Published in final edited form as:

J Bone Joint Surg Am. 2020 October 07; 102(19): 1703–1713. doi:10.2106/JBJS.19.01056.

Surgical outcome and oncological survival of Osteofibrous dysplasia-like- and classic Adamantinomas: an international multicenter study of 318 cases

EM Schutgens[a,c], **P Picci**[b], **D Baumhoer**[c], **R Pollock**[d], **JVMG Bovee**[e], **PCW Hogendoorn**[e], **AJ Rueten-Budde**[f], **PC Jutte**[g], **F Traub**[h], **A Leithner**[i], **PU Tunn**[j], **P Funovics**[k], **G Sys**[l], **M Julian**[m], **GR Schaap**[n], **HR Dürr**[o], **J Hardes**[p], **J Healy**[q], **R Capanna**[r], **D Biau**[s], **A Gomez-Brouchet**[t], **J Wunder**[u], **T Cosker**[v], **M Laitinen**[w], **X Niu**[x], **V Kostiuk**[y], **Adamantinoma research group**[z], **MAJ van de Sande**[a]

[a]Orthopedic Surgery, Leiden University Medical Center, Leiden, The Netherlands

[b]Medical Oncology, Musculoskeletal Oncology Department, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy

[c]Bone Tumour Reference Centre, Institute of Pathology, University Hospital and University of Basel, Basel, Switzerland

[d]London Sarcoma Service, Royal National Orthopedic Hospital, Stanmore, United Kingdom

[e]Department of histopathology, Leiden University Medical Center, Leiden, The Netherlands

[f]Mathematical Institute, Leiden University, Leiden, the Netherlands

[g]Department of Orthopedics, University Medical Center, University of Groningen, Groningen, The Netherlands

[h]Orthopedic Surgery, University of Tubingen, Tubingen, Germany

[i]Department of Orthopedics and Trauma, Medical University of Graz, Graz, Austria

[j]Orthopedic Surgery, Helios-Clinics, Berlin, Germany

[k]Orthopedic Surgery, Medical University of Vienna, Vienna, Austria

[l]Orthopedic Surgery, Ghent University Hospital, Ghent, Belgium

[m]Orthopedic Surgery, University of Navara, Pamplona, Spain

[n]Orthopedic Surgery, Academic Medical Center, Amsterdam, The Netherlands

[o]Orthopedic Surgery, University Hospital München, München, Germany

[p]Musculoskeletal Oncology, Department of Orthopedic Surgery, Physical Medicine and Rehabilitation, University Hospital, LMU Munich, Germany

Contact Emile Schutgens, Muriel Sands Building 1st floor, Brockley Hill, Stanmore, Middlesex HA7 4LP, United Kingdom, Emile.Schutgens@nhs.net, Michiel van de Sande, Stafsecretariaat Orthopaedie, Postzone J11R, Postbus 9600, 2300 RC Leiden, Leiden University Medical Center Leiden, The Netherlands, MAJvandeSande@lumc.nl.

[q]Orthopedic Surgery, Memorial Sloan Kettering Cancer Center, New York, United States of America

[r]Orthopedic Surgery, Careggi University Hospital, Florence, Italy

[s]Orthopedic Surgery, Cochin Hospital, Paris, France

[t]Department of Histopathology, University medical Center, Toulouse, France

[u]University Musculoskeletal Oncology Unit, Mount Sinai Hospital, Toronto, Canada

[v]Orthopedic Surgery, Nuffield Orthopedic Center, Oxford, United Kingdom

[w]Orthopedic Surgery, Helsinki University Hospital, Helsinki, Finland

[x]Department of Orthopedic Oncology, Beijing Jishuitan Hospital, Beijing, China

[y]Orthopedic Surgery, National Cancer Institute Ukraine, Kiev, Ukraine

[z]Adamantinoma Research group

Abstract

BACKGROUND—Osteofibrous-dysplasia-like adamantinoma (OFD-AD) and classic adamantinoma (AD) are rare, neoplastic diseases with only limited data supporting current treatment protocols. A retrospective multicenter cohort study resulted in the largest analysis of adamantinoma patients to date. Primarily we describe the disease characteristics and evaluate the oncological outcomes. Secondly, we identify risk factors for local recurrence (LR) after surgical treatment and propose treatment guidelines.

METHODS—318 confirmed cases of OFD-AD and AD (primary treatment between 1985 and 2015) were submitted by 22 tertiary bone tumor centers. Proposed clinical risk factors for LR such as size, type, margins were identified using univariable and multivariable cox regression.

RESULTS—Of 318 cases, 128 were OFD-AD and 190 AD. 53% of patients were female. Mean age at diagnosis for OFD-AD was 17 years (median 14.5) and 32 years (median 28) for AD. Mean combined tumor size was 7.7cm measured histologically. 21% of patients suffered a pathological fracture prior to treatment. LR occurred in 22% of OFD-AD and 24% of AD cases. None of the recurrences in OFD-AD patients progressed to AD. Metastatic disease (MD) was found in 19% of AD cases and fatal disease in 9% of AD cases. No MD, nor fatal disease outcome was reported in OFD-AD. Multivariable Cox regression analysis demonstrated that uncontaminated resection margins (HR 0.164, CI 0.092–0.290, $p<0.001$), pathological fracture (HR 1.968, CI 1.076–3.600, $p=0.028$) and sex (female vs. male HR 0.535, CI 0.300–0.952, $p=0.033$) are associated with LR.

CONCLUSIONS—OFD-AD and AD are parts of a spectrum but should be regarded as different entities. Our results support reclassification of OFD-AD to the intermediate locally aggressive category, based on the LR-rate of 22% and absence of metastases. Metastatic disease (19%) is restricted to AD. In both cases we advocate wide resection with uncontaminated margins including bone and involved periosteum.

LEVEL IV study: Retrospective Cohort study.

INTRODUCTION

Osteofibrous dysplasia like-adamantinoma (OFD-AD) and classic adamantinoma (AD) are rare bone tumors that occur mostly in the anterior diaphysis of the tibia before the age of thirty. Combined they comprise around 0.2% to 0.4% of all primary bone tumors(1–4). Today they are recognized as distinct histopathological entities on a spectrum(5). The WHO definition of AD is: a malignant biphasic tumor characterized as clusters of epithelial cells, surrounded by a relatively bland spindle-cell osteofibrous component(4). Histologically OFD-AD differs from OFD by the inclusion of abundant isolated or small clusters of epithelial cells spread throughout the lesion while AD tumors have easily identifiable islands of epithelial tissue. AD is regarded as a malignant lesion with metastatic potential while OFD-AD is seen as a variant of AD with a less obvious epithelial component. There is an ongoing discussion as to whether OFD-AD should remain to be considered as a subtype of AD(6). Controversy exists as to the potential for OFD-AD to transform into AD(7). Proof of this potential would possibly result in different treatment strategies. Currently, it is important to clearly distinguish OFD-AD and AD based on histology as treatment and follow-up strategies may differ(7).

Adamantinomas are almost exclusively found in the anterior tibial cortex with occasional involvement of the ipsilateral fibula (figure 1). The origin of adamantinoma remains disputed, however, the most favored hypotheses are epithelial cell transfer during embryological development or direct trauma to the anterior cortex of the tibia where it is closest to the skin(8,9).

