Chondrosarcoma in Norway 1990-2013;

Risk stratification without histology.

Thesis for the degree Philosophiae Doctor (PhD)

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Acknowledgements

This section is positioned first, but was written last. It is my name is on the cover, but this is clearly a team effort and many people have taken part on many different levels.

This work was somewhat ironically initiated by the hospitals effort to reduce staff numbers. My mentor and former boss Sigmund Skjeldal took the initiative to get me onto the PhD program as this was weighted heavily in the criteria for jobs. The general topic of chondrosarcoma was also his idea. He gave me two weeks study leave to get stuck into the literature and the outline for a chondrosarcoma project started to take form. Sigmund along with his partner in crime, Gunnar Follerås started and developed sarcoma surgery in Norway as the true pioneers. Much of what we in fact are studying in this PhD is their work.

My supervisors Olga Zaikova, Ole-Jacob Norum and Øyvind Bruland deserve my most sincere thanks. Although I am an independent type by nature, the world of academia is new and foreign to me. They have helped me navigate the hurdles and bumps in the road. They have been key in planning. They have organized the department such that I have had the actual time to do the work in the midst of a busy clinical department and home life, as well as a very limited budget. Thank you for your patient support and generous encouragement.

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We were fortunate enough to contribute a cover image for the Journal of Surgical Oncology for article 2. Photographer Ine Eriksen from the University of Oslo photo/ video service delivered a graphical abstract which was accepted and nicely summarised our findings. Thank you Ine, for your efforts with this, as well as other figures and desperate questions about "dpi and TIFF file resolution".

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My family has always followed with interest this strange academic world and my slow progress in its realm. Thanks to my mum Ellen and dad Lasse for the pillars of a solid education, the contagious curiosity for discovering the world and every opportunity in it. Thank you also for the support of my brothers Thomas, Theo and "big bro" and orthopeadic colleague Rasmus. Following Rasmus' own phd process has been inspiring.

Most importantly I want to celebrate my beacon of inspiration; my intelligent, patient and beautiful wife Marte. You truly understand and accept my level of engagement in this project and what it means for me to put my name to something. You have had ample opportunity to get really sick of chondrosarcoma, but instead you have been tremendous and continuous in your support. This has spanned a busy time of our lives with the building of a home, three brilliantly intense children and sickness for us both. Your support and interest makes me strong and confident. It gives me the naive energy to take on the world with the attitude "of course I can do this!" I am very lucky to be in the middle of your "circle of trust!" It makes every day interesting and worthwhile.

Silje (5), Lotte (8) and Sofie (10).This has been what I am thinking about when I lose my place in a book or a goodnight song. It has been what I have been thinking about when I stare into space, take too long in the bathroom or don't listen properly to what you are telling me. I

hope you all can find some sort of inspiration in this work, at some point in the future. Please continue to discover the world in exactly the way you are doing already. Never stop asking why and how? Never stop laughing, listening, reading and discovering. You are all brilliant and the world is lucky for it! I am so very proud of you all.

Vollen 11.02.21

Joachim Thorkildsen

Scientific environment

This PhD project is based at the Faculty of Medicine, University of Oslo while I have held a full time surgical consultant post at the Division of Orthopaedic surgery, Oslo University Hospital, Norwegian Radium Hospital. At the same time I have been associated with the Cancer Registry of Norway (CRN) from where all data gathering has occurred.

The close proximity of the Radium Hospital and CRN has been a clear advantage with regards to the intellectual cooperation between parties. This is always easier once the parties have met and a trusting relationship has been established. It has been an advantage for the project as a whole, as well as the involved departments on both sites.

The project topic is central to the clinical work in both the surgical oncology unit, but also the whole multidisciplinary sarcoma unit. The close daily cooperation between a spectrum of clinicians, radiologist, pathologist, nurses and physiotherapists has been core to many of the insights and definitions that apply. The reciprocal advantages to both research and clinical communities from this cooperation have been tremendous, but are difficult to measure.

The project has been supported financially the by the Astri and Birger Torstedts Legacy, the Radium Hospital Legacy as well as the National Advisory Unit for Sarcoma in Norway.

