



Cartilage survival of the knee strongly depends on malalignment: a survival analysis from the Osteoarthritis Initiative (OAI)

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Abstract

Purpose Progression of osteoarthritis over time is poorly understood. The aim of the current study was to establish a timeline of “cartilage survival rate” per subregion of the knee in relation to mechanical alignment of the lower extremity. The study hypothesized that there are differences in progression of osteoarthritis between varus, valgus and physiologic lower extremity alignment.

Methods Based on hip-knee-ankle standing radiographs at baseline, 234 knees had physiologic ($180^\circ \pm 3^\circ$, mean 179.7°), 158 knees had varus ($< 177^\circ$; mean 174.5°) and 66 knees valgus ($> 183^\circ$; mean 185.2°) alignment (consecutive knees of the OAI “Index Knee” group, $n = 458$; mean age 61.7; 264 females). The Osteoarthritis Initiative (OAI; a multi-center, longitudinal, prospective observational study of knee osteoarthritis [30] using MRIs) defines progressive OA as a mean decrease of cartilage thickness of $136 \mu\text{m}/\text{year}$ and a mean decrease of cartilage volume by 5% over 1 year (DESS sequences, MRI). A Kaplan–Meier curve was generated for osteoarthritis progression based on OAI criteria.

Results Osteoarthritis progression based on volume decrease of 5% in varus knees occurred after 30.8 months (medial femoral condyle), after 37 months (medial tibia), after 42.9 months (lateral femoral condyle) and 43.4 months (lateral tibia), respectively. In a valgus alignment progression was detectable after 31.5 months (lateral tibia), after 36.2 months (lateral femoral condyle), after 40.4 months (medial femoral condyle) and 43.8 months (medial tibia), respectively. The physiological alignment shows a progression after 37.8 months (medial femoral condyle), after 41.6 months (lateral tibia), after 41.7 months (medial tibia) and after 43 months (lateral femoral condyle), respectively.

Conclusion Based on data from the OAI, the rate and location (subregion) of osteoarthritis progression of the knee is strongly associated with lower extremity mechanical alignment.

Level of evidence Level I (prognostic study).

Keywords Cartilage survival · Timeline of osteoarthritis · Limb alignment

Introduction

Knee osteoarthritis (OA) has a global prevalence of 3.8% [25] and is a major source of socioeconomic costs [18]. It has an increasing burden (years lived with disorder) of 64% over the last 2 decades [25] and is the most common cause of knee arthroplasty [2, 3].

In the past, an indirect approximation of articular cartilage measuring the minimum joint space width on radiographs represents the standard to detect progression of knee OA [1, 12]. Measuring minimum joint space width on radiographs is an indirect approach and is subject to error secondary to reproducibility of position of the joint, beam alignment, and distance between the joint and film [23]. The current gold standard to detect progression of knee OA is

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magnetic resonance imaging (MRI) [12, 40, 43]. MRI provides excellent soft tissue imaging and is accurate in measuring cartilage volume, thickness, and surface area [11, 14, 41, 42].

The Osteoarthritis Initiative (OAI) is a public free of charge database used to conduct longitudinal studies using prospective MRI data to analyze cartilage alterations in knee OA. A number of studies [13, 14, 26, 28, 42, 43] reported on changes in cartilage volume and thickness in ten tibial and six femoral subregions. Maschek et al. [26] showed a minimum loss of cartilage thickness of 136 μm in the most affected subregion (OV1) in knees with Kellgren and Lawrence grade (KLG) 2–4. Wluka et al. [45] defined OA progression as annual change in cartilage volume of 5.3%/year.

A number of factors are associated with progression of OA (age, previous knee injury, obesity) [18, 37]. Inter alia (BMI, physical activity, meniscal pathologies, cartilage or bone marrow lesions) [4, 24], limb alignment represents a risk factor for progression of OA of the knee [17, 20, 34–36]. Sharma et al. [36] showed a fourfold higher risk of OA progression with varus alignment ($> 5^\circ$) and a odds ratio of 4.89 for progression of OA in valgus alignment ($> 5^\circ$).

Although the quantitative loss of cartilage thickness and volume has been described in previous studies, nobody has studied yet, to our knowledge, the survival rate (Kaplan–Meier survival rate) over the time and can show a detailed timeline of cartilage loss in subregions of the knee.

Based on the OAI dataset, the study wants to describe a detailed timeline of cartilage survival. Progression of OA was analyzed to answer the following research questions: (1) Does mechanical alignment of the lower limb affect progression of OA (timeline of cartilage survival) in the different subregions of the knee? (2) Are there differences in the change of cartilage thickness and cartilage volume between the subregions of the knee?

