

# Evaluation of tumor-prostheses over time: Complications, functional outcome, and comparative statistical analysis after resection and reconstruction in orthopedic oncologic conditions in the lower extremities

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## Abstract

**Objectives:** Previous multicenter studies report variable outcomes and failure rates after tumor-prosthetic reconstructions. The purpose of this study was (1) to evaluate implant survival, limb survival, and functional outcome in a cohort of patients who underwent resection of primary malignancies or aggressive benign bone tumors and reconstruction with modern tumor-prostheses in the lower extremities and (2) to provide comparison to a historical cohort on previous generations of tumor-prostheses from the same center.

**Methods:** A longitudinal retrospective single-center study of 72 consecutive patients (F/M = 30/42), mean age = 44 (range = 7–84) years with bone, soft tissue sarcoma adjacent to bone (n = 69), and aggressive benign bone tumors (n = 3) having surgery between 2006 and 2016 with bone resection and reconstruction with tumor-prostheses were compared to a historical cohort from 1985 to 2005. Revisions were classified as major and minor revisions. Causes of failure were classified according to the Henderson classification. Fine and Gray competing risk analysis was used for assessing cumulative incidence for implant revision and limb amputation. Functional outcome was evaluated with Musculoskeletal Tumor Society Score system.

**Results:** Forty-seven patients were alive at the end of the study. Mean follow-up was 6 years (range = 2–13 years). Ten-year cumulative risk of major revision was 18% (95% confidence interval = 9%–28%). Deep infection and recurrence of tumor caused most revisions in modern tumor-prostheses. Ten-year cumulative incidence of limb amputation was 11% (95% confidence interval = 3%–18%). According to the Henderson classification, the overall predominant failure mode was non-mechanical (n = 20, 51%). Mean Musculoskeletal Tumor Society Score was 20 (67%) (range = 0–30).

**Conclusion:** A minimum of 2 years follow-up with modern modular tumor-prostheses demonstrated a relatively low risk of implant failure and amputation and also an acceptable functional outcome. No statistical difference of, implant survival, limb survival and functional outcome between tumor-prostheses over two time periods was observed, possibly explained by Type 2 error.

## Keywords

Tumor-prostheses, complications, limb sparing surgery, functional outcome

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## Introduction

Advances in treatment of bone sarcomas have over the past decades led to a gradually increased patient survival from 15% in the 1970s to present 60%–70%.<sup>1</sup> This improvement is generally a result of the introduction of neo-adjuvant and adjuvant chemotherapy combined with surgery.<sup>2</sup> The possibility to downstage tumors before surgery facilitated the

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development of limb-sparing tumor resection and reconstruction instead of amputation. The advances in diagnostic and imaging techniques allowing more accurate pre-surgical planning have additionally resulted in limb sparing surgery (LSS) as the method of choice now offered to 90%–95% of all patients.<sup>3,4</sup> Limb sparing surgery with tumor-prostheses is the preferred surgical principle for several reasons: they provide immediate fixation, allowing early weight bearing and also maintenance of function (14,56). Development of orthopedic implant designs and possibilities has continuously aimed to optimize function and prevent implant complications and revisions. The evolution regarding the knees has moved from early fully constrained or fixed-hinge custom-made designs, to modern modular rotating-hinge designs with cemented or uncemented fixation, and various coatings have been suggested to improve bone ingrowth. Although the introduction of modular fixed-hinge knee systems in the 1980s provided more patients-specific prostheses,<sup>5,6</sup> the design caused high stress in the bone–implant interface.<sup>7</sup> Introduction of rotating-hinge prostheses is therefore considered to be one of the most central improvements to modern treatment with LSS due to reduction in mechanical stress and bone resorption in the bone–implant interface.<sup>8</sup> Despite advances, the incidence of revisions and complications of tumor-prostheses is continuously described higher compared to primary arthroplasty.<sup>4,7,9–11</sup> In 2011, Henderson et al.<sup>12</sup> introduced a classification system that classifies five different types of implant failures, aiming to facilitate clearer interstudy comparison and understanding of failure modes and their causes. The Henderson classification is now widely used in studies reporting outcome after insertion of tumor-prosthesis.<sup>11,13–15</sup>

Aseptic loosening and deep infection are the most common reported causes for revision and implant failure.<sup>11,16,17</sup> Sarcoma patients are prone to infection due to the wide resections, loss of tissue, prolonged surgery time and often also radiation or chemotherapy.<sup>18</sup> The two most commonly reported causes for amputation after LSS are deep infection and local recurrence.<sup>19,20</sup> While risk of recurrence in some long-term studies has demonstrated to decrease with time, the risk of deep infection has been demonstrated to persist or increase with time.<sup>16</sup> Thus, deep infection is to be considered the current greatest threat for limb survival, although local recurrence additionally represents a risk of reduced overall survival.

