Orthopaedic surgery, Leiden University Medical Center, Leiden, The Netherlands
2. Department of Orthopaedic surgery, traumatology and plastic surgery, University Hospital Cologne, Cologne, Germany
3. Department of Orthopaedic surgery, traumatological institute Teodore Gebauer, Santiago, Chile
4. Center for Pediatric Oncology, Princess Maxima Center, Utrecht, The Netherlands
5. Mathematical institute Leiden University, Leiden, The Netherlands
6. Department of Biomedical Science, section Medical Statistics, Leiden University Medical Center, Leiden, The Netherlands
7. Department of Orthopaedic surgery, Oslo University Hospital, Oslo, Norway

Journal of Bone and Joint Surgery, February 2025

Abstract

Background: Over time, the locking mechanism of Modular Universal Tumour and Revision System (MUTARS) knee arthroplasties changed from polyethylene (PE) to polyether-ether-ketone Optima (PEEK) and metal-on-metal (MoM) in an attempt to reduce the risk of mechanical failure. In this study, we aimed to assess the cumulative incidence of locking mechanism revision for symptomatic instability by type of material, and assess potential associated risk factors. Methods: The MUTARS Orthopaedic Registry Europe was used for a retrospective review of 316 patients (54% male (n = 170), median age 44 years (IQR 23 to 61)) who underwent a MUTARS knee arthroplasty for oncological indications between December 1995 and January 2023. The minimum follow-up was 12 months, and the median follow-up was 7.9 years (IQR 3.3 to 13.0). A competing risk model was used to estimate the cumulative incidence of first locking mechanism revision with death and revision for any other reason as competing events. Possible risk factors were assessed employing a univariate cause-specific hazards regression model. Results Symptomatic instability of the hinge or locking mechanism due to wear (n = 20) or breakage (n = 14) occurred in 34 patients (11%): 9% of PE (n = 4/45), 20% of PEEK (n = 9/44), and 9% of MoM locking mechanisms (n = 21/227). The cumulative incidences of revision for instability due to wear or locking mechanism breakage at two, five, and ten years were 0%, 5% (95% CI 1 to 15), and 5% (95% CI 1 to 15) for PE, 5% (95% CI 1 to 14), 14% (95% CI 5 to 26), and 16% (95% CI 7 to 29) for PEEK, and 0%, 3% (95% CI 1 to 6), and 10% (95% CI 5 to 16) for MoM. With PE as the reference category, the cause-specific hazard ratio for PEEK and MoM were 3.6 (95% CI 1.1 to 11.9; p = 0.036) and 3.2 (95% CI 1.1 to 9.5; p = 0.043), respectively. Age, BMI, resection length, and extra-articular resections were not associated with the time to locking mechanism revision. Conclusion: Alterations in prosthetic materials have not decreased the revision risk for locking mechanism failure. Besides locking mechanism material, no other patient- or prosthesis-related risk factors for locking mechanism failure were identified. Improvement of the locking mechanism is warranted since revision exposes patients to the risk of serious secondary complications.

Introduction

The Modular Universal Tumour and Revision System (MUTARS; Implantcast, Germany), introduced in 1992, is one of the most commonly used systems for reconstruction of large tumour defects around the knee. The knee endoprostheses consist of a femoral and tibial component, connected with a hinged locking mechanism. Originally, the locking mechanisms of the distal femoral reconstructions were constructed of metal-on-polyethylene interface (PE). Previous studies reported that in 13% to 19% of cases, wear or even breakage of the locking mechanism occurred, leading to severe instability of the endoprosthesis and often necessitating revision of the locking mechanism(1-4). In an attempt to reduce the risk of early structural failure, the PE was replaced by polyether-ether-ketone Optima (PEEK) in 2003. Although PEEK has obvious mechanical advantages over PE,(5) other studies reported early to mid-term breakage of the locking mechanism in 11% to 38% of cases(3, 4, 6, 7). The locking mechanisms of distal femur reconstructions were changed to a metal-on-metal (MoM) version in 2013, aiming to reduce this risk of mechanical failure. Proximal tibia reconstructions, on the other hand, were equipped with a MoM locking mechanism from the beginning. Despite the use of MoM hinges, locking mechanism failure persisted, affecting up to 25% of cases according to previous reports(3, 4, 8). To date, larger series focusing on locking mechanism failure of MUTARS knee arthroplasties are lacking.

Therefore, we aimed to: report the incidence of locking mechanism revision for symptomatic instability due to hinge wear or breakage; identify associated risk factors for locking mechanism failure; and evaluate the cumulative incidences of locking mechanism revision for symptomatic instability for PE, PEEK, and MoM at two, five, and ten years.

Material and methods

In this international multicentre observational retrospective study, data from the MUTARS Orthopaedic Registry Europe (MORE) were used. All patients who had a MUTARS distal femur, proximal tibia, total knee (distal femur and proximal tibia arthroplasty combined), or total femur reconstruction for an oncological indication between December 1995 and January 2023 were included. Patients with a follow-up of less than 12 months were excluded. A total of 316 patients from four tertiary referral centres were included (54% male (n = 170), median age 44 years (IQR 23 to 61)). The median follow-up was 7.9 years (IQR 3.3 to 13.0), with time to failure estimated using the reverse Kaplan-Meier methodology(9). A total of 45 (14%) patients received a PE locking mechanism, 45 (14%) a PEEK-Optima, and 226 (72%) a MoM (Table 1.). Overall, 83 (26%) patients had prior surgery to the same site. The median resection length was 16 cm (IQR 13 to 20), and 67 patients (25%) underwent an extra-articular resection.

Table 1. Study population

Variable	***Number (% of total)***
Sex	**316**
Male	170 (54)
Female	146 (46)
Age, median (IQR)	44 (23-61)
BMI, median (IQR)	24 (21-27)
ASA score	**288**
ASA 1	93 (32)
ASA 2	161 (56)
ASA 3	34 (12)
Smoking	**196**
Yes, currently	36 (18)
Yes, former (stopped > 6 months)	29 (15)
Diabetes	9/243 (4)
Indication for reconstruction	**316**
Osteosarcoma	142 (45)
Chondrosarcoma	43 (14)
Soft-tissue sarcoma	26 (8)
Ewing sarcoma	14 (4)
Metastatic carcinoma	41 (13)
Giant cell tumor (GCT)	29 (9)

Sarcoma NOS	5 (2)
Leiomyosarcoma of bone	7 (2)
Other	9 (3)
Previous surgery at same site	83/316 (26)
Reconstruction lower extremity	43 (52)
Arthroplasty	3 (4)
Excision / curettage tumor	17 (20)
Osteosynthesis for oncological reasons	10 (12)
Osteosynthesis after trauma	4 (5)
Arthroscopy	3 (4)
Other	3 (4)
Soft tissue involvement	197/267 (74)
Pathological fracture at diagnosis	60/300 (20)
Neoadjuvant chemotherapy	125/298 (42)
Neoadjuvant radiotherapy	15/296 (5)
Adjuvant chemotherapy	131/293 (45)
Adjuvant radiotherapy	19/295 (6)
Resection type	**263**
Intra-articular	196 (75)
Extra-articular	67 (25)
Location of reconstruction	**316**
Distal femur	223 (71)
Uncemented	163/223 (73)
Proximal stem cemented	16/223 (7)
Distal stem cemented	20/223 (9)
Proximal and distal cemented	24/223 (11)
Proximal tibia	82 (26)
Uncemented	71/82 (87)
Proximal stem cemented	5/82 (6)
Distal stem cemented	1/82 (1)
Proximal and distal cemented	3/82 (4)
Total knee	2 (1)
Distal stem cemented	1/1 (100)
Total femur	9 (3)
Uncemented	8/9 (89)
Distal stem cemented	1/9 (11)
Material of locking-mechanism	316
Polyethylene (PE)	45 (14)
Polyether-ether-ketone (PEEK)	44 (14)
Metal-on-metal (MoM)	227 (72)

Legend: ASA, American Society of Anesthesiologists; NOS, not otherwise specified.

Prosthetic details

The MUTARS system consists of a hexagonal stem that is available in different sizes, both for uncemented and cemented fixation. Uncemented press-fit fixation of a hydroxyapatite-coated stem was preferred, unless adequate primary stability could not be obtained (for example in case of conically shaped bones, or poor bone quality such as that of irradiated bones). Extension pieces are used to add to the desired implant implant reconstruction length. The femoral and tibial components are connected with a rotating hinged locking mechanism.

Variables

Demographics, surgical and prosthesis details, and complications were obtained from the electronic patient records. Locking mechanism failure was defined as symptomatic instability or a restricted range of motion requiring revision surgery due to bushing wear or breakage of the locking mechanism. Complications and the reason for implant revision were scored according to the Henderson classification(10).

Statistical analysis

A competing risks model was used to estimate the cumulative incidence of locking mechanism revision with death and revision for any other reason as competing events. To assess the difference among the cumulative incidences of different locking mechanism materials, a Gray test was used. A univariate cause-specific hazards regression model was employed to study the effect of possible prognostic risk factors on locking mechanism failure. Cause-specific hazard ratio (HRcs) with 95% CIs are reported. The log-rank test was employed to assess the effect of prognostic factors on the outcome. The score test was employed to assess the validity of the proportional hazards assumption for each prognostic factor and a visual inspection of the Schoenfeld Residuals was performed. Median time and IQR for revision due to locking mechanism revision were calculated. Data analysis was performed using SPSS v. 25.0. (IBM, USA), and R v. 4.2.1 (R Foundation for Statistical Computing, Austria). The R-studio package ‘cmprsk’ was used to estimate the cumulative incidence of implant revision. The level of significance was set at a p-value < 0.05.

Results

Revision of the PE, PEEK, and MoM locking-mechanisms

Surgical revision for instability due to wear or breakage (Henderson 3A) was observed in 34/316 patients. Of these 34 patients, five were previously revised for aseptic loosening (n = 2) or infection (n = 3), and were later revised for symptomatic instability due to hinge-wear or breakage. These patients had a median age of 36 years (IQR 20 to 52), versus 46 years (IQR 23 to 62) for those without locking mechanism failure. The median time to first locking mechanism revision for 14 patients experiencing breakage was 5.1 years (IQR 3.4 to 6.7) versus 8.7 years (IQR 4.7 to 11.7) for 20 patients requiring a revision due to wear. Nine patients (3%) had recurrent locking mechanism failures: six patients had two revisions, three patients had three revisions. The median time to first locking mechanism failure for patients with recurrent failures was 4.1 years (IQR 2.7 to 7.0), versus 7.7 years (IQR 4.3 to 10.3) for those with a single failure.

Revision of the PE locking-mechanism

Four out of 45 patients (9%) with a PE locking mechanism were revised: three (7%) due to hinge-wear, and one (2%) due to breakage. All revised implants were distal femoral reconstructions. The median time to first locking mechanism revision was 6.8 years (IQR 3.7 to 12.5). One patient underwent three revisions; the initial reconstruction was with a PE locking mechanism, which was revised to PEEK, and then subsequent PEEK revisions due to wear and recurrent breakage (Table 2.).

Revision of the PEEK locking-mechanism

Nine out of 44 patients (20%) with a PEEK locking mechanism were revised: five (11%) due to hinge-wear, and four (9%) due to breakage. All revised implants were distal femoral reconstructions. The median time to first locking mechanism revision was 4.5 years (IQR 2.9 to 7.3). Two patients underwent three revisions from PEEK to MoM and subsequent MoM revisions due to recurrent wear and breakage (Table 2.).

Revision of the MoM locking-mechanism

A total of 21 out of 227 patients (9%) with a MoM locking mechanism were revised: 12 (5%) due to hinge-wear, and nine (4%) due to breakage. Among the revised implants, 11 were distal femoral, eight proximal tibial, one total knee, and one total femoral. The median time to first locking mechanism revision was 7.5 years (IQR 4.1 to 10.5). Six patients underwent two revisions from MoM to MoM due to recurrent hinge-wear or breakage (Table 2.).

Table 2. Information on patients suffering of recurrent locking-mechanism failures

ID	Sex	Age	BMI	Nr. LM failures	Initial LM	2nd LM	3rd LM	4th LM	Location	Problem	Years till next revision
1	M	54	29	2	MoM	MoM	MoM		PT	Wear, wear	5.1, 3.3
2	M	25	21	2	MoM	MoM	MoM		PT	Breakage, wear	2.7, 3.8
3	M	52	35	2	MoM	MoM	MoM		DF	Breakage, breakage	2.6, 3.3
4	M	22	20	2	MoM	MoM	MoM		PT	Wear, wear	8.8, 6.7
5	F	14	24	2	MoM	MoM	MoM		PT	Wear, acute symptomatic instability without evident abnormalities	12.0, 0.8
6	M	58	-	2	MoM	MoM	MoM		DF	Breakage, breakage	4.1, 0.7
7	F	15	25	3	PEEK	PEEK	PEEK	MoM	DF	Wear, breakage, wear	4.4, 3.6, 3.3
8	M	19	19	3	PEEK	PEEK	PEEK	MoM	DF	Breakage, wear, breakage	1.7, 0.8, 2.9
9	M	24	-	3	PE	PEEK	PEEK	PEEK	DF	Wear, breakage, breakage	3.9, 1.7, 5.5

Legend: M = male, F = female, LM = locking-mechanism, PE = polyethylene, PEEK = Polyether-ether-ketone, MoM = Metal-on-metal, PT = proximal tibia, DF = distal femur

Risk factors for locking-mechanism failure

With PE as the reference category, the cause-specific hazard ratio (HRcs) for PEEK and MoM locking mechanisms were 3.6 (95% CI 1.1 to 11.9; p = 0.036), and 3.2 (95% CI 1.0 to 9.5; p = 0.043), respectively. Age, BMI, resection length, and extra-articular resections were not associated with the time to locking mechanism revision (Table 3.). The proportional hazards assumption was not violated for all risk factors.

Table 3. Cause-specific hazard ratios (HRcs) along with the 95% confidence interval for locking-mechanism failure

Potential risk factors	**HRcs (95%CI)**	**p-value**
Age	0.99 (0.98-1.02)	0.658
Gender (male)	1.39 (0.70-2.76)	0.346
BMI (kg/m2)	1.02 (0.96-1.09)	0.513
Surgical duration (hours)	0.99 (0.75-1.)	0.920
Blood loss (L)	1.90 (0.92-3.94)	0.083
Resection length (cm)	1.03 (0.99-1.08)	0.120
Location of reconstruction		
Distal femur*	Reference	
Proximal tibia	0.78 (0.35-1.74)	0.543
Type of resection		
Intra-articular resection*		
Extra articular resection	0.76 (0.33-1.80)	0.537
Locking-mechanism material		
PE*	Reference	
PEEK	3.59 (1.08-11.92)	0.036
MoM	3.15 (1.04-9.53)	0.043

*Legend: HRcs = cause-specific hazard ratio, 95% CI = 95% confidence interval, BMI = body mass index, * = reference category, PE = polyethylene, PEEK = polyether-ether-ketone, MoM = metal-on-metal*

Cumulative incidence of first locking-mechanism failure

The cumulative incidence of locking mechanism failure as reason for first revision at two, five, and ten years were 0%, 5% (95% CI 1 to 15), and 5% (95% CI 1 to 15) for PE, 5% (95% CI 1 to 14), 14% (95% CI 5 to 26), and 16% (95% CI 7 to 29) for PEEK, and 0%, 3% (95% CI 1 to 6), and 10% (95% CI 5 to 16) for MoM, respectively (Figure 1).

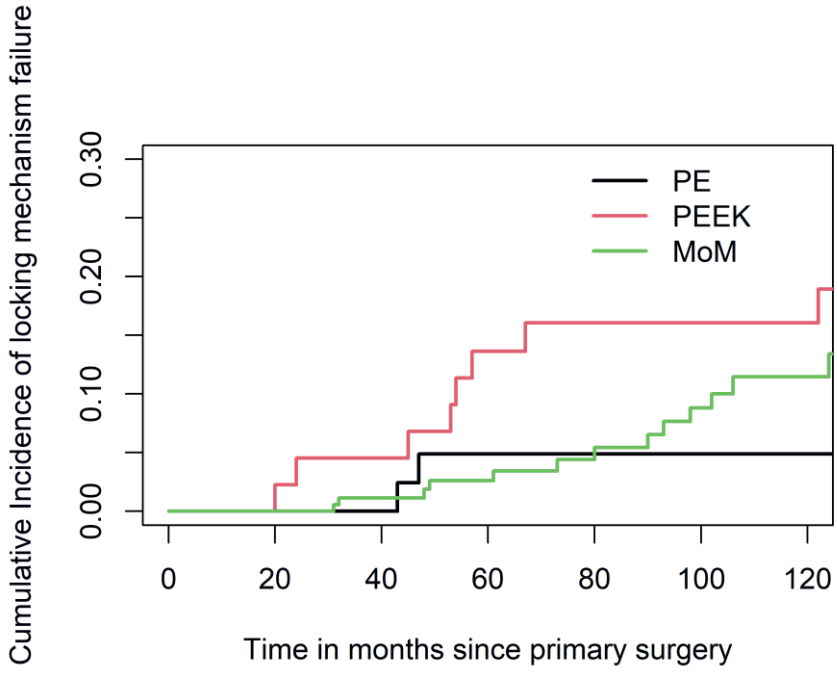


Figure 1. Cumulative incidence of implant revision due to wear or breakage for polyethylene (PE), polyether-ether-ketone (PEEK), and metal-on-metal (MoM).