Materials and methods

Cohort

The study investigates the Osteoarthritis Initiative (OAI) database, a multi-center, longitudinal, prospective observational study of knee OA [30]. A total of 4791 subjects aged between 45 and 79 years at risk of developing knee OA were enrolled in the OAI. Annual radiographs, MRI, and clinical assessment of knees and disease activity were performed for all participants over a period of 8 years.

The “Core Image Assessment sample” at OAI was designed to provide longitudinal structural outcomes. 600 knees, part of the “Core Image Assessment sample”, were defined as “Index knees”: symptomatic knees with Kellgren and Lawrence (K&L) grades 2 or 3 radiographic evidence

of OA at baseline [30]. Eckstein et al. [13, 42] performed quantitative cartilage measurements on MRI (sagittal DESS sequence) of these knees at baseline, 12, 24 and 48 months (kMRI quant Cart sagDESS, Project 9A) [31]. Of the 600 index knees, the hip-knee-ankle standing radiographs were assessed to determine limb alignment (available at a single measurement at 12 months by Cooke et al. [30] (“fXR Knee Alignment Cooke”), ICC 0.99). 142 knees were excluded because no alignment measurements were available leaving 458 knees to be included in the current study. Subjects were grouped based on lower limb alignment into varus alignment ($n = 158$, hip-knee-ankle angle $< 177^\circ$), physiologic alignment ($n = 234$, hip-knee-ankle angle $180^\circ \pm 3^\circ$) and valgus alignment ($n = 66$, hip-knee-ankle angle $> 183^\circ$). 458 knees were available for analysis at baseline, 451 knees at 12 months, 458 at 24 months and 56 at 48 months.

Image analyses

The cartilage volume and cartilage thickness were analyzed on sagittal double-echo steady-state (DESS) sequences. Reporting details and nomenclature for MRI evaluation are reported on the OAI website [30, 31] and by Eckstein et al. [10]. The medial and lateral femorotibial cartilage was segmented manually, using proprietary software (Chondrometrics GmbH), with two readers blinded to disease severity, alignment, and the order of image acquisition [44]. One expert reader, with more than 5 years of MRI-based cartilage segmentation experience, performed quality control readings of all segmentations.

The following cartilage volume parameters were analyzed (Fig. 1): central medial femur (total, OAI variable “BMFVCL”, in mm^3 and normalized, “BMFVCN”, in mm), central lateral femur (total, “BLFVCL”, in mm^3 and normalized, “BLFVCN”, in mm), central medial tibia (total, “WMTVCL”, in mm^3 and normalized, “WMTVCN”, in mm) and central lateral tibia (total, “WLTVCL”, in mm^3 and normalized, “WLTVCN”, in mm). The following thickness parameters (in mm) as femoral subregions were analyzed: central area of the weight-bearing lateral femur (“BLFMTH”), central area of the weight-bearing medial femur (“CBMFMTH”), internal part of the weight-bearing medial femur (“IBMFMTH”), external part of the weight-bearing medial femur (“EBMFMTH”). Following thickness parameters (in mm) as tibial subregions were analyzed: internal part of the weight-bearing medial (“IMTMTH”) and lateral (“ILTMTH”) tibia, central area of the medial (“CMTMTH”) and lateral (“CLTMTH”) tibia, external area of the medial (“EMTMTH”) and lateral (“ELTMTH”) tibia, anterior part of the medial (“AMTMTH”) and lateral (“ALTMTH”) tibia as well as posterior area of the medial (“PMTMTH”) and lateral (“PLTMTH”) tibia.

