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Prognostic factors of recurrence after an intralesional excision of benign bone tumour in the peripheral skeleton

Napovedni dejavniki za recidiv po intralezijski izpraznitvi benignega kostnega tumorja perifernega skeleta

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Abstract

Background: Most aggressive benign bone tumours are treated surgically by an intralesional excision and bone defect filling. The primary aim of our study was to evaluate prognostic factors of recurrence after an intralesional excision of a benign bone tumour in the peripheral skeleton. We asked whether patient age and gender, maximal tumour diameter, histological diagnosis, and the tumour's location statistically significantly impact postoperative tumour recurrences. The secondary aim was to evaluate preoperative differences between different histopathological groups of benign bone tumours and the impact of age and gender, maximal tumour diameter, histological diagnosis, and the tumour location on the number of diagnostic biopsies and curative surgical procedures.

Methods: Retrospective analysis of prospectively collected data included a cohort of patients operated on at a single tertiary tumour centre between 2010 and 2020 with at least one-year follow-up. Ordinal logistic regression was used to assess the influence of input variables on the number of diagnostic/curative surgical procedures and postoperative recurrences.

Results: The cohort analysis included 261 patients with 61 local recurrences. The risk of tumour recurrence was significantly lower with higher patient age ($p = 0.001$) and tumour location in the distal femur ($p = 0.033$). Higher number of diagnostical procedures correlated with higher patient age ($p = 0.028$), larger maximal tumour diameter ($p = 0.035$) and connective tissue tumour diagnosis ($p = 0.027$). Higher number of curative procedures correlated with larger maximal tumour diameter ($p = 0.008$) and lower patient age ($p = 0.001$).

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Ključne besede: kostni tumorji; recidiv tumorja, lokalni; napoved izida; intralezijska izpraznitev

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Conclusions: Preoperative features of benign bone tumours significant impact the number of surgical procedures needed to treat the tumour and the risk of postoperative recurrence. Although most of these factors are nonmodifiable, they represent an incentive to create evidence-based guidelines for biopsy indications, surgical techniques and consistent postoperative follow-up.

Izvleček

Izhodišča: Večina agresivnih benignih kostnih tumorjev se zdravi kirurško s t.i. intralezijsko izpraznitvijo in zapolnitvijo kostnega defekta. Glavni cilj naše študije je oceniti napredne dejavnike ponovitve po intralezijski izpraznitvi benignega kostnega tumorja v perifernem skeletu. Preučili smo vprašanje, ali starost in spol bolnika, največji premer tumorja, histološka diagnoza in umestitev tumorja statistično pomembno vplivajo na tveganje za recidiv tumorja po operaciji. Sekundarni cilj je bil oceniti razlike med različnimi histopatološkimi skupinami benignih kostnih tumorjev, ocenjenimi pred operacijo, ter vpliv starosti in spola, največjega premera tumorja, histološke diagnoze in umestitve tumorja na število diagnostičnih biopsij in kurativnih kirurških posegov.

Metode: Retrospektivna analiza prospektivno zbranih podatkov je vključevala kohorto bolnikov, operiranih v enem samem terciarnem tumorskem centru med letoma 2010 in 2020 z vsaj enoletnim spremljanjem. Za oceno vpliva vhodnih spremenljivk na število diagnostičnih in kurativnih kirurških posegov in recidivov po posegu smo uporabili statistično metodo ordinalne logistične regresije.

Rezultati: Kohortna analiza je vključevala 261 bolnikov z 61 lokalnimi recidivi. Tveganje za recidiv tumorja je bilo pomembno manjše ob višji starosti bolnika (p = 0,001) in umeščenosti tumorja v distalnem delu stegnenice (p = 0,033). Večje število diagnostičnih posegov je bilo v soodvisnosti z višjo starostjo bolnika (p = 0,028), večjim maksimalnim premerom tumorja (p = 0,035) in diagnozo vezivnega tumorja (p = 0,027). Večje število kurativnih posegov je bilo v soodvisnosti z večjim maksimalnim premerom tumorja (p = 0,008) in nižjo starostjo bolnika (p = 0,001).

Zaključek: Značilnosti benignih kostnih tumorjev, ugotovljenih pred operacijo, pomembno vplivajo na število kirurških posegov, potrebnih za zdravljenje tumorja in za tveganje recidiva. Čeprav večine teh dejavnikov ni mogoče spremeniti, so osnova za sprejemanje z dokazi podprtih smernic glede indikacij za biopsijo, izbiro kirurške tehnike in oblikovanje enotnih načel spremljanja po operaciji.