Abbreviations

ASI	Age specific incidence
ASR	Age standardized rates
CCCS	Central conventional chondrosarcoma
CI	Confidence interval
CRN	Cancer Registry of Norway (denoted NCR=National Cancer Registry in paper 1.)
CS	Chondrosarcoma
CT	Computed Tomography
DSS	Disease specific survival
HR	Hazard Ratio
ICD code	International statistical Classification of Disease code
IPS	Indeterminate Pulmonary Nodules
K-M	Kaplan-Meier
LR	Local recurrence
LRFS	Local recurrence free survival
LR-test	Likelihood ratio test
Met	Rate of metastasis
MFS	Metastasis free survival
NCIN	National Cancer Intelligence Network
MO	Multiple Osteochondromatosis
MRI	Magnetic Resonance Imaging
OR	Odds Ratio
OS	Overall Survival
SEER	Surveillance, Epidemiology and End Result program
SLICED	Skeletal Lesions Interobserver Correlation among Expert Diagnosticians study group
Yr.	Year

Thesis summary

Norway has a well renowned cancer registry which gives us the opportunity to study rare diseases with complete and population based data. My PhD project is a study of basic epidemiological trends and prognostic analysis of a rare form of cancer called chondrosarcoma of bone at the Cancer Registry of Norway (CRN).

Chondrosarcoma (CS) of bone is a term used to denote a group of malignant tumour forming diseases originating in the skeleton with a common feature that they are made up of malignant cartilage cells and matrix. CS can be differentiated into different subtypes by their location of origin and morphological picture into central conventional, peripheral, periosteal, dedifferentiated, mesenchymal and clear cell subtypes. CS has commonly been studied together in mixed CS cohorts, but the differing subtypes of CS are different diseases, with different behaviour and management. As such mixed cohorts must be interpreted with caution and future study must be at a subtype level. The most common subtype is central conventional CS (CCCS) of bone, which originates within the bone marrow or intramedullary space. It has a wide range of behaviour ranging from a very indolent and locally aggressive course to a high risk of lung metastasis and death.

For the last 50 years we have used histological grade ascertained by microscopy to predict behaviour, but have gradually become aware of the subjective nature and limitations of this assessment.

The thesis is entirely based on analysis from the Cancer Registry of Norway (CRN) CS of bone cohort. This was constructed in 2016 by searching the CRN for all CS from 1990-2013 and retrieving clinical files for all patients to expand and control the entries for each case. Tumour databases at the four University hospitals treating CS through the time period were also searched. Further we carried out review of radiological images for 223 cases and histological slides for 112 cases. The cohort consists of 311 cases of tissue verified CS of all subtypes analysed for incidence, and 306 with a full data set and documented follow-up for further prognostic analysis at subtype level.

All papers are observational studies in that we have studied the real life management course during the study period. It is one of the key aims of this thesis to help better understand and predict which course a given tumour will take within this setting.

In paper 1 we calculated the incidence of CS in Norway during the study period for CS overall and at a subtype level to assess any change. We have also calculated incidence for specific age groups, overall and at subtype level. We presented rates of local recurrence, rates of metastasis and disease specific survival at 2, 5 and 10 years overall and for each subtype. We found the total incidence in the study period to be 2.85 per million per year overall, with an increase driven by an increase in the most common CCCS subtype through the study period. Each subtype has its unique patterns and frequency of local recurrence, metastasis and survival. The current recommendation is that all of these patients be followed for 10 years, but our data suggest that 5 years is sufficient for most patients with specific exceptions. We then looked at the main subtype; CCCS and entered the variables age at diagnosis, sex, tumour

size, skeletal location, histological grade and presence/ absence of soft tissue extension and metastatic status at diagnosis into a statistical model to predict which factors influence behaviour (prognostics). We found that the presence of a soft tissue component was associated with increased rates of local recurrence, metastasis and reduced survival while histological grade III predicted adverse levels of metastasis. Metastasis at diagnosis was the most influential predictor of death.