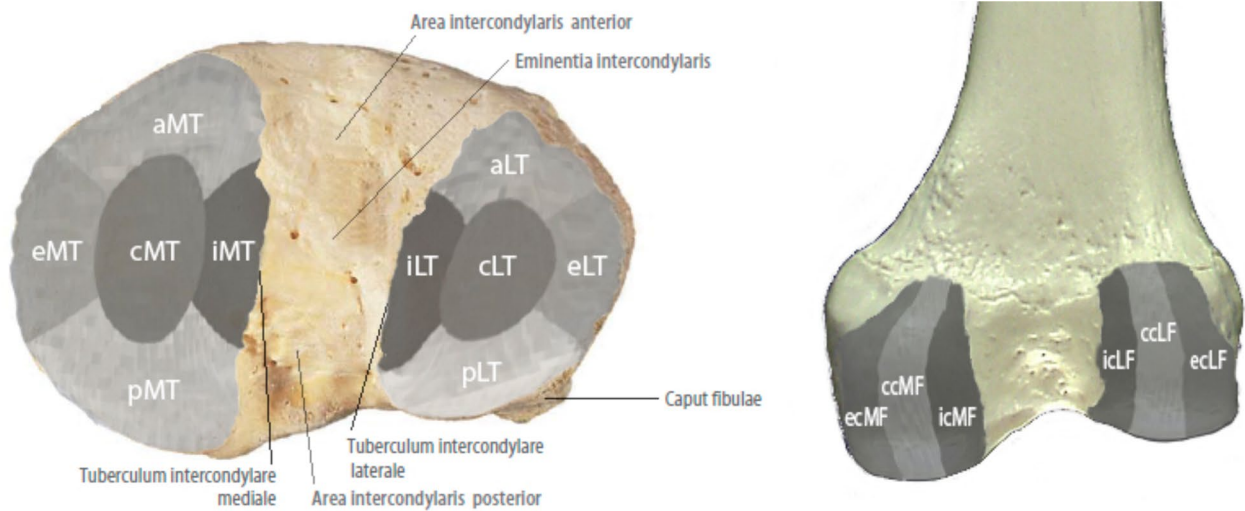


Fig. 1 The analyzed subregions at the tibia (left) and the femur (right). Central medial tibia (cMT) includes variables “WMTVCL”, “WMTVCN” and “CMTMTH”, external medial tibia (eMT) includes “EMTMTH”, internal medial tibia (iMT) includes “IMTMTH”, anterior medial tibia (aMT) includes “AMTMTH”, posterior medial tibia (pMT) includes “PMTMTH”. At the lateral tibia following subregions with variables are described: central lateral tibia (cLT) with variables “WLTVCL”, “WLTVCN” and “CLTMTH”; external lateral

tibia (eLT) with “ELTMTH”; internal lateral tibia (iLT) with “ILTMTH”; anterior lateral tibia (aLT) with “ALTMTH” and posterior lateral tibia (pLT) with “PLTMTH”. At the femur subregion central medial femur (ccMF) includes variables “BMFVCL”, “BMFVCN” and “CBMFMTH”; external central medial femur (ecMF) includes “EBMFMTH”; internal central medial femur (icMF) includes “IBMFMTH”; on the lateral femur subregion central lateral femur (ccLF) with “BLFVCL”, “BLFVCN” and “BLFMTH” is analyzed

Limb alignment (varus, valgus, physiologic) was identified on hip-knee-ankle radiographs (parameter: fXR_KneeAlign_Cooke01). Frontal alignment was defined as the angle between the mechanical axes of the femur and tibia [6, 7].

In the current study, progression of knee OA per year was defined by a minimum thickness loss of 136 μm [26] or/with volume loss of minimum 5% [45].

The study received IRB approval by the institutional review board at the authors’ institution (Hospital for Special Surgery, NY, USA, IRB #15013).

Statistical analyses

Demographics are shown in Table 1. Possible confounders (age, BMI and previous surgery) are analyzed using Student’s *t* test (BMI, age) and Pearson’s Chi square test (previous surgery) (Table 2).

Kaplan–Meier survival curves were generated for cartilage survival. A loss of more than 136 μm or 5% of volume was counted as progression of OA (“event” in Kaplan–Meier survival analysis). Cases without an event were censored. For every subregion (volume: 2 femoral, 2 tibial; thickness: 4 femoral, 10 tibial), three survival curves (alignment dependent: varus, valgus and

Table 1 Demographics of 600 knees summarized at the “Core Image Assessment sample” (symptomatic knees with Kellgren and Lawrence grades 2 or 3 radiographic evidence of OA)

Demographics	Mean	Range
Age	61.7	45–79
BMI	29.7	18.2–47.7
Sex	264 females, 194 males	
<i>n</i>		
Any knee surgery		115
Arthroscopy		97
	With meniscectomy/meniscus repair	81
	With ACL repair	16
Others		18

Table 2 Possible confounding factors such as BMI, age and previous knee surgery do not show any statistical significant differences between knees reaching the endpoint of cartilage loss and knees with cartilage survival

	Reaching endpoint	Cartilage survival	<i>p</i> value
BMI (mean, ±SD)	30.1 (± 5.3)	29.5 (±4.6)	n.s.
Age (mean, ±SD)	61.8 (± 7.7)	61.7 (±9)	n.s.
Previous knee surgery (<i>n</i>)	29	86	n.s.

T test was used for BMI and age, Pearson Chi square test for “Previous Knee Surgery”. The subgroup of the medial femoral condyle is shown (other subgroups do not show any statistical significance too)

physiological) were prepared. Significant differences in survival time between each subregion and/or alignment type were determined by log-rank tests. Effect size was calculated according to Hedge’s *g*. A *p* value of less than 0.05 was considered to be statistically significant. All statistical analyses were performed using IBM SPSS Statistics software version 23 (Armonk, NY: IBM Corp.).