Secondary infections

Among 34 patients with revision for locking mechanism failure, nine (26%) developed acute secondary infections (within two months after revision surgery). Eight were successfully treated; six with debridement, antibiotics, and implant retention, and two with two-stage procedures. One patient developed a chronic infection (occurring after the third locking mechanism revision) which was non-responsive to antibiotics and surgical therapy, and resulted in an amputation.

Discussion

In this MORE study, the clinical outcomes of three different locking mechanism materials of the MUTARS knee reconstructions were evaluated, with a particular emphasis on implant wear or breakage. Regardless of the type of articulation, we observed symptomatic instability caused by wear or fractures of the locking mechanism, necessitating revision surgery. Furthermore, we identified that PEEK and MoM locking mechanisms have a significantly increased revision risk for locking mechanism failure over time compared to PE.

In the current study, the cumulative incidence of revision surgery for implant wear or breakage of 5% (95% CI 1 to 15) at both five and ten years, and an overall locking mechanism revision rate of 9% for PE locking mechanisms, compares favourable to previous studies, with reported incidences ranging from 13% to 19%(1-4). However, caution should be used when interpreting these results, since the statistical analyses used in these studies did not account for patients who died without revision, nor for patients requiring revision for other reasons. Additionally, Hardes et al. (4) only included extra-articular resections, while these resections are presumed to increase the risk of mechanical failure. Kinkel et al. (1) observed an overall locking mechanism failure rate of 19% in MUTARS PE locking mechanisms and identified a significant correlation with extra-articular resections, or cemented implants. Notably, 80% of their 11 patients with locking mechanism failure underwent extra-articular resections, and 73% received cemented femoral fixation. This contrasts our results with none of the cemented resections and one (25%) extra-articular resection among the four PE locking mechanism failures. Furthermore, the authors state that their aggressive approach toward tumours with potential joint capsule invasion or knee effusion leads to frequent extra-articular resections with accompanying extensive resection of stabilizing structures around the knee(1). They believed that this results in higher mechanical stress on the joint coupling mechanism, although our results showed no difference between intra- and extra-articular resections.

There are several other commonly used systems for endoprosthetic knee reconstructions available, with revision rates for locking mechanism or bushing failure ranging from 0% to 42%(2, 11, 12). Myers et al.(2) found a 16% locking-mechanism revision rate, and 2% locking-mechanism breakage in a cohort of 428 Stanmore distal femur reconstructions with PE bushing, which is comparable to the results of the MUTARS knee reconstructions. Capanna et al.(11) report a 42% locking-mechanism revision rate in a cohort of 95 uncemented Kotz Modular Femur-Tiba Reconstruction System (Stryker, UK) distal femur reconstructions with PE bushing, with a mean of 5.3 years after implantation. On the other hand, Ilyas et al.(12) reported no PE bushing fractures or revisions due to wear in a cohort of 48 patients reconstructed with an uncemented HMRS distal femur (Stryker), with a median follow-up of 5.6 years. Additionally, Sharma et al.(13) reported no bushing fractures or revisions due to wear in a cohort of 77 cemented HMRS distal femur reconstructions, but observed a 4% fracture rate of the tibial bearing component. Variations in implant designs and approaches to tumour implants may yield distinct failure patterns. The use of a “sloppy” hinge as opposed to a more rigid constrained system might reduce mechanical stresses on the stem, although the clinical relevance remains uncertain at this moment.

In the current study, the cumulative incidence of revision surgery for implant wear or breakage at five and ten years of 14% (95% CI 5 to 26) and 16% (7 to 29), and an overall locking mechanism revision rate of 20% for PEEK locking mechanisms, are comparable to previous studies describing an overall locking mechanism failure rate of 11% to 18% in patients reconstructed with the MUTARS PEEK locking mechanism(3, 4, 6). Cho et al.(6) observed a higher BMI in ten patients with locking mechanism breakage (BMI 24 kg/m2 (standard error (SE) 2.1) compared to those without (BMI 22 kg/m2 (SE 3.3); p = 0.05). Remarkably, they reported a median time to locking mechanism failure of 2.2 years (range 1.0 to 6.0), compared to 6.4 years (IQR 4.0 to 9.7; range 1.7 to 19.4) years in our cohort. However, a proper comparison cannot be made due to differences in statistical methodology and the fact that we included all revisions for symptomatic instability due to breakage or wear, whereas Cho et al.(6) focused on breakage only. Hardes et al.(8) reported a 20% locking mechanism failure rate and a mean of 3.6 years (0.8 to 6.8) after

implantation, in a cohort of patients with MUTARS endoprosthetic reconstructions after extra-articular resections of the knee. Three of 16 (19%) were PE, 3/17 (18%) PEEK, and 6/24 (25%) MoM locking mechanisms. In line with our results, they found no association between locking mechanism failure and patient BMI or resection length. According to Hardes et al.(4) the extent of resection of the extensor apparatus contributed to the relatively high proportion of patients experiencing locking-mechanism failure, due to high mechanical demands(4). Interestingly, Merose et al.(7) observed a 38% overall locking mechanism failure rate in 56 PEEK hinged MUTARS distal femur reconstructions. They identified male sex and higher weight at failure as significant risk factors, contrary to our findings. New-onset knee instability, often triggered by physical activity, was commonly observed years after implantation. A retrieval analysis from Merose et al.(7) for three failed locking mechanisms revealed fretting and microcracks in high-stress areas, culminating in complete fracture at the tip of the PEEK slot in full extension.

The cumulative incidence of revision for implant wear or breakage of the MoM locking mechanisms at five and ten years is 3% (95% CI 1 to 6) and 10% (95% CI 5 to 16), respectively. Additionally, the overall locking mechanism revision rate for MoM in the current study is 9%, which is favourable compared to previous studies describing an overall locking mechanism revision rate of 20% to 25% for locking mechanism wear in patients reconstructed with the rotating MoM hinge(4, 8). Hardes et al. observed no prosthetic fractures in a cohort of 98 patients who underwent an intra-articular resection and subsequent proximal tibia reconstruction, which is in contrast with our 3% MoM locking mechanism revision for breakage. However, they found a 20% locking mechanism revision rate for wear at a median of 5.8 years (range 0.7 to 14.3) after implantation(8).

A retrieval analysis conducted by Bormann et al.(14) identified a relatively high incidence of locking-mechanism wear, assessed through a semi-quantitative scoring-system and coordinate measurements. As expected, increased wear was observed in patients who had the implant in situ for a longer durationIn turn, corrosion and mechanical wear of the MoM locking mechanism can lead to both local metallosis and systemic metal ion side effects. Local reactions include adverse reactions to metal debris, resulting in osteolysis

and pseudotumour formation(15,16). This is especially concerning in high-demand young patients reconstructed with MoM articulations, as prolonged exposure may result in elevated metal-ion levels of cobalt and chromium. Such elevated metal ion levels may result in systemic cardiovascular and neurological adverse effects(17-19). Moreover, repetitive hyperextension of the knee during the landing phase may contribute to cyclic fretting damage and therefore locking mechanism failure. Based on our results, the question arises about the appropriate course of action to improve implant survival. Should it involve the development of new materials possessing enhanced strength and non-toxic properties, or should the focus be on modifying the implant design? Currently, a new carbon-reinforced PEEK locking mechanism is under post-marketing surveillance; however, clinical results are not yet available.

Limitations

This study has several limitations. First, our dataset contained a limited number of patients with a PE or PEEK reconstruction. Second, investigating the degree of quadriceps compromise resulting from tumour resection and conducting gait analysis would be valuable, as it could influence mechanical stresses on the locking mechanism, potentially serving as an indicator for locking mechanism failure. To address this limitation, we evaluated whether the resection was intra- or extra-articular, yet identified no significant association with the occurrence of locking mechanism revision over time. Future studies should evaluate the impact of compromised knee muscles and conduct gait analysis in patients with MUTARS knee reconstructions to determine their potential association with locking mechanism failure.

Conclusion

This study showed that the cumulative incidence of locking mechanism revision for symptomatic instability due to hinge breakage or wear was comparable or favourable compared to other systems. Thus far, alterations in prosthetic materials have not decreased the risk of locking mechanism failure. Besides locking mechanism material, no additional factors contributing to locking mechanism failure were identified. Improvement of the locking mechanism is warranted since recurrent revision of the locking mechanism

increases the risk of serious secondary complications. Anticipated advancements could come with the introduction of a novel carbon-reinforced PEEK locking mechanism design.

Take home messages

- This multicentre series represents the largest cohort to date, studying various locking mechanisms in Modular Universal Tumour and Revision System knee reconstructions.
- Thus far, alterations in prosthetic materials have not decreased the risk of locking mechanism failure.
- The cumulative incidences of locking mechanism revision at ten years were 5% for polyethylene, 16% for polyether-ether-ketone, and 10% for metal-on-metal.

Other information

Ethical review statement

This study was approved by the scientific committee of the Leiden University Medical Centre, and waived informed consent (W.22.005/2022 to 031). Participating centres obtained approval from their local ethical review board.

Source of funding

This investigator-initiated study was funded by an unconditional research grant of Implantcast GmbH, Buxtehude, Germany.

Conflicts of interest

The funder (and also producer of the MUTARS knee reconstructions) was not involved with the design, conduction, or analysis of the study results. The authors declare no competing interest.

Accessibility of protocol, and raw data

The study protocol can be requested at the corresponding author (R.E. Evenhuis). Anonymized data is available on request.

References

1. Kinkel S, Lehner B, Kleinhans JA, Jakubowitz E, Ewerbeck V, Heisel C. Medium to long-term results after reconstruction of bone defects at the knee with tumor endoprostheses. J Surg Oncol. 2010;101(2):166-9.
2. Myers GJ, Abudu AT, Carter SR, Tillman RM, Grimer RJ. Endoprosthetic replacement of the distal femur for bone tumours: long-term results. J Bone Joint Surg Br. 2007;89(4):521-6.
3. Bus MPA, van de Sande MAJ, Fiocco M, Schaap GR, Bramer JAM, Dijkstra PDS. What Are the Long-term Results of MUTARS(®) Modular Endoprostheses for Reconstruction of Tumor Resection of the Distal Femur and Proximal Tibia? Clin Orthop Relat Res. 2017;475(3):708-18.
4. Hardes J, Henrichs MP, Gosheger G, Gebert C, Höll S, Dieckmann R, et al. Endoprosthetic replacement after extra-articular resection of bone and soft-tissue tumours around the knee. The Bone & Joint Journal. 2013;95-B(10):1425-31.
5. Ma H, Suonan A, Zhou J, Yuan Q, Liu L, Zhao X, et al. PEEK (Polyether-ether-ketone) and its composite materials in orthopaedic implantation. Arabian Journal of Chemistry. 2021;14(3):102977.
6. Cho W-H, Jeon D-G, Kong C-B, Lee HS, Song WS. Locking Mechanism Failure after Distal Femoral Reconstruction with Modular Universal Tumor and Revision System (MUTARS) Tumor Prosthesis. jkoa. 2017;52(5):435-41.
7. Merose O, Factor S, Gortzak Y, Dadia S, Segal O, Vituri A, et al. Mechanical failure of distal femur mega prosthesis due to polyaryl-ether-ether-ketone (PEEK) hinge component. Arch Orthop Trauma Surg. 2024.
8. Hardes J, Henrichs M-P, Gosheger G, Guder W, Nottrott M, Andreou D, et al. Tumour endoprosthesis replacement in the proximal tibia after intra-articular knee resection in patients with sarcoma and recurrent giant cell tumour. Int Orthop. 2018;42(10):2475-81.
9. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Controlled Clinical Trials. 1996;17(4):343-6.
10. Henderson ER , O'Connor MI , Ruggieri P , et al. Classification of failure of limb salvage after reconstructive surgery for bone tumours: a modified system Including biological and expandable reconstructions . Bone Joint J . 2014 ; 96-B (11): 1436 – 1440 .
11. Capanna R, Morris HG, Campanacci D, Del Ben M, Campanacci M. Modular uncemented prosthetic reconstruction after resection of tumours of the distal femur. J Bone Joint Surg Br. 1994;76(2):178-86.
12. Ilyas I, Kurar A, Moreau PG, Younge DA. Modular megaprosthesis for distal femoral tumors. Int Orthop. 2001;25(6):375-7.
13. Sharma S, Turcotte RE, Isler MH, Wong C. Cemented Rotating Hinge Endoprosthesis for Limb Salvage of Distal Femur Tumors. Clinical Orthopaedics and Related Research®. 2006;450:28-32.
14. Bormann T, Jäger S, Kretzer JP, Nebel L, Clarius L, Omlor G, et al. Retrieval Analysis of Modern Knee Tumor Megaendoprosthesis Shows Considerable Volumetric Metal Wear Generated at the Rotating Hinge. Materials (Basel). 2020;13(7).
15. Sutphen SA, MacLaughlin LH, Madsen AA, Russell JH, McShane MA. Prevalence of Pseudotumor in Patients After Metal-On-Metal Hip Arthroplasty Evaluated with Metal Ion Analysis and MARS-MRI. J Arthroplasty. 2016;31(1):260-3.
16. Langton DJ, Joyce TJ, Jameson SS, Lord J, Van Orsouw M, Holland JP, et al. Adverse reaction to metal debris following hip resurfacing: the influence of component type, orientation and volumetric wear. J Bone Joint Surg Br. 2011;93(2):164-71.
17. de Smidt KQ, Spierenburg G, Evenhuis RE, Bosma SE, van der Wal RJP, Broekhuis D, et al. Systemic Metal Ion Concentrations in Patients With Hip and Knee Megaprostheses: A Prospective Cohort Study. Arthroplasty Today. 2022;18:191-201.e1.

18. Gessner BD, Steck T, Woelber E, Tower SS. A Systematic Review of Systemic Cobaltism After Wear or Corrosion of Chrome-Cobalt Hip Implants. J Patient Saf. 2019;15(2):97-104.
19. Vasukutty NL, Minhas TH. Systemic effects of cobalt toxicity after revision hip replacement can manifest in intermediate to long term follow-up. Hip Int. 2016;26(4):e31-4.

Chapter 7

Proximal humeral endoprosthetic reconstruction for tumor defects: clinical outcomes of 165 patients from the MUTARS Orthopaedic Registry Europe (MORE)

R.E. Evenhuis[1], M.P.A. Bus[1], S. Sellevold[2], E.F. Dierselhuis[3], I.G. Trikoupis[4], M. Scorianz[5], S.G. Walter[6], J. Cabrolier[7], M. Fiocco[8,9,10], M.A.J. van de Sande[1,8], and the MORE study group*.

* Members of the MORE study group

J. Von Harras BSc[1], R.J.P. van der Wal MD PhD[1], Prof. P.J. Papagelopoulos MD PhD[4], Prof. V. Kontogeorgakos MD PhD[4], Prof. D.A. Campanacci MD PhD[5], O. Ceballos MD PhD[7], Prof. P.C. Jutte MD PhD[11].

