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APPENDIX I - Participating international sarcoma reference centres

1. Leiden University Medical Center, **Leiden**, The Netherlands
2. Radboud University Nijmegen Medical Center, **Nijmegen**, The Netherlands
3. IRCCS Istituto Ortopedico Rizzoli, **Bologna**, Italy
4. Fondazione IRCCS Istituto Nazionale dei Tumori, **Milano**, Italy
5. Istituto Ortopedico Gaetano Pini, **Milano**, Italy
6. Mount Sinai School of Medicine, **New York**, USA
7. Medical University Graz, **Graz**, Austria
8. Halen İstanbul Üniversitesi, **Istanbul**, Turkey
9. AOU Città della Salute e della Scienza, **Torino**, Italy
10. Orthopedic Hospital Gersthof, **Vienna**, Austria
11. Careggi University-Hospital, **Firenze**, Italy
12. University Medical Center Groningen, **Groningen**, The Netherlands
13. Academic Medical Center, **Amsterdam**, The Netherlands
14. Mount Sinai Hospital, **Toronto**, Canada
15. Beijing Jishuitan Hospital, **Beijing**, 100035, China
16. Institut Roi Albert II, **Brussels**, Belgium
17. Royal National Orthopedic Hospital, **London**, the United Kingdom
18. Hospital de Navarra, **Pamplona**, Spain
19. Centre hospitalier universitaire de Nantes, **Nantes**, France
20. Ludwig-Maximilians-University Munich, **Munich**, Germany
21. Medical University of Innsbruck, **Innsbruck**, Austria
22. Massachusetts General Hospital Harvard, **Boston**, United States of America
23. Chiba Cancer Center, **Chiba**, Japan
24. National Cancer Center, **Tokyo**, Japan
25. Kanazawa University Graduate School of Medical Sciences, **Kanazawa**, Japan
26. Sytenko Institute of Spine and Joint Pathology, **Kharkiv**, Ukraine
27. Universitätsklinikum Jena, **Jena**, Germany
28. University of the Phil-Phil General Hospital, **Manila**, Philippines
29. Catholic University of Korea, **Seoul**, Korea
30. Cairo University, **Cairo**, Egypt
31. Wilhelmsburger Krankenhaus Groß Sand, **Hamburg**, Germany

APPENDIX II - Patient-, tumour and treatment characteristics

Table 1 Collected patient-, tumour and treatment characteristics with corresponding definitions.

Characteristic	**Definition**
TGCT-type	Localized-/diffuse-TGCT as defined by the 2013 WHO[1, 2]
Admission status	Previously treated*
Sex	Male/female
Age at initial treatment	Age at initial treatment
Side	Left/right
Localization	TGCT affected joint
Bone involvement	Discontinuation of cortex by tumour ingrowth*
Date first diagnosis	Date first diagnosis
Duration of symptoms	Duration of symptoms in months
Pain, swelling, stiffness and limited range of motion prior to initial treatment and at last follow-up	(Clinically relevant) Pain, swelling, stiffness[+] and limited range of motion prior to initial treatment* and at last follow-up
Total number surgeries	All surgeries related to TGCT, including re-operations for complications
Date initial treatment**	Date initial treatment at tertiary centre and date(s) of consecutive treatment(s)
Initial treatment**	Type of initial treatment and consecutive treatment(s): arthroscopic resection, one-staged open resection, two-staged open resection, endoprosthetic reconstruction, amputation, wait and see[++], resection not specified
Tumour size	Largest size in any dimension (cm), according to the 2013 WHO classification[1, 2], <5 and ≥5 cm were compared
Adjuvant therapy	Nothing, radiotherapy, 90Yttrium, targeted therapy, cryosurgery, other
Date complication	Date complication related to surgical treatment
Complication	Type of complication related to surgical treatment: no complication, superficial wound infection, deep wound infection, joint stiffness[+], haemorrhage, neurovascular damage, thrombosis, other, unknown
Total number recurrences	Total number local recurrences
Date final follow-up	Date final follow-up
Status last follow-up	No evidence of disease, alive with disease wait and see, alive with disease planned surgery of adjuvant therapy, death of disease, death of other disease, lost (<6 months follow-up)
Chronic analgesic treatment at last follow-up	Chronic analgesic treatment at last follow-up