Results

Comparison between alignments showed statistical significant differences (Tables 3, 4), effect sizes showed a large effect in every comparison (Hedge’s *g* 2.13–9.03), except at the lateral femoral condyle (varus vs physiologic alignment Hedge’s *g* 0.15).

Cartilage thickness survival rates and subregion differences in varus knees are demonstrated in Table 5. Table 6 summarizes the cartilage thickness survival rates and each difference between subregions in knees with valgus alignment. Physiologic aligned osteoarthritic knees showed differences in cartilage thickness survival rates as well as in their subregion analyses (Table 7).

Varus knees showed shortest cartilage volume survival rates at the medial femur (30.8 months, CI 95% 28.2–33.4), followed by the medial tibia (36.9 months, CI 95% 34.5–39.4) (Table 3). Valgus knees showed shortest cartilage volume survival at the lateral tibia (31.5 months, CI 95% 27.6–35.4) and at the lateral femur (36.2 months, CI 95% 32.4–40) (Table 7). Physiologic aligned osteoarthritic knees showed shortest volume survival rates at the medial femur (37.8 months, CI 95% 36–39.7) (Table 8).

Table 3 Survival rates (in months) of cartilage volume depending on limb alignment (varus, valgus and physiologic)

		Variable	Varus		p-value (varus vs physiologic)	Physiologic		p-value (physiologic vs valgus)	Valgus		p-value (varus vs valgus)
			Mean Survival (months)	CI 95%		Mean Survival (months)	CI 95%		Mean Survival (months)	CI 95%	
Medial Femur	Vol.	BMFVCL	31.7	29-34.3	0.001	37.2	35.3-39.1	0.096	40.2	36.9-43.5	0.000
	Nor. Vol.	BMFVCN	30.8	28.2-33.4	0.000	37.8	36-39.7	0.144	40.4	37-43.7	0.000
Lateral Femur	Vol.	BLFVCL	42.5	40.5-44.4	0.814	42.8	41.3-44.3	0.024	38.5	35-42.1	0.033
	Nor. Vol.	BLFVCN	42.9	41.1-44.8	0.869	43	41.5-44.5	0.000	36.2	32.4-40	0.000
Medial Tibia	Vol.	WMTVCL	36.9	34.5-39.4	0.006	40.8	39.1-42.5	0.071	44.2	41.5-46.9	0.001
	Nor. Vol.	WMTVCN	37	34.6-39.4	0.000	41.7	40.1-43.4	0.218	43.8	41.2-46.4	0.001
Lateral Tibia	Vol.	WLTVCL	41.6	39.7-43.6	0.986	41.8	40.2-43.4	0.000	30.7	26.8-34.7	0.000
	Nor. Vol.	WLTVCN	43.4	41.6-45.1	0.087	41.6	40-43.2	0.000	31.5	27.6-35.4	0.000

Statistical significant differences between Kaplan–Meier survival rates (by log-rank test) were shown (varus vs valgus, varus vs physiologic, valgus vs physiologic)

Statistically differences are highlighted

Table 4 Survival rates (Kaplan–Meier curve) of cartilage thickness in months depending on limb alignment

		Varus		p-value (varus vs physiologic)	Physiological		p-value (physiologic vs valgus)	Valgus		p-value (varus vs valgus)
		Mean Survival (months)	CI 95%		Mean Survival (months)	CI 95%		Mean Survival (months)	CI 95%	
Medial Femur	Central	31.2	28.6-33.8	0.000	37.6	35.7-39.6	0.029	41.6	38.5-44.8	0.000
	Internal	39.6	37.5-41.8	0.854	39.3	37.4-41.1	0.170	41.6	38.5-44.8	0.160
	External	37.3	34.9-39.7	0.001	41.5	39.9-43.1	0.017	45.3	43.1-47.4	0.000
Lateral Femur	Central	45.5	44.1-46.9	0.673	45.1	43.8-46.3	0.000	39.8	36.5-43.1	0.000
Medial Tibia	Central	33.6	31-36.1	0.002	38.4	36.5-40.3	0.017	42.7	39.8-45.6	0.000
	Internal	40	37.9-42.2	0.744	39.5	37.7-41.3	0.688	40.4	36.9-43.8	0.881
	External	36.9	34.5-39.3	0.001	41.7	40-43.3	0.259	43.3	40.5-46	0.001
	Anterior	43.6	41.9-45.3	0.422	45	43.8-46.2	0.246	46.2	44.4-47.9	0.077
	Posterior	44.5	42.9-46.1	0.076	46.2	45.2-47.1	0.890	46	43.8-48.2	0.308
Lateral Tibia	Central	38.7	36.5-41	0.340	37.7	35.9-39.6	0.001	30	26-34	0.000
	Internal	37.3	35-39.6	0.283	38.7	36.8-40.5	0.030	34	30.2-37.8	0.196
	External	41.8	39.8-43.8	0.028	44.7	43.5-46	0.000	38.9	35.5-42.3	0.123
	Anterior	45.3	43.8-46.7	0.834	45.9	45-46.9	0.002	41.8	38.9-44.8	0.014
	Posterior	44.1	42.5-45.8	0.845	44.1	42.7-45.4	0.002	40.2	36.9-43.4	0.002