As a result of the improved implant possibilities, we at our center introduced the Global Modular Replacement System (GMRS, Stryker®, Inc., Rutherford, NJ, USA) prostheses in 2005, and the Zimmer® Segmental system (Zimmer® Biomet, Warsaw, IN, USA) prostheses in 2011 as modern second-generation prostheses. Both prostheses are highly modular systems with porous-coated or trabecular metal surfaces for soft tissue attachment, cemented/cementless stem options, and rotating-hinge knee joints.

The aim of this study was to evaluate the incidence of pre-defined revisions, amputation, and functional outcome after resection and reconstruction with tumor-prostheses over

time. We hypothesized that the general improvements over time in orthopedic implant possibilities, surgical technique, diagnostic imaging, and the use of post-operative antibiotics would lead to a lower incidence of revision, amputation, and improved functional outcome.

## Material and methods

The study is a longitudinal retrospective study. In order to compare outcomes between two time periods, the present cohort, henceforward named the late cohort, is compared to a historical cohort described by Holm et al.<sup>21</sup> henceforward named the early cohort due to an earlier surgery period but from the same center. Both cohorts were consecutive cohorts according to the below mentioned inclusion criteria. Since all patients of interest were included, we did not perform power calculation. Due to the Danish Civil Registration System, no patients were lost to follow up and exact date of death was known for all patients.<sup>22</sup>

### Late cohort

A consecutive retrospective cohort of all patients who underwent LSS and reconstruction with tumor-prostheses at the Musculoskeletal Tumor section, Department of Orthopedic surgery, Rigshospitalet in Copenhagen between January 2006 and 31 December 2016. Patients were identified by manually screening our institutional surgical planning system. Inclusion criteria were as follows: patients of all ages who underwent resection and reconstruction with tumor-prostheses due to primary bone sarcoma, soft tissue sarcoma adjacent to bone or joint, and aggressive benign tumor in the lower extremities. Patients with aggressive benign tumors were offered LSS with tumor-prostheses if they had repeated recurrences followed by curettage or joint destruction. Exclusion criterion was as follows: patients with other types of surgical treatment or revision of prior implants. Patients were followed until death or end of study (1 January 2018) resulting in a minimum of 2-year follow-up.

We included 72 patients (F/M=30/42, mean age=44 (range=7–84) years) who underwent LSS and reconstruction with a tumor-prosthesis for a bone sarcoma (n=60), soft tissue sarcoma adjacent to bone (n=9), or aggressive benign bone tumor (n=3). From patient records, we obtained the following: gender, age, date of diagnosis, date of surgery, anatomical tumor site, and type of implant. Also, from patient records, we registered all subsequent types of surgeries related to the prosthesis. From the Danish National Pathology Registry (DNPR),<sup>23</sup> we found histopathological diagnosis and date for debut of cancer. In a few patients (n=5), pre-operative biopsies were inconclusive. Final histopathological diagnosis was defined post-surgically. The anatomic sites of reconstruction were as follows: distal femur (n=33), proximal femur (n=24), proximal tibia (n=12) and entire femur (n=3). The following types of implants were used for reconstruction: GMRS (Stryker®, Stryker Orthopaedics, Mahwah,

**Table 1.** Summarizing patient characteristics.

	All patients	Early cohort	Late cohort	p-value
Number of patients	n = 122	n = 50	n = 72	
Female/male	54/68	24/26	30/42	p = 0.58 <sup>a</sup>
Patients alive at end of study	75	28 (56%)	47 (65%)	p = 0.35 <sup>a</sup>
Mean age at surgery (range)	39 (6–84)	34 (6–74)	44 (7–84)	p = 0.02 <sup>c</sup>
Location				
Hip	33 (27%)	9 (18%)	24 (33%)	p = 0.06 <sup>a</sup>
Knee	83 (68%)	38 (76%)	45 (63%)	p = 0.17 <sup>a</sup>
Distal femur	62 (51%)	29 (58%)	33 (46%)	N/A
Proximal tibia	21 (17%)	9 (18%)	12 (17%)	N/A
Total femur	6 (5%)	3 (6%)	3 (4%)	p = 0.68 <sup>a</sup>
Total number of revisions	137	78	59	p = 0.27 <sup>a</sup>
Osteosarcoma	59 (48%)	30 (60%)	29 (40%)	p = 0.9 <sup>b</sup>
Chondrosarcoma	30 (25%)	9 (18%)	21 (29%)	p = 0.02 <sup>b</sup>
Ewing sarcoma (of bone)	8 (7%)	3 (6%)	5 (7%)	N/A
Giant cell bone tumor	9 (7%)	6 (12%)	3 (4%)	p = 0.3 <sup>b</sup>
Myofibrosarcoma	5 (4%)	–	5 (8%)	N/A
Synovial cell sarcoma	1 (1%)	–	1 (1%)	N/A
Rhabdomyosarcoma	1 (1%)	–	1 (1%)	N/A
Leiomyosarcoma	1 (1%)	–	1 (1%)	N/A
Sarcoma NOS	5 (4%)	–	5 (7%)	N/A
Angiosarcoma	4 (3%)	2 (4%)	2 (3%)	p = 1 <sup>b</sup>

NOS: not otherwise specified; N/A: not available.