1 Introduction

1.1 Benign bone tumours

The Latin meaning of the word tumour, in its broader sense, is used to designate every macroscopically visible increase in the tissue or organ volume. In the past, tumour marked one of the five cardinal signs of inflammation; however, today, it is used in a stricter sense and designates a neoplasm (1). In terms of the invasive or disseminative potential of tumours, they are divided into benign or malignant tumours (2). Benign neoplasms are collections of well-differentiated cells that are very similar or the same as the cells from which they originated (1,2). The processes in these cells resemble those performed by normal original cells; mitoses are also rare, particularly in well-differentiated tumours (2). Their growth is mostly slow and they all remain localized in their site of origin. They usually grow expansively and only push the surrounding tissue away (1), as they do not possess the ability to infiltrate, invade or metastasize into surrounding tissue or organs – this is the main differentiating feature from malignant tumours (2).

Primary benign bone tumours substantially outnumber their malignant counterparts and are 100 times more frequent (3), especially in patients up to 40 years of age (2). The most often discovered benign bone tumours include fibrous tumours and matrix forming tumours, out of which non-ossifying fibroma is the most common (4). The 5th edition WHO Classification of Soft Tissue and Bone Tumours includes 27 different benign bone tumours (4), but for the purposes of our research, we sorted them into nine different groups of related diagnoses.

Modern orthopaedic surgery offers multiple ways of treating benign bone tumours. Some neoplasms require only regular radiological follow-up, while others require surgical treatment after a previous thorough diagnostic evaluation (5,6).

Fundamentally, the extent of the surgical intervention

into the bone can be divided into four groups, according to the attained surgical margins (7):

- intralesional excision: the plane of dissection runs directly through the tumourous tissue,
- marginal excision: the plane of dissection runs tightly around the lesion but not through it,
- wide excision: the plane of dissection runs through the surrounding healthy tissue close to the tumour,
- radical excision: the entire bone or tumour compartment is removed.

When performing an intralesional excision, the lesion is accessed through a surgically made bone window. The pathologically altered tissue is removed using different surgical instruments; most often, the tissue is removed by scraping it with a curette. The hence-made bone defect may then be filled with polymethylmethacrylate (PMMA, i.e., the bone cement), bone substitutes of different origin (e.g., calcium triphosphate) or bone transplants, either from the patient himself (autologous graft) or from a bone graft bank (homologous graft of another human individual). Different methods of osteosynthesis are sometimes needed to strengthen the bone if it was weakened with surgical excision (5,8).

1.2 The exploratory research questions

The presented study's primary aim was to determine the prognostic factors for recurrence after an intralesional excision of benign bone tumours in the peripheral skeleton. The study protocol included 261 consecutive patients diagnosed with a benign bone tumour in the peripheral skeleton and surgically treated with an intralesional excision between 1 January 2010 and 31 December 2021 at the Department of Orthopaedic Surgery, University Medical Centre Ljubljana, Slovenia. For each patient, the following data were collected prospectively: date of birth, gender, histopathological diagnosis, tumour location, tumour dimensions and estimated tumour volume, number of preoperative pathological fractures, dates and content of diagnostic and curative procedures, number of postoperative tumour recurrences and the name of the operating surgeon who performed the surgical treatment.

The following exploratory research questions were analysed:

1. Do patients' age, gender, maximal tumour dimension, tumour localization, and histopathological diagnosis correlate with the number of postoperative recurrences after an intralesional excision of a benign bone tumour?
2. Do preoperative features of benign bone tumours, such as patients' age at the first surgery, maximal tumour dimension, estimated tumour volume, and the number of preoperative pathological fractures, differ between groups of histopathological diagnoses?
3. Do patients' age, gender, maximal tumour dimension, tumour localization, and histopathological diagnosis correlate with the number of diagnostic surgical procedures and curative surgical procedures performed in a patient with a benign bone tumour?

2 Methods

2.1 Patients

Our retrospective analysis of prospectively collected data included all patients surgically treated with an intralesional excision of a benign bone tumour in the peripheral skeleton between January 1, 2010 and December 31, 2021 at the only tertiary orthopaedic hospital in the Republic of Slovenia to treat bone tumours (University Medical Centre Ljubljana, Department of Orthopaedic Surgery). The presented cohort, therefore, includes the vast nationwide majority of all patients in Slovenia who have undergone such procedures in the designated period. All data were collected from the digital medical archives of treatment records and the radiological imaging database.

2.2 Inclusion and exclusion criteria

The main inclusion criterion was the surgical treatment of the patient between 1 January 2010 and 31 December 2021 with an intralesional excision of a benign bone tumour in the peripheral skeleton, with or without subsequent filling of the bone defect. This period was chosen because of the wide availability of digital medical records and radiographic images since 2010.

The exclusion criteria were: no clear histological diagnosis after excision (four patients excluded) and unavailability of required medical documentation because the patient was or later became a resident of a foreign country (five patients excluded).