Current treatment strategies for OFD-AD include observation, curettage and resection(10). AD is usually treated according to oncological principles for a malignant tumor. Yet, despite wide surgery, the reported incidence for LR is reported between 20–30%(1,7). It is not clear which factors contribute to this high recurrence rate or if there are factors that predict the likelihood of LR.

This multicenter retrospective cohort study presents the following goals: 1) describe the treatment and outcome of the largest cohort of OFD-AD and AD cases with a minimum of 2 years follow-up. 2) determine which factors contribute to LR and the development of metastatic disease. 3) provide insights regarding the hypothesized progression of OFD-AD to AD based on the dataset.

MATERIALS AND METHODS

A multicenter retrospective database analysis was set up. Surgeons and histopathologists from orthopedic oncological centers around Europe, North America and Asia were asked to provide data on histologically proven cases of OFD-AD and AD. Centers were invited at European Musculoskeletal Oncological Society and International Society of Limb Salvage meetings. For each identified case information was entered into a database (table 1). All consecutive cases were included if histopathologically proven and treated between 1985 and 2015.

OFD-AD was defined as the presence of solitary epithelial cells staining positive on immunohistochemical analysis for keratin within osteofibrous stroma(11). AD was diagnosed when clusters of epithelial cells are present(12). The final diagnosis as established on the surgical resection specimen was used to provide the diagnosis for the database. The inclusion criteria of patient cases were based on an unequivocal histological diagnosis of OFD-AD or AD and 2 years of follow-up after first surgical treatment.

22 specialized centers provided a total of 322 cases for inclusion into the EMSOS+ Adamantinoma database.

Statistical analysis

To investigate the effect of risk factors on the occurrence of LR univariable and multivariate Cox regression analyses were performed.

Risk factors of interest were sex (female vs. male), tumor size (<=5cm vs. >5cm), pathological fracture (yes vs. no), age (<18 vs >=18), AD (yes vs no), perioperative spill (yes vs. no), uncontaminated resection margin (yes vs no), high volume center (yes vs no). High volume was arbitrarily defined as centers contributing 20 or more cases.

All risk factors were studied using univariable Cox regression analyses. Death was not considered a competing event since only 3 patients died without LR.

Based on clinical expertise and the findings of the univariable analyses a multivariate Cox regression analysis was conducted using as covariates sex, tumor size, pathological fracture, uncontaminated margins and AD (yes vs no).

Statistical analysis was carried out using SPSS version 22 and R version 3.5.1.

Ethical consideration

This study is conducted according to the Declaration of Helsinki (October 2013) and approved by the institutional review board of the Leiden University Medical Center (March 10th, 2016; G16.012).

SOURCES OF FUNDING

No sources of funding or roles in this project for sources of funding are reported.

RESULTS

In four cases the histopathological diagnosis remained doubtful; these were excluded from further analysis, leaving 318 cases for study. The overall study group demographics are presented in table 2. The majority of patients included were AD cases (59.7%). Mean age at diagnosis for OFD-AD was 17 (median 14.5, range 1–65) years compared to 32 (median 28, range 1–81) years for AD. Combined average tumor size was 7.7cm (median 7, range 0.5–22) as measured on macroscopy (7.0cm (median 6, range 0.6–22) in OFD-AD and 8.3cm (median 7, range 0.5–26) in AD). Local recurrence occurred in 28 (21.9%) cases for OFD-AD tumors and 46 (24.2%) for AD cases.

Data included in regression analysis

From the total of 318 cases, patients with missing LR information (n=60) were excluded leaving 258 patients for further statistical analyses. Biopsy diagnosis matched resection specimen diagnosis in all cases for this subset. Characteristics of this dataset are presented in table 3. In this subset 40% of patients were pediatric (below 18 years of age) at inclusion. 17% of patients experienced pathological fracture. Mean combined tumor size was 7.8cm. Histopathologically demonstrated tumor free resection margins were reported in 68% of cases and missing or inconclusive in 12%. Median follow-up was 83 months (95% CI: 75 to 103). Of the 258 patients considered for risk analysis, 18 patients died, of which 15 experienced LR, 73 patients developed a LR and 24 patients developed distant metastases mostly situated in the lungs (table 3).

Data on risk factors was partially incomplete for multiple variables (appendix 1). For the univariable Cox analysis all available information was used. For the multivariate Cox regression analysis, a subset of the data with complete information on all covariates was used (n=210).

Clinical presentation

Patients often presented to an orthopedic clinic with deformity, pain and a palpable lesion of the anterolateral tibia. A history of pain was present in the majority of cases (60% OFD-AD, 72% AD) often for more than one year (mean 16 months) and up to 18% presented with pathological fracture. A history of trauma to the site of tumor was reported only in up to a third of cases (33% OFD-AD, 25% AD).

Tumor location

In the entire dataset of 318 cases 99% of OFD-AD tumors were localized either in the tibia, fibula or both osseous sites. One case was located in the ulna. For AD 97.7% cases were found in the tibia, fibula or both locations simultaneously. There were 3 cases in the femur, 2 cases in the humerus and one case in the foot. No cases were reported for disease localized to the spine. Most tumors in the tibia were localized to the anterolateral diaphysis. Very few cases were found in the metaphysis and even fewer in the epiphysis (figure 2).

Local recurrence

Results of the univariable analysis are available in the online supplement (table 4). Multivariate Cox regression analyses presented in table 5, demonstrated significant hazard ratios ($p<0.05$) for uncontaminated resection margins (0.164, CI 0.092–0.290).

The unadjusted cumulative incidence for LR did significantly differ between AD and OFD-AD, figure 3. At every time point the unadjusted cumulative incidence for LR was higher if a pathological fracture was reported, figure 4A. LR was also more likely if resection margins were contaminated (figure 4B). Similarly, when peri-operative spill was reported the cumulative incidence for LR was much higher, (figure 4C). The unadjusted cumulative incidence for LR is also higher for male patients at all ages, figure 4D. The unadjusted cumulative incidence for LR in patients under the age of 18 did not significantly differ,

neither was a difference seen in centers where more or less than 20 patients were treated, appendices 2 & 3.

Metastatic potential

Metastatic disease was restricted to AD patients. In total there were 24 patients with metastatic disease (majority presenting to the lungs), representing 9.3% of the analyzed subset data subset and 17.3% of all AD cases (table 3). There was no metastatic disease in OFD-AD. Only 4 out of 24 cases of metastasis were present in patients that had no prior LR. The time to diagnosis of metastatic disease is demonstrated in figure 5. DM was predominantly seen in adult patients (mean age 39 years, median 33 years, range 20–68), with only 2 patients under the age of 18, (9 and 12).

Fatal disease

Disease progression to fatal patient outcome was recorded in 18 patients representing 7.0% of the analyzed data subset and 12.9% of AD patients. Fatal patient outcome was recorded in 16 out of 24 metastatic patients, 8 patients were alive with metastases at the time of submission of the dataset. All deaths were reported in patients with metastatic AD.