<sup>a</sup>Fisher's exact test.

<sup>b</sup>Chi-square test.

<sup>c</sup>Student's unpaired t-test.

NJ) (n=37), Zimmer<sup>®</sup> Segmental system (Zimmer<sup>®</sup> Biomet, Warsaw, IN, USA) (n=27), Megasystem-C (Waldemar Link<sup>®</sup>, CMBH&CD, Germany) (n=5), and Link<sup>®</sup> custom-made growing prostheses (Waldemar Link<sup>®</sup>, CMBH&CD, Germany) (n=3). GMRS (Stryker<sup>®</sup>, Stryker Orthopaedics, Mahwah, NJ) was used in the vast majority of patients from the introduction of the prostheses in 2005 until 2011 when the Zimmer<sup>®</sup> Segmental prostheses were introduced at our center and became the mainly used tumor-prostheses until present. The remaining eight custom-made prostheses were primarily used for children (n=6) and due to surgeon preferences (n=2). Patient characteristics and tumor histology are summarized in Table 1.

### Early cohort

The early cohort has previously been described by Holm et al.<sup>21</sup> In short, inclusion criteria were as follows: patients who underwent LSS and reconstruction with a mega-prosthesis due to bone sarcoma or a giant cell tumor of bone in the lower extremities at our musculoskeletal tumor center between 1985 and 2005 (Table 1). Fifty patients who underwent resection and reconstruction with mainly early prostheses due to a primary bone sarcoma (n=44) were included. The indication for LSS in patients with in aggressive benign bone tumors (n=6) was as in the late cohort mentioned above. Exclusion criterion was as follows: patients with

other types of surgical treatment. Patient characteristics and tumor histology are summarized in Table 1.

### Implant follow-up

In the competing risk analysis, revisions were defined as follows: *Major revisions*: change or removal of bone-anchored parts of the implant or amputation of the extremity for any cause. *Minor revisions*: all implant-related surgeries without removal of bone-anchored parts, including change of polyethylene, local recurrence without contamination of the prosthesis, brisement forcé, DAIR (debridement, antibiotics, and implant retention), closed and open hip repositions with or without insertion of a constrained liner due to dislocation. Aseptic superficial wound revisions in local anesthesia were not defined as revisions. Two-stage surgery due to deep infection was considered as two major revisions. No planned extensions of growing prostheses were defined as revisions. All revisions were registered until death or end of the study period 31 December 2018.

Endoprosthetic complications and failures were classified according to the Henderson Failure Mode Classification<sup>12</sup> in five failure types: Type 1 (mechanical failure due to soft tissue problems, such as debridement, peroneal nerve palsy, dislocation of joint (closed reduction), and superficial infections), Type 2 (aseptic loosening), Type 3 (structural failures, such as periprosthetic fractures and hip dislocation requiring

surgical treatment), Type 4 (non-mechanical failures, such as deep infection), and Type 5 (tumor progression).

### Limb follow-up

In the competing risk analysis, amputation was defined as amputation of the extremity for all causes, as such also analyzed per se. Patients were followed until death or end of study (1 January 2018).

### Clinical follow-up

For patients alive in the study period, post-operative functional outcome was evaluated with the Musculoskeletal Tumor Society Score (MSTS) system.<sup>24</sup> The MSTS was introduced in 1983 by Enneking et al.<sup>25</sup> and modified in 1993 for evaluation of the functional outcome after treatment of sarcomas. The system estimates from bad to very good with parallel assigned values from 0 to 5 in six categories in the lower extremities: Pain, Function, Emotional acceptance, Supports, Walking, and Gait. Subsequently, the six values are added and divided by the maximum value of 30 and a percent rating is calculated.