Paper 2 is a deeper assessment of prognostics for the CCCS subtype. We explored the influence of the size of the soft tissue component for those cases where this was available measured by standardized means. Creating a combined variable of tumours in the axial skeleton with large soft tissue components (≥1cm), we found that we could divide the cohort into a small high risk group (39 cases with 33% risk of metastasis) and a large low risk group (103 cases with 2% risk of metastasis) without the use of histological grade, reaching statistical significance. This is the first organization of a CCCS cohort into differing risk groups without the use of histological grade.

Paper 3 is an analysis of the patterns and impact of local recurrence (LR) in CCCS. We found that only half of LR CCCS were symptomatic and the other half successfully uncovered by routine surveillance. We also wanted to quantify the concept of "upgrading" where a LR appears to have a higher histological grade than the primary tumour (only a single case in this cohort) or dedifferentiation where the tumour clearly changes into another more aggressive subtype (only two cases in this cohort) and found this to be far less frequent than in previous studies. We performed statistical analysis accounting for the concept of immortal time bias and found that LR was associated with an increased risk of metastasis and death overall. This was not valid for all subgroups, but appeared to follow similar predictors of risk as in the primary treatment setting. Those with more aggressive disease at the outset are also those with more aggressive disease in the case of local recurrence. The most useful distinction was that proposed in paper 2 (called Oslo high/low risk) subgroups, leaving only 26% of the cohort at increased risk metastasis in the event of local recurrence. This finding needs validation in larger populations.

In conclusion, we have presented basic epidemiological data for chondrosarcoma of bone, in Norway. We have used these data to develop a simple method of assessing risk of metastasis, without the need for histological grade. This creates a small high risk group and a large low risk group. This method appears to predict risk both at the point of primary diagnosis as well as in the setting of local recurrence. Our findings need validation in larger cohorts.

Articles in the thesis

Paper 1

Thorkildsen J, Taksdal I, Bjerkehagen B, Haugland HK, Borge Johannesen T, Viset T, Norum OJ, Bruland O, Zaikova O. Chondrosarcoma in Norway 1990-2013; an epidemiological and prognostic observational study of a complete national cohort. *Acta Oncol.* 2019:1-10.

Paper 2

Thorkildsen J, Taksdal I, Bjerkehagen B, Norum OJ, Myklebust TA, Zaikova O. Risk stratification for central conventional chondrosarcoma of bone: A novel system predicting risk of metastasis and death in the Cancer Registry of Norway cohort. *J. Surg. Oncol.* 2020

Paper 3

Thorkildsen J, Norum OJ, Myklebust TA, Zaikova O. Chondrosarcoma local recurrence in the Cancer Registry of Norway cohort (1990-2013): Patterns and impact. *J Surg Oncol.* 2020.

Norwegian thesis summary

Norge har ett anerkjent Krefteregister som gir mulighet til å studere sjeldne sykdommer med populasjonsbaserte data. Mitt phd prosjekt er en studie av de grunnleggende epidemiologiske dataene og en prognostisk analyse av en sjelden kreftsykdom som heter kondrosarkom, hos Kreftregisteret.

Kondrosarkom er et samlet begrep for en gruppe kreftsvulster som oppstår i skjelettet og som ligner på bruskvev. Kondrosarkom kan deles inn i subtyper basert på hvor i skjelettet de oppstår sammen med hvordan de ser ut ved mikroskopisk undersøkelse. Subtypene betegnes som sentralt konvensjonelt, perifert, periostalt, dedifferensiert, mesenchymalt og klarcellet kondrosarkom.

Kondrosarkom har vanligvis vært studert med alle subtypene i en samlet gruppe, men vi vet nå at de forskjellige subtypene er forskjellige sykdommer med ulik behandling og prognose. Funn fra studier basert på blandete grupper må derfor tolkes med forsiktighet. Den vanligste subtypen oppstår i benmarg og heter sentral konvensjonell kondrosarkom. Den har et bredt spenn av mulige forløp, fra å være en begrenset og lokalt aggressiv sykdom, til å ha en høy risiko for spredning til lungene og for død.

De siste 50 årene har det vitenskapelige miljøet hovedsakelig brukt vurdering av aggressivitet ved mikroskopisk vevsundersøkelse (malignitetsgrad 1-3) for å prøve å forutsi sykdomsforløp. Man er gradvis blitt oppmerksom på den kvalitative og derved subjektive naturen av denne metoden og dens påfølgende begrensninger.