2.3 Gathered data

For each patient, the following data were gathered: date of birth, gender (male, female), histopathological diagnosis (the diagnoses were combined into 9 groups as follows: aneurismal bone cysts, enchondromas and chondromas, unicameral bone cysts, connective tissue

tumours, giant cell tumours of bone, vascular tumours, chondroblastomas, nonossifying fibromas, other diagnoses), tumour location (pelvis, proximal femur, distal femur, proximal tibia, distal tibia, fibula, small bones of hand/foot, humerus), tumour dimensions (length/width/height) and estimated tumour volume, number of preoperative pathological fractures, dates of diagnostical procedures, dates of curative procedures, number of postoperative tumour relapses and number of other postoperative complications.

2.4 Statistical analysis

The statistical analysis of the gathered data was performed with Microsoft Excel 2019 (Microsoft Corporation, Redmond, ZDA) and IBM SPSS 23.0 for Windows (IBM Corporation, Armonk, USA). The differences between mean parameter values of histopathological diagnoses groups were evaluated by the chi-square test for categorical variables (number of males/females, number of preoperative pathological fractures) and one-way ANOVA for numerical variables (mean age at first surgery, mean maximal tumour diameter, mean estimated tumour volume).

The impact of independent variables (patient age and gender, maximal tumour dimension, histopathological diagnosis, localization) on the number of procedures and the number of recurrences was evaluated with ordinal regression. The key assumption in ordinal regression is that the effects of any explanatory variables are consistent or proportional across the different thresholds (i.e., the proportionality of odds). Therefore, they are assumed to have the same effect on the odds regardless of the threshold. A separate statistical model of ordinal regression was designed for each dependent variable: the number of diagnostical procedures, the number of curative procedures and the outcome with at least one recurrence.

2.5 Ethical approval

The presented non-interventional observational retrospective study of medical archive data was approved by the National Medical Ethics Committee of the Republic of Slovenia on 20 October 2020, case No. 0120-456/2020-3). The data for this study were collected prospectively during regular clinical work and then analysed retrospectively without any direct or indirect contact with the participants. No medical interventions, examinations, diagnostic or therapeutic procedures were performed during the research. Participation in the study was not financially compensated, nor did any expenses emerge. No recognizable patient data were disclosed or relevant for this purpose.

3 Results

3.1 Preoperative results

After all the required data were gathered, 261 patients were included in the study based on the aforementioned inclusion criteria, four patients were excluded due to unclear postoperative histological diagnosis and five due to the unavailability of required medical documentation. Table 1 shows the numerical distribution of patients into nine histopathological diagnosis groups based on four preoperative features (mean patients' age at first surgery, mean maximal tumour dimension, mean estimated tumour volume, and the number of preoperative pathological fractures). A p-value is given for each preoperative feature, indicating whether the features statistically significantly differ in average values among different histopathological diagnosis groups.

Out of 261 patients in the study, 138 were female (52%), and 123 were male (48%). The gender ratio was fairly equal throughout the entire study; the only noticeable deviation occurred in the enchondroma or chondroma diagnosis group (1.6 times more often in male patients) and in the unicameral bone cyst diagnosis group (2.5 times more prevalent in female patients). The most frequent diagnosis was a unicameral bone cyst, followed by enchondroma/chondroma and aneurismal bone cyst. The mean age of the entire patient cohort was 24.4. years, with the highest age in the other diagnoses group, followed by the enchondroma/chondroma diagnosis group and the giant-cell tumour of the bone group, respectively. The lowest age was present in the non-ossifying fibroma group, followed by the chondroblastoma group, while the aneurismal bone cyst group had the third lowest average age, and these differences were statistically significant ($p < 0.01$).

The largest average maximal tumour dimensions were measured in the giant cell tumour of the bone group (59 mm) and were almost the same as in the unicameral bone cyst group (58 mm). The smallest average maximal tumour dimensions were recorded in the chondroblastoma (29 mm) and enchondroma/chondroma (31 mm) groups of diagnoses. Once again, the differences in the average maximal tumour dimensions were statistically significant ($p < 0.01$).

Among the calculated average tumour volumes, the giant cell tumour of the bone group had the largest

Table 1: Preoperative features of different histopathological diagnosis groups.