### Statistical analysis

Since the Kaplan–Meier method assumes identical risk in censored and uncensored patients, a competing risk model (Aalen–Johansson estimate) was used to assess the cumulated incidence of major and minor implant revisions with death and amputation as competing risks, and with death as competing risk when calculating the cumulative incidence of amputation. Cumulative incidence of failures according to the Henderson classifications was calculated using the competing risk analysis. Gray's test, log-rank test, and chi-square test were used to assess differences between groups. Confidence intervals are reported as 95% confidence intervals (95% CI) and  $p$ -values  $< 0.05$  are considered statistically significant. Statistical analysis was performed using software R (R Foundation, Vienna, Austria).

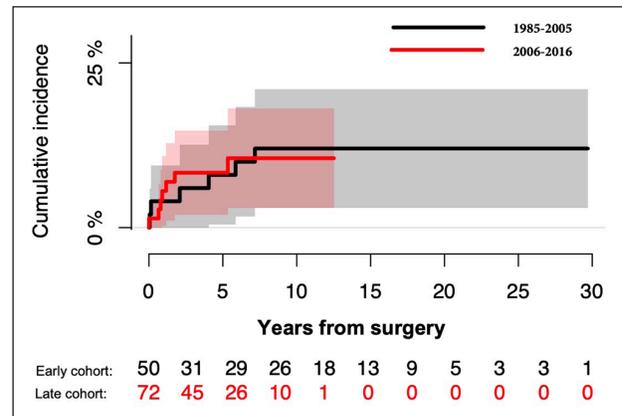
### Ethics

The study was approved by the Danish Data Protection Agency (j.nr: 2012-58-0004) and the Danish Health and Medicine Authority (3-3013-2578/1). Informed oral and written consent was obtained from all individual participants still alive at inclusion in the study.

## Results

### Limb survival

Eight patients in the late cohort were amputated (11%) (resection site: knee ( $n=5$ ); hip ( $n=3$ )) after a mean of



**Figure 1.** The Aalen–Johansen estimate of the risk of amputation in the early and late cohort ( $p=0.9$ ).

1.5 years (range = 1 day–5 years). Seven patients (10%) were amputated due to recurrence of tumor, and one patient (1%) due to acute ischemia. The 2-, 5-, and 10-year cumulative incidence of amputation was 8% (95% CI = 2%–15%), 8% (95% CI = 2%–15%), and 11% (95% CI = 3%–18%), respectively (Figure 1). We did not find any significant difference between anatomic sites (hip vs knee) ( $p=0.8$ ). We found no difference comparing cumulative incidence for amputation between the early and late cohort ( $p=0.9$ ) (Figure 1).

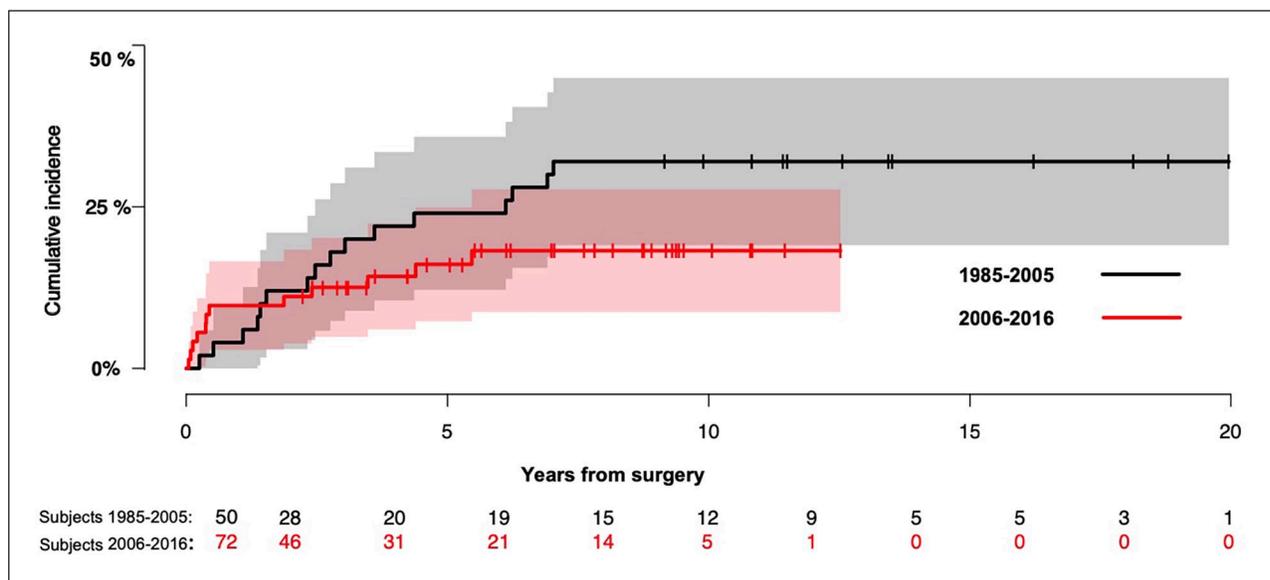
### Incidence of revisions

In the late cohort, 28 patients (39%) underwent revision surgery for all causes (i.e. major and minor revisions). A total of 50 revisions were conducted in the late cohort. Distribution of all revisions for both cohorts is described in Table 2. Average time from primary surgery to first revision was 1.2 years (1 day–7.4 years).