Progression of OFD-AD to AD

1 patient was identified that showed progression of an untreated OFD-AD to AD. This case was initially diagnosed as OFD in 1987 and was followed-up using plain film radiographs for several years after which the patients was lost to FU. In 2016 the patient revisited the clinic with a painful new swelling in the tibia that was diagnosed as AD in a larger area of OFD-AD (Figure 6). Further imaging and histology are presented in the appendix 4. Hatori et al. present a very similar case with a patient treated at young age for OFD-AD who presented more than a decade later with painful progression in the same area, diagnosed as AD after resection(13).

DISCUSSION

The results of this study offer interesting insights into the treatment outcome of patients with OFD-AD and AD. The greatest strength of this dataset is that it represents the largest collection of adamantinoma in the scientific literature, with a median follow-up was 83 months (95% CI: 75 to 103) including a subgroup (n = 87) of patients with long term follow-up (>10 years).

Several other series have been published in literature (table 7 in online supplement). The majority of these series focus on AD. They report rates of metastatic disease of 0–43% and rates of fatal disease 0–33%. Before 1989 no distinction was made in the literature between OFD-AD and AD. In all the combined published series only 36 cases of OFD-AD are reported on. We strongly surpass this in this study.

The WHO classification distinguishes OFD, OFD-AD and AD. It is now well established that AD is malignant, which is supported by the data from our series. The malignant potential of OFD-AD is not completely understood in literature, as it does not metastasize

but behaves locally aggressive(14). Results from this study clearly confirm the locally aggressive, non-metastatic behavior of OFD-AD in more than 150 cases. Within this dataset only one OFD-AD case was left untreated for a longer period of time and showed progression to AD after 29 years (appendix 4).

Reduction in local recurrence

The combined observed local recurrence for OFD-AD and AD is 28%. We have demonstrated that the risk for LR is multifactorial. These risks can be divided into modifiable and non-modifiable. The latter include patient sex, tumor size, and disease type. We have identified several modifiable factors, which we suspect may reduce the risk of LR after surgery. These include preventing pathologic fracture after diagnosis and achieving free margins after resection. Patients in this study were not treated with adjuvant chemotherapy or radiotherapy as there is currently little evidence to support this(29).

28 cases that had uncontaminated margins (histologically reported) at resection experienced LR (OFD-AD 9, AD 19). We presume that a proportion of these recurrences is due to undetected skip lesions as well as the possible presence of disease in the periosteum. This would underline the importance of an uncontaminated resection of the involved bone including the periosteum at the time of surgery.

Study limitations

We recognize that the quality of the histopathological reports determines the quality of our data. Some reports are several decades old. To remedy this, we would have to carry out a central histopathological review of the original specimen blocks by a single center. For this study only a re-review was possible on a sample of data provided by 4 centers totaling 136 cases (70 OFD-AD). No changes were reported in the submitted data. Review of all was logistically not possible. Excluding cases that were not re-confirmed would significantly reduce the numbers available to study.

This study has been of exploratory nature. We conducted multiple univariable analysis to investigate risk factors before deciding on a multivariable model. In this approach multiple comparisons are made, and the final multivariable model may be subject to overfitting and must be interpreted with caution. Results may not be translatable to other centers, they can however motivate future research.

Another limitation of our study is the long time period in which the data was collected. There may be differences in outcomes for patients treated at different times which we did not account for.

Treatment guidelines

AD is a malignant entity that requires wide surgical resection including the periosteum (involved in 38.8% of cases in our series), after complete preoperative analyses including radiograph, MRI of the involved bone, representative biopsy and CT chest in AD cases. Follow-up should be long-term with at least chest radiographs (lungs are the most likely site for metastasis) and local surgical site radiographs or MRI as this there were 6 out of 28

(27%) recurrent AD patients that were diagnosed with LR after more than 10 years of follow in this series.

In OFD-AD cases, we advocate that if surgical treatment is undertaken that it be personalized to the patient's requirements. We suggest marginal but R0 resection to reduce the risk of local recurrence. As OFD-AD should be regarded a locally aggressive but benign disease, the timing of surgical resection could be tailored around the preference of the patients (and parents) and should take into account the growth potential of the involved bone, but also the risk for fracture, bone deformity and pain. In patients where even a marginal excision might cause significant functional deficits, especially in the growing skeleton, one may postpone surgery, as the metastatic potential is extremely small and progression to AD is an exceedingly rare event. Close follow-up may be an option before surgery. Surgical resection should also anticipate the growth of small and possibly undiagnosed skip lesions. Some centers have published results of intralesional resection which have demonstrated a significantly higher risk of local recurrence and thus of re-operation (1,7,17,18). In very young patients one should consider planning the resection after the age of 6–8 years and apply careful observation with consideration of protective weightbearing if appropriate.

Reclassification of OFD-AD

In the current WHO classification OFD-AD is considered a subtype of AD, and both are considered malignant. Our data would support that OFD-AD should be considered locally aggressive instead of having full malignant potential. Evidence for this includes no reported cases in the literature, nor in our series, of metastatic disease in OFD-AD and a very low incidence of progression of OFD-AD to AD. We report on one case where this has occurred, while Hatori et al(13) have described another. In addition, OFD-AD presents at an earlier age as compared to AD and therefore also our demographic data would support that OFD-AD and AD should be considered two separate entities within a single spectrum.

Conclusion

Our AD series from 22 different bone tumor referral centers support that AD has full malignant potential. Our exploratory study suggests that AD could benefit from aggressive surgical treatment. This should involve uncontaminated resection, where possible at the earliest possible convenience. For OFD-AD our series confirm locally aggressive behavior, without metastatic potential. We therefore advocate an uncontaminated resection, but the timing can be amended to optimal functional reconstruction. Waiting for further skeletal maturity may be an option in some cases especially in metaphyseal locations and be indicated to facilitate surgical reconstruction in very young patients. As OFD-AD should be considered locally aggressive, of low metastatic potential, the benefits of increased bone stock should be weighed against the risk of progression in size, pathological fractures and decreased remodeling capacity after allograft / autograft reconstruction. For both entities we highlight the importance of long-term follow-up as tumors of this type have recurred up to 20 years after primary treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations

AD	Classic adamantinoma
OFD-AD	Osteofibrous dysplasia like adamantinoma
LR	Local recurrence
95% CI	95% Confidence Interval
CI	Cumulative incidence