1. Department of Orthopaedic Surgery, Leiden University Medical Center, Leiden, the Netherlands
2. Department of Orthopaedic Surgery, Oslo University Hospital, Oslo, Norway
3. Department of Orthopaedic Surgery, Radboudumc, Nijmegen, the Netherlands
4. First Department of Orthopaedic Surgery, National and Kapodistrian University of Athens, Attikon University General Hospital, Athens, Greece
5. Department of Orthopaedic Oncology, University Hospital Careggi, Florence, Italy
6. Department of Orthopaedic Surgery, Traumatology and Reconstructive Surgery, University Hospital Cologne, Germany
7. Institute of Traumatology, Teodoro Gebauer, Santiago, Chile
8. Center for Pediatric Oncology, Prinses Maxima Center, Utrecht, the Netherlands
9. Mathematical Institute Leiden University, Leiden, the Netherlands
10. Department of Biomedical Science, section Medical Statistics, Leiden University Medical Center, Leiden, the Netherlands
11. Department of Orthopaedic Surgery, University Medical Center Groningen, Groningen, The Netherlands

Accepted for publication in the Bone and Joint open on the 14th of January 2025

Abstract

Introduction: Tumor defects of the proximal humerus can be reconstructed using hemiarthroplasty, reverse- (RSA) or anatomic total shoulder arthroplasty (TSA). This study aimed to evaluate clinical and functional outcomes of reconstructions of proximal humeral tumor defects with MUTARS endoprostheses. Methods: 165 reconstructions were included; 98(59%) hemiarthroplasties, 61(37%) RSAs, and six(4%) TSAs. Median age was 54 years(IQR 31-68). Median follow-up time was 5.9 years(range 0-19). Competing risks models were employed to estimate the cumulative incidences of revision (CIR) for mechanical reasons and infection with local recurrence and mortality as competing events. The range of motion (ROM) was reported using descriptive statistics. Results: Axillary nerve preservation, and deltoid muscle reattachment was observed in 89% and 96% of cases respectively, without significant differences among implant types. Rotator cuff refixation was less frequent in RSA(78%) compared to hemiarthroplasty(91%). Twenty-six implants(16%) were revised, for mechanical complications (dislocation n=11, loosening n=2, peri-prosthetic fracture n=3), and infection (n=10). Patients with previous surgery at same site had a higher revision risk due to instability (cause-specific hazard ratio [HRcs] 3.7, 95%CI 1.3-10.8). The CIR for mechanical reasons (Henderson 1 to 3) in the entire population at 2, 5, and 10 years were 7%(95%CI 3-11), 11%(6-17), and 13%(7-20) respectively. For PJI (Henderson 4), the CIR was 5%(2-10), 7%(3-12), and 7%(3-12). Compared with hemiarthroplasty, RSA offered superior anteflexion (73°[IQR 40-90] vs 30°[5-45]), abduction (70°[38-90] vs 30°[5-45]), and external rotation (15°[0-28] vs 5°[0-19]). Conclusions: MUTARS proximal humerus reconstruction outcomes are satisfying, particularly in terms of mechanical failure. RSA and hemiarthroplasty exhibit comparable revision risks, with previous surgery at same site as prognostic factor for revision due to dislocation. RSA appears to provide the best functional outcome.

Introduction

The proximal humerus is relatively frequently affected by primary bone sarcomas and metastatic lesions(1, 2). Wide resection of tumors around the shoulder compromises crucial structures for shoulder stability and function, and may include the axillary nerve, deltoid muscle, rotator cuff, and bone(3-6). Consequently, it is challenging to obtain a well-functioning reconstruction, and functional outcomes may be limited in terms of stability range of motion (ROM).

The choice of reconstruction method can vary depending on the tumor extent, although a reconstruction consensus is lacking(4, 7, 8). Endoprostheses are commonly used after proximal humeral tumor resection, particularly for reconstruction following Malawer type I (intra-articular proximal humeral resection) and Malawer type V (extra-articular humeral and glenoid resection)(9, 10). However, the risk of complications such as dislocation (4-23%), aseptic loosening (0-5%), and infection (3-9%) remains substantial(4, 11-13). MUTARS (implantcast GmbH, Buxtehude, Germany) offers a modular system for reconstructions of the proximal humerus. Due to its rarity, there are no large systematic studies on the clinical outcomes of individual proximal humerus endoprotheses. As mentionend, there is currently no consensus on when to use hemiarthroplasty, reverse, or anatomic total shoulder replacement, although some studies suggest that reverse shoulder arthroplasty may result in superior functional results in case the rotator cuff is to be resected(3, 4, 12, 14, 15).

This study aims to assess the clinical outcomes of MUTARS proximal humeral reconstructions for oncological indications, using data from the MUTARS Orthopaedic Registry Europe (MORE)(16). We evaluated (1) the complications and reasons for implant revision, and the associated risk factors, (2) the cumulative incidence of implant revision (CIR) at 2, 5, and 10 years, and (3) the functional outcomes in terms of range of motion (ROM) for hemiarthroplasty, reverse shoulder arthroplasty (RSA), and total shoulder arthroplasty (TSA).

Methods

In this international multicenter observational retrospective study, data from the MUTARS Orthopaedic Registry Europe (MORE) was used. Patients who received a MUTARS proximal humerus reconstruction for an oncological indication between 2001 and 2023 were included, from eight participating centers in six different countries. Patients with a follow-up of less than 24 months, and custom-made shoulder reconstructions were excluded.

A total of 165 patients (51% female) were included, with a median-follow-up of 5.9 years (range, 0-19), estimated using the reverse Kaplan-Meier method(17). The median age was 54 years [IQR 31-68] for the entire cohort, 57 years [36-68] for those with hemiarthroplasty, 47 years [22-61] for RSA, and 59 years [20-68] for TSA. Hemiarthroplasty was performed in 98 patients (59%), while 61 (37%) received RSA, and six (4%) underwent TSA (Table 1). The indication for proximal humerus resection was a primary bone tumor in 106 patients (64%), while 54 (33%) were treated for metastatic carcinoma. Among the 165 reconstructions, 106 (64%) were uncemented, 57 (35%) were cemented, and for 2 (1%) it was unknown. Additionally, 73 patients (44%) received a silver-coated implant, 67 (41%) did not, and for 25 (15%) it was unknown. The majority of the cemented reconstructions (74%) were performed for metastatic lesions. Nineteen (12%) patients underwent prior surgery to the same site, consisting of a previous reconstruction (n=10, 6%), osteosynthesis for oncological reasons such as prophylactic fixation (n=1, 1%), and osteosynthesis for a pathological fracture (n=1, 1%), osteosynthesis after trauma (n=1, 1%), or excision or curettage of a tumor (n=6, 4%). The median resection length was 12 cm (IQR 10-16).

Prosthetic details

The MUTARS system is a modular endoprosthetic system, using a hexagonal stem that is available in different sizes, both for uncemented and cemented fixation. Uncemented press-fit fixation of a hydroxyapatite coated stem was preferred, unless adequate primary stability could not be obtained (for example in case of poor bone quality). Extension pieces can be used to obtain the appropriate length in 1 cm increments, with or withour silver

coating. In the majority of cases, tendons and muscle insertions were attached to the prosthesis using a Trevira tube.

Variables

Demographics, surgical and prosthesis details, and complications were obtained from the (electronical) patient records. Implant revision was defined as any surgical procedure in which (part of) the implant was removed or replaced. Complications and the reason for implant revision were scored according to the Henderson classification(18).

Statistical analysis

Descriptive statistics were employed for baseline characteristics, the incidence of complications, and functional outcomes. Univariate cause-specific hazards regression models were employed to study the effect of possible prognostic risk factors on implant revision. Cause-specific hazard ratio (HRcs) along with 95% confidence interval (CI) are reported. Two competing risks models(19) were used to estimate the CIR. In model 1, the CIR among the entire study population for mechanical reasons and for infection was estimated considering revision for local recurrence and death as competing events. In model 2, the CIR due to mechanical reasons and infection was estimated, for RSA and hemiarthroplasty separately, with revision for local recurrence and death as competing events (Figure 1).

Analysis of data was performed using SPSS version 25.0. (IBM Corp. Armonk, NY), and R-studio version 4.2.1(20). The R-studio package ‘cmprsk’ was used to estimate the CIR. The level of significance was set at a p-value < 0.05.

Study ethics

This study was approved by the scientific committee of the Leiden University Medical Center, and waived informed consent(W.22.005/2022-031). Participating centers obtained approval by their local ethical review board.

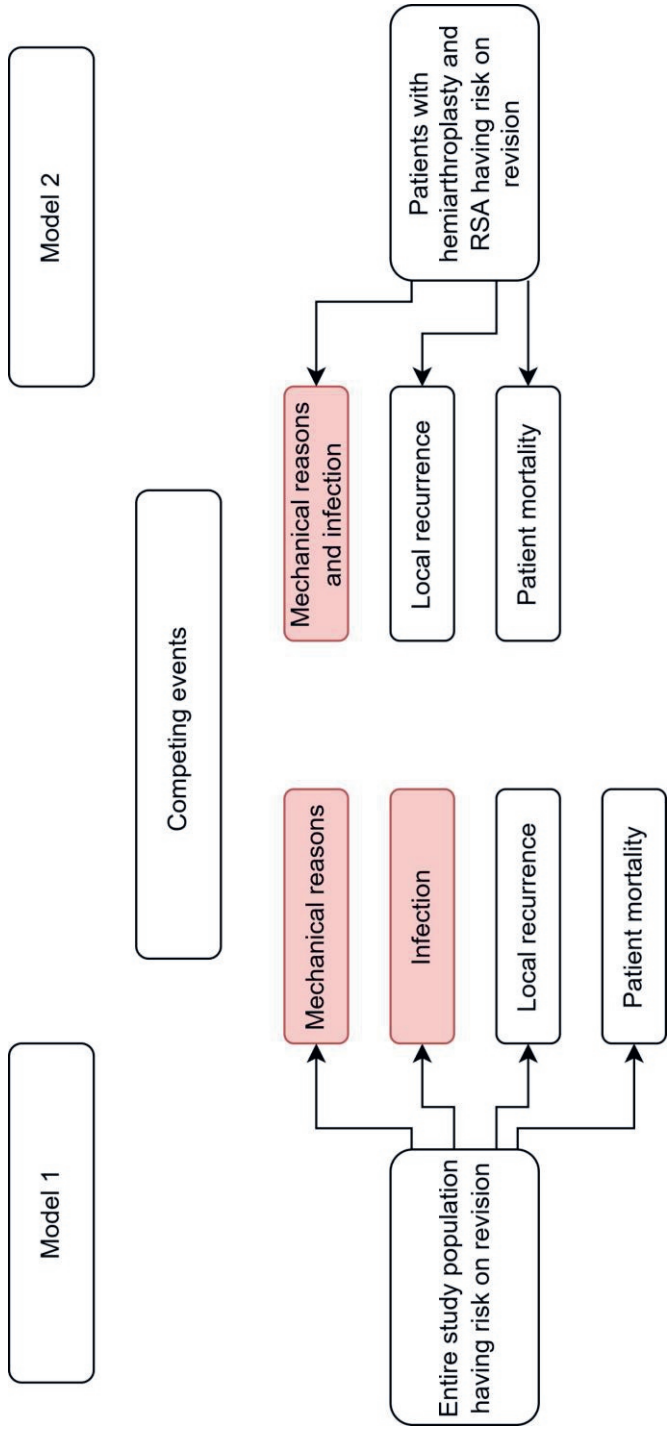


Figure 1. Competing risk model with 4 competing events (left panel), and with 3 competing events (right panel).

Table 1. Study population.

Variable	*Number (% of total)*
Sex	**165** (100)
Male	81(49)
Female	84 (51)
Age (median [IQR])	54 [31-68]
ASA score	**156** (95)
ASA 1	38 (24)
ASA 2	82 (53)
ASA 3	35 (22)
ASA 4	1 (1)
Smoking	**97** (58)
Yes, currently	15 (16)
Yes, former (stopped > 6 months)	10 (10)
Diabetes	11/108 (10)
Indication for reconstruction	**165** (100)
Primary malignant tumors	*106 (64)*
Chondrosarcoma	53 (32)
Osteosarcoma	41 (25)
Ewing sarcoma	4 (2)
Soft-tissue sarcoma	3 (2)
Multiple myeloma	2 (1)
Other high-grade sarcomas	3 (2)
Metastatic carcinoma	*54 (33)*
Benign aggressive lesions	*5 (3)*
GCTB	2 (1)
Osteoblastoma	2 (1)
Intraosseous hemangioma	1 (1)
Previous surgery at same site	19 (12)
Previous reconstruction	10 (6)
Osteosynthesis for oncological reasons	2 (1)
Osteosynthesis after trauma	1 (1)
Curettage or excision of (benign) tumor	6 (4)
Soft tissue involvement	98/149 (66)
Pathological fracture at diagnosis	63/163 (39)
Neoadjuvant chemotherapy	43/159 (27)
Neoadjuvant radiotherapy	9/156 (6)
Adjuvant chemotherapy	55/157 (35)
Adjuvant radiotherapy	21/155 (14)

Legend: ASA= American Society of Anesthesiologists physical status, GCTB= giant cell tumor of bone

Results

The axillary nerve was spared in 89% of resections, 96% of the patients had a partial or complete reattachment of the deltoid muscle, and 86% of the patients had a partial or complete reattachment of the rotator cuff (Table 2). Less patients (45/58, 78%) with RSA had a partial or complete reattachment of their rotator cuff compared to hemiarthroplasty (81/89, 91%) and TSA (5/5, 100%). In total, 40 patients (24%) experienced one or more complications during the follow-up period.

Table 2. Surgical and prosthesis details.

Variable	Number (% of total)
Type of reconstruction	**165** (100)
Hemiarthroplasty	98 (59)
Reverse shoulder arthroplasty	61 (37)
Anatomic total shoulder arthroplasty	6 (4)
Surgical approach	**162** (98)
Deltopectoral	157 (97)
Deltoid flap	2 (1)
Other	3 (2)
Resection length (median [IQR])	12 [10-16]
Surgical duration in hrs (median [IQR])	3 [2.5-3.8]
Blood loss in L (median [IQR])	0.6 [0.3-0.9]
Silver coating	73/140 (52)
Cemented prosthesis	57/163 (35)
Metastatic carcinoma as indication	42/57 (74)
Trevira tube	136/164 (83)
Sacrifice (part of) axillary nerve	**17/161** (11)
TSA	0/6 (0)
RSA	8/59 (14)
Hemiarthroplasty	9/96 (9)
Partial or complete deltoid reattachment	**133/139** (96)
TSA	3/4 (75)
RSA	52/55 (95)
Hemiarthroplasty	78/80 (98)
Partial or complete rotator cuff reattachment	**131/152** (86)
TSA	5/5 (100)
RSA	45/58 (78)
Hemiarthroplasty	81/89 (91)

Legend: hrs = hours, L = liter, TSA = total shoulder arthroplasty, RSA = reverse shoulder arthroplasty

Dislocation(s) (Henderson 1A) occurred in 15 patients (9%).
The first dislocation occurred within 6 months in three cases (20%), between 6-12 months in two (13%), and between 1-8 years in ten (67%). Fourteen patients (8%) underwent a single procedure for dislocation(s). Specifically, five patients were revised from hemiarthroplasty (5/98, 5%) to RSA. Of the RSAs, two (2/61, 3%) were revised to different component sizes, two underwent stabilizing soft tissue procedures, while others either underwent revision to a constrained design, offset adjustment, rotational cup adjustment, open reduction, or closed reduction under general anesthesia. One patient, initially reconstructed with RSA, underwent three revisions for recurrent instability and ultimately the RSA was revised to a hemiarthroplasty without glenoid reconstruction, 9 years after initial implantation.

In total, 10 out of 147 patients (7%) without previous surgery at same site suffered from (recurrent) dislocations. In contrast, 5 out of 19 patients (26%) with previous surgery at same site experienced (recurrent) dislocations requiring reoperation. Among these five patients, one had previously undergone reconstruction with an allograft prosthetic composite (APC) which required revision due to local recurrence. The other four had previously undergone curettage or excision of a tumor and suffered from local recurrence. Patients with previous surgery at same site had a higher dislocation risk (HRcs 3.7, 95%CI 1.3-10.8) compared to those without. No other prognostic factors were identified (table 3).

Aseptic loosening (Henderson 2) was observed in three patients (3/165, 2%), all hemiarthroplasties. Two uncemented stems loosened (2/106, 2%) after nine months, of which one was revised to an uncemented RSA, and one was revised to a cemented stem (which loosened again after two years and was again revised with a new cemented stem). One cemented stem (1/57, 2%) loosened after 14 years and was revised to a new cemented stem.

Implant breakage or wear (Henderson 3A) was not observed.

Periprosthetic fractures (Henderson 3B) were observed in 4 patients (2%). One occurred during primary implantation and was managed with cerclage wires. Two fractures resulted from trauma; one at 9 months post-implantation in a hemiarthroplasty, treated with open reposition and internal fixation using an allograft, strut graft and cerclage wires; and one in RSA at 42 months, treated with conversion to a total humerus prosthesis. The last case was a hemiarthroplasty with a pathological periprosthetic fracture due to local recurrence at 9 months, for which revision to a cemented stem was performed.