Major revision by anatomic site included knee ( $n=10$ ), hip ( $n=2$ ) and for minor revision, knee ( $n=7$ ), hip ( $n=6$ ), and total femur ( $n=1$ ). Main causes for first revision in general in the present late cohort were deep infection ( $n=6$ ; 8%) followed by wear of polyethylene ( $n=5$ ; 7%) and aseptic loosening ( $n=5$ ; 7%). Average time from surgery to major revision was 4.1 years (range = 17 days–12.5 years). The 2-, 5-, and 10-year cumulative incidence of major revision was 11% (95% CI = 4%–18%), 16% (95% CI = 7%–25%), and 18% (95% CI = 9%–28%), respectively (Figure 2). The 2-, 5-, and 10-year cumulative incidence of minor revision was 15% (95% CI = 7%–24%), 20% (95% CI = 11%–30%), and 25% (95% CI = 14%–36%), respectively (Figure 3). Nine patients developed secondary recurrence: osteosarcoma ( $n=2$ ), myofibrosarcoma ( $n=2$ ), sarcoma not otherwise specified (NOS) ( $n=2$ ), chondrosarcoma ( $n=2$ ), and synovial sarcoma ( $n=1$ ). Secondary recurrence caused in total 10 revisions: minor revisions ( $n=3$ ) and major revisions ( $n=7$ ).

**Table 2.** Causes and numbers of performed revisions in general.

All patients		Early cohort	Late cohort	p-value
Number of revisions	n = 128	n = 78	n = 50	0.31
Aseptic loosening	25	18	7	0.33
Polyethylene wear	20	16	4	0.007
Deep infection	36	19	17	0.6
Instability	15	10	5	1
Fractured stem	7	5	2	0.6
Periprosthetic fracture	4	4	0	0.05
Recurrence or progression of tumor	12	2	10	0.20
Severe symptoms from earlier revision	1	1	0	1
Compartment	1	1	0	0.4
Reduced function (brisement forcé)	3	0	3	1
Ulceration through acetabulum	1	1	0	0.4
Ischemia	1	0	1	1
Unknown	1	1	0	0.8

**Figure 2.** The Aalen-Johansen estimate for risk of major revision in the early and late cohort ( $p=0.2$ ).

Comparison of cumulative incidence for major ( $p=0.2$ ) and minor ( $p=0.9$ ) revisions between the early and late cohort demonstrated no statistically significant differences; however, a clear tendency toward lower major revision risk in the late cohort was observed (Figures 2 and 3).

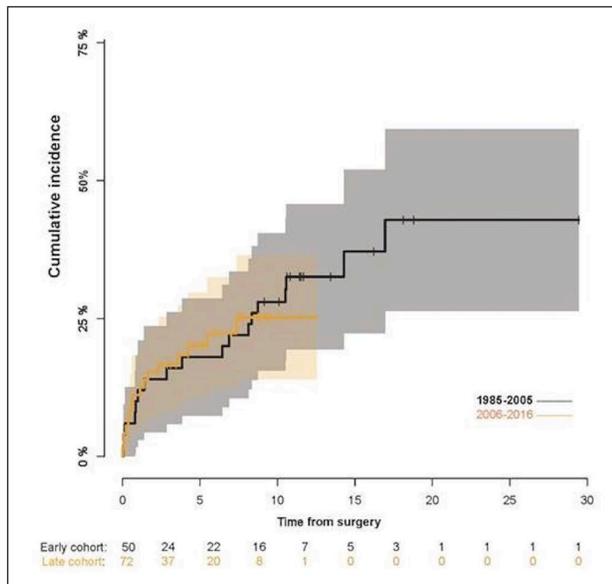
### Deep infections

In the late cohort, 8 patients (11%) had a total of 17 major ( $n=15$ ) and minor ( $n=2$ ) revisions due to deep infection. The 5- and 10-year cumulative incidence for deep infection was 11% (95% CI=4%–19%) and 11% (95% CI=4%–19%), respectively (Figure 4). We found no difference between the two cohorts ( $p=0.9$ ) (Figure 4). Seven patients (10%) had