*These parameters were answered by absent or present

**(Date) initial treatment, initial treatment in a tertiary centre is not necessarily first treatment of the patient

[+]Joint stiffness requiring manipulation under anaesthesia

[++]Wait and see and conservative treatment are considered similar

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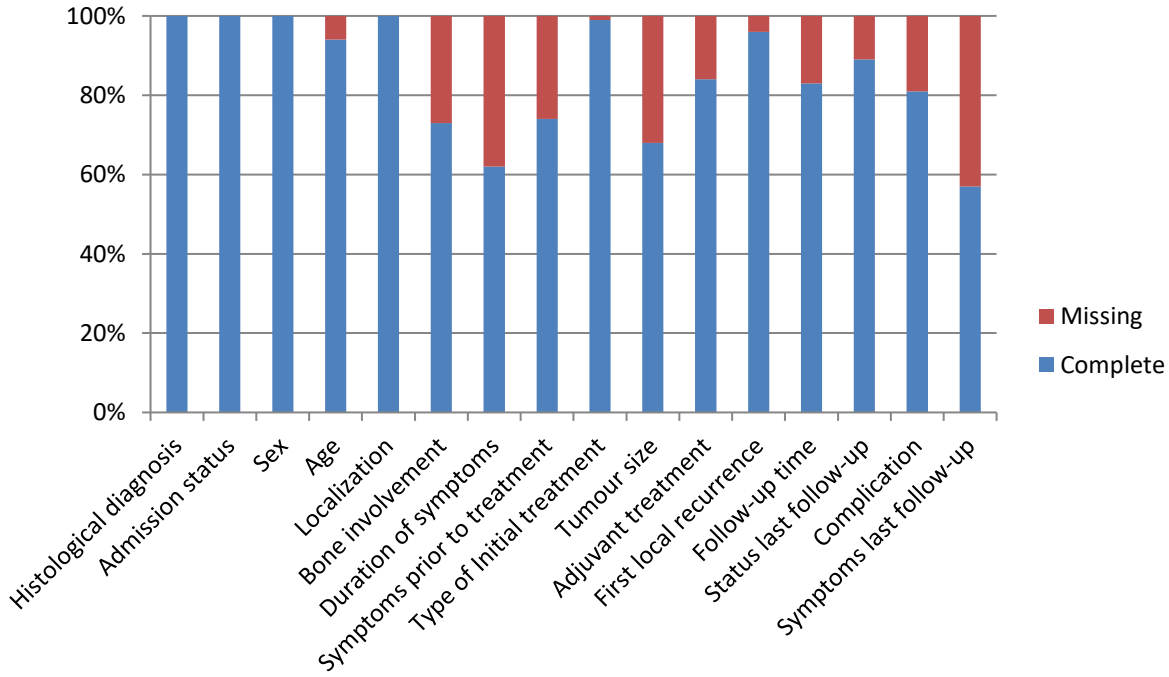
APPENDIX III - Data missing per variable

Figure 1 Proportion of data missing per variable in localized-TGCT (N=941).
Symptoms prior to initial treatment at tertiary centre include pain, swelling, stiffness and limited range of motion. Symptoms at last follow-up include pain, swelling, stiffness, limited range of motion and chronic analgesic treatment at last follow-up.



APPENDIX IV - Exact survival information and statistical methods

For some cases exact survival information was not available (appendix figure 1). In 7 out of 61 cases, we could recover the missing recurrence indicator: in 2 cases patients had a second treatment and in 5 cases patients had follow-up status 'alive with disease' and were classified as recurrent disease. If the exact time of recurrence was not recorded, an approximation was sometimes possible. If the date of surgery to treat a local recurrence was known, this was used instead (N=33). If this information was missing as well, then the date of last recurrence was used as an upper bound (N=5). Otherwise the date of last recorded follow-up was used as an upper bound (N=69). If data on recurrence status or date of recurrence was missing and could not be recovered as described, patients were excluded for risk- and survival analyses (N=64).
Some centres did not record follow-up time in patients without recurrent disease. To prevent exclusion of these patients, we imputed their follow-up time (N=97). Multiple imputation technique was applied and 5 complete data sets were imputed using the R-package Amelia II[18]. Statistical analyses were conducted on all data sets and the results were then pooled following Rubin's rule[19].

As a consequence of the approximation of the time of recurrence by upper bounds in some cases, common survival methods (Kaplan-Meier estimate, log rank test) were substituted by methods that allow interval censoring. Observed survival curves and probabilities were computed using non-parametric maximum likelihood estimates for interval censored data with the R-package interval[20]. P-values for the univariate analyses were calculated with the score test of Sun (1996)[21].
Covariates that were found to have a significant association with local recurrence free survival in the univariate analysis were included in a multivariate Cox regression analysis using the icenReg R-package, which allows for interval censored data[22].

APPENDIX V – Recurrence free survival probabilities for each localization

Table 2 Recurrence free survival probabilities for localized-TGCT

Admission status	Localization	N+	%RFS at 3 years	95% CI	%RFS at 5 years	95% CI	%RFS at 10 years	95% CI
primary	knee	529	89	87-93	85	81-89	81	76-87
primary	foot/ankle	156	90	84-96	84	76-93	81	71-91
primary	upper extremity*	82	93	86-100	90	81-98	86	74-97
recurrent	knee	16	44	19-68	44	19-68	**	
recurrent	foot/ankle	11	30	3-57	18	0-41	18	0-41
recurrent	upper extremity*	3	67	13-100	67	13-100	67	13-100

Since the hip was affected sporadically (primary N=24; recurrent N=2) without recurrent disease during follow-up, reliable analyses were not possible.

+N: number at baseline (time point = 0), *Upper extremity including other localization, **Survival estimates of recurrent knee patients at 10 years could not be estimated (due to lack of follow-up information). Primary: patient was first seen at a tertiary centre with therapy-naïve disease, recurrent: patient was initially treated elsewhere, 95%CI: 95% Confidence interval.

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