References

1. Keeney GL, Unni KK, Beabout JW, Pritchard DJ. Adamantinoma of long bones. A clinicopathologic study of 85 cases. Cancer. 1989 8;64(3):730–7. [PubMed: 2743266]
2. Huvos AG. Bone tumors: Diagnosis, treatment and prognosis. Second edition. 1987.
3. Moon NF, Mori H. Adamantinoma of the appendicular skeleton--updated. Clin Orthop Relat Res [Internet]. 1986 3 [cited 2019 Mar 12];(204):215–37. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3514033
4. Fletcher CDM, Organization WH. WHO Classification of Tumours of Soft Tissue and Bone [Internet]. IARC Press; 2013. (IARC WHO Classification of Tumours Series). Available from: https://books.google.co.uk/books?id=G0fdMgEACAAJ
5. Kahn LB. Adamantinoma, osteofibrous dysplasia and differentiated adamantinoma. Skeletal Radiol [Internet]. 2003 5 [cited 2017 Nov 9];32(5):245–58. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12679847
6. Most MJ, Sim FH, Inwards CY. Osteofibrous dysplasia and adamantinoma. J Am Acad Orthop Surg. 2010 6;18(6):358–66. [PubMed: 20511441]
7. Scholfield DW, Sadozai Z, Ghali C, Sumathi V, Douis H, Gaston L, et al. Does osteofibrous dysplasia progress to adamantinoma and how should they be treated? Bone Joint J [Internet]. 2017 3 1 [cited 2017 Nov 9];99-B(3):409–16. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28249983
8. Jain D, Jain VK, Vasishta RK, Ranjan P, Kumar Y. Adamantinoma: a clinicopathological review and update. Diagn Pathol [Internet]. 2008 2 15 [cited 2018 Feb 22];3(1):8.
9. Hazelbag HM, Fleuren GJ, vd Broek LJ, Taminiau AH, Hogendoorn PC. Adamantinoma of the long bones: keratin subclass immunoreactivity pattern with reference to its histogenesis. Am J Surg Pathol. 1993 12;17(12):1225–33. [PubMed: 7694513]
10. Qureshi AA, Shott S, Mallin BA, Gitelis S. Current trends in the management of adamantinoma of long bones. An international study. J Bone Joint Surg Am [Internet]. 2000 8 [cited 2018 Oct 19];82-A(8):1122–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10954102
11. Vigorita V, Hogendoorn P, Sawyer J. Osteofibrous dysplasia. In: Fletcher C, Bridge J, Hogendoorn P, Mertens F, editors. WHO Classification of Tumours of Soft Tissue and Bone. 4th ed. Lyon: IARC Press; 2013. p. 354–5.
12. Hogendoorn P, Kanamori M. Adamantinoma. In: Fletcher C, Bridge J, Hogendoorn P, Mertens F, editors. WHO Classification of Tumours of Soft Tissue and Bone. 4th ed. Lyon: IARC Press; 2013. p. 343–5.
13. Hatori M, Watanabe M, Hosaka M, Sasano H, Narita M, Kokubun S. A classic adamantinoma arising from osteofibrous dysplasia-like adamantinoma in the lower leg: a case report and review of the literature. Tohoku J Exp Med. 2006 5;209(1):53–9. [PubMed: 16636523]

14. Hazelbag HM, Taminiau AH, Fleuren GJ, Hogendoorn PC. Adamantinoma of the long bones. A clinicopathological study of thirty-two patients with emphasis on histological subtype, precursor lesion, and biological behavior. J bone Jt surgeryAmerican Vol. 1994 10;76(10):1482–99.
15. Zumárraga JP, Cartolano R, Kohara MT, Baptista AM, Dos Santos FG, de Camargo OP. TIBIAL ADAMANTINOMA: ANALYSIS OF SEVEN CONSECUTIVE CASES IN A SINGLE INSTITUTION. Acta Ortop Bras [Internet]. 2018 8 [cited 2019 Mar 26];26(4):252–4. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1413-78522018000400252&lng=en&tlng=en
16. Houdek MT, Sherman CE, Inwards CY, Wenger DE, Rose PS, Sim FH. Adamantinoma of bone: Long-term follow-up of 46 consecutive patients. J Surg Oncol [Internet]. 2018 12 [cited 2019 Mar 26];118(7):1150–4.
17. Puchner SE, Varga R, Hobusch GM, Kasparek M, Panotopoulos J, Lang S, et al. Long-term outcome following treatment of Adamantinoma and Osteofibrous dysplasia of long bones. Orthop Traumatol Surg Res [Internet]. 2016 11 [cited 2018 Dec 13];102(7):925–32. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27745864
18. Szendroi M, Antal I, Arato G. Adamantinoma of long bones: a long-term follow-up study of 11 cases. Pathol Oncol Res. 2009 6;15(2):209–16. [PubMed: 19048403]
19. Gleason BC, Liegl-Atzwanger B, Kozakewich HP, Connolly S, Gebhardt MC, Fletcher JA, et al. Osteofibrous dysplasia and adamantinoma in children and adolescents: a clinicopathologic reappraisal. Am J Surg Pathol. 2008 3;32(3):363–76. [PubMed: 18300815]
20. Desai SS, Jambhekar N, Agarwal M, Puri A, Merchant N. Adamantinoma of tibia: a study of 12 cases. J Surg Oncol [Internet]. 2006 4 1 [cited 2019 Mar 26];93(5):429–33.
21. Van Rijn R, Bras J, Schaap G, van den Berg H, Maas M. Adamantinoma in childhood: report of six cases and review of the literature. Pediatr Radiol [Internet]. 2006 10 12 [cited 2019 Mar 26];36(10):1068–74.
22. Kuruvilla G, Steiner GC. Osteofibrous dysplasia-like adamantinoma of bone: a report of five cases with immunohistochemical and ultrastructural studies. Hum Pathol [Internet]. 1998 8 [cited 2019 Mar 26];29(8):809–14. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9712421
23. Jundt G, Remberger K, Roessner A, Schulz A, Bohndorf K. Adamantinoma of long bones. A histopathological and immunohistochemical study of 23 cases. Pathol Res Pract [Internet]. 1995 3 [cited 2019 Mar 26];191(2):112–20. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0344033811805601
24. Czerniak B, Rojas-Corona RR, Dorfman HD. Morphologic diversity of long bone adamantinoma. The concept of differentiated (regressing) adamantinoma and its relationship to osteofibrous dysplasia. Cancer [Internet]. 1989 12 1 [cited 2019 Mar 12];64(11):2319–34. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2804923
25. Campanacci M, Giunti A, Bertoni F, Laus M, Gitelis S. Adamantinoma of the long bones. The experience at the Istituto Ortopedico Rizzoli. Am J Surg Pathol [Internet]. 1981 9 [cited 2019 Mar 23];5(6):533–42. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7325273
26. Weiss SW, Dorfman HD. Adamantinoma of long bone. An analysis of nine new cases with emphasis on metastasizing lesions and fibrous dysplasia-like changes. Hum Pathol [Internet]. 1977 3 [cited 2019 Mar 26];8(2):141–53. Available from: http://www.ncbi.nlm.nih.gov/pubmed/852865
27. Huvos AG, Marcove RC. Adamantinoma of long bones. A clinicopathological study of fourteen cases with vascular origin suggested. J Bone Joint Surg Am [Internet]. 1975 3 [cited 2019 Mar 26];57(2):148–54. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1112840
28. BAKER PL, DOCKERTY MB, COVENTRY MB. Adamantinoma (so-called) of the long bones; review of the literature and report of three new cases. J Bone Joint Surg Am [Internet]. 1954 7 [cited 2019 Mar 23];36-A(4):704–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/13174600
29. Lokich J Metastatic adamantinoma of bone to lung. A case report of the natural history and the use of chemotherapy and radiation therapy. Am J Clin Oncol [Internet]. 1994 4 [cited 2019 May 2];17(2):157–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7511328