Prosthetic joint infection (Henderson 4) was observed in 16 patients (10%), 8 hemiarthroplasties (8%), 6 RSAs (10%), and 2 TSAs (33%). Two infections (13%) occurred within the first month after implantation, three (19%) between 1-6 months, five (31%) between 6-12 months, and six (38%) >12 months postoperatively. In one patient, the PJI followed after a revision procedure for loosening 14 years post-implantation. In the remaining 15 patients, the reoperation for PJI was their first reoperation. Four PJIs were successfully treated with one DAIR, and seven PJIs were successfully treated with one-stage or two-stage procedures. Five PJIs necessitated implant removal, without further reconstruction. No significant risk factors for PJI were identified (Table 3).

Local recurrence (H5B) was observed in 10 patients (6%). Among these, eight underwent amputation, while two underwent re-resection and received a revision implant.

Cumulative incidence of implant revision and reconstruction status at final follow-up
The CIR for mechanical reasons (Henderson 1 to 3) among the entire study population at 2, 5, and 10 years were 7% (95%CI 3-11), 11% (6-17), and 13% (7-20) respectively. For PJI (Henderson 4), these were 5% (2-10), 7% (3-12), and 7% (3-12) (Model 1, Figure 2). Specifically for RSA, the CIR for mechanical reasons and infection (Henderson 1 to 4) at 2, 5, and 10 years were 9% (3-18), 22% (11-37), and 24% (11-37). For hemiarthroplasty, these were 13% (7-21), 16% (9-24), and 18% (10-27) (Model 2, Figure 3). The number TSAs (n=6) was too small to provide an adequate estimation of the CIR. At final follow-up, 153 patients (93%) had a (revised) implant in situ.

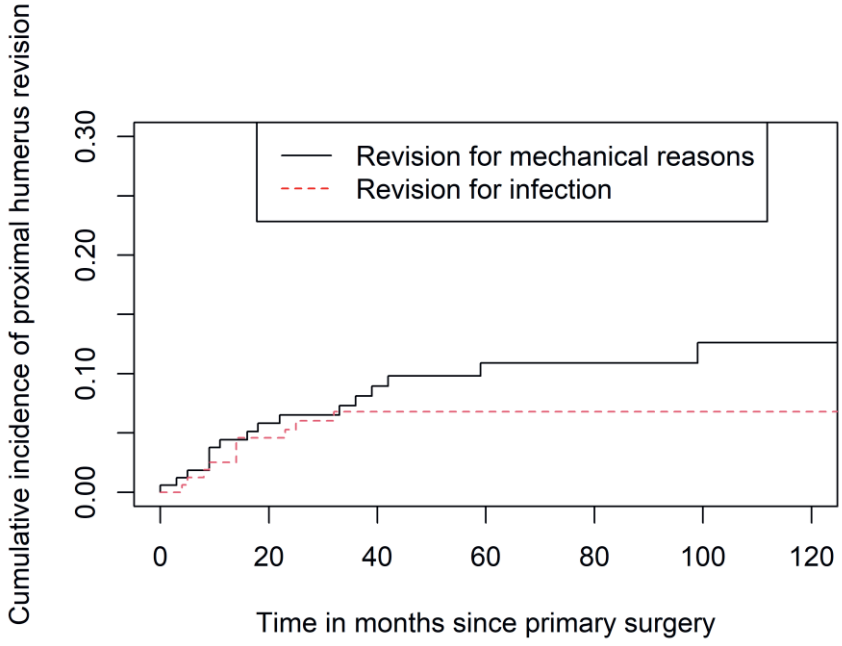


Figure 2. Cumulative incidence of revision for mechanical reasons or infection.

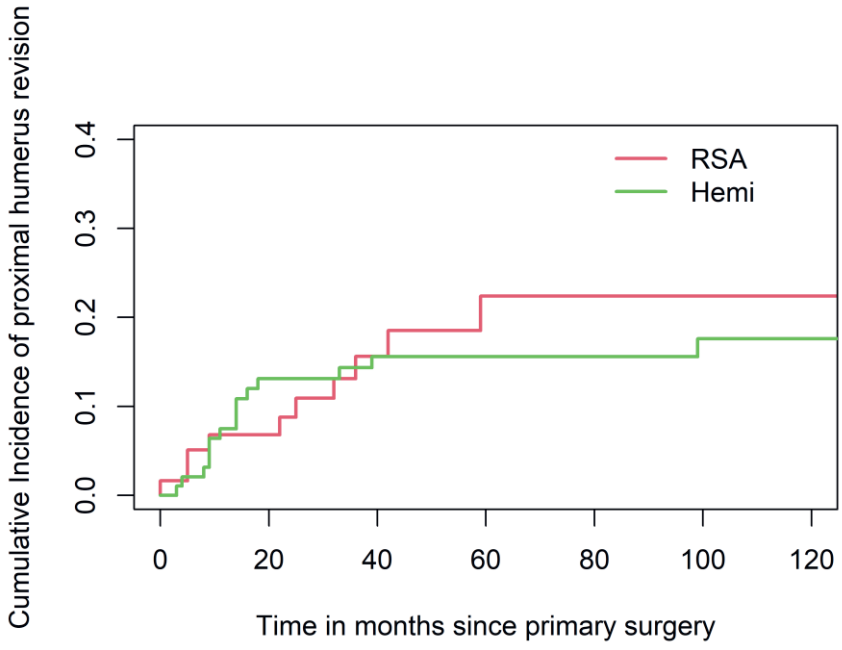


Figure 3. Cumulative incidence of revision for both mechanical reasons and infection as event of interest, by type of proximal humerus reconstruction. *Legend: RSA = reverse shoulder arthroplasty, Hemi = hemiarthroplasty.*

Functional outcome

In patients with RSA, the median (IQR) active anteflexion, abduction, and external rotation were 73º (40-90), 70º (38-90) and 15º (0-28) respectively (data available for 42 patients, 69%). For those with a hemiarthroplasty, these were 30º (5-45), 30º (5-45) and 5º (0-19) respectively (data available for 56 patients, 57%). Additionally, a subanalysis of patients without a reattached rotator cuff in both the RSA and hemiarthroplasty groups showed that RSA led to better functional outcomes (table 4). The sample size for TSAs was too small to provide an adequate estimation of the ROM.

Table 3. Univariate Cox proportional hazards regression model for possible prognostic factors on the occurrence of dislocation (left) and PJI (right) along with the 95% confidence interval.

Possible risk factors	**Dislocation**		**PJI**	
	HR	95% CI	HR	95% CI
Sex				
Female*				
Male	1.02	0.37-2.80	1.50	0.56-4.04
Age	1.00	0.98-1.03	0.98	0.95-1.00
BMI			0.92	0.81-1.04
ASA classification				
ASA I +II*				
ASA III + IV	1.86	0.50-6.93	0.64	0.14-2.83
Previous surgery at same site				
No*				
Yes	**3.70**	**1.26-10.84**	0.94	0.21-4.15
Type of reconstruction				
Reverse arthroplasty*				
Hemiarthroplasty	0.94	0.34-2.71	0.83	0.28-2.41
Resection length (cm)	0.88	0.77-1.01	1.03	0.94-1.14
Surgical duration (hours)	0.78	0.47-1.32	1.21	0.78-1.87
Blood loss (liter)			1.00	0.99-1.00
Use of silver-coating				
No*				
Yes			1.42	0.51-3.99
Use of Trevira® tube				
No*				
Yes	0.40	0.14-1.18	1.39	0.31-6.16

*Legend: * = Reference category, PJI = prosthetic joint infection, HR = hazard ratio, 95% CI = 95% confidence interval, ASA = American Society of Anesthesiologists physical status, n.a. = not applicable.*

Table 4. functional outcomes of patients reconstructed with a MUTARS proximal humerus reconstruction

	All patients	**Patients without reattachment rotator cuff**
	Median [IQR]	Median [IQR]
RSA	*(42/61)	*(12/13)
Anteflexion	73 [40-90]	80 [66-102]
Abduction	70 [38-90]	81 [63-90]
External rotation	15 [0-28]	15 [10-18]
Hemiarthroplasty	*(56/98)	*(5/8)
Anteflexion	30 [5-45]	52 [35-59]
Abduction	30 [5-45]	51 [38-65]
External rotation	5 [0-19]	10 [10-10]

*Legend: IQR = interquartile range, RSA = reverse shoulder arthroplasty, * = available cases for analysis of functional outcomes*

Discussion

This study evaluates the clinical outcomes of proximal humeral reconstructions for a tumor defect with either a MUTARS hemiarthroplasty, reverse shoulder arthroplasty, or (anatomic) total shoulder arthroplasty. It represents the largest series of proximal humerus reconstructions to date. We found satisfactory mechanical complications rates, although dislocation and infection remain relatively frequent causes for implant revision. RSA demonstrated good functional outcomes despite the fact that the rotator cuff was more often sacrificed in these patients.

Our dislocation rate (9%) is consistent with Raiss et al.(21), who reported a 10% dislocation rate in 39 patients with MUTARS proximal humerus endoprostheses. Our results are favorable compared to other studies on MUTARS hemiarthroplasty and RSA, ranging from 22% to 33%(4, 22, 23). We identified previous surgery at same site as a prognostic factor for revision due to dislocation. Other studies, possibly due to smaller sample sizes, did not identify any possible risk factors for dislocation. Sharma et al. reported a 14% dislocation rate in 21 cemented Stryker endoprostheses, and Kumar et al. described a 2% reoperation

rate for dislocation in 100 Stanmore custom-made endoprosthetic reconstructions(24, 25). Our results are equal to or favorable in comparison to alternative reconstructive techniques. Teunis et al. reviewed the literature and found a 0-31% dislocation rate among proximal humeral endoprostheses, 0-62% among allografts, and 0-21% in APCs. They concluded that there was no significant difference in dislocation rates between reconstruction techniques(26). However, caution is warranted when interpreting these findings as sample sizes of the studies in the review were typically limited.

We found loosening in 2% of our patients, which is in line with the findings of Raiss et al. (3% in 39 uncemented MUTARS)(21). Trikoupis et al.(4) reported a 5% loosening rate in a cohort of 40 patients reconstructed with either hemiartroplasty or RSA. Similarly, Trovarelli et al.(23) documented one case of loosening in an uncemented stem in their cohort of 22 patients, of which 10 were uncemented. Streitburger et al.(12) and Guven et al.(27), on the other hand, observed no loosenings, although the follow-up in their studies was short, and sample sizes were small. Kumar et al. observed three loosenings in 100 patients reconstructed with cemented custom-made Stanmore endoprostheses(25), while Sharma et al. found no loosenings in 21 cemented Stryker endoprostheses(24). Our results are favorable compared to the loosening rates in endoprostheses (0-20%) and APCs (0-17%) described by Teunis et al(26).

Our PJI risk (10%) was somewhat higher compared to other publications with infection rates of 0-6% in MUTARS endoprosthetic reconstructions(4, 12, 21, 23, 27). A possible explanation is longer follow-up period, as we observed that 38% of our PJIs occurred later than one year postoperatively. Trovarelli et al. noted that they had no PJIs in silver-coated implants(23). Although we present the largest series to date, we found no difference for silver coating, nor did we identify other risk factors, which might be attributable to the multifactorial cause of PJI. Van de Sande et al. identified comparable infection rates for allografts (1/13 patients, 8%), and APCs (1/10 patients, 10%), whereas Rödl et al. observed a 27% (4/15 patients) infection rate in clavicula pro humeri reconstructions(28, 29). Our PJI risk is comparable or favorable to the infection rate in endoprosthesis (0-20%), allografts (0-25%), and APCs (0-13%) as described by Teunis et al(26). However, it is important to

note that there is a substantial variability and uncertainty regarding complication rates due to limited sample sizes and heterogenous study populations.

The 10-year CIR for mechanical reasons and infection for hemiarthroplasty and RSA were 18% and 24% respectively, which is in line with other studies reporting a 5-32% implant revision rate. However, comparisons are difficult due to differences in statistical methodology: We employed competing risks models to estimate the CIR, while others use the Kaplan-Meier method. In addition, most previous studies had shorter follow-up periods(4, 12, 21, 23, 27). Interestingly, a plateau in the risk of revision over time can be observed in our cohort, suggesting that patients have a relatively low risk of revision once they have passed the initial postoperative years without revisions. As for alternative reconstructive techniques, Van de Sande et al. reported a poor 5-year implant survival of 9% for osteoarticular allografts, and 60% for APCs with implant revision as the endpoint. With implant removal as the endpoint, the 5-year implant survival for osteoarticular allografts was 61%, and 90% for APCs(6). Rödl et al. reported a 10-year cumulative survival of 79% for the clavicula pro humeri procedure, 75% for osteoarticular allografts, and 83% for endoprostheses(29). In the systematic review by Teunis et al., the survival rates of endoprostheses (38-100%) were comparable to osteoarticular allografts (33-100%) and APCs (33-100%)(26).

As previously reported, RSA seem to offer significantly better functional results compared to anatomical reconstructions, particularly for those with sacrificed rotator cuff muscles(4, 27, 30). This improvement can be attributed to the fact that the center of rotation is moved medially and inferiorly, which increases the deltoid muscle's moment arm(31). Another factor could be an indication bias favoring RSA, as these patients were generally younger and potentially more active. The range of motion after RSA in our study was comparable to those in other studies with active flexion ranging from 88-117º, abduction from 80-103º, and external rotation of 13º(4, 12, 23, 27). Similarly, the ROM of patients with hemiarthroplasty or anatomical reconstructions were comparable with other studies, showing active anteflexion ranging from 34-60º, abduction from 33-55º, and external rotation of 12º(4, 21).

Several limitations must be acknowledged. First, the relatively small number of TSA cases limits the generalizability of the findings related to this implant type. However, there is limited indication for TSA in oncological patients, as TSAs require an intact rotator cuff to function properly, while the cuff is often sacrificed during tumor resection. Second, the MORE focuses on complications requiring reoperation, which likely leads to an underestimation of the true incidence of complications, most notably dislocations. Nevertheless, patients who do not choose or require revision for instability often continue to live well despite having an unstable shoulder joint. Third, despite the fact that we present the largest series to date, the limited number of events per complication hampered the multivariate analyses. At last, the absence of patient-reported outcome measures (PROMS) prevented their use in this study. To effectively evaluate patient outcomes, centers should systematically collect PROMS as a standard of care.

This is the largest series on proximal humerus reconstructions to date and could serve as a benchmark for future studies, given the current lack of large-cohort comprehensive studies with adequate follow-up on these reconstructions. Clinical outcomes are satisfying, particularly in terms of mechanical failure. RSA and hemiarthroplasty exhibit comparable revision risks. The risk of dislocation is higher in patients with previous surgery at the same site. RSA appears to provide good functional outcomes, even in the absence of a functioning rotator cuff. These findings suggest that clinicians should consider using reverse shoulder arthroplasty over hemiarthroplasty, given its comparable revision risk and superior functional outcomes.

Other information

Source of funding

This investigator-initiated study was funded by an unconditional research grant of Implantcast GmbH, Buxtehude, Germany.

Conflicts of interest

The funder (and also producer of the MUTARS proximal humerus endoprostheses) was not involved with the design, conduction, or analysis of the study results. The authors declare no competing interest.

Accessibility of protocol, and raw data

The study protocol can be requested at the corresponding author (RE Evenhuis). Anonymized data is available on request.