p values following log-rank test to determine statistical significant differences between each Kaplan–Meier curve (varus vs valgus, varus vs physiologic, valgus vs physiologic)

Statistically differences are highlighted

Discussion

The main finding of the current study, as one of the first, is the detection of a cartilage survival rate over time (Kaplan–Meier) and shows a strong relation to malalignment. Varus and valgus alignment accelerate the OA progression rate compared to osteoarthritic knees with physiologic alignment. Differences of cartilage survival in subregions contribute to more precisely understanding of an “OA-progression-timeline” and create a “time-map” of cartilage survival.

The study reveals that the cartilage survival is strongly influenced by limb alignment similar to prior reports in the literature [27, 28, 34, 36]. The current study suggests that in knees with physiologic alignment, a more homogeneous progression of OA is observed compared to the varus or valgus group. In contrast, varus knees show a broader time range of the cartilage loss in the anterior and posterior subregion of the medial compartment suggesting that little posterior translation of the femur occurs. In valgus knees, however, posterior translation characterizes the progression of OA. These findings might be explained by differences in normal kinematics of the knee with a relatively constant medial condyle and posterior translation of the lateral condyle contact point during a knee bending [8, 9, 38].

In relation to cartilage thickness in varus and valgus alignment, a statistical significant difference of survival rates can be shown in the anterior and posterior subregion of the lateral compartment (lateral tibia anterior: $p = 0.014$; lateral tibia posterior: $p = 0.002$). This suggests that in valgus knees an anterior to posterior translation characterizes the progression of OA, whereas in varus knees direction of progression is in medial direction (medial tibia central: $p = 0.001$ medial external tibia: $p = 0.001$).

A closer look into differences between subregions in each alignment type shows in varus knees in the central medial tibia and central medial femur the shortest survival rates. Not surprisingly, external subregions on the medial tibia and femur are affected early too and the shortest survival rate of the contralateral compartment was determined in the internal lateral tibia. This might be related to beginning medial subluxation [21, 22].

The last affected regions were anterior and posterior. These findings lead to following assumptions: (1) prior studies reported that insufficiency of the ACL is a main factor for posterior medial wear in varus OA knees [19, 29]. Therefore, degeneration of the ACL may not be present in the majority of subjects in the OAI cohort. (2) Anteromedial wear pattern in varus OA knees are reported in anatomical studies analyzing bone wafers collected from total knee arthroplasties [19, 32, 39]. However, these findings cannot be confirmed with

Table 5 “OA-progression-timeline” in varus aligned, osteoarthritic knees with mean cartilage thickness survival rates (in months) are demonstrated

Varus-Alignment		Variable	Mean Survival (months)	CI 95%	p-value 1	p-value 2	p-value 3	p-value 4	p-value 5	p-value 6	p-value 7	p-value 8	p-value 9	p-value 10	p-value 11	p-value 12	p-value 13
Med. Femur	Central	1	CBFMTH	31.2	28.6-33.8												
	Internal	2	IBFMTH	39.6	37.5-41.8	.000											
	External	3	EBFMTH	37.3	34.9-39.7	.002	.151										
Lat. Femur	Central	4	BLFMTH	45.5	44.1-46.9	.000	.000	.000									
Med. Tibia	Central	5	CMTMTH	33.6	31-36.1	.263	.001	.044	.000								
	Internal	6	IMTMTH	40	37.9-42.2	.000	.694	.067	.000	.000							
	External	7	EMTMTH	36.9	34.5-39.3	.003	.107	.861	.000	.066	.046						
	Anterior	8	AMTMTH	43.6	41.9-45.3	.019	.001	.512	.001	.055	.003	.000					
	Posterior	9	PMTMTH	44.5	42.9-46.1	.000	.000	.000	.163	.000	.002	.000	.840				
Lat. Tibia	Central	10	CLTMTH	38.7	36.5-41	.000	.642	.329	.000	.003	.390	.253	.000	.000			
	Internal	11	ILTMTH	37.3	35-39.6	.002	.119	.904	.000	.055	.051	.951	.000	.000	.272		
	External	12	ELTMTH	41.8	39.8-43.8	.000	.062	.001	.003	.000	.135	.001	.140	.092	.020	.001	
	Anterior	13	ALTMTH	45.3	43.8-46.7	.000	.000	.000	.850	.000	.000	.000	.166	.223	.000	.000	.005
	Posterior	14	PLTMTH	44.1	42.5-45.8	.000	.001	.000	.127	.000	.002	.000	.000	.906	.000	.000	.124