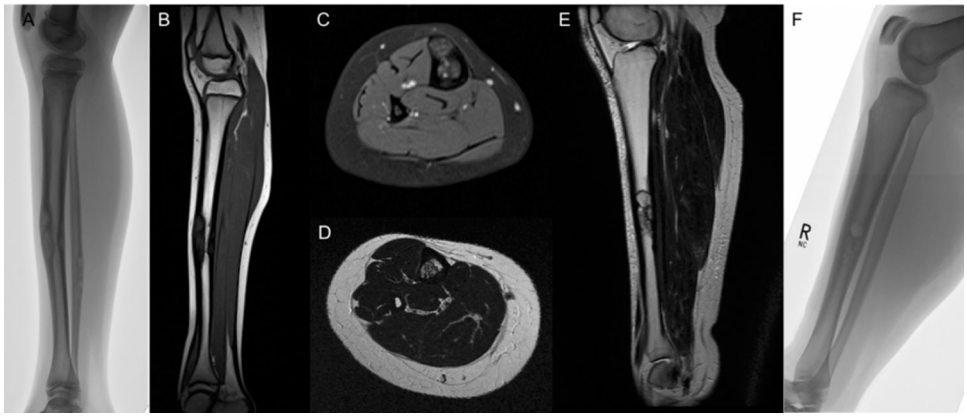

Figure 1.

Osteofibrous dysplasia like-adamantinoma in a 9-year-old female. Lateral X-Ray (A), Sagittal T2 MRI (B) and axial T1 MRI (C). Classic adamantinoma in a 42-year-old female. Axial and sagittal T2 MRI (D,E) and lateral X-Ray (F).

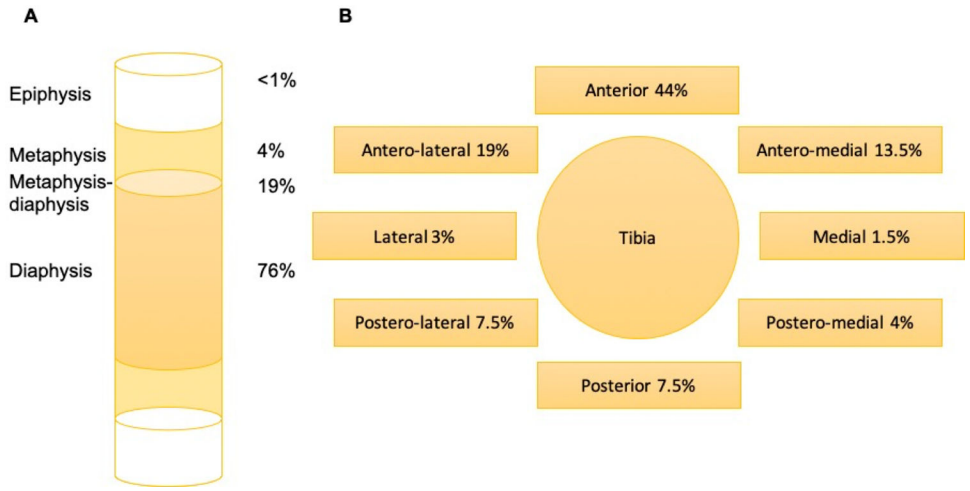

Figure 2.

Proportions of OFD-AD and AD cases within the tibia only for both sides combined (A). Proportions of tumors and their origins reported from axials CT and MRI images (B).

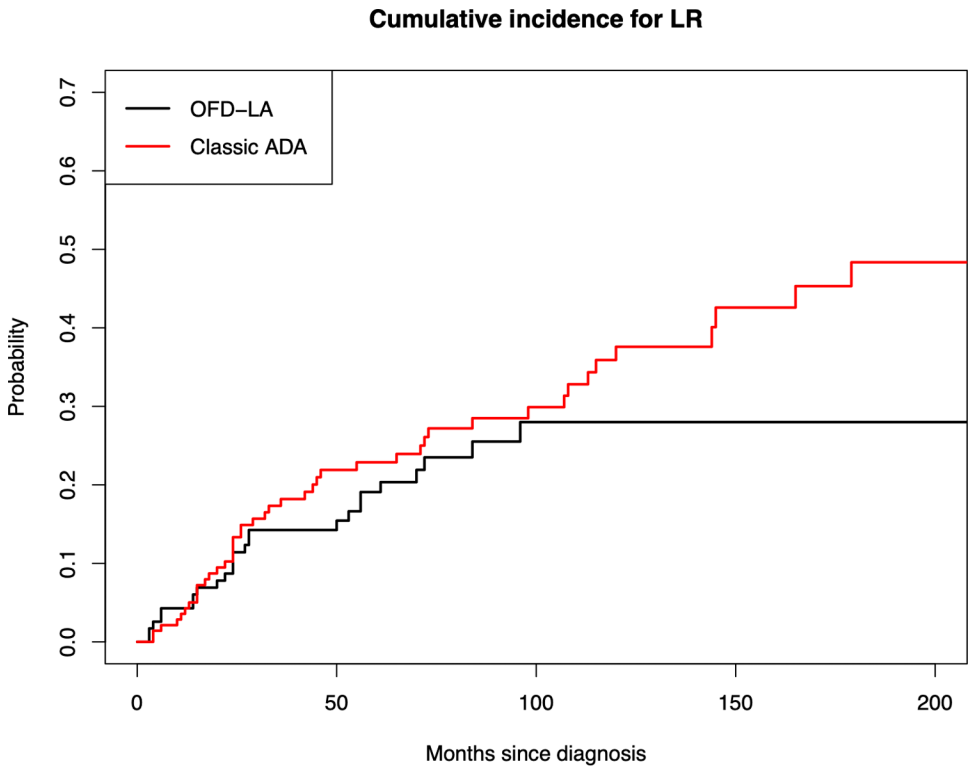

Figure 3.
Unadjusted cumulative incidence for LR in the months following treatment OFD-AD vs AD.