References

1. Wittig JC, Bickels J, Kellar-Graney KL, Kim FH, Malawer MM. Osteosarcoma of the proximal humerus: long-term results with limb-sparing surgery. Clin Orthop Relat Res. 2002(397):156-76.
2. Hage WD, Aboulafia AJ, Aboulafia DM. INCIDENCE, LOCATION, AND DIAGNOSTIC EVALUATION OF METASTATIC BONE DISEASE. Orthopaedic Clinics of North America. 2000;31(4):515-28.
3. Rachbauer AM, Schneider KN, Gosheger G, Deventer N. Endoprosthetic Reconstruction of the Proximal Humerus with an Inverse Tumor Prosthesis. Cancers (Basel). 2023;15(22).
4. Trikoupis IG, Savvidou OD, Tsantes AG, Papadopoulos DV, Goumenos SD, Vottis C, et al. Prosthetic Reconstruction of the Shoulder After Resection of Proximal Humerus Bone Tumor. Orthopaedics. 2022;45(6):e335-e41.
5. Sirveaux F. Reconstruction techniques after proximal humerus tumour resection. Orthopaedics & Traumatology: Surgery & Research. 2019;105(1, Supplement):S153-S64.
6. van de Sande MA, Dijkstra PD, Taminiau AH. Proximal humerus reconstruction after tumour resection: biological versus endoprosthetic reconstruction. Int Orthop. 2011;35(9):1375-80.
7. Kumar D, Grimer RJ, Abudu A, Carter SR, Tillman RM. Endoprosthetic replacement of the proximal humerus. The Journal of Bone & Joint Surgery British Volume. 2003;85-B(5):717-22.
8. Scorianz M, Houdek MT, Sherman CE, Sim FH, O'Connor MI. Survival, Tumor Recurrence, and Function Following Shoulder Girdle Limb Salvage at 24 to 35 Years of Follow-up. Orthopaedics. 2019;42(6):e514-e20.
9. Malawer MM, Chou LB. Prosthetic survival and clinical results with use of large-segment replacements in the treatment of high-grade bone sarcomas. J Bone Joint Surg Am. 1995;77(8):1154-65.
10. Schmolders J, Koob S, Schepers P, Kehrer M, Frey SP, Wirtz DC, et al. Silver-coated endoprosthetic replacement of the proximal humerus in case of tumour-is there an increased risk of periprosthetic infection by using a trevira tube? Int Orthop. 2017;41(2):423-8.
11. Gosheger G, Gebert C, Ahrens H, Streitbuerger A, Winkelmann W, Hardes J. Endoprosthetic Reconstruction in 250 Patients with Sarcoma. Clinical Orthopaedics and Related Research®. 2006;450:164-71.
12. Streitbuerger A, Henrichs M, Gosheger G, Ahrens H, Nottrott M, Guder W, et al. Improvement of the shoulder function after large segment resection of the proximal humerus with the use of an inverse tumour prosthesis. Int Orthop. 2015;39(2):355-61.
13. Pala E, Trovarelli G, Ippolito V, Berizzi A, Ruggieri P. A long-term experience with Mutars tumor megaprostheses: analysis of 187 cases. European Journal of Trauma and Emergency Surgery. 2021.
14. De Wilde LF, Van Ovost E, Uyttendaele D, Verdonk R. [Results of an inverted shoulder prosthesis after resection for tumor of the proximal humerus]. Rev Chir Orthop Reparatrice Appar Mot. 2002;88(4):373-8.
15. Denissen J, Koenders N, van Hinte G, Groen F, van der Wees PJ, van der Geest ICM, et al. Functional outcomes after reverse shoulder megaprosthesis following resection of malignant bone tumor in the proximal humerus: a systematic review and meta-analysis. JSES Int. 2023;7(4):592-600.
16. Evenhuis RE, van de Sande MAJ, Fiocco M, Dierselhuis EF, Broekhuis D, Bus MPA, et al. LUMiC Endoprosthetic Reconstruction of Periacetabular Tumor Defects: A Multicenter Follow-up Study. JBJS. 2024;106(14):1309-16.
17. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Controlled Clinical Trials. 1996;17(4):343-6.
18. Henderson ER, O'Connor MI, Ruggieri P, Windhager R, Funovics PT, Gibbons CL, et al. Classification of failure of limb salvage after reconstructive surgery for bone tumours : a modified system Including biological and expandable reconstructions. Bone Joint J. 2014;96-b(11):1436-40.

19. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med. 2007;26(11):2389-430.
20. The R Project for Statistical Computing. 2017.
21. Raiss P, Kinkel S, Sauter U, Bruckner T, Lehner B. Replacement of the proximal humerus with MUTARS tumor endoprostheses. European Journal of Surgical Oncology (EJSO). 2010;36(4):371-7.
22. Streitbuerger A, Henrichs M, Gosheger G, Ahrens H, Nottrott M, Guder W, et al. Improvement of the shoulder function after large segment resection of the proximal humerus with the use of an inverse tumour prosthesis. Int Orthop. 2015;39(2):355-61.
23. Trovarelli G, Cappellari A, Angelini A, Pala E, Ruggieri P. What Is the Survival and Function of Modular Reverse Total Shoulder Prostheses in Patients Undergoing Tumor Resections in Whom an Innervated Deltoid Muscle Can Be Preserved? Clinical Orthopaedics and Related Research®. 2019;477(11):2495-507.
24. Sharma S, Turcotte RE, Isler MH, Wong C. Experience with Cemented Large Segment Endoprostheses for Tumors. Clinical Orthopaedics and Related Research®. 2007;459:54-9.
25. Kumar D, Grimer RJ, Abudu A, Carter SR, Tillman RM. Endoprosthetic replacement of the proximal humerus. Long-term results. J Bone Joint Surg Br. 2003;85(5):717-22.
26. Teunis T, Nota SP, Hornicek FJ, Schwab JH, Lozano-Calderón SA. Outcome after reconstruction of the proximal humerus for tumor resection: a systematic review. Clin Orthop Relat Res. 2014;472(7):2245-53.
27. Guven MF, Aslan L, Botanlioglu H, Kaynak G, Kesmezacar H, Babacan M. Functional outcome of reverse shoulder tumor prosthesis in the treatment of proximal humerus tumors. Journal of Shoulder and Elbow Surgery. 2016;25(1):e1-e6.
28. van de Sande MAJ, Dijkstra PDS, Taminiau AHM. Proximal humerus reconstruction after tumour resection: biological versus endoprosthetic reconstruction. Int Orthop. 2011;35(9):1375-80.
29. Rödl RW, Gosheger G, Gebert C, Lindner N, Ozaki T, Winkelmann W. Reconstruction of the proximal humerus after wide resection of tumours. J Bone Joint Surg Br. 2002;84(7):1004-8.
30. De Wilde LF, Plasschaert FS, Audenaert EA, Verdonk RC. Functional Recovery after a Reverse Prosthesis for Reconstruction of the Proximal Humerus in Tumor Surgery. Clinical Orthopaedics and Related Research®. 2005;430.
31. Ackland DC, Roshan-Zamir S, Richardson M, Pandy MG. Moment Arms of the Shoulder Musculature After Reverse Total Shoulder Arthroplasty. JBJS. 2010;92(5):1221-30.

Chapter 8

General summary, discussion, and future perspectives

The overall purpose of the dissertation

Clinical outcomes and improvements in patient care in orthopaedic oncology depend on both accurate diagnostic and prognostic processes, as well as well-balanced surgical resections and reconstructive surgeries. Therefore, this thesis consists of two parts.

Part I aims to assess a novel diagnostic tool for chondrosarcoma and improve our understanding of prognostic factors for survival in osteosarcoma patients. Additionally, it evaluates an innovative, non-invasive prognostic tool for predicting chemotherapy response in osteosarcoma patients

Part II aims to contribute to the understanding of clinical outcomes in endoprosthetic reconstructions by evaluating risk factors for complications and implant failures. It utilizes high-quality, global multicenter studies focused on MUTARS endoprosthetic reconstructions.

Part I Advances in the evaluation of diagnosis and prognosis in patients with bone tumors

A potential novel non-invasive diagnostic tool for chondrosarcoma of bone

Accurate diagnosis and classification of cartilage tumors is vital since treatment varies with tumor grade. Benign or low-grade cartilaginous tumors may be managed with curettage or supervised observation, whereas high-grade chondrosarcomas usually require extensive surgery and consequent reconstructions(1-3). However, distinguishing between low-grade or benign cartilaginous tumors and high-grade chondrosarcoma remains challenging due to significant interobserver variability in current radiological and histological methods(4, 5). To address this challenge, novel diagnostic tools are explored. The eNose analyzes volatile organic compounds (VOCs) through pattern recognition and requires training with a dataset to develop its diagnostic capabilities(6-9). In an earlier study of Acem et al., the eNose showed promise as a non-invasive diagnostic biomarker for detecting soft tissue sarcomas (STS) with good performance(9). However, in our explorative pilot study presented in **Chapter 2**, the eNose showed limited sensitivity and specificity of 75% and 65% respectively, with an AUC of 0.66. These findings suggest that the eNose is not yet reliable for routine clinical use.

Risk factors, oncological outcomes, and predictive biomarkers in osteosarcoma

Although there has been a remarkable increase in survival rates for osteosarcoma patients since the 1970s, 5-year survival outcomes still vary widely, ranging from 21% to 86%(10-13). A key question is: what causes this variation in survival outcomes? An important first step in addressing this question is to identify what are the possible prognostic factors that may be associated to survival outcomes. In **Chapter 3,** age was identified as a prognostic factor for survival, even when adjusted for other demographic and treatment factors. Adolescents and young adults (AYAs) aged between 16 to 40, as well as older adults aged ≥40, had less favorable outcome compared to children under the age of 16 years, which is

partially explained by different patient and treatment characteristics. Older adults present more frequently with axial located tumors, pathological fractures, and were more often treated with Adriamycin and Cisplatin (AP) chemotherapy instead of high-dose Methotrexate combined with AP (MAP). Additionally, chemotherapy seems to have a less profound effect in older patients, as they are less likely to have a good histological response to chemotherapy. This is partly due to dose limitations caused by comorbidities, age-related organ dysfunction, or chemotherapy-related toxicity. Besides age, risk factors for survival included tumor size, distant metastasis at presentation, histological response to chemotherapy, and local tumor relapse. While assessing risk factors for survival is crucial for accurate prognosis estimation, their clinical implications are limited since many factors are either fixed at diagnosis or become apparent after surgical resection, such as the response to neo-adjuvant chemotherapy.

Chapter 4 introduces a novel prognostic biomarker which can be obtained before tumor resection. The relative wash-in rate (rWIR), derived from dynamic contrast-enhanced (DCE-) MRI, reflects changes in tumor perfusion before and after neo-adjuvant chemotherapy and has been associated with response to chemotherapy by Kalisvaart et al.(14). Our subsequent study showed that the rWIR is associated with event-free survival (EFS), adjusted for traditional prognostic factors. Moreover, the 2- and 5-year EFS for patients with rWIR ≥ 2.3 were 85% (95% CI 74-96%) and 75% (62-89%), compared to 55% (40-70%) and 50% (35-66%) for those with rWIR < 2.3. These finding suggest that rWIR could be a valuable tool for personalizing treatment strategies and adjusting chemotherapy in non-responsive patients in future trials, as it can be determined pre-operatively and before adjuvant chemotherapy.

Strengths and limitations - part I

In **part I** of this thesis, we explored novel non-invasive tools to enhance diagnostic and prognostic accuracy in patients with bone tumors. These studies had several strengths. First, they describe a novel non-invasive technique to differentiate between healthy individuals and those with chondrosarcoma of bone. While this technique has shown

significant potential for diagnosing other types of cancer, its application to chondrosarcoma has not been previously described. Furthermore, a large single-center cohort of osteosarcoma patients was studied, to better explore risk factors for survival. At last, they introduce a novel method for assessing the response to neo-adjuvant chemotherapy at an early stage (pre-resection), which has been found to be associated with event-free survival – a previously undocumented correlation. These innovations could pave the way for new research into additional therapies, patient- and risk-tailored protocols, potentially leading to improved survival outcomes for patients with bone tumors. Despite the promise of quantitative data (omics) in prognostic and diagnostic models, the integration of such methods into daily practice remains limited. Challenges include small sample sizes, complex and hard-to-reproduce methods, and a lack of external validation, which affect reproducibility and generalizability(15, 16). Therefore, it is essential for future studies to utilize larger cohorts, adopt transparent methodologies, and incorporate external validation to improve the generalizability and accuracy of these (prediction) models.

Future perspectives and clinical implications - part I

Future research should address several key areas to advance the field of bone tumor diagnostics, prognostics, and treatment. For the eNose, investigations are needed to determine if distinct VOC patterns are associated with different types or stages of chondrosarcoma. Longitudinal studies could reveal whether changes in VOC patterns over time correlate with disease progression, treatment response, or recurrence, potentially offering a non-invasive method for ongoing patient monitoring and tailored personalized treatment adjustments. Additionally, exploring the use of artificial intelligence (AI) and deep-learning models to automatically detect and stage primary bone tumors, based on quantitative imaging features or complex pattern recognition, could significantly enhance the accuracy of detecting and staging primary bone tumors(17, 18). Statistical models rely on predefined features, while deep learning models have the potential to automatically learn and extract relevant features directly from raw data. Furthermore, in the context of

osteosarcoma, research should explore how treatment protocols can be customized for various age groups, with a particular focus on adolescents and young adults (AYAs) as well as older adults. This includes evaluating the effectiveness of age-specific chemotherapy regimens and developing personalized treatment strategies that consider biological differences across age groups. Addressing the poor chemotherapy responses observed in some patients, especially older adults, is crucial. Molecular and genetic research should aim to identify biomarkers associated with poor histological outcomes. Potential new treatment approaches could involve combining immunotherapy, chemotherapy, and anti-angiogenesis therapies to overcome chemotherapy resistance and improve survival rates, as suggested by Garcia-Ortega et al.(19).

Moreover, the rWIR as a prognostic biomarker, should be (externally) validated in large future multicenter studies to confirm its applicability across different demographics, tumor subtypes, and treatment protocols. Integrating rWIR into standard diagnostic procedures and evaluating its impact on treatment decisions, including chemotherapy regimens and surgical timing, is crucial. Additionally, developing protocols for ongoing monitoring with rWIR could be valuable for detecting changes in tumor dynamics, potentially indicating relapse or chemotherapy resistance and facilitating timely intervention(20).

Part II MUTARS reconstructions in patients with extensive bone defects following orthopaedic oncological resections

The surgical management of bone defects, utilizing MUTARS endoprosthesis

Modular endoprosthetic reconstructions, such as the Modular Universal Tumor And Revision System (MUTARS) offer benefits like off-the-shelf availability, relative ease of implantation, intra-operative flexibility with adjustable components, and support for early weight-bearing(21, 22). However, they still carry significant complication and cumulative revision risks, as patients are generally young and active, and the endoprostheses are subject to long-term mechanical stresses(22, 23). Our understanding of these risks is limited due to the scarcity of high-quality studies, and variability in study cohorts and follow-up. To address this, we established the MUTARS Orthopaedic Registry Europe (MORE), to evaluate the long-term safety and efficacy of several MUTARS endoprostheses.

Chapter 5 presents the clinical outcomes of the largest series to date, evaluating the reconstruction of pelvic tumor defects using the LUMiC prosthesis in 166 patients. Almost half of the patients required at least one reoperation of which the majority was performed within the first 6 months post-reconstruction, primarily due to dislocation and periprosthetic joint infection (PJI). Notably, a plateau phase in complications can be observed after the first post-operative year, suggesting that patients face the highest risk of complications in the early post-operative period, after which the risk significantly decreases. The cumulative incidences of revision for mechanical reasons and PJI (Henderson 1 to 4) at 2, 5, and 10 years were 11% (95% confidence interval [CI], 7% to 17%), 18% (12% to 25%), and 24% (16% to 33%), respectively. Previous surgery at same site was identified as a risk factor for dislocation, while more extensive resection (including P3) was a risk factor for the occurrence of PJI. The LUMiC prosthesis showed durability concerning implant loosening, which was rarely observed during the follow-up period. In **Chapter 6,** the clinical outcomes of the largest oncological series of MUTARS knee reconstructions to date are presented, with a particular focus on locking-mechanism

failure, in a total of 316 patients. While PJI is a common complication in lower-limb endoprosthetic reconstructions, structural failure of the implant is also a relative frequent issue. The MUTARS knee reconstruction's locking-mechanism, can break or experience significant wear, leading to symptomatic instability. The cumulative incidences of revision for instability due to wear or locking-mechanism breakage were 0% (95% CI 0-0), 5% (1-15), and 5% (1-15) for PE; 5% (1-14), 14% (5-26), and 16% (7-29) for PEEK; and 0%, 3% (1-6), and 10% (5-16) for MoM at 2, 5, and 10 years, respectively. Despite adjusting the locking-mechanism material from PE to PEEK and to MoM, the risk of revision has not decreased. In fact, PEEK and MoM locking mechanisms were associated with a higher risk of locking-mechanism failure than PE. Other potential risk factors such as age, BMI, and resection length were not associated with locking-mechanism failure. This underscores the need for design improvements to reduce the risk of complications and the need for revisions. **Chapter 7** presents clinical and functional outcomes of the largest oncological series of proximal humerus endoprosthetic reconstructions to date, involving 165 patients. Our findings indicate that dislocation (9%) and PJI (10%) were the most common complications and primary reasons for revision. Despite the substantial reoperation risk, we observed a plateau phase, indicating that most complications occurred in the early post-operative phase. The cumulative incidences of revision for mechanical reasons (Henderson 1 to 3) in the entire population at 2, 5, and 10 years were 7%(95%CI 3-11), 11%(6-17), and 13%(7-20) respectively. For PJI (Henderson 4), the cumulative incidences of revision were 5%(2-10), 7%(3-12), and 7%(3-12). Previous surgery at same site was identified as a risk factor for dislocation. Both reverse shoulder arthroplasty (RSA) and hemiarthroplasty exhibited comparable revision risks. However, RSA provides superior functional outcomes. The relative low revision rates in the mid-term combined with better functional results of RSA, suggest that clinicians should consider using RSA over hemiarthroplasty for reconstruction of tumor defects of the proximal humerus.