Histopathological diagnosis groups	Number of patients [female / male]	Mean patient age at first surgery [years]	Mean maximal tumour dimension [mm]	Mean estimated tumour volume [cm³]	Number of pre-operative pathological fractures [no. of patients]
Aneurismal bone cysts	38 [19 / 19]	20.5 ± 16.5	44 ± 24	20.1 ± 30.0	4 [4]
Enchondromas and chondromas	71 [27/44]	40.4 ± 15.2	31 ± 24	8.5 ± 13.5	3 [3]
Unicameral bone cysts	76 [54/22]	19.6 ± 18.5	58 ± 30	24.5 ± 26.8	44 [29]
Connective tissue tumours	11 [7/4]	33.3 ± 17.9	47 ± 17	14.6 ± 10.5	1 [1]
Giant cell tumours of the bone	23 [11/12]	36.9 ± 16.4	59 ± 23	74.4 ± 74.5	2 [2]
Vascular tumours	6 [2/4]	35.3 ± 20.6	37 ± 25	13.5 ± 18.8	0 [0]
Chondroblastomas	9 [6/3]	18.5 ± 7.9	29 ± 13	10.1 ± 12.1	0 [0]
Nonossifying fibromas	10 [5/5]	16.4 ± 9.5	48 ± 16	15.7 ± 14.2	2 [2]
Other diagnoses	17 [7/10]	43.2 ± 18.3	45 ± 27	12.1 ± 11.5	0 [0]
p-value	/	< 0.01	< 0.01	< 0.01	< 0.01

average volume (74.4 cm³), while the enchondroma group of diagnoses had the smallest average volume (8.5 cm³). The difference between the average calculated tumour volumes was statistically significant ($p < 0.01$).

The highest number of preoperative pathological fractures, almost 80 % of all cases, was observed in the unicameral bone cyst group. The mean number of fractures per patient amounted to 1.5, which means that most patients in the unicameral bone cyst group endured more than one preoperative fracture.

Analysis of collected data was then performed with three separate statistical models of ordinal regression in order to evaluate the impact of a set of independent variables on three separate dependent variables: the number of diagnostic procedures per patient, number of curative procedures per patient and the outcome with at least one postoperative recurrence.

3.2 Postoperative recurrences

In the entire cohort of the analysed 261 study patients, we observed 78 postoperative recurrences of a benign bone tumour in 68 patients (23% of the entire cohort). The highest percentage of patients with at least one postoperative recurrence was present in unicameral bone cysts (38% of patients with this diagnosis), while 0% recurrence risk was observed in the non-ossifying fibroma and vascular tumour group (Figure 1).

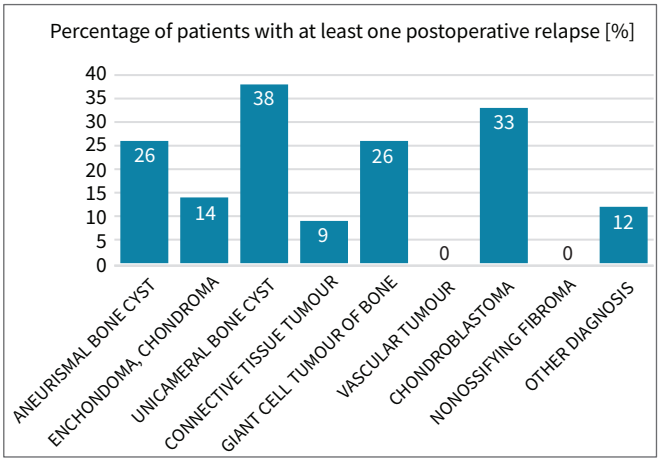

Figure 1: Percentage of patients with at least one postoperative recurrence.

Table 2: Ordinal regression analysis of the impact of independent variables on the outcome of postoperative tumour recurrence.

	B	SE	95% CI of B (lower limit)	95% CI of B (upper limit)	Sig.
Age	-0.049	0.014	-0.077	-0.021	0.001
Maximal tumour dimension	0.014	0.007	0.000	0.027	0.050
Gender					
• female	-0.310	0.392	-1.078	0.458	0.429
• male	0	/	/	/	/
Diagnosis					
• aneurismal bone cyst	0.823	0.953	-1.045	2.691	0.388
• enchondroma/ chondroma	0.712	0.979	-1.207	2.631	0.467
• unicameral bone cyst	0.488	0.965	-1.403	2.379	0.613
• connective tissue tumour	1.341	1.025	-0.669	3.350	0.191
• giant cell tumour of bone	-0.282	1.399	-3.024	2.460	0.840
• vascular tumour	-18.9	8534.0	-16745.2	16707.4	0.998
• chondroblastoma	0.597	1.157	-1.671	2.866	0.606
• nonossifying fibroma	-17.7	0.000	-17.7	-17.7	/
• other	0	/	/	/	/
Localization					
• small bone hand/foot	-0.514	0.642	-1.772	0.744	0.424
• pelvis	-19.401	0.000	-19.401	-19.401	/
• proximal femur	-0.547	0.486	-1.499	0.405	0.260
• distal femur	-1.380	0.648	-2.650	-0.110	0.033
• proximal tibia	0.612	0.631	-0.625	1.848	0.332
• distal tibia	-1.681	1.129	-3.894	0.531	0.136
• fibula	-1.595	1.202	-3.951	0.761	0.185
• humerus	0	/	/	/	/

Legend: B – ordinal regression coefficient; SE – standard error; CI – confidence interval; Sig. – significance (p-value).