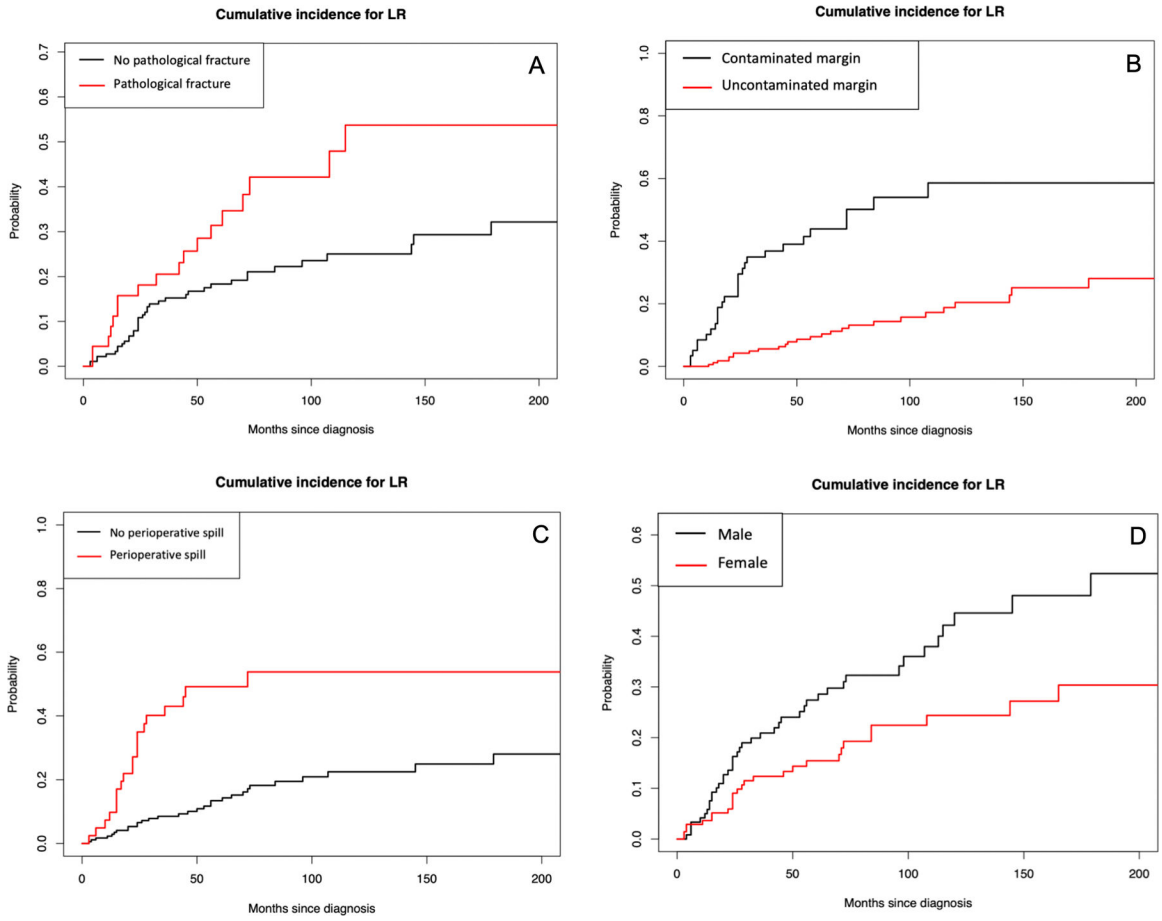

Figure 4.

Unadjusted cumulative incidence plots for OFD-AD and AD combined: history of pathological fracture vs no history of pathological fracture (A), contaminated vs uncontaminated surgical margins from histopathology report (B), no perioperative spill vs perioperative spill (C) and Female vs male patient sex (D).

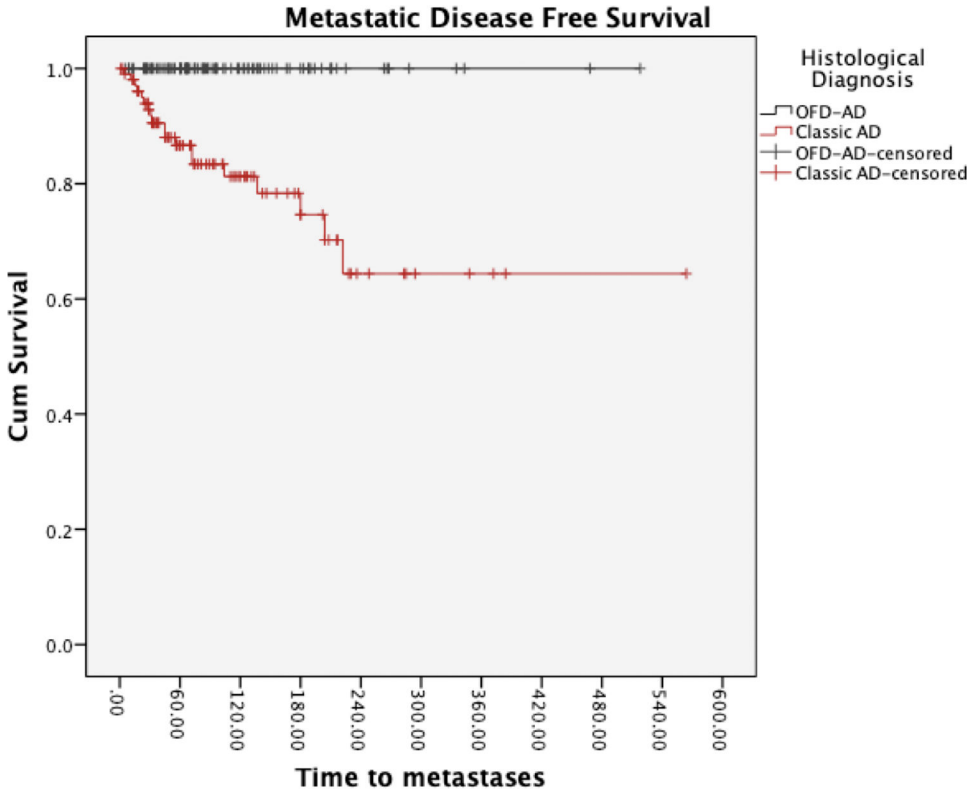

Figure 5.

Kaplan Meier plot showing time (months) to detection of metastasis stratified per OFD-AD and AD.

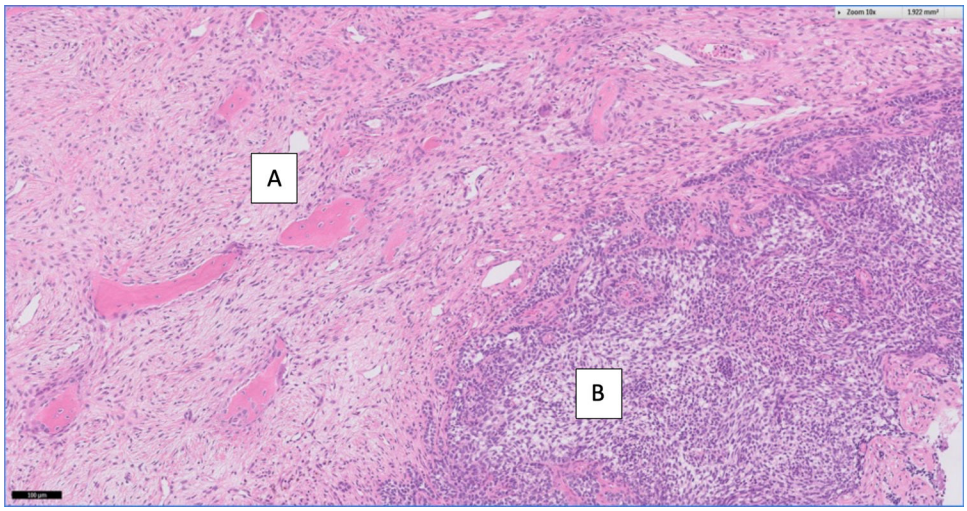

Figure 6.

Hematoxylin and eosin stain slide of the resection specimen removed in 2016. Area of OFD-AD (A) surrounding and area of AD (B). Black bar left lower corner represents 100μm.

Table 1

Patient characteristics collected.