Denne avhandlingen er basert på analyse av populasjonsbaserte data fra Kreftregisteret i Norge. Det ble utført søk i Kreftregisteret for alle pasienter med diagnosen kondrosarkom i perioden 1990-2013. Dette ble kvalitetssikret og utdypet ved gjennomgang av pasient journaler for alle kasus. Videre ble søket kontrollert mot databasene på de fire universitetssykehusene som utredet og behandlet kondrosarkom i Norge i den samme tidsperioden. En videre gjennomgang av radiologi for 223 kasus og histologi for 112 kasus har gitt en studiekohort med 311 kasus for insidens analyse og 306 for analyse av prognose. Vi mener at studiekohorten er unik med hensyn til at vi har nærmest komplette nasjonale data med mange variabler på subtype nivå.

All artikler som er del av denne avhandlingen er observasjonstudier som analyser den reelle behandlingen og forløpet av disse sykdommene i perioden. Ett av hovedmålene med avhandlingen er å studere kriterier for best mulig prognostisering av sykdomsforløp.

I den første artikklen har vi beregnet insidens av kondrosarkom i Norge i studieperioden, både totalt og for hver subtype over tid. Vi har også presentert insidens av kondrosarkom for forskjellige aldersgrupper samlet og på subtype nivå. Vi presenterte lokal residiv frekvens, metastase frekvens og risiko for sykdomsrelatert død ved 2, 5 og 10 års oppfølgning per subtype.

Vi fant at total insidens for perioden var 2.85 per million per år, men med en økning gjennom studieperioden drevet av en økning av den mest vanlige subtypen; sentralt konvensjonelt

kondrosarkom. Hver subtype har sitt eget mønster og sin egen frekvens av lokalt residiv, metastaser og risiko for død. Den gjeldende anbefaling er at alle pasienter med kondrosarkom bør følges for tilbakefall i 10 år etter behandling. Våre data tyder på at 5 år er nok for de fleste, med konkrete unntak.

Videre studerte vi prognostiske kriterier for den sentrale konvensjonelle subtypen. De faktorer som er antatt å ha betydning for prognose(alder, kjønn, tumor størrelse, beliggenhet, malignitetsgrad, tilstedeværelse av bløtdelskomponent og metastaser ved diagnose) ble vurdert i en multivariat statistisk modell. Påvist bløtdelskomponent var assosiert med økt risiko for lokale residiv, økt metastasering og død. Malignitetsgrad 3 var forbundet med økt metastasefrekvens, mens påvist metastasestatus ved diagnosetidspunktet ga høyest risiko for død.

I artikkel 2 har vi gjort en dypere prognostisk analyse for sentralt konvensjonelt kondrosarkom. Vi har vurdert påvirkningskonsekvensen av en standardisert metode for å måle størrelsen på bløtdelskomponenten. Basert på en videre statistisk analyse av hvilke faktorer som er forbundet med økt metastase risiko har vi konstruert en ny variabel. Denne kombinerer svulster som har sin beliggenhet i aksialt skjelett med samtidig bløtdelskomponent som er større enn 1cm. Basert på denne variabelen kunne vi dele kohorten inn en liten gruppe med høy risiko (39 pasienter med 33% metastasefrekvens) og en stor lav risiko gruppe (103 pasienter med 2% metastasefrekvens). Dette er den første vurderingen risiko inndelingen for kondrosarkom pasienter uten bruk av histologisk grad. Vi har kalt inndelingen for «Oslo høy/lav risiko».

I artikkel 3 studerte vi lokale tilbakefall for sentralt konvensjonelt kondrosarkom. Vi studerte mønsteret av lokale tilbakefall og dens påvirkning på sykdomsforløpet. Vi fant at halvparten av lokale residiv ble oppdaget på grunn av symptomer. Den andre halvparten var asymptomatiske og ble oppdaget ved rutinemessig oppfølgning. Vi ønsket å kvantifisere frekvensen av «oppgradering»; et konsept hvor et lokalt residiv er histologisk vurdert mere aggressiv enn primærtumor. Vi fant kun ett tilfelle av dette i kohorten mens det var to tilfeller av dedifferensiering hvor residivet er endret til en mer aggressiv subtype. Dette var tydelig mindre hyppig enn rapportert i litteraturen.