The ordinal regression analysis (Table 2) showed a statistically significant impact of patients' age on postoperative recurrences ($p = 0.001$): the odds of recurrence decreased with higher age ($exp(B) = 0.952$). Along with patient age, the localization of a tumour on the distal part of the femur was also shown to have an influence on recurrences ($p = 0.033$). Patients who had a tumour in the distal part of the femur had a lower number of recurrences than other localizations ($exp(B) = 0.871$). Patient gender ($p = 0.429$), histopathological diagnosis (p (for all diagnoses) > 0.05) and maximal tumour dimension ($p = 0.050$) had no statistically significant impact in this regard.

3.3 Diagnostic procedures

Altogether 90 diagnostic procedures were performed on 261 patients, which amounts to an average of 0.34 diagnostic procedures per patient. As shown in Figure 2, the highest mean number of diagnostic procedures was performed in the giant cell tumours of bone (0.83) and the lowest in the unicameral bone cyst (0.09). The overall mean of diagnostic procedures is lower than 1 because not all surgeons decided on a separate diagnostic procedure before a curative one. A separate diagnostic procedure is medically indicated in tumours with an aggressive radiological appearance and in tumours of large volume.

The ordinal regression analysis (Table 3) showed a statistically significant impact of patients' age on the number of diagnostic procedures per patient ($p = 0.028$), i.e., the higher the age, the higher the number of diagnostic procedures ($\exp(B) = 1.022$). Likewise, the maximal tumour dimension was significantly related ($p = 0.028$) to higher number of diagnostic procedures ($\exp(B) = 1.015$). Two histological diagnosis groups statistically significantly influenced the number of diagnostic procedures per patient: aneurismal bone cyst ($p = 0.017$) and connective tissue tumour ($p = 0.027$). An aneurismal bone cyst had a lower number ($\exp(B) = 0.167$), and connective tissue tumours had a higher number ($\exp(B) = 5.275$) of diagnostic procedures per patient in comparison to other diagnoses. The influence of patient gender ($p = 0.234$) and tumour localization p (for all localizations) > 0.05) was not statistically significant.

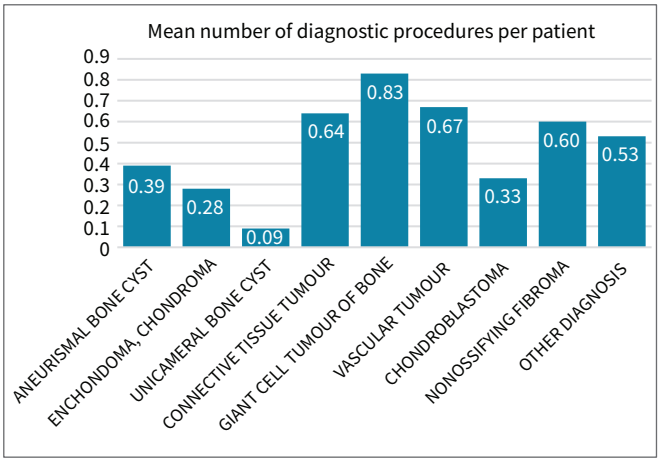

Figure 2: Mean number of diagnostic procedures per patient.

Curative procedures were performed most often on unicameral bone cysts (1.68) and least often on non-ossifying fibroma (1.00) (Figure 3). The ordinal regression analysis (Table 4) showed a statistically significant impact of patient age ($p = 0.001$) and maximal tumour dimension ($p = 0.008$) on the number of curative procedures. Contrary to the observed correlation between young age and a higher number of diagnostic procedures, the number of curative procedures decreased with higher patient age ($\exp(B) = 0.942$). An increase in the number of curative procedures was also related to the maximal tumour dimension ($\exp(B) = 1.017$). Histopathologic diagnosis (p for all diagnoses > 0.05), tumour localization (p for all localizations > 0.05) or patient gender ($p = 0.774$) did not exhibit any statistically significant influence in this regard.

3.4 Curative procedures

A total of 368 curative procedures were performed on 261 patients in the cohort of the presented study, i.e., a mean of 1.41 curative procedures per patient. The mean number of curative surgical procedures was more than one procedure per patient in all but one group of diagnoses. In this context, the curative procedures included possible revision surgery due to the residual tumour tissue (the postoperative imaging showed the tumour was not excochleated in its entirety), possible postoperative complications (e.g., infection), removal of osteosynthesis material (e.g., removal of drainage screw in case of a simple bone cyst) or revision surgery due to tumour recurrence (total macroscopic removal at the primary operation, recurrence occurred later).