Patient characteristics: Sex (m/f) Relevant medical history (any) Date of diagnosis (dd/mm/yyyy) Age at diagnosis (months) Trauma history (y/n) History of pain (y/n) Duration of pain (months) Pathological fracture (y/n) History of biopsy (y/n)	**Macroscopic characteristics:** Left/right Location of lesion (i.e. tibia) Region within bone (i.e. diaphysis) Location within region (i.e. proximal) Location on the clock (i.e. 12 o'clock on axial image) Number of lesions Size of lesion (widest diameter in cm) Lesion type (singular, multiple) Periosteal involvement (none, partial, complete) Soft tissue expansion (y/n)
Radiological characteristics: Imaging modality used for reporting radiological characteristics (XR, CT, MRI) Gadolinium enhanced scanning (y/n) Positive on Gadolinium enhanced scanning (y/n) Size of lesion (widest diameter in cm) Number of lesions Medulla involvement (none, partial, complete) Extra-cortical expansion (y/n) Periosteal involvement (y/n) Soft tissue expansion (y/n)	**Microscopic characteristics:** Histological diagnosis (OFD-AD, AD) Keratin positive cell arrangement (i.e. clusters) Uncontaminated resection margins (y/n) Extra-cortical expansion (y/n) Periosteal involvement (y/n) Soft tissue expansion (y/n)
Treatment characteristics: Planned treatment type (intralesional, narrow, wide resection) Reconstructive treatment (i.e. allograft) Per-operative exposure of lesion (y/n) Free resection margins at surgery (y/n) Periosteal resection (none, partial, complete) Biopsy tract resection (y/n)	**Outcome characteristics:** Local Recurrence (y/n) Recurrence histologically confirmed (y/n) Time to recurrence (months) Metastatic disease Location & amount of metastases Time to metastasis (months) Fatal disease Time to fatal disease (months)

Table 2

Patients demographics for all cases submitted to the EMSOS+ Adamantinoma database with a known diagnosis.

Diagnosis	Total/Combined	OFD-AD	Classic AD
n	318 (100%)	128 **(40.3%)**	190 **(59.7%)**
Patient demographics			
Mean age (yrs)	26 (SD 17.8)	17 (SD 11.6)	32 (SD 18.8)
Sex: male/female	47%/53%	39%/61%	53%/47%
Tumour characteristics			
Lesion size (mean, cm)	7.7 (SD 4.9)	7.0 (SD 4.5)	8.3 (SD 5.2)
Lesions (single vs multiple)	24% multiple	25% multiple	23% multiple
Radiology			
Tibia location	305 **(95.9%)**	125 **(97.7%)**	180 **(94.7%)**
Diaphyseal location	230 **(72.3%)**	101 **(78.9%)**	129 **(67.9%)**
Microscopic periosteal involvement	168 **(52.8%)**	44 **(34.4%)**	105 **(55.3%)**
Reported pathological fracture	51 **(16.0%)**	23 **(18.0%)**	28 **(14.7%)**
Outcome			
n recurrence	74 **(23.3%)**	28 **(21.9%)**	46 **(24.2%)**
n metastatic disease **(entire dataset)**	35 **(11.0%)**	0	35 **(18.4%)**
n fatal disease	18 **(5.7%)**	0	18 **(9.5%)**

Table 3

Demographics of patient cases included in the multivariable analysis (258 cases).

Diagnosis	Total/Combined	OFD-AD	Classic AD
n	258 (100%)	119 **(46.1%)**	139 **(53.9%)**
Patient demographics			
Mean age (yrs)	25 (SD 17)	16.5 (SD 11.1)	32 (SD 18.0)
Sex: male/female	47%/53%	51%/49%	39%/61%
Tumour Characteristics			
Lesion size (mean, cm)	7.8 (SD 4.5)	6.3 (SD 4.0)	8.3 (SD 5.0)
Pathological fracture			
No	172 **(66.7%)**	87 **(73.1%)**	85 **(61.1%)**
Yes	44 **(17.1%)**	26 **(21.8%)**	18 **(12.9%)**
Missing	42 **(16.3%)**		
Uncontaminated margins at index treatment (R0)			
No	46 **(17.8%)**	29 **(24.4%)**	17 **(12.2%)**
Yes	176 **(68.2%)**	79 **(66.4%)**	97 **(69.8%)**
Inconclusive/missing	36 **(14.0%)**		
Primary surgical treatment type/intention			
Amputation (R0)	12 **(5.8%)**	0 **(0.0%)**	12 **(8.6%)**
Intralesional resection (R2)(intentional) inc curettage	43 **(16.7%)**	27 **(22.7%)**	16 **(11.5%)**
Marginal surgical resection (R0)	58 **(22.5%)**	37 **(31.1%)**	21 **(15.1%)**
Wide surgical margins (R0)	145 **(56.2%)**	74 **(62.2%)**	71 **(51.1%)**
Oncological outcome			
Local recurrence	73 **(28.3%)**	29 **(24.4%)**	44 **(31.7%)**
Metastasis	24 **(9.3%)**	0 **(0.0%)**	24 **(17.3%)**
Fatal disease	18 **(7.0%)**	0 **(0.0%)**	18 **(12.9%)**

Table 4

Univariate analysis of multiple factors.

Variable	Available numbers for analysis	HR	0.95 CI	P value
Sex: female	258	0.568	0.356–0.907	0.018*
Size > 5cm	225	0.989	0.572–1.708	0.968
Pathological fracture	228	1.947	1.129–3.359	0.017*
Uncontaminated resection margins (R0)	233	0.205	0.121–0.347	<0.001*
Under 18 years of age	258	1.428	0.9–2.263	0.130
Classic adamantinoma	258	1.254	0.781–2.012	0.349
Intralesional resection (R2)$^{\Sigma}$	216	4.179	2.381–7.333	<0.001*
High volume centre$^{\Omega}$	258	1.413	0.885–2.256	0.148
Operative resection margin narrow (R0)$^{\Psi}$	184	0.399	0.212–0.751	0.004*
Operative resection margin wide (R0)^{Z}	184	0.147	0.079–0.272	<0.001*

$^{\Sigma}$Intralesional is defined as surgery where en-bloc resection was not attempted. This includes curettage and surgeries where macroscopic tumour was left (R2).

$^{\Omega}$Centres that have submitted more than 20 (arbitrary) cases.

$^{\Psi}$Where the histopathological margins were described as R0 but narrow (arbitrary)

^{Z}Where the histopathological margins were described as R0 but wide (arbitrary)

Table 5

Multivariable Cox regression model outcomes for LR.

Variable	HR	0.95 CI	P value
Sex: female	0.535	0.3 −0.952	0.033*
Size >5cm	1.384	0.734–2.608	0.315
Pathological fracture	1.968	1.076–3.6	0.028*
Uncontaminated margins (R0)	0.164	0.092–0.29	<0.001*
Classic adamantinoma	1.549	0.849–2.828	0.154

Table 6

Multivariate Cox regression analysis stratified for histological subtype.

	OFD-AD			Classic AD		
Variable	**HR**	**0.95 CI**	**P value**	**HR**	**0.95 CI**	**P Value**
Sex: female	0.422	0.172–1.037	0.060	0.617	0.275–1.386	0.242
Size >5cm	1.731	0.701–4.27	0.234	0.897	0.371–2.169	0.810
Pathological fracture	1.328	0.495–3.566	0.574	2.927	1.283–6.679	0.011*
Contaminated margins	6.579	2.681–16.129	<0.001*	6.410	2.985–13.698	<0.001*

Table 7.

published datasets of adamantinomas of the long bones.