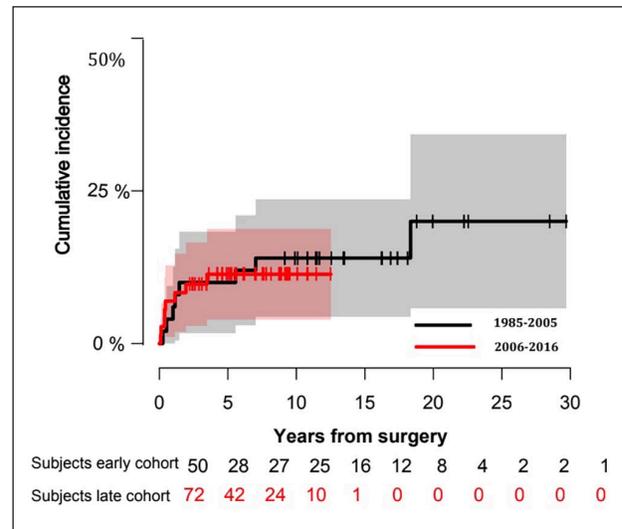
deep infection in a primary implant; three patients (4%) had re-infection and their secondary implant and one patient (1%) had infection in a secondary implant inserted for other causes than infection. The 5- and 10-year cumulative incidence for deep infection after revision was 17% (95% CI=2%–32%) and 17% (95% CI=2%–32%), respectively. We found no difference for deep infection after revision between the two cohorts ( $p=0.81$ ).

### The Henderson classification

Complications according to Henderson et al.<sup>12</sup> are summarized in Table 3. Out of a total of 50 major and minor revisions according to the Henderson classification, 39 could be classified.



**Figure 3.** The Aalen-Johansen estimate for risk of minor revision in early and late cohort ( $p=0.9$ ).



**Figure 4.** The Aalen-Johansen estimate for risk of deep infection in the early and late cohort ( $p=0.9$ ).

**Table 3.** Showing the Aalen-Johansen estimate of the 5- and 10-year risk of complications to surgery classified according to Henderson et al.<sup>12</sup> of both cohorts, using Gray's test to assess the difference between cohorts.

	Number of primary implants	Type 1 (soft tissue failure)	Type 2 (aseptic loosening)	Type 3 (structural failure)	Type 4 (infection)	Type 5 (tumor progression)	Total complications
<b>Old cohort</b>	n = 50	n = 10 (20%)	n = 18 (36%)	n = 26 (52%)	n = 15 (30%)	n = 2 (4%)	n = 71
Cumulative incidence							
5 year		8.0%	12.0%	10.0%	10.0%	2.0%	
10 year		8.0%	14.0%	24.0%	14.0%	4.0%	
<b>Late cohort</b>	n = 72	n = 5 (7%)	n = 6 (8%)	n = 8 (11%)	n = 15 (21%)	n = 6 (8%)	n = 39
Cumulative incidence							
5-year		4.7%	4.5%	6.0%	10%	8.3%	
10-year		4.7%	9.0%	11.0%	10%	8.3%	
<b>Gray's test</b>		$p=0.4$	$p=0.3$	$p=0.2$	$p=0.6$	$p=0.3$	

The overall predominant failure mode was non-mechanical ( $n=20$ , 51%), whereas mechanical failures constituted 49% ( $n=19$ ) (Table 3). We found no differences in failure mode Types 1–5 between the early and late cohort (Table 3).

### Functional outcome

In the late cohort, 47 patients were alive during the entire study period, and functional outcome was evaluated in 40 patients after an average of 6 (1.7–12) years post-operatively. Seven patients did not have a functional outcome evaluation due to amputation ( $n=3$ ) or lost to follow-up for various reasons ( $n=4$ ). The mean (range) individual MSTS score

parameters were as follows: pain 3.5 (0–5), function 2.6 (0–5), emotional acceptance 3.5 (0–5), support 3.8 (0–5), walking ability 3.7 (0–5), and gait 3 (0–5). Mean MSTS score was 20.2 (range=6–30), representing a mean score of 67%.

### Discussion

The 2-, 5-, and 10-year cumulative incidence of major revisions was 11%, 16%, and 18%, respectively. The 2-, 5-, and 10-year cumulative incidence for amputation was 8%, 8%, and 11%, respectively. Deep infection and recurrence of tumor caused most revisions. According to the Henderson classification, non-mechanical endoprosthetic failures were the most frequent type of failure.

The incidence of major revisions in modern tumor-prostheses was improved even if no significant difference was found. The reported literature on the two mainly used modern prostheses in this study is sparse. Pala et al.<sup>8,26</sup> and Yilmaz et al.<sup>27</sup> evaluated the rotating-hinge GMRS (Stryker®, Inc.) prosthesis. They report higher implant survival than us; however, Pala et al.<sup>26</sup> excluded soft tissue failures and revisions caused by local recurrence. Although our results are not directly comparable to Pala et al.<sup>26</sup> due to diverse statistical analyses, we also found a clear tendency toward lower major revision risk in the late cohort.