Statistically significant differences in survival rates between three medial femoral, one lateral femoral, five medial tibial and five lateral tibial subregions are shown. The shortest survival rates show medial central femur (31.2 months) and medial central tibia (33.6 months). A mediolateral expansion can be seen [external medial tibia: 36.9 months, internal lateral tibia: 37.3, external medial (37.3 months) and internal medial (39.6) femur]. Anterior and posterior subregions (medial and lateral) show the longest survival rates

Statistically differences are highlighted

Table 6 “OA-progression-timeline” in valgus aligned, osteoarthritic knees with mean cartilage thickness survival rates (in months) are demonstrated

Valgus-Alignment		Variable	Mean Survival (months)	CI 95%	p-value 1	p-value 2	p-value 3	p-value 4	p-value 5	p-value 6	p-value 7	p-value 8	p-value 9	p-value 10	p-value 11	p-value 12	p-value 13
Med. Femur	Central	1	CBFMTH	41.6	38.5-44.8												
	Internal	2	IBFMTH	41.6	38.5-44.8	1											
	External	3	EBFMTH	45.3	43.1-47.4	.080	.080										
Lat. Femur	Central	4	BLFMTH	39.8	36.5-43.1	.338	.338	.007									
Med. Tibia	Central	5	CMTMTH	42.7	39.8-45.6	.646	.646	.191	.155								
	Internal	6	IMTMTH	40.4	36.9-43.8	.412	.412	.011	.847	.201							
	External	7	EMTMTH	43.3	40.5-46	.483	.483	.283	.096	.808	.129						
	Anterior	8	AMTMTH	46.2	44.4-47.9	.019	.019	.512	.001	.055	.002	.090					
	Posterior	9	PMTMTH	46	43.8-48.2	.044	.044	.760	.003	.113	.005	.175	.730				
Lat. Tibia	Central	10	CLTMTH	30	26-34	.000	.000	.000	.001	.000	.000	.000	.000				
	Internal	11	ILTMTH	34	30.2-37.8	.002	.002	.000	.028	.000	.019	.000	.000	.178			
	External	12	ELTMTH	38.9	35.5-42.3	.184	.184	.002	.703	.073	.596	.042	.000	.001	.002	.067	
	Anterior	13	ALTMTH	41.8	38.9-44.8	.888	.888	.055	.402	.543	.507	.393	.012	.027	.000	.003	.223
	Posterior	14	PLTMTH	40.2	36.9-43.4	.192	.192	.002	.825	.076	.648	.044	.000	.001	.001	.046	.925

Statistically significant differences in survival rates between three medial femoral, one lateral femoral, five medial tibial and five lateral tibial subregions are shown. The focus is on lateral tibial subregions with the shortest survival rates (central 30 months, internal 34 months), also a posterior component (40.2 months) is apparent

Statistically differences are highlighted

Table 7 “OA-progression-timeline” in physiological aligned, osteoarthritic knees with mean cartilage thickness survival rates (in months) are demonstrated

Physiologic-Alignment		Variable	Mean Survival (months)	CI 95%	p-value 1	p-value 2	p-value 3	p-value 4	p-value 5	p-value 6	p-value 7	p-value 8	p-value 9	p-value 10	p-value 11	p-value 12	p-value 13
Med. Femur	Central	1	CBFMTH	37.6	35.7-39.6												
	Internal	2	IBFMTH	39.3	37.4-41.1	.170											
	External	3	EBFMTH	41.5	39.9-43.1	.003	.117										
Lat. Femur	Central	4	BLFMTH	45.1	43.8-46.3	.000	.000	.000									
Med. Tibia	Central	5	CMTMTH	38.4	36.5-40.3	.638	.364	.014	.000								
	Internal	6	IMTMTH	39.5	37.7-41.3	.190	.939	.103	.000	.399							
	External	7	EMTMTH	41.7	40-43.3	.002	.099	.895	.000	.009	.079						
	Anterior	8	AMTMTH	45	43.8-46.2	.000	.000	.001	.568	.000	.000	.002					
	Posterior	9	PMTMTH	46.2	45.2-47.1	.000	.000	.000	.407	.000	.000	.000	.161				
Lat. Tibia	Central	10	CLTMTH	37.7	35.9-39.6	.754	.089	.001	.000	.421	.096	.001	.000	.000			
	Internal	11	ILTMTH	38.7	36.8-40.5	.542	.445	.019	.000	.905	.466	.012	.000	.000	.363		
	External	12	ELTMTH	44.7	43.5-46	.000	.000	.003	.377	.000	.000	.005	.739	.083	.000	.000	
	Anterior	13	ALTMTH	45.9	45-46.9	.000	.000	.000	.637	.000	.000	.000	.309	.693	.000	.000	.174
	Posterior	14	PLTMTH	44.1	42.7-45.4	.000	.000	.022	.121	.000	.000	.034	.308	.016	.000	.000	.487