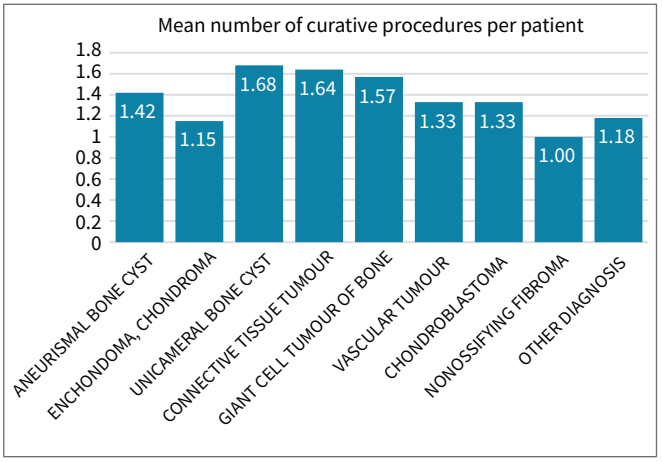

Figure 3: Mean number of curative procedures per patient.

Table 3: Ordinal regression analysis of the impact of independent variables on the number of diagnostic procedures.

	B	SE	95% CI of B (lower limit)	95% CI of B (upper limit)	Sig.
Age	0.022	0.010	0.002	0.042	0.028
Maximal tumour dimension	0.015	0.007	0.001	0.029	0.035
Gender					
• female	0.405	0.340	-0.262	1.072	0.234
• male	0	/	/	/	/
Diagnosis					
• aneurismal bone cyst	-1.787	0.751	-3.259	-0.316	0.017
• enchondroma/ chondroma	-0.340	0.652	-1.618	0.938	0.602
• unicameral bone cyst	0.274	0.691	-1.079	1.628	0.691
• connective tissue tumour	1.663	0.752	0.188	3.138	0.027
• giant cell tumour of bone	0.748	0.824	-0.867	2.362	0.364
• vascular tumour	1.291	0.960	-0.592	3.173	0.179
• chondroblastoma	0.139	0.996	-1.813	2.090	0.889
• nonossifying fibroma	1.220	1.040	-0.818	3.258	0.241
• other	0	/	/	/	/
Localization					
• small bone hand/foot	-1.047	0.627	-2.275	0.181	0.095
• pelvis	0.808	0.978	-1.110	2.726	0.409
• proximal femur	-0.008	0.564	-1.113	1.098	0.989
• distal femur	0.160	0.538	-0.896	1.215	0.767
• proximal tibia	-0.058	0.571	-1.177	1.061	0.920
• distal tibia	-0.113	0.691	-1.467	1.240	0.870
• fibula	-0.820	0.879	-2.544	0.904	0.351
• humerus	0	/	/	/	/

Legend: B – ordinal regression coefficient; SE – standard error; CI – confidence interval; Sig. – significance (p-value).

4 Discussion

4.1 Key findings

In our study, we asked three main exploratory research questions. The primary aim was to find out if the preoperative characteristics of different benign bone tumours (patient age, patient gender, maximal tumour diameter, histopathological diagnosis and tumour localization) correlate with the number of postoperative recurrences after an intralesional exchochelation of such a tumour. Multivariate analysis showed a correlation between higher patient age and tumour localization on the distal part of the femur with a lower number of postoperative recurrences, while other characteristics had no statistically significant impact

Table 4: Ordinal regression analysis of the impact of independent variables on the number of curative procedures.

	B	SE	95% CI of B (lower limit)	95% CI of B (upper limit)	Sig.
Age	-0.060	0.013	-0.087	-0.034	0.001
Maximal tumour dimension	0.017	0.007	0.005	0.030	0.008
Gender					
• female	-0.103	0.358	-0.806	0.599	0.774
• male	0	/	/	/	/
Diagnosis					
• aneurismal bone cyst	0.375	0.873	-1.337	2.087	0.668
• enchondroma/ chondroma	0.461	0.898	-1.299	2.221	0.608
• unicameral bone cyst	0.021	0.884	-1.712	1.753	0.981
• connective tissue tumour	1.462	0.926	-0.353	3.278	0.114
• giant cell tumour of bone	0.865	1.054	-1.201	2.931	0.412
• vascular tumour	-20.366	0.000	-20.366	-20.366	/
• chondroblastoma	0.016	1.085	-2.110	2.143	0.988
• nonossifying fibroma	1.208	1.253	-1.247	3.664	0.335
• other	0	/	/	/	/
Localization					
• small bone hand/foot	-0.659	0.629	-1.891	0.574	0.295
• pelvis	-20.617	0.000	-20.617	-20.617	/
• proximal femur	-0.255	0.447	-1.132	0.621	0.568
• distal femur	-0.598	0.538	-1.652	0.456	0.266
• proximal tibia	0.494	0.607	-0.695	1.683	0.415
• distal tibia	-1.327	0.872	-3.037	0.382	0.128
• fibula	-2.012	1.233	-4.429	0.405	0.103
• humerus	0	/	/	/	/

Legend: B – ordinal regression coefficient; SE – standard error; CI – confidence interval; Sig. – significance (p-value).

on the recurrence risk. The secondary aim was to find out whether the preoperative characteristics of benign bone tumours differ significantly between different histopathological diagnoses. All four analysed preoperative parameters showed statistically significant differences between nine groups of histopathological diagnoses: the mean patient age at first surgery, the mean maximal tumour diameter, the mean estimated tumour volume, and the number of preoperative pathological fractures. Finally, we wanted to evaluate the impact of prognostic factors (patient age, patient gender, maximal tumour diameter, histopathological diagnosis, and tumour localization) on the number of performed diagnostic and curative surgical procedures.