As opposed to previous decades, the vast majority of all patients with bone sarcomas are currently offered LSS regardless of life expectancy,<sup>3</sup> and the subsequently heterogeneity in terms of diagnosis, staging, and adjuvant oncological treatment undoubtedly has affected the comorbidity and risk for post-surgical complications between the cohorts. Thus, we speculate that our findings is a reflection of the change in patient selection over time, in combination with low sample size and consequently risk of Type 2 errors, as indicated by the wide CIs. Also, the difference in revision rates reported from the previous studies<sup>9,26</sup> could in part be explained by the lack of using a competing risk model for calculation of risk of implant revision. We believe that this is particularly important when estimating risks for patients with sarcoma because of their high mortality rates and increased risk of revision over time due to implant wear-out, especially in long-term follow-up studies.

In a systematic review, Thornley et al.<sup>17</sup> recently described low quality of reporting and inconsistency with regard to follow-up and surveillance among studies, hence limiting inter-study comparison due to heterogeneity. Henderson et al.<sup>12</sup> have suggested five classifications of failure mode in order to obtain consistency. However, any comparison across studies between five subgroups with competing risk analysis will be limited due to the often small sample sizes. Previous findings with chi-square test do not take revisions over time into consideration. To detect any potential differences with competing risk models across studies, we suggest broader consistency with fewer categories, and thus larger sample sizes.

Secondary amputation after LSS is a devastating event for any patient and especially for patients with a severe course of illness and perhaps sparse residual life expectancy. Various rates from 6% to 23%<sup>28</sup> of secondary amputation after LSS have been reported.<sup>16,20</sup> We found our results in the late cohort (11%, 8 out of 72) comparable to the literature. It is well-known that it is difficult to achieve free margins with soft tissue sarcomas since they are often poorly circumscribed.<sup>29</sup> Recurrence of soft tissue sarcomas or highly malignant sarcomas with significant soft tissue components at various locations was the main cause for amputation in present late cohort (n=6). We found significant poorer overall survival in patients with secondary recurrence. This is possibly explained by the broader selection of patients who are now offered LSS and hence a potential

higher risk of local recurrence due to, for example, large soft tissue components. There exist conflicting reports whether local recurrence in osteosarcoma patients is independently associated with overall survival separately from chemotherapy response.<sup>30,31</sup> Since the patient survival in general has plateaued parallel with significant improvements in imaging and surgical techniques, the assumed surgical improvements may not affect overall survival. As stated by Anderson,<sup>30</sup> there has come to be an acceptance of higher rates of local recurrence in LSS compared to amputation. To what extent this affects overall survival is controversial. Bacci et al.<sup>32</sup> demonstrated that free margins and poor chemotherapy response yielded better overall survival compared to poor margins and good chemotherapy response. Bertrand et al.<sup>33</sup> reported inferior survival in patients with poor margins in a review comprising 241 patients treated between 1999 and 2001, and Ferguson and Goorin<sup>34</sup> stated that failure to achieve complete gross resection with free margins leads to high risk of local recurrence and poor overall survival. However, Grimer et al.<sup>35</sup> reported that increased rates of local recurrence did not affect overall survival, and thus advocated to choose LSS despite poor chemotherapy response. The same findings with increased local recurrence rates, without compromising overall survival, were found by Myers et al.<sup>19</sup> In a recent systematic review, Thornley et al.<sup>17</sup> reported that incidence of local recurrence was only reported in 5% of all patients, and hence, the previous reverse findings may be caused by varied and inconsistent reporting.

Incidence of aseptic loosening has been reported with various rates from 2% to 11%.<sup>8,19,36,37</sup> Rotating-hinge prostheses, as in present late cohort, has been reported to reduce the torsional stress in the bone-implant interface, hence reducing aseptic loosening and stem breakage when compared to fixed-hinge prostheses.<sup>7,12,19</sup> Furthermore, by allowing multiple degrees of movement, rotating-hinge prostheses intend to reduce wear by dispersing stress throughout the condylar surfaces.<sup>38</sup> Our findings suggest the same mechanical improvements of implants: in the early cohort, aseptic loosening constituted the vast majority of all revisions (23%)<sup>21</sup> as opposed to the present cohort where aseptic loosening constituted fewest major revisions. This is also demonstrated by the difference between Henderson Type 3 failures in the early (30%) and the late cohort (11%) that is wear of polyethylene and stem-fractures. We consider these results to support the hypothesis that rotating-hinge prostheses reduce the mechanical stress, although our result undoubtedly also reflects the relatively sparse follow-up time. We found our demonstrated risk of 5% and 9% after 5 and 10 years, respectively (Table 3) fully comparable to Puchner et al.<sup>39</sup> who by competing risk analysis demonstrated the true incidence of aseptic loosening of 6% and 16% at 5 and 10 years, respectively. By comparison between rotating-hinge and fixed-hinge prostheses, Puchner et al.<sup>39</sup> did not demonstrate significant differences, which could

be caused by Type 2 error due to the low sample size as in this study.