Statistically significant differences in survival rates between three medial femoral, one lateral femoral, five medial tibial and five lateral tibial subregions are shown. Physiological aligned knees show a narrow timeline of cartilage survival (37.6–46.2 months) with no typical outliers as in varus (central medial tibia and femur) or valgus (central and internal lateral tibia) knees

Statistically differences are highlighted

OAI–MRI measurements. Rajgopal et al. [32] described an anteromedial pattern of varus OA knees, although 87% showed an intact ACL. In 99.5%, anteromedial wear was present. White et al. [39] described ACL sufficient knees with anteromedial wear pattern in 40% (zone B) and in 43% with central medial wear pattern (zone BC).

These differences to the current study might be an expression of different definitions of medial tibial subregions. Rajgopal et al. [32] described three medial tibial subregions, White et al. [39] defined four medial tibial subregions, from anterior to posterior, respectively. Exact cutoff values were not reported. On the other hand, Raju et al. [33] showed in a cadaver study a more central medial cartilage wear. Biswal et al. [5] showed in a longitudinal MRI study that cartilage lesions located in the central region of the medial compartment progress faster than cartilage lesions in the anterior and posterior portions of the medial compartment. Everhart et al. [16] described a more rapid progress of cartilage defects in the medial compartment than in the lateral compartment.

In valgus OA knees, lateral central and internal tibial cartilage thickness shows the shortest survival rates. Lateral femoral cartilage thickness shows a significant cartilage loss relatively late. The shortest survival time at the tibial subregions, followed by femoral subregions is an important differentiation to varus aligned knees. Eckstein et al. [15] also showed the highest amount of cartilage loss at the internal and central lateral tibia followed by lateral

femoral subregions in valgus knees. In valgus knees, the contralateral medial compartment shows a mean thickness cartilage survival rate of 43.7 months (medial tibial subregions), whereas in varus knee the contralateral compartment shows a mean thickness cartilage survival rate of 41.4 months (lateral tibial subregions). These findings suggest that the valgus osteoarthritic remains longer a uni-compartmental disease than knees with varus OA.

Physiologic aligned osteoarthritic knees show a very homogeneous pattern of cartilage thickness loss. Central femoral cartilage thickness shows shortest cartilage survival rate followed by the central lateral tibial. The longest survival rate was detected in the posterior medial tibial subregion (46.2 months). A comparable pattern to varus aligned knees (central medial femur, central medial tibia and external medial tibia) or valgus aligned knees (central lateral tibia, internal lateral tibia and external lateral tibia) could not be shown.

The current study has several limitations. First, the cutoff values (cartilage loss of 136 μm thickness or 5% volume over 1 year) are described in recent studies, but are selected randomly in the current study. Second, these cutoff values are signs of cartilage-loss’ only, they do not predict progression of clinical symptoms as increased pain, decreased range of motion or decreased quality of life. The cutoff values are no disease value itself.

Table 8 Mean volume cartilage survival rates (in months) depending on limb alignment. Statistically significant differences between medial and lateral femur and medial and lateral tibia are shown