Higher patient age, larger maximal tumour diameter, and connective tissue tumour diagnosis correlated with a higher mean number of diagnostic procedures per patient, while the diagnosis of an aneurismal bone cyst was linked to a lower number of procedures. Furthermore, larger maximal tumour diameter correlated with a higher mean number of curative procedures per patient, and higher age was linked to a lower mean number of procedures.

4.2 Study limitations

The first limitation of our study was the fact that five different orthopaedic surgeons of the Department of Orthopaedic Surgery, University Medical Centre Ljubljana, performed the analysed surgical procedures. This circumstance had no impact on the preoperative (prognostic) factors; however, it might have affected postoperative results. The decisions of performing an exclusively diagnostic procedure before a curative one, whether a curative procedure is not needed after a diagnostic one or whether a diagnostic and curative procedure can be combined into one procedure depended on each individual orthopaedic surgeon. Extensive professional guidelines on treating benign bone tumours exist, but a subjective influence cannot be entirely excluded. Moreover, the surgeon's experience or the thoroughness of his surgical technique may have affected the postoperative recurrence risk, and some of the surgeons were prone to take over more demanding cases by choice. The impact of this confounding variable (i.e., different surgeons) was reduced by selecting a cohort of patients treated at the University Medical Centre Ljubljana, Department of Orthopaedic Surgery, in a uniform environment with uniform clinical guidelines and conditions of surgical work.

The second limitation of our study was the retrospective nature of the study. Only retrospective cohort studies provide a sufficiently large number of participants when the researched events are rare, which is the case in certain histopathological diagnoses, pathological fractures, or tumour recurrences. Other prognostic factors may also exist which were not taken into account and would require too much time to search for in archives or were not recorded when the study was being designed (e.g., patient height and weight). Furthermore, the archival image data was in part incomplete; for example, no 3-dimensional radiological imaging was available in some older cases, or mismatched data from different archival sources was present.

4.3 Literature review

The analysis of patient gender distribution in different diagnosis groups showed considerable asymmetry in a relatively large group of patients with enchondromas/chondromas and unicameral bone cysts. Contrary to our findings, the literature review suggests a male gender predilection of unicameral bone cysts (4,5,6). Enchondromas and chondromas are supposed to have no gender predilection (4,5). The most frequent histopathological diagnosis in our study was unicameral bone cyst, followed by enchondroma/chondroma. The frequency of unicameral bone cysts (9) and enchondromas (10) is very low in comparison to non-ossifying fibroma, as both diagnoses contribute 3% and 2% (respectively) to the entire prevalence of benign bone tumours. Nonetheless, most nonossifying fibromas do not require surgical treatment, while bone cysts are much more likely to require an operation. The prevalence of unicameral bone cyst is not known with certainty because some of them are never discovered due to their frequent asymptomatic nature (11). The same applies to nonossifying fibromas (10).

The highest patient age in our cohort was marked in the other diagnoses group, followed by the enchondroma/chondroma group and the giant cell bone tumour group. Most enchondromas are diagnosed between ages 20 to 40 (12,13), which places our average on the upper limit of the age interval. Giant cell bone tumours are most commonly discovered in patients aged 20 to 40 years (14,15), which corresponds well to the mean patient age of our cohort. The diagnosis group with the lowest average patient age was the non-ossifying fibroma group, followed by the chondroblastoma group and the unicameral bone cyst group. Non-ossifying fibroma is one of the most common benign bone lesions in children (16,17), which matches our results, and the majority of chondroblastomas are diagnosed in the second or third decade of life, on average between 19 and 23 years of age (18), which is close to the average age of our study group. According to our results, unicameral bone cysts occur most commonly in children or adolescents (19,20).

The largest mean maximal tumour diameter was recorded in the giant cell tumour of the bone group, closely followed by the unicameral bone cyst group. Our mean maximal tumour diameter of the giant cell tumour of bone closely matches the one measured by the Tianjin Hospital researchers by less than 10 mm - in a cohort of 250 patients, the mean was 58 mm or 69 mm, depending on the localization (21). The smallest

mean maximal diameter was observed in the chondroblastoma group and the enchondroma group. On average, chondroblastomas measure from 30 - 60 mm (22,23), which places our average close to the bottom limit of the interval. Enchondromas are typically lesions measuring less than 30 mm (24); in the study, conducted by M.J Walden et al., including 449 patients, the average diameter was 19 mm (25), 12 mm more than our average.