Since rotating-hinge prosthesis has been taken into use, many studies now report deep infection as the most common cause for revisions<sup>4,11,40,41</sup> due to the higher risks in terms of wide resections, loss of tissue and prolonged surgery time, and often also adjuvant oncological treatment.<sup>18</sup> The most common cause for revision in present modern tumor-prostheses was deep infection, with distal femur (n=3) and proximal tibia (n=3) as the most common sites. We found no difference in the risk of deep infection between the two cohorts. Our findings (11%, 8 out of 72) are comparable to Fujiwara et al.<sup>42</sup> who in a retrospective study evaluated tumor-prostheses in the lower extremities and demonstrated a rate of 12% in 121 both fixed- and rotating-hinge tumor-prostheses. Proximal tibia is the predominant location for deep infection, and hence also the most common place for amputations caused by deep infection. This has been suggested to be associated with insufficient wound coverage after extensor mechanism reconstruction.<sup>7,18,43</sup> The consisting higher incidence of infections in the proximal tibia is confirmed in a recent multicenter study by Mazaleyra et al.<sup>44</sup> who compared survival between distal femoral and proximal tibial reconstruction prostheses. In addition, Puchner et al.<sup>39</sup> recently demonstrated a 5- and 10-year cumulated incidence of infection of 17% and 22%, respectively, when evaluating LSS and reconstruction with tumor-prostheses of the proximal tibia. Using competing risk analysis, these results are fully comparable to present results from late cohort (11%), although they demonstrate a fairly higher incidence of infections. However, the cohort by Puchner et al.<sup>39</sup> as well comprised patients suffering from metabolic bone disease (MBD) who are more prone to infections due to immune-suppression and a poor general health condition.

All patients in this study had salvage after revision for deep infection with no need for subsequent amputation at final follow-up. However, the 5- and 10-year incidence for deep infection after revision was 17%, with deep infection constituting the majority of the prior revisions. These findings were also demonstrated by Theil et al.,<sup>45</sup> who found type of first complication to be associated with the type of second complication. Although all patients had salvage after deep infection, our results emphasize that deep infection remains a severe complication after reconstruction despite improved adjuvant oncological treatment, implant possibilities, and surgical techniques. Several studies suggest the use of silver-coated implants.<sup>40,42,46,47</sup> Streitbuenger et al.<sup>47</sup> demonstrated promising results when comparing silver-coated implants with standard implants and Pala et al.<sup>40</sup> advocate using silver- and iodine-coated implants in high-risk patients to reduce re-infection rate. However, none of the studies demonstrated statistical difference when comparing silver-coated and standard implants. Demonstration of genuine association by coated implants is warranted.

We found no improvement in mean MSTS score in the late cohort compared to the early cohort. Reviewing the literature, mean MSTS score ranges from 66% to 82%.<sup>48,49</sup> We speculate that the lack of improvement with modern tumor-prostheses partly reflects that only patients with high functional status in the early cohort were offered LSS.

### Limitations

Some limitations to this study need to be discussed. This study is a retrospective study with a small sample size for statistical comparison. We included all patients available with none lost to follow-up, and our cohorts should therefore in principle be representative to the population of interest. This does, however, not exclude the risk of underpower and risk of Type 2 errors as indicated by wide CIs. Also, although comparisons were drawn between subgroups, present cohorts were prone to confounding in terms of diagnosis, staging adjuvant and neo-adjuvant treatment, which undoubtedly has affected outcome and hence the interpretation.

### Conclusion

In conclusion, at a minimum of 2 years follow-up with modern modular tumor-prostheses, we demonstrated a relatively low risk of implant failure and amputation, and also an acceptable functional outcome. Deep infection remains a severe high-risk complication after reconstruction despite improved adjuvant oncological treatment, implant possibilities, and surgical techniques. No statistical difference of implant survival, limb survival, and functional outcome between tumor-prostheses over two time periods was observed, possibly explained by Type 2 error as indicated by wide CIs and patient group heterogeneity. For future evaluations of tumor-prostheses, we advocate using competing risk analysis to achieve valid estimates of implant and limb survival and to enhance interstudy comparison.

### Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Ethical approval

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### Informed consent

Informed oral and written consent was obtained from all individual participants still alive at inclusion in the study.

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