Varus-Alignment			Variable	Mean Survival (months)	CI 95%	p-value 1	p-value 2	p-value 3	p-value 4	p-value 5	p-value 6	p-value 7
Med. Femur	Vol.	1	BMFVCL	31.7	29-34.3							
	Nor. Vol.	2	BMFVCN	30.8	28.2-33.4	.694						
Lat. Femur	Vol.	3	BLFVCL	42.5	40.5-44.4	.000	.000					
	Nor. Vol.	4	BLFVCN	42.9	41.1-44.8	.000	.000	.943				
Med. Tibia	Vol.	5	WMTVCL	36.9	34.5-39.4	.005	.001	.000	.000			
	Nor. Vol.	6	WMTVCN	37	34.6-39.4	.005	.001	.000	.000	.987		
Lat. Tibia	Vol.	7	WLTVCL	41.6	39.7-43.6	.000	.000	.159	.128	.008	.008	
	Nor. Vol.	8	WLTVCN	43.4	41.6-45.1	.000	.000	.872	.936	.000	.000	.102
Valgus-Alignment			Variable	Mean Survival (months)	CI 95%	p-value 1	p-value 2	p-value 3	p-value 4	p-value 5	p-value 6	p-value 7
Med. Femur	Vol.	1	BMFVCL	40.2	36.9-43.5							
	Nor. Vol.	2	BMFVCN	40.4	37-43.7	.870						
Lat. Femur	Vol.	3	BLFVCL	38.5	35-42.1	.541	.443					
	Nor. Vol.	4	BLFVCN	36.2	32.4-40	.095	.066	.303				
Med. Tibia	Vol.	5	WMTVCL	44.2	41.5-46.9	.085	.129	.020	.001			
	Nor. Vol.	6	WMTVCN	43.8	41.2-46.4	.083	.118	.021	.001	1		
Lat. Tibia	Vol.	7	WLTVCL	30.7	26.8-34.7	.001	.000	.005	.065	.000	.000	
	Nor. Vol.	8	WLTVCN	31.5	27.6-35.4	.001	.001	.009	.113	.000	.000	.817
Physiologic-Alignment			Variable	Mean Survival (months)	CI 95%	p-value 1	p-value 2	p-value 3	p-value 4	p-value 5	p-value 6	p-value 7
Med. Femur	Vol.	1	BMFVCL	37.2	35.3-39.1							
	Nor. Vol.	2	BMFVCN	37.8	36-39.7	.484						
Lat. Femur	Vol.	3	BLFVCL	42.8	41.3-44.3	.000	.000					
	Nor. Vol.	4	BLFVCN	43	41.5-44.5	.000	.000	.583				
Med. Tibia	Vol.	5	WMTVCL	40.8	39.1-42.5	.003	.021	.108	.034			
	Nor. Vol.	6	WMTVCN	41.7	40.1-43.4	.000	.001	.523	.239	.346		
Lat. Tibia	Vol.	7	WLTVCL	41.8	40.2-43.4	.001	.008	.194	.067	.731	.515	
	Nor. Vol.	8	WLTVCN	41.6	40-43.2	.001	.009	.190	.066	.749	.508	.980

Two parameters (volume and normalized volume) are shown for each variable. Normalized volume represents the remaining volume per area. Depending on limb alignment typically timelines can be derived (varus: medial femur, medial tibia, lateral femur and lateral tibia; valgus: lateral tibia, lateral femur, medial femur, medial tibia; physiological: medial femur, medial tibia, lateral tibia and lateral femur)

Statistically differences are highlighted

Conclusion

Data of the current study suggest that in varus OA, the main cartilage loss occurs on the medial femur (central and external), medial tibia (central and external) and internal lateral tibia. In valgus knees, the lateral tibia (central subregion first, followed by internal and external subregion) with a posterior component are affected first. This study is the first to determine the rate of OA progression depending on lower limb alignment. Therefore, we can now inform our patients in detail about when a significant loss of cartilage is to be expected and in which subregion this will occur. The therapy regimen may need to be adapted after reaching the cutoff values. OA progression occurred after an average of 37.6 months in physiologic aligned knees, 31.2 months in varus knees and 30 months in valgus knees. This confirms a considerable influence of limb alignment on cartilage survival.

Author contributions FM: planning/conception of the study, collection of data, analysis and interpretation, statistical analysis, writing and revising article; (orthopedic surgeon). KM: collection of data, analysis and interpretation, statistical analysis; (resident). SP, WW: collection of data, critical revision of the article; (resident, orthopedic surgeon). RH, BF: critical revision of the article, final approval of the article, overall responsibility; (surgeon in chief University of Ulm; orthopedic surgeon, attending at HSS).

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Compliance with ethical standards

Conflict of interest We certify that we have not signed any agreement with commercial interest related to this study, which would in any way limit publication of any and all data generated for the study or to delay publication for any reason. Dr. Boettner reports personal fees from Smith & Nephew, personal fees from Ortho Development Corporation, personal fees from Depuy, outside the submitted work. Dr. Faschingbauer reports personal fees from Deutsche Forschungsgemeinschaft (Research Fellowship, FA 1271/1-1, <http://www.dfg.de>), during the conduct of the study.

Ethical statement The authors' institutional review board approved this study.

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