The largest average calculated volume was found in the giant cell tumour of the bone group and the smallest in the enchondroma group. The latter finding is supported by enchondromas often being discovered in small carpal and tarsal bones with comparatively small diameters (4,13). Furthermore, the shape of these tumours is often ellipsoid, which explains why this group was the smallest in volume – one of the diameters could have been relatively larger, but the remaining two were very small. Most preoperative pathological fractures occurred in the unicameral bone cyst group. This finding corresponds well with the literature, which suggests that the unicameral bone cyst is one of the most frequent (26) causes of a pathological fracture caused by a benign bone lesion.

To date, no study has been published to include more than 250 patients from the same hospital, who were all surgically treated with intralesional excision due to different benign bone tumours and would contain an analysis of predictive factors for the number of diagnostic procedures, curative procedures and postoperative recurrences.

The only study with a similar basic design was published in 1985 by A. Kreicbergs et al., Karolinska Hospital, Sweden (27). The study included a cohort of 155 patients surgically treated by intralesional curettage due to different benign bone tumours. A subsequent analysis of possible predictive factors for recurrence was performed. A recurrence occurred in 23% of patients, which is an astonishingly similar result to our study. Patient gender and histological diagnosis were also found to be statistically significant predictive factors of recurrence. Furthermore, the diagnoses of an aneurismal bone cyst and a giant cell tumour of bone were found to be predictive factors of recurrence for the female study participants, whereas the diagnosis of a unicameral bone cyst was the predictive factor for participants up to 9 years of age. A correlation between an individual histological diagnosis and the occurrence of a recurrence was not proven in our study; however, there was a correlation between tumour localization and patient age with tumour recurrence.

Other similar studies are mostly based on a single histological diagnosis, most frequently the diagnosis of a giant cell tumour of bone (28-39). Predictive factors of recurrence after intralesional excision were sometimes only identified, and other times also statistically evaluated. For example, patient gender and age were the researched predictive factors in a study conducted by Mohaidat et al. (28): male gender and lower age were linked to a higher number of recurrences. On the contrary, C. Errani et al. concluded that none of the predictive factors were statistically insignificant (29); the same conclusion was stated by Teixera et al. (30).

Predictive factors, researched in other studies, include tumour localization (31), the occurrence of another bone tumour simultaneously with a giant cell tumour of bone (32), usage of different surgical adjuvants (bone cement (33,34), phenol (35)), occurrence of pathological fractures (36) and microscopic characteristics of surrounding tissue (37). Other histological diagnoses to be more frequently found in similar studies are chondroblastoma (38-41), aneurismal bone cyst (42), osteoblastoma (43), and enchondroma (44). Predictive factors of recurrence included biological aggressiveness of a tumour (39), patient gender (40,41), tumour size (42), and the usage of phenol as a surgical adjuvant (43), to name a few.

Ours is the first clinical study to research the field of active and aggressive benign bone tumours in the Republic of Slovenia. Its findings and conclusions have direct clinical applicability in forming guidelines for surgical treatment and postoperative follow-up of benign bone tumours. The study was also the first to analyse the predictive factors of recurrence among different diagnosis groups in a cohort greater than 250 patients. It was shown that higher patient age and the localization of a tumour on the distal femur correlate with a lower number of postoperative recurrences.

5 Conclusion

The preoperative features of benign bone tumours (patient age at first surgery, maximal tumour diameter, estimated tumour volume, and the number of preoperative pathological fractures) statistically significantly differ among different histopathological diagnosis groups. A higher number of diagnostic procedures in the treatment of benign bone tumours is statistically significantly linked to patient age, maximal tumour diameter, and the diagnosis of a connective tissue tumour. A lower number is linked to a diagnosis of an aneurysmal bone cyst. Other variables (patient gender,

other diagnosis groups, and tumour localization) have no statistically significant impact.

A higher number of curative procedures in the treatment of benign bone tumours is statistically significantly linked to maximal tumour diameter and a lower number to patient age. Other variables (patient gender, histopathological diagnosis and tumour localization) have no statistically significant impact on the number of curative surgical procedures. A lower risk of postoperative recurrences after an intralesional excision of a benign bone tumour is statistically significantly linked to a higher patient age and a higher number of recurrences to the tumour localization on the distal femur.

Therefore, the characteristics of benign bone tumours significantly impact the number of surgical procedures needed to treat the tumour and the risk of postoperative recurrence. Although most of these factors are nonmodifiable, they represent the incentive to create evidence-based guidelines for biopsy indications, surgical techniques, and consistent postoperative follow-up.

Conflict of interest

None declared.

Editorial note

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