Strengths and limitations - part II

The studies in **part 2** of this thesis have several strengths. First, they are distinguished by their large sample sizes, as there are no other studies of similar scale focusing on location-specific oncological MUTARS reconstructions. Furthermore, these studies, based on data of the MORE registry, systematically evaluate complications using the Henderson classification, facilitating easy comparison with other studies(24). They employ appropriate statistical methodologies, including competing risks models, to assess the risk of implant failure. The use of competing risk models is crucial because Kaplan-Meier's methodology overestimates the cumulative risk of implant failure by not accounting for competing events such as death or revision for other reasons(25). At last, the MORE, being the first and largest global tumor endoprostheses registry, serves as a benchmark for potential future initiatives and comparable studies on clinical outcomes of endoprostheses from different manufacturers. This registry aims to improve the understanding of long-term efficacy and safety of MUTARS endoprostheses.

However, there are limitations to consider. The Henderson classification, used in the MORE, focuses on failures, needing revision surgery of (modular) components, rather than overall complications, leading to underreporting of complications without subsequent revision procedures, and misclassifying less invasive procedures as failures. The classification is also broad, often missing specific details, like the exact cause of implant failure or the type of infection (acute hematogenic, or delayed/chronic), which are crucial for treatment decisions. To address these gaps, the MORE has added questions for detailed complication data and adapted the classification to distinguish between less invasive maintenance (e.g. liner exchange, locking-mechanism revision, rotational adjustment) and true failures (e.g. one- and two-stage revision, implant removal). Bus et al. have also suggested modifications to enhance its accuracy in future research(26). Furthermore, the multicenter retrospective design introduced variability in peri-operative protocols and resulted in missing data, which could have affected clinical outcomes and introduced biases. The relatively small number of events per complication also limited the ability to perform detailed multivariable risk factor analyses using Cox regression models.

This is crucial in orthopaedic oncology due to the complex multi-factorial nature of complications. As the registry incorporates both retrospective and prospective data, data completeness is expected to improve, addressing gaps in older patient records. At last, registries are also prone to biases such as selection and reporting biases, and concerns about data privacy and security may impact center participation. Despite these limitations, global initiatives like MORE are essential for establishing a solid foundation and validating research on endoprosthetic reconstructions, as individual case series contribute minimally to current knowledge and can lead to coincident findings that add scientific "noise".

Future perspectives and clinical implications - part II

Risk factor analyses

Future studies in even larger cohorts should focus on multivariable risk factor analyses for common complications in endoprosthetic reconstructions, such as dislocation and PJI. Moreover, larger sample sizes will enable the use of multi-state models. These are statistical models used to describe the evolution of the status of the patient, where transitions between different states (i.e. revision(s) with different causes, or death) over time are possible. While multi-state models have been employed to evaluate oncological outcomes like local tumor relapse or distant metastases after (neo-)adjuvant radiotherapy, they have not yet been applied to tumor endoprostheses due to insufficient data on recurrent revisions(27). Such models could enhance our understanding of factors contributing to recurrent revisions.

Dislocation management

Future research should address stability issues in pelvic and proximal humerus reconstructions, which are prone to dislocation. Given that previous surgery increases dislocation risk, tailored surgical techniques or customized post-operative protocols may be valuable. Although dual-mobility cups have shown reduced dislocation rates compared to conventional cups in general hip arthroplasty and LUMiC reconstructions, this thesis did not find a significant association between dual-mobility cups and lower dislocation risk(28, 29). Exploring the use of more constrained acetabular cups might further reduce the dislocation risk. While constrained designs could theoretically improve stability in shoulder

reconstructions as well, evidence of their benefit is limited(30-32). However, its use in combination with the LUMiC prosthesis, with its relatively low loosening rates, remains a promising option for further minimizing dislocations while preserving implant integrity(33). Another area of interest is the impact of an altered center of rotation (COR) in patients reconstructed with the LUMiC prosthesis. A previous study on endoprosthetic periacetabular reconstructions, has shown that a vertical shift of the COR >18mm and a sagittal shift >20mm increases the dislocation risk(34). Understanding these factors could lead to different surgical strategies for patients with an anticipated significantly altered center of rotation. One potential solution might be to modify the current design, such as by adding an extension piece to the LUMiC stem to allow for COR adjustments. However, future bio-mechanical studies, like implant migration CT-RSA studies, are needed to determine whether this could increase the risk of periprosthetic fractures or implant migration and ultimately implant loosening(35, 36). Such supporting studies are needed to proof clinical evidence of class III medical devices under the MDR (Medical Device Regulations)(37). Alternatively, custom-made implants could be considered for such cases. Additionally, since most dislocations occur within the first months after surgery and patients with prior surgeries at the same site are at a higher risk, future research should explore less aggressive post-operative mobilization, or personalized rehabilitation protocols.

At last, resection of an acetabular tumor disrupts the pelvic ring, potentially leading to decreased stability, reduced functional outcomes, and increased pain(38). While several reconstructive methods for restoring pelvic ring have been described, the effectiveness of these methods remains debated(39). An emerging alternative is the use of 3D-printed custom-made acetabular implants to reconstruct the bone defect and restore the pelvic ring. This relative new method shows promise for the reconstruction of pelvic bone defects in terms of complications and implant survival(40). However, most studies are single-center with small sample sizes and limited follow-up, leaving some uncertainty about their effectiveness after tumor resection(41, 42). Moreover, a significant disadvantage of 3D-printed custom-made implants in orthopaedic oncology is the lack of intraoperative adjustability, making precise pre-operative planning and implantation crucial(40, 43). In

light of these considerations, we recommend using the LUMiC prosthesis, particularly for aggressive malignancies that require urgent surgery, such as high-grade chondrosarcomas and metastases. The time constraints associated with these tumors often make custom-made implants impractical, although future advancements may shorten production times. Conversely, for patients with osteosarcoma or Ewing sarcoma undergoing neo-adjuvant chemotherapy – where treatment spans 10-18 weeks before definitive surgery – there is generally enough time to produce custom-made implants. Thus, the optimal treatment can be tailored based on patient and tumor characteristics in these scenarios. For tumors extending into the ilium and sacrum (P1-2 resections), the LUMiC prosthesis might be unsuitable due to its stem requiring sufficient medial ilium bone stock for proper insertion. However, for more extensive resections, including the os pubis (P3), the LUMiC prosthesis may be preferable over custom-made implants. This preference is due in part to the higher risk of periprosthetic joint infection (PJI) associated with P2-3 resections. The modular design of the LUMiC facilitates easier and quicker component exchanges during debridement, antibiotics, and implant retention (DAIR) procedures, or in one- or two-stage revisions, potentially improving infection management. Additionally, the higher cost of custom-made implants, combined with the elevated infection risk, can result in significantly increased expenses(38). Therefore, in such cases, an off-the-shelf LUMiC prosthesis may offer a more cost-effective and flexible solution..

Structural failure

Some patients need (recurrent) revisions of their locking-mechanism. However, it remains unclear why certain patients require multiple revisions due to locking-mechanism failure. One hypothesis is that extensive surgical resections around the knee compromises the stabilizing structures(44), and alters gait(45), potentially leading to increased stresses through repetitive knee hyperextension. Future studies should therefore focus on gait analysis after endoprosthetic reconstruction, and quantitative MRI studies to evaluate muscle volume around the knee, such as the quadriceps and hamstrings, both pre- and post-operatively. Moreover, Implantcast has introduced carbon-reinforced PEEK locking-mechanisms, which may offer improved durability, although clinical outcomes should be awaited.

Prevention and treatment of PJIs

PJI remains the most common reason for revision in endoprosthetic reconstructions(46, 47). To address this, future studies should focus on prevention strategies. One approach involves optimizing patient health before surgery by improving physical fitness, nutrition, glycemic control, quitting smoking, and managing comorbidities. Although specific studies on endoprostheses in orthopaedic oncology are lacking, these measures can help reduce postoperative infections(48-50). A multi-disciplinary team involving an orthopaedic surgeon, anesthesiologist, nutritionist, infectiologist, medical oncologist, and physiotherapist should collaborate to enhance overall health and educate patients on risks and lifestyle modifications. Additionally, exploring the use of muscle flaps or other methods for robust soft tissue coverage and antimicrobial protection could be beneficial(51). Some centers use well-vascularized myocutaneous flaps to cover implants and eliminate large wound spaces following pelvic reconstruction, though these procedures can be associated with longer surgical durations, increased blood loss, donor site morbidity, and persistently high risk of wound complications(52, 53).

Another potential strategy to reduce the risk of PJIs is the use of silver-coated endoprostheses, which have antibacterial properties targeting a wide range of bacteria associated with PJIs(54). Retrospective studies on MUTARS silver-coated implants suggest an increased likelihood of successful revision surgery in patients suffering PJI(55, 56). However, their effectiveness in preventing primary PJI remains uncertain, as neither our studies nor others have found a significant reduction on the PJI risk. While some studies have reported argyria from locally elevated silver ion levels, systemic toxicological side effects are generally not observed(57-59). Considering their potential benefits in treating PJIs, we believe the continued use of silver-coated implants is justified. Future larger studies comparing non-coated and silver-coated implants should determine whether they indeed reduce the incidence of PJI. At last, for high-risk patients, especially those with extensive tumors or poor anticipated functional outcomes, alternative approaches like resection arthroplasty or flail joint procedures, rotationplasty, or amputation should be considered. This may significantly reduce the risk of PJI, and patients may still experience a relatively good function(60, 61).

Overall conclusions

This thesis addresses advancements and ongoing challenges in the broad array of orthopaedic oncology. It reviews progress in diagnostic and prognostic tools, including the evaluation of the eNose for chondrosarcoma and the use of relative wash-in rate as a radiomics-based prognostic marker for early prediction of prognosis in osteosarcoma patients. These tools hold significant potential for personalized treatment and the development of new therapies. However, refinement and external validation is warranted before these tools can be clinically adopted.

The second part of this thesis underlines the crucial role of international registries in evaluating treatments for orphan diseases, with a particular focus on endoprosthetic reconstructions. It presents clinical outcomes of various MUTARS endoprostheses through the first international multicenter initiative, the MUTARS Orthopaedic Registry Europe (MORE). Expanding this registry will facilitate more detailed analyses of specific complication and less common reconstructions, such as growing prostheses, intercalary reconstructions, or custom-made implants. The successful implementation of MORE represents a significant advance in orthopaedic oncology, providing a valuable platform for other centers to contribute to and utilize registry data for ongoing research. By collaborating with global experts, we can focus on addressing critical issues and advancing research that aims to improve clinical outcomes and overall patient care.

References

1. Dierselhuis EF, Goulding KA, Stevens M, Jutte PC. Intralesional treatment versus wide resection for central low-grade chondrosarcoma of the long bones. Cochrane Database Syst Rev. 2019;3(3):Cd010778.
2. Deckers C, de Leijer EM, Flucke U, de Rooy JWJ, Schreuder HWB, Dierselhuis EF, et al. Curettage and cryosurgery for enchondroma and atypical cartilaginous tumors of the long bones: Oncological results of a large series. J Surg Oncol. 2021;123(8):1821-7.
3. Gelderblom H, Hogendoorn PC, Dijkstra SD, van Rijswijk CS, Krol AD, Taminiau AH, et al. The clinical approach towards chondrosarcoma. Oncologist. 2008;13(3):320-9.
4. Alhumaid SM, Alharbi At, Aljubair H. Magnetic Resonance Imaging Role in the Differentiation Between Atypical Cartilaginous Tumors and High-Grade Chondrosarcoma: An Updated Systematic Review. Cureus. 2020;12(10):e11237.
5. Reliability of histopathologic and radiologic grading of cartilaginous neoplasms in long bones. J Bone Joint Surg Am. 2007;89(10):2113-23.
6. Scheepers M, Al-Difaie Z, Brandts L, Peeters A, van Grinsven B, Bouvy ND. Diagnostic Performance of Electronic Noses in Cancer Diagnoses Using Exhaled Breath: A Systematic Review and Meta-analysis. JAMA Netw Open. 2022;5(6):e2219372.
7. Anzivino R, Sciancalepore PI, Dragonieri S, Quaranta VN, Petrone P, Petrone D, et al. The Role of a Polymer-Based E-Nose in the Detection of Head and Neck Cancer from Exhaled Breath. Sensors (Basel). 2022;22(17).
8. Gardner JW, Bartlett PN. A brief history of electronic noses. Sensors and Actuators B: Chemical. 1994;18(1):210-1.
9. Acem I, van Praag VM, Mostert CQ, van der Wal RJ, Neijenhuis RM, Verhoef C, et al. Noninvasive detection of soft tissue sarcoma using volatile organic compounds in exhaled breath: a pilot study. Future Oncol. 2023;19(10):697-704.
10. Jaffe N. Historical perspective on the introduction and use of chemotherapy for the treatment of osteosarcoma. Adv Exp Med Biol. 2014;804:1-30.
11. Smeland S, Bielack SS, Whelan J, Bernstein M, Hogendoorn P, Krailo MD, et al. Survival and prognosis with osteosarcoma: outcomes in more than 2000 patients in the EURAMOS-1 (European and American Osteosarcoma Study) cohort. Eur J Cancer. 2019;109:36-50.
12. Williams LA, Barragan S, Lu Z, Weigel BJ, Spector LG. Sex differences in osteosarcoma survival across the age spectrum: A National Cancer Database analysis (2004–2016). Cancer Epidemiology. 2024:102565.
13. Ottaviani G, Jaffe N. The epidemiology of osteosarcoma. Cancer Treat Res. 2009;152:3-13.
14. Kalisvaart GM, Van Den Berghe T, Grootjans W, Lejoly M, Huysse WCJ, Bovée J, et al. Evaluation of response to neoadjuvant chemotherapy in osteosarcoma using dynamic contrast-enhanced MRI: development and external validation of a model. Skeletal Radiol. 2023.
15. Crombé A, Fadli D, Italiano A, Saut O, Buy X, Kind M. Systematic review of sarcomas radiomics studies: Bridging the gap between concepts and clinical applications? Eur J Radiol. 2020;132:109283.
16. Fanciullo C, Gitto S, Carlicchi E, Albano D, Messina C, Sconfienza LM. Radiomics of Musculoskeletal Sarcomas: A Narrative Review. J Imaging. 2022;8(2).
17. Salehi MA, Mohammadi S, Harandi H, Zakavi SS, Jahanshahi A, Shahrabi Farahani M, et al. Diagnostic Performance of Artificial Intelligence in Detection of Primary Malignant Bone Tumors: a Meta-Analysis. J Imaging Inform Med. 2024;37(2):766-77.
18. Park CW, Oh SJ, Kim KS, Jang MC, Kim IS, Lee YK, et al. Artificial intelligence-based classification of bone tumors in the proximal femur on plain radiographs: System development and validation. PLoS One. 2022;17(2):e0264140.