Author	Year	Histological diagnosis (*n*)	Mean age (years)	Mean tumor size (cm)	Mean follow-up (months)	Local Recurrence % (*n*)	Metastatic Disease % (*n*)	Fatal Disease % (*n*)	Remarks	Reference
Zumarraga et al (Sao Paulo, Brazil)	2018	7 classic AD	28.5 (17–49)	9.16 (4.1–12.8)	180 (36–324)	0%	Classic AD 28.6% (2)	Classic AD 0% (0)		(15)
Houdek et al (Rochester, USA)	2018	46 classic AD	24 (7–79)	7 (1–17)	192 (36–504)	7.5–15%	Classic AD 26.1% (12)	Classic AD 21.7% (10)		(16)
Scholfield et al (Birmingham, United Kingdom)	2017	21 classic AD 10 OFD-AD	Classic AD 38 (14–86) OFD-AD 13.4 (6–28)	Not reported	Classic AD 139 (4–396) OFD-AD 118 (36–315)	Classic AD 28.5% (6) OFD-AD 30% (3)	Classic AD 42.8% (9)	Classic AD 33.3% (7)	Classic AD included 4 cases of Ewing's like Adamantinoma.	(7)
Puchner et al (Vienna, Austria)	2016	10 classic AD 1 OFD-AD	Classic AD 28 (5–62) OFD-AD 26	Not reported	Classic AD 232 (48–564) OFD-AD 60	Classic AD 40% (4) OFD-AD 0% (0)	Classic AD 20% (2)	Classic AD 10% (1)		(17)
Szendroi et al (Budapest, Hungary)	2009	11 Classic AD	Classic AD 29 (4–80)	14.3 (2–16)	Classic AD 152 (36–480)	Classic AD 36% (4)	Classic AD 18% (2)	Classic AD 9% (1)		(18)
Gleason et al (Boston, USA)	2008	3 Classic AD 5 OFD-AD	Classic AD 16.3 (13–18) OFD-AD 13.6 (9–17)	Not Reported	Classic AD 156 (108–216) OFD-AD 94 (30–144)	Classic AD 0% (0) OFD-AD 0% (0)	Classic AD 33.3% (1)	Classic AD 33.3% (1)		(19)
Desai et al (Mumbai, India)	2006	12 Classic AD	Classic AD 30 (18–65)	5 (maximum 11)		Classic AD 25% (3)	Classic AD 8.3% (1)	Classic AD 0% (0)	1 patient lost to follow-up after diagnosis	(20)
Van Rijn et al (Amsterdam, The Netherlands)	2006	6 Classic AD	Classic AD 7.7 (3–14)	Not Reported	Classic AD 72 (19–144)	Classic AD 0% (0)	Classic AD 0% (0)	Classic AD 0% (0)	Only reported on children. Included in this paper	(21)
Qureshi et al (USA, Canada, Italy)	2000	70 Classic AD	Classic AD 31 (7–86)	Not Reported	Classic AD 84 (14–188)	Classic AD 18.6% at 10 years	Classic AD 10% (7)	Classic AD 12.8% at 10 years	23 contributing centers	(11)
Kuruvilla et al (New York, USA)	1998	5 OFD-AD	OFD-AD 8.3 (4.5–14)	Not Reported	OFD-AD 42–180	OFD-AD 60% (3)	OFD-AD 0% (0)	OFD-AD 0% (0)	No evidence of progression to classic AD, all cases treated y curettage	(22)

J Bone Joint Surg Am. Author manuscript; available in PMC 2021 November 05.

Author	Year	Histological diagnosis (*n*)	Mean age (years)	Mean tumor size (cm)	Mean follow-up (months)	Local Recurrence % (*n*)	Metastatic Disease % (*n*)	Fatal Disease % (*n*)	Remarks	Reference
Jundt et al (Swtizerland, Germany)	1995	23 Classic AD	Classic AD 25.4 (5–67)	Not Reported	Classic AD 72 (6–156) (19/23 cases)	Classic AD 21.7% (5)	Classic AD 13% (3)	Classic AD 13% (3)		(23)
Hazelbag et al (Leiden, The Netherlands)	1994	25 classic AD 7 OFD-AD	Classic AD 28.7 (4–70) OFD-AD 22 (5–64)	Not Reported	122 (11–350)	Classic AD 24% (6) OFD-AD 42.8% (3)	Classic AD 32% (8)	Classic AD 28% (7)	OFD-Ad seen as a subtype of classic AD. Included in this paper	(13)
Czerniak et al (New York, USA)	1989	17 Classic AD 8 OFD-AD	Classic AD 40 (15–65) OFD-AD 11 (3–17)	1–12 (combined)	Not Reported	Not Reported	Not Reported	Not Reported		(24)
Keeney et al (Rochester, USA)	1989	85 adamantinomas	25.9 (3–72)	Not Reported	108 (1–564)	31% (26)	15% (13)	13% (11)	Not clear if distinction was made between Classic AD and OFD-AD	(1)
Moon and Mori (Japan, USA)	1986	195 adamantinoma	32.9 (4–74)	Not Reported	Not Reported	Not Reported	Not Reported	18% (36)	Meta-analysis, 180 cases from literature. Not clear if distinction was made between Classic AD and OFD-AD	(3)
Campanacci et al. (bologna, Italy)	1981	9 adamantinomas	26.6 (8–57)	Not Reported	76 (12–264)	44% (4)	0% (0)	0% (0)	Not clear if distinction was made between Classic AD and OFD-AD	(25)
Weiss et al (Baltimore, USA)	1977	9 adamantinomas	38 (15–65)	Not Reported	(0–120)	11% (1)	22% (2)	11% (1)	Not clear if distinction was made between Classic AD and OFD-AD	(26)
Huvos et al (New York, USA)	1975	14 adamantinomas	40 (13–67)	Not Reported	144 (0–408)	71% (10)	14% (2)	14% (2)	10/14 patients treated with curettage initially. Not clear if distinction was made between Classic AD and OFD-AD	(27)

Author	Year	Histological diagnosis (*n*)	Mean age (years)	Mean tumor size (cm)	Mean follow-up (months)	Local Recurrence % (*n*)	Metastatic Disease % (*n*)	Fatal Disease % (*n*)	Remarks	Reference
Baker et al (Rochester, USA)	1954	27 adamantinomas	31 (12–57)	Not Reported	134 (12–276) For only 8 cases	55.6% (15)	29.6% (8)	22.2% (6)	24 cases from literature. Not clear if distinction was made between Classic AD and OFD-AD	(28)
Total										
Classic AD		251	7.7–38			0–40%	0–42.8%	0–33.3%		
OFD-AD		36	8.3–26			0–60%	0%	0%		
Adamantinomas*		339	25.9–40			11–71%	0–29.6%	0–22.2%		

J Bone Joint Surg Am. Author manuscript; available in PMC 2021 November 05.