19. Garcia-Ortega DY, Cabrera-Nieto SA, Caro-Sánchez HS, Cruz-Ramos M. An overview of resistance to chemotherapy in osteosarcoma and future perspectives. Cancer Drug Resist. 2022;5(3):762-93.
20. Erber BM, Reidler P, Goller SS, Ricke J, Dürr HR, Klein A, et al. Impact of Dynamic Contrast Enhanced and Diffusion-Weighted MR Imaging on Detection of Early Local Recurrence of Soft Tissue Sarcoma. J Magn Reson Imaging. 2023;57(2):622-30.
21. Myers GJ, Abudu AT, Carter SR, Tillman RM, Grimer RJ. Endoprosthetic replacement of the distal femur for bone tumours: long-term results. J Bone Joint Surg Br. 2007;89(4):521-6.
22. Bus MPA, van de Sande MAJ, Fiocco M, Schaap GR, Bramer JAM, Dijkstra PDS. What Are the Long-term Results of MUTARS(®) Modular Endoprostheses for Reconstruction of Tumor Resection of the Distal Femur and Proximal Tibia? Clin Orthop Relat Res. 2017;475(3):708-18.
23. Pala E, Trovarelli G, Ippolito V, Berizzi A, Ruggieri P. A long-term experience with Mutars tumor megaprostheses: analysis of 187 cases. European Journal of Trauma and Emergency Surgery. 2021.
24. Henderson ER, O'Connor MI, Ruggieri P, Windhager R, Funovics PT, Gibbons CL, et al. Classification of failure of limb salvage after reconstructive surgery for bone tumours : a modified system Including biological and expandable reconstructions. Bone Joint J. 2014;96-b(11):1436-40.
25. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med. 2007;26(11):2389-430.
26. Bus MP. Reconstructive techniques in musculoskeletal tumor surgery : management of pelvic and extremity bone tumors. 2018.
27. Willeumier JJ, Rueten-Budde AJ, Jeys LM, Laitinen M, Pollock R, Aston W, et al. Individualised risk assessment for local recurrence and distant metastases in a retrospective transatlantic cohort of 687 patients with high-grade soft tissue sarcomas of the extremities: a multistate model. BMJ Open. 2017;7(2):e012930.
28. Bus MPA, Szafranski A, Sellevold S, Goryn T, Jutte PC, Bramer JAM, et al. LUMiC(®) Endoprosthetic Reconstruction After Periacetabular Tumor Resection: Short-term Results. Clin Orthop Relat Res. 2017;475(3):686-95.
29. Williams JT, Jr., Ragland PS, Clarke S. Constrained components for the unstable hip following total hip arthroplasty: a literature review. Int Orthop. 2007;31(3):273-7.
30. Goodloe JB, Denard PJ, Lederman E, Gobezie R, Werner BC. No difference in range of motion in reverse total shoulder arthroplasty using standard or constrained liners: a matched cohort study. JSES Int. 2022;6(6):929-34.
31. Cundy WJ, McArthur MS, Dickinson IC, Rowell PD, Sommerville SMM. Constrained or unconstrained shoulder replacement for musculoskeletal tumor resections? Journal of Shoulder and Elbow Surgery. 2020;29(10):2104-10.
32. Post M. Constrained Arthroplasty of the Shoulder. Orthopedic Clinics of North America. 1987;18(3):455-62.
33. Berend KR, Lombardi AV, Mallory TH, Adams JB, Russell JH, Groseth KL. The Long-term Outcome of 755 Consecutive Constrained Acetabular Components in Total Hip Arthroplasty: Examining the Successes and Failures. The Journal of Arthroplasty. 2005;20:93-102.
34. Qu H, Mou H, Wang K, Tao H, Huang X, Yan X, et al. Risk factor investigation for hip dislocation after periacetabular tumour resection and endoprosthetic reconstruction via thin-slice CT-based 3D model. The Bone & Joint Journal. 2022;104-B(10):1180-8.
35. Kaptein BL, Pijls B, Koster L, Kärrholm J, Hull M, Niesen A, et al. Guideline for RSA and CT-RSA implant migration measurements: an update of standardizations and recommendations. Acta Orthop. 2024;95:256-67.
36. Overgaard S, Grupp TM, Nelissen RG, Cristofolini L, Lübbeke A, Jäger M, et al. Introduction of innovations in joint arthroplasty: Recommendations from the 'EFORT implant and patient safety initiative'. EFORT Open Rev. 2023;8(7):509-21.

37. Fraser AG, Nelissen R, Kjærsgaard-Andersen P, Szymański P, Melvin T, Piscoi P. Improved clinical investigation and evaluation of high-risk medical devices: the rationale and objectives of CORE-MD (Coordinating Research and Evidence for Medical Devices). Eur Heart J Qual Care Clin Outcomes. 2022;8(3):249-58.
38. Laitinen MK, Parry MC, Albergo JI, umathi VS, Jeys LM, Grimer RJ. Resection of the ilium in patients with a sarcoma. The Bone & Joint Journal. 2017;99-B(4):538-43.
39. Schwameis E, Dominkus M, Krepler P, Dorotka R, Lang S, Windhager R, et al. Reconstruction of the Pelvis After Tumor Resection in Children and Adolescents. Clinical Orthopaedics and Related Research®. 2002;402:220-35.
40. Hu X, Lu M, Wang Y, Luo Y, Zhou Y, Yang X, et al. Advanced Pelvic Girdle Reconstruction with three dimensional-printed Custom Hemipelvic Endoprostheses following Pelvic Tumour Resection. Int Orthop. 2024;48(8):2217-31.
41. Broekhuis D, Boyle R, Karunaratne S, Chua A, Stalley P. Custom designed and 3D-printed titanium pelvic implants for acetabular reconstruction after tumour resection. HIP International. 2022:11207000221135068.
42. Xu S, Guo Z, Shen Q, Peng Y, Li J, Li S, et al. Reconstruction of tumor-induced pelvic defects with customized, three-dimensional printed prostheses. Frontiers in Oncology. 2022;12:935059.
43. Hu X, Lu M, Zhang Y, Li Z, Wang J, Wang Y, et al. Pelvic-girdle reconstruction with three-dimensional-printed endoprostheses after limb-salvage surgery for pelvic sarcomas: current landscape. British Journal of Surgery. 2023;110(12):1712-22.
44. Johansen ML, Eriksrud O, Thorkildsen J, Norum O-J, Wisløff T, Taksdal I, et al. Muscle strength characteristics following megaprosthetic knee reconstruction for bone sarcoma. Surgical Oncology. 2023;48:101944.
45. Singh VA, Heng CW, Yasin NF. Gait Analysis in Patients with Wide Resection and Endoprosthesis Replacement Around the Knee. Indian J Orthop. 2018;52(1):65-72.
46. Zuidhof R-JWJ, Löwik CAM, Ploegmakers JJW, Dijkstra SPD, Wouthuyzen-Bakker M, Jutte PC. Periprosthetic joint infection in orthopaedic surgical oncology. Annals of Joint. 2019;4.
47. Smolle MA, Andreou D, Tunn PU, Leithner A. Advances in tumour endoprostheses: a systematic review. EFORT Open Rev. 2019;4(7):445-59.
48. Ellenberger C, Schorer R, Bedat B, Hagerman A, Triponez F, Karenovics W, et al. How can we minimize the risks by optimizing patient's condition shortly before thoracic surgery? Saudi J Anaesth. 2021;15(3):264-71.
49. Warwick E, Moonesinghe SR. Chronic Disease Management and Optimization of Functional Status Before Surgery: Does This Improve Long-Term Postoperative Outcomes? Current Anesthesiology Reports. 2023;13(4):324-34.
50. Baek SH. Identification and preoperative optimization of risk factors to prevent periprosthetic joint infection. World J Orthop. 2014;5(3):362-7.
51. Buchner M, Zeifang F, Bernd L. Medial gastrocnemius muscle flap in limb-sparing surgery of malignant bone tumors of the proximal tibia: mid-term results in 25 patients. Ann Plast Surg. 2003;51(3):266-72.
52. Barrientos-Ruiz I, Ortiz-Cruz EJ, Peleteiro-Pensado M. Reconstruction After Hemipelvectomy With the Ice-Cream Cone Prosthesis: What Are the Short-term Clinical Results? Clin Orthop Relat Res. 2017;475(3):735-41.
53. Ogura K, Miyamoto S, Sakuraba M, Chuman H, Fujiwara T, Kawai A. Immediate soft-tissue reconstruction using a rectus abdominis myocutaneous flap following wide resection of malignant bone tumours of the pelvis. The Bone & Joint Journal. 2014;96-B(2):270-3.
54. Hetrick EM, Schoenfisch MH. Reducing implant-related infections: active release strategies. Chemical Society Reviews. 2006;35(9):780-9.

55. Wafa H, Grimer RJ, Reddy K, Jeys L, Abudu A, Carter SR, et al. Retrospective evaluation of the incidence of early periprosthetic infection with silver-treated endoprostheses in high-risk patients: case-control study. Bone Joint J. 2015;97-b(2):252-7.
56. Fiore M, Sambri A, Zucchini R, Giannini C, Donati DM, De Paolis M. Silver-coated megaprosthesis in prevention and treatment of peri-prosthetic infections: a systematic review and meta-analysis about efficacy and toxicity in primary and revision surgery. Eur J Orthop Surg Traumatol. 2021;31(2):201-20.
57. Hardes J, Ahrens H, Gebert C, Streitbuerger A, Buerger H, Erren M, et al. Lack of toxicological side-effects in silver-coated megaprostheses in humans. Biomaterials. 2007;28(18):2869-75.
58. Glehr M, Leithner A, Friesenbichler J, Goessler W, Avian A, Andreou D, et al. Argyria following the use of silver-coated megaprostheses: no association between the development of local argyria and elevated silver levels. Bone Joint J. 2013;95-b(7):988-92.
59. Li H, Wang D, Zhang W, Xu G, Xu C, Liu W, et al. Potential side effects of antibacterial coatings in orthopaedic implants: A systematic review of clinical studies. Front Bioeng Biotechnol. 2023;11:1111386.
60. Takami M, Ieguchi M, Aono M, Hoshi M, Takada J, Oebisu N, et al. Flail hip joint following periacetabular tumor resection of the pelvis using upper surface of the femoral neck as a saddle: A case report. Oncol Lett. 2015;10(6):3529-31.
61. Takami M, Ieguchi M, Takamatsu K, Kitano T, Aono M, Ishida T, et al. Functional evaluation of flail hip joint after periacetabular resection of the pelvis. Osaka City Med J. 1997;43(2):173-83.

Chapter 9

Summary in Dutch (Nederlandse samenvatting)

Het doel van dit proefschrift

De klinische uitkomsten en verbeteringen in de patientenzorg binnen de orthopaedische oncologie zijn afhankelijk van zowel adequate en nauwkeurige diagnostische en prognostische processen, als goed afgewogen chirurgische resecties en reconstructieve operaties. Daarom bestaat dit proefschrift uit twee delen.

Deel I richt zich op de evaluatie van een nieuw diagnostisch hulpmiddel voor chondrosarcoom en op het verbeteren van ons begrip van prognostische factoren voor overleving bij osteosacoom patienten. Daarnaast evalueert het een innovatief, niet-invasief prognostisch hulpmiddel voor het voorspellen van de respons op chemotherapie bij osteosarcoom patienten.
Deel II beoogt bij te dragen aan het inzicht op de klinische uitkomsten van endoprothetische reconstructies door risicofactoren voor complicaties en implantaatfalen te evalueren. Het maakt gebruik van hoogwaardige, wereldwijde multicenter studies gericht op verscheidene MUTARS endoprothesen.

Deel I Vooruitgang in de evaluatie van diagnose en prognose bij patiënten met bottumoren

Een potentieel nieuw niet-invasief diagnostisch hulpmiddel voor chondrosarcoom

Een nauwkeurige diagnose en classificatie van kraakbeentumoren is cruciaal, aangezien de behandeling varieert naargelang de tumorgraad. Goedaardige of laaggradige kraakbeentumoren kunnen vaak worden behandeld met curettage of gesuperviseerde observatie, terwijl hooggradige chondrosarcomen meestal uitgebreide chirurgie en reconstructie vereisen. Het onderscheid tussen laaggradige of goedaardige kraakbeentumoren en hooggradige chondrosarcomen is echter lastig, vanwege aanzienlijke interobserver variabiliteit in de huidige radiologische en histologische methoden. Om dit probleem aan te pakken, worden nieuwe diagnostische hulpmiddelen onderzocht. De eNose analyseert vluchtige organische stoffen (VOCs) met behulp van

patroonherkenning en moet worden getraind met een dataset om zijn diagnostische mogelijkheden te ontwikkelen. In een eerdere studie van Acem et al. toonde de eNose veelbelovende resultaten als niet-invasieve biomarker voor het opsporen van wekedelen sarcomen (STS) met een goed onderscheidend vermogen. In onze verkennende pilotstudie, gepresenteerd in **Hoofdstuk 2**, liet de eNose echter een beperkte gevoeligheid en specificiteit zien van respectievelijk 75% en 65%, met een AUC van 0,66. Deze resultaten suggereren dat de eNose nog niet betrouwbaar genoeg is voor routinematig klinisch gebruik.

Risicofactoren, oncologische uitkomsten en voorspellende biomarkers bij osteosarcoom

Hoewel de overlevingskansen voor patiënten met osteosarcoom sinds de jaren 1970 aanzienlijk zijn verbeterd, variëren de 5-jaars overlevingsresultaten nog steeds sterk, van 21% tot 86%. Een belangrijke vraag die blijft bestaan is wat deze variatie in overlevingsresultaten veroorzaakt. Een eerste stap in het beantwoorden van deze vraag is het identificeren van mogelijke prognostische factoren die verband houden met overlevingsuitkomsten. In **hoofdstuk 3** werd leeftijd geïdentificeerd als een prognostische factor voor overleving, zelfs wanneer gecorrigeerd voor andere demografische en behandelingsfactoren. Adolescenten en jongvolwassenen (AYAs) tussen 16 en 40 jaar, evenals oudere volwassenen van ≥40 jaar, hadden een minder gunstige uitkomst vergeleken met kinderen jonger dan 16 jaar, wat gedeeltelijk wordt verklaard door verschillende patiënt- en behandelingskenmerken.

Oudere volwassenen presenteren zich vaker met axiaal gelokaliseerde tumoren, pathologische fracturen, en werden vaker behandeld met Adriamycin en Cisplatine (AP) chemotherapie in plaats van hoge dosis Methotrexaat gecombineerd met AP (MAP). Daarnaast lijkt chemotherapie minder effectief te zijn bij oudere patiënten, aangezien zij minder vaak een goede histologische reactie op chemotherapie vertonen. Dit is gedeeltelijk te wijten aan dosisbeperkingen veroorzaakt door comorbiditeiten, leeftijdsgebonden orgaanfunctiestoornissen of toxiciteit van de chemotherapie. Naast leeftijd waren risicofactoren voor overleving tumorgrootte, metastasen op afstand bij presentatie, histologische respons op chemotherapie en lokaal tumor recidief. Hoewel het beoordelen van risicofactoren voor overleving cruciaal is voor een nauwkeurige prognose,

zijn de klinische implicaties beperkt aangezien veel factoren vastliggen bij diagnose of pas na chirurgische resectie duidelijk worden, zoals de respons op neo-adjuvante chemotherapie.

Hoofdstuk 4 introduceert een nieuwe prognostische biomarker die al vóór tumorresectie kan worden verkregen: de relatieve wash-in rate (rWIR). Deze wordt bepaald met dynamische contrast-versterkte MRI en weerspiegelt veranderingen in tumorperfusie vóór en na neo-adjuvante chemotherapie. Daarnaast is de rWIR geassocieerd met de respons op chemotherapie. Onze daaropvolgende studie toonde aan dat de rWIR geassocieerd is met event-vrije overleving (EFS), zelfs wanneer gecorrigeerd voor de eerder genoemde prognostische factoren. Bovendien waren de 2- en 5-jaars EFS voor patiënten met rWIR ≥ 2.3 respectievelijk 85% en 75%, vergeleken met 55% en 50% voor degenen met rWIR < 2.3. Deze bevindingen suggereren dat rWIR een waardevol hulpmiddel kan zijn voor het personaliseren van behandelstrategieën en het aanpassen van chemotherapie bij patiënten die onvoldoende reageren, aangezien het pre-operatief en vóór adjuvante chemotherapie kan worden bepaald.

Deel II MUTARS-reconstructies bij patiënten met uitgebreide botdefecten na orthopaedische oncologische resecties

De chirurgische behandeling van botdefecten met behulp van MUTARS-endoprothesen

Modulaire endoprothetische reconstructies, zoals het Modular Universal Tumor And Revision System (MUTARS), bieden voordelen zoals directe beschikbaarheid, relatief gemakkelijke implantatie, intra-operatieve flexibiliteit met aanpasbare componenten en de mogelijkheid tot vroege belasting na de operatie. Ze brengen echter nog steeds aanzienlijke complicatie- en cumulatieve revisierisico's met zich mee, omdat patiënten over het algemeen jong en actief zijn, en de endoprothesen onderhevig zijn aan langdurige biomechanische belasting. Het huidige begrip van deze risico's is beperkt door het gebrek aan hoogwaardige studies en variabiliteit in studiecohorten en follow-up. Om dit aan te pakken, hebben we het MUTARS Orthopaedic Registry Europe (MORE) opgericht om de

lange termijn veiligheid en effectiviteit van verschillende MUTARS-endoprothesen te evalueren.

Hoofdstuk 5 presenteert de grootste serie bekkenreconstructies tot nu toe en beschrijft de klinische uitkomsten van 166 LUMiC reconstructies na periacetabulaire tumorresectie. Bij bijna de helft van de patiënten was minstens één heroperatie nodig, waarvan de meeste werden uitgevoerd binnen de eerste 6 maanden na de reconstructie, voornamelijk vanwege dislocatie en periprothetische gewrichtsinfectie (PJI). Opvallend is dat na het eerste postoperatieve jaar een plateau in complicaties kan worden waargenomen, wat suggereert dat patiënten het hoogste risico op complicaties lopen in de vroege postoperatieve periode, waarna het risico aanzienlijk afneemt. De cumulatieve incidenties van revisie door mechanische redenen en PJI (Henderson 1 tot 4) op 2, 5 en 10 jaar waren respectievelijk 11% (95% betrouwbaarheidsinterval [BI], 7% tot 17%), 18% (12% tot 25%) en 24% (16% tot 33%). Eerdere chirurgie op dezelfde locatie werd geïdentificeerd als een risicofactor voor dislocatie, terwijl uitgebreidere resectie (inclusief het os pubis en os ischium [P3]) een risicofactor was voor het optreden van PJI. De LUMiC-prothese toonde duurzaamheid met betrekking tot implantaatloslating, wat zelden werd waargenomen tijdens de follow-up periode. **Hoofdstuk 6** presenteert de klinische uitkomsten van 316 patiënten met een MUTARS knie-reconstructie en een bijzondere focus op het falen van het scharniermechanisme. Dit is de grootste oncologische serie van MUTARS knie-reconstructies tot nu toe. Terwijl PJI een veelvoorkomende complicatie is bij endoprothetische reconstructies van de onderste ledematen, is structureel falen van het implantaat ook een relatief frequent probleem. Het scharniermechanisme van de MUTARS knieconstructie kan breken of aanzienlijke slijtage vertonen, wat leidt tot symptomatische instabiliteit. De cumulatieve incidenties van revisie door instabiliteit als gevolg van slijtage of breuk van het scharniermechanisme waren 0% (95% BI 0-0), 5% (1-15) en 5% (1-15) voor PE; 5% (1-14), 14% (5-26) en 16% (7-29) voor PEEK; en 0%, 3% (1-6) en 10% (5-16) voor MoM op respectievelijk 2, 5 en 10 jaar. Ondanks de aanpassing van het vergrendelmechanisme van PE naar PEEK en vervolgens naar MoM, is het risico op revisie niet afgenomen. PEEK- en MoM-scharniermechanismen waren geassocieerd met een hoger risico op falen van het scharniermechanisme dan PE. Andere potentiële

risicofactoren zoals leeftijd, BMI en resectielengte waren niet geassocieerd met falen van het scharniermechanisme. Dit onderstreept de noodzaak van ontwerpverbeteringen om het risico op complicaties en de noodzaak van revisies te verminderen. **Hoofdstuk 7** presenteert de klinische en functionele uitkomsten van de grootste oncologische serie van proximale humerus endoprothetische reconstructies tot nu toe, met 165 patiënten. Onze bevindingen tonen aan dat dislocatie (9%) en PJI (10%) de meest voorkomende complicaties en de belangrijkste redenen voor revisie waren. Ondanks het aanzienlijke risico op heroperatie, observeerden we een plateaufase, wat aangeeft dat de meeste complicaties optraden in de vroege postoperatieve fase. De cumulatieve incidenties van revisie voor mechanische redenen (Henderson 1 tot 3) in de gehele populatie waren op 2, 5 en 10 jaar respectievelijk 7% (95% BI 3-11), 11% (6-17) en 13% (7-20). Voor PJI (Henderson 4) waren de cumulatieve incidenties van revisie 5% (2-10), 7% (3-12) en 7% (3-12). Eerdere operaties op dezelfde locatie werden geïdentificeerd als een risicofactor voor dislocatie. Zowel de omgekeerde schouderprothese (RSA) als hemiarthroplastiek vertoonden vergelijkbare revisierisico's. Echter, RSA biedt betere functionele resultaten. De relatief lage revisie risico’s op de middellange termijn, gecombineerde met de betere functionele resultaten van RSA, suggereren dat clinici moeten overwegen RSA te gebruiken in plaats van hemiarthroplastiek voor de reconstructie van de proximale humerus.

Algemene conclusies

Deze thesis belicht belangrijke vorderingen en voortdurende uitdagingen in de orthopaedische oncologie. Het evalueert de voortgang in diagnostische en prognostische hulpmiddelen, waaronder de evaluatie van de eNose voor chondrosarcoom en het gebruik van de relatieve wash-in rate als een radiomics-gebaseerde prognostische marker voor de vroege voorspelling van de prognose bij osteosarcoom patienten. Deze hulpmiddelen hebben aanzienlijk potentieel voor gepersonaliseerde behandeling en de ontwikkeling van nieuwe therapieën. Echter verdere optimalisatie en externe validatie zijn nodig voordat deze hulpmiddelen breed kunnen worden toegepast in de klinische praktijk.

Het tweede deel van deze thesis benadrukt de cruciale rol van internationale registers bij het evalueren van behandelingen voor zeldzame ziekten, met een bijzonder focus op endoprothetische reconstructies. Het presenteert klinische uitkomsten van diverse MUTARS-endoprothesen via het eerste internationale multicenter initiatief, het MUTARS Orthopaedic Registry Europe (MORE). Het uitbreiden van dit register zal gedetailleerde analyses van specifieke complicaties en minder voorkomende reconstructies, zoals groeiprothesen, intercalaire reconstructies of custom-made implantaten mogelijk maken. De succesvolle implementatie van MORE vertegenwoordigt een belangrijke vooruitgang in de orthopedische oncologie en biedt een waardevol platform voor andere centra om bij te dragen aan en gebruik te maken van de gegevens uit de registratie voor lopend onderzoek. Door samen te werken met wereldwijde experts kunnen we ons richten op het aanpakken van cruciale kwesties en het bevorderen van onderzoek dat gericht is op het verbeteren van klinische uitkomsten en de algehele patiëntenzorg.

Appendices

List of publications, acknowledgements, curriculum vitae

List of publications

Survival Analysis of 3 Different Age Groups and Prognostic Factors among 402 Patients with Skeletal High-Grade Osteosarcoma. Real World Data from a Single Tertiary Sarcoma Center. **R.E.Evenhuis,** I. Acem, A.J. Rueten-Budde, D.S.A. Karis, M. Fiocco, D.M.J. Dorleijn, F.M. Speetjens, J. Anninga, H. Gelderblom, M.A.J. van de Sande. Cancers (Basel). 2021 Jan 27;13(3):486. doi: 10.3390/cancers13030486. PMID: 33513855; PMCID: PMC7865349.

Risk of venous thromboembolism and major bleeding in the clinical course of osteosarcoma and Ewing sarcoma. F.H.J. Kaptein, M.A.M. Stals, **R.E. Evenhuis**, H. Gelderblom, M.V. Huisman, D.S.A. Karis, R.W.D. Noten, S.C. Cannegieter, F.M. Speetjens, A.J. Verschoor, H.H. Versteeg, M.A.J. van de Sande MAJ, F.A. Klok. Thromb Res. 2023 Jan;221:19-25. doi: 10.1016/j.thromres.2022.11.007. Epub 2022 Nov 18. PMID: 36435048.

Systemic metal ion concentrations in patients with hip and knee megaprostheses: a prospective cohort study. K.Q. de Smidt, G. Spierenburg, **R.E. Evenhuis**, S.E. Bosma, R.J.P. van der Wal, D. Broekhuis, M.A.J. van de Sande. Arthroplast Today. 2022 Oct 21;18:191-201.e1. doi: 10.1016/j.artd.2022.08.006. PMID: 36561551; PMCID: PMC9764025.

Impact of age at diagnosis on cardiotoxicity in high-grade osteosarcoma and ewing sarcoma patients. J.C. Heemelaar, F.M. Speetjens, A.A.M. Al Jaff, **R.E. Evenhuis**, E.A.S. Polomski, B.J.A. Mertens, J.W. Jukema, H. Gelderblom, M.A.J. van de Sande, M.L. Antoni. JACC CardioOncol. 2023 Feb 21;5(1):117-127. doi: 10.1016/j.jaccao.2022.11.016. PMID: 36875898; PMCID: PMC9982211.

LUMiC endoprosthetic reconstruction of periacetabular tumor defects: a multicenter follow-up study. **R.E. Evenhuis,** M.A.J. van de Sande, M. Fiocco, D. Broekhuis, M.P.A. Bus; LUMiC® Study Group. J Bone Joint Surg Am. 2024 May 23. doi: 10.2106/JBJS.23.01082. Epub ahead of print. PMID: 38781319.

Diagnosis of chondrosarcoma in a noninvasive way using volatile organic compounds in exhaled breath: a pilot study. **R.E. Evenhuis,** I. Acem, V.M. van Praag, R.J.P. van der Wal, M.P.A. Bus, M.A.J. van de Sande. Future Oncol. 2024 Jun 12:1-8. doi: 10.1080/14796694.2024.2355080. Epub ahead of print. PMID: 38864668.

Relative wash-in rate in dynamic contrast-enhanced magnetic resonance imaging as a new prognostic biomarker for event-free survival in 82 patients with osteosarcoma: a multicenter study. G.M. Kalisvaart*, **R.E. Evenhuis*,** W. Grootjans, T. Van Den Berghe, M. Callens, J.V.M.G. Bovée, D. Creytens, H. Gelderblom, F.M. Speetjens, L. Lapeire, G. Sys, M. Fiocco, K.L. Verstraete, M.A.J. van de Sande, J.L. Bloem. Cancers (Basel). 2024 May 21;16(11):1954. doi: 10.3390/cancers16111954. PMID: 38893075; PMCID: PMC11171179.

* *These authors contributed equally to this work*

Evaluating polyethylene, polyether-ether-ketone, and metal-on-metal locking mechanism survival in Modular Universal Tumour and Revision System knee reconstructions for oncological indications : insights from the MUTARS Orthopedic Registry Europe. **R.E. Evenhuis,** M.P.A. Bus, J. van Nes, S.G. Walter, J. Cabrolier, M. Fiocco, R.J.P. van der Wal, D. Broekhuis, S. Sellevold, M.A.J. van de Sande. Bone Joint J. 2025 Feb 1;107-B(2):239-245. doi: 10.1302/0301-620X.107B2.BJJ-2024-0623. PMID: 39889752.

Proximal humeral endoprosthetic reconstruction for tumor defects: clinical outcomes of 165 patients from the MUTARS Orthopaedic Registry Europe (MORE)
Accepted for publication in the Bone and Joint Open (January 2025)
***R.E. Evenhuis**, M.P.A. Bus, S. Sellevold, E.F. Dierselhuis, J. Von Harras, R.J.P. van der Wal, I.G. Trikoupis, P.J. Papagelopoulos, V. Kontogeorgakos, M. Scorianz, D.A. Campanacci, P.C. Jutte, S.G. Walter, O. Ceballos, J. Cabrolier, M. Fiocco, M.A.J. van de Sande.*

Acknowledgements / dankwoord

Prof. dr. M.A.J. van de Sande, hooggeleerde promotor, beste Michiel
Dankzij jouw begeleiding en verbindende kracht heb ik met inspirerende mensen samengewerkt en mijn proefschrift tot een succes kunnen brengen. Ik ben je zeer dankbaar voor je ruimte en motivatie om me zowel professioneel als persoonlijk te ontwikkelen.

Prof. dr. M. Fiocco, hooggeleerde promotor, beste Marta
Dankzij jouw enthousiasme voor statistiek en de waardevolle gesprekken op het Mathematische Instituut (inclusief heerlijke espresso's) heb ik mijn kennis enorm kunnen uitbreiden. Ik ben je dankbaar voor je begeleiding en je rol in mijn promotiecommissie.

Dr. M.P.A. Bus, hooggeleerde co-promotor, beste Michaël
Jouw ideeën, kritische feedback, en energie waren van onschatbare waarde. Daarnaast heb ik er een vriend bij gekregen waarmee ik kon sparren over het onderzoek tijdens borrels op het dakterras, congressen en gedurende onze potjes squash.

Prof. R.G.H.H. Nelissen, beste Rob
Ik bewonder jouw eindeloze energie en motivatie om de (orthopaedische) wereld op een eerlijke en transparante manier beter te maken. Je hebt een enorm mooi team om je heen gebouwd wat de afdeling orthopaedie in het LUMC een bijzonder fijne werkplek maakt. Veel dank!

Collega onderzoekers van C2-C3-D1 Leiden
Ondanks de verhuizingen zijn we altijd een team gebleven. Jullie hielpen me door de soms frustrerende wereld van wetenschappelijk onderzoek. De gezellige koffiemomenten, uitjes, en borrels zullen me altijd bijblijven.

Team onco

Michiel, Robert, Demien, Michael, Lizz, Jasper, Geert, Zeger, Maartje, Claire, Anouk, Marloes, Nicolette, bedankt voor de geweldige tijd gedurende de congressen die we samen hebben meegemaakt. Ik heb fenomenale herinneringen aan de EMSOS congressen met jullie.

Zeger, Anouk, Thies

Jullie aanwezigheid en vriendschap hebben gemaakt dat ik enorm heb genoten de afgelopen jaren. Ik ben jullie dankbaar voor de onbaatzuchtige hulp met mijn onderzoek, en de prachtige herinneringen die we samen hebben gemaakt. De veelvuldige Anoukjes, en Zegermeister(s) zal ik blijven herinneren.

Beste assistenten en staf van de orthopaedie in het LUMC

Dank voor de kans om mee te draaien op de polikliniek en in de OK. De afwisseling in mijn werk was van groot belang, en ik heb genoten van de ski-reis en andere uitjes.

Secretariaat orthopaedie

Marisa, Eveline, en Anika, bedankt voor de fijne samenwerking en ondersteuning tijdens mijn PhD-traject. Hopelijk tot snel!

JC Gulden

Waarde clubgenoten, wat hebben wij een mooie tijd gehad. De warme afwisseling van het medische wereldje met jullie nuchtere en soms saaie gesprekken over de advocatuur of andere fiscale ongein, rare herinneringen en prachtige reizen hebben mij veel energie gegeven. Op naar de toekomst!

Oud-huisgenoten van de Bronx

Wat we samen hebben meegemaakt, is onbeschrijfelijk. Jullie zijn vrienden voor het leven, en ik weet zeker dat jullie een grote rol in mijn toekomst zullen blijven spelen.

Frank Haasnoot en Philip Oldenburg (paranimfen),

Frenk en Oldie, als Haagse boeven en Bronxianen hebben we veel mooie momenten beleefd. Jullie vriendschap betekent ontzettend veel voor mij, en met jullie als paranimfen weet ik zeker dat het feestje helemaal goedkomt.

Lieve pap en mam,

Dankzij jullie ben ik geworden wie ik ben. Jullie onvoorwaardelijke steun en liefde hebben mij geholpen dit proefschrift te voltooien. Dit werk is dan ook net zo goed jullie werk. Ik houd van jullie.

*William, Carlijn, Fenna & Siem**

Lieve Willie, je was altijd daar voor me en ik heb ontzettend veel van je geleerd. Lieve Car, Fenna en Siem, het maakt mij blij en trots dat jullie samen met mijn grote broer een prachtig gezin vormen. Lieve Siem, we missen je hier, maar je schittert daar.

Juliette en Fons

Lieve Juul, wat ben ik geprezen met zo een fijne zus. Ik bewonder jouw avontuurlijke, energieke en bovenal lieve attente karakter. Fons, wat fijn dat jij er bij bent gekomen. Vakanties, feestjes en diners met jullie zijn onvergetelijk en betekenen veel voor mij.

Lieve Lidewij

Zoals mijn familie ook graag benadrukt; zonder jou had ik waarschijnlijk de studie geneeskunde niet gehaald, laat staan mijn PhD. Je bent een bron van inspiratie voor mij en voor vele andere mensen. Maar bovenal ben je de liefde van mijn leven. Ik houd van je.

About the author

Richard Eduard Evenhuis was born on May 28, 1995, in Glane, the Netherlands. He grew up in the beautiful region of Twente with his parents, older brother William, and older sister Juliette. After completing his secondary school at the Twentse Carmel College Lyceumstraat in Oldenzaal, he moved to Leiden in 2013 to begin medical school at Leiden University Medical Center (LUMC).

In 2018, Richard began his medical internships, during which his interest in orthopaedic surgery was sparked. Concurrently, he started his first research project at the orthopaedic department under the supervision of Prof. M.A.J. van de Sande. After completing his medical internships, he concluded it with an extended research internship on prognostic factors for osteosarcoma survival, and a clinical internship at the surgical department of Haga Hospital in The Hague, which led to a position as a medical doctor at the end of 2020.

In 2022, Richard started his PhD program at the LUMC. His research was conducted under the guidance of Prof. M.A.J. van de Sande, Prof. M. Fiocco, and Dr. M.P.A. Bus. During this time, Richard led several clinical studies on novel diagnostic and prognostic tools for bone tumors and played a key role in establishing the MUTARS Orthopaedic Registry Europe (MORE), which formed the basis for his studies on clinical outcomes in patients reconstructed with MUTARS endoprostheses.

Richard presented his work at several international musculoskeletal oncology conferences and supervised multiple (technical) medical students during their scientific internships. Within less than three years, he completed the majority of his PhD program. In October 2024, he joined the orthopaedic department of Alrijne Hospital as a resident-not-in-training. He has since been accepted into the orthopaedic surgery residency program, which he will begin in January 2026.