Statistisk analyse viste at lokalt tilbakefall var assosiert med en forhøyet risiko for metastaser og for død for kohorten samlet. Dette gjaldt ikke alle subgrupper men fulgte risikoprofil som ved primær diagnose. De med aggressiv sykdom ved initial diagnose hadde også mere aggressiv sykdom ved residiv. Den mest nyttige inndelingen var vår variabel fra artikkel 2; «Oslo høy/lav risiko». Dette innebærer at bare 26% av kohorten har økt risiko for metastaser ved lokalt residiv, mens det klare flertall ikke har det.

Samlet har vi bidratt til å belyse grunnleggende epidemiologiske data for en sjelden kreftsykdom; kondrosarkom. Videre har vi utviklet en metode for risikovurdering uten bruk av mikroskopisk vevsundersøkelse som skaper en liten høyrisiko gruppe og en stor lavrisiko gruppe. Denne inndelingen virker å gjelde både ved primær diagnose og ved lokalt tilbakefall. Funnene våre må valideres i større kohorter.

Introduction/ Background

Cartilage is a form of connective tissue composed of an extracellular matrix and cells called chondrocytes. The matrix serves as a route for the diffusion of substances between adjacent blood vessels and chondrocytes. It also gives the specific mechanical properties depending on its composition. Different characteristics of the matrix give rise to the definition of three different type of cartilage as hyaline cartilage, fibrocartilage and elastic cartilage.

Hyaline cartilage is distinguished by the presence of a glassy homogenous matrix, it is highly hydrated giving it pliable, adaptive and resilient properties making it ideal for weight bearing and frictionless movement of joints. Hyaline cartilage forms the framework of the initial fetal skeleton (for all bones except skull, mandible and clavicle) that forms by a process called enchondral ossification. It also serves as the epiphyseal growth plate as long as the bone grows in longitudinal length. In an adult it is present as a highly organized layer at the articular surface of joints, and as a structural framework for the trachea, bronchi, larynx, nose and at the end of the ribs.

Chondrosarcoma (CS) of bone is a group of tumour forming diseases originating inside the bone marrow or on the non-articular surface of the skeleton with a common feature that they are made up of abundant hyaline cartilage matrix in lobular patterns. The cartilage of articular surface is actually one of few structures in the body in which cancer does not occur. Key features of CS micro environment are a slow proliferation rate, poor vascularity, dense extracellular matrix, hypoxia and multidrugresistance protein overexpression [1] CS is termed a primary malignancy of bone in that it arises in bone and can spread to other parts of the body (mostly lungs) from there. The subtype is distinguished by the location of origin as well as their morphological picture. The most common subtype often stated to represent about 85% of all cases is central conventional CS (CCCS) of bone. This originates within the bone marrow or intramedullary space. It can expand within the same intramedullary space or destroy the constraining hard bone that surrounds it and grow into the surrounding soft tissues and spread into the blood stream. It has a wide range of behaviour ranging from locally aggressive course to a high risk of metastasis and death. Other subtypes include peripheral CS, and dedifferentiated CS. Historically these have been studied together as one group, but we now know them to have different etiology, treatment and prognosis and should as such be studied separately although they share common features when looked upon through the microscope[2].

All sarcomas are rare, and in Norway there are approximately 50-60 new cases of bone sarcoma per year[3]. The three most common types of bone sarcomas are osteosarcoma, chondrosarcoma and Ewing sarcoma [4,5]. In Norway there are approximately 15-20 new cases of CS per year. The tradition of centralisation of care and international collaboration for sarcoma patients in Norway and Scandinavia is longstanding. Up to 2007, CS patients were managed in four regional referral centres (Oslo, Bergen, Trondheim and Tromsø). Since 2007, all bone sarcoma has been referred for treatment to the university hospitals in Oslo or Bergen. Radiation and chemotherapy have a very limited influence on CS growth, which is primarily treated by surgical means.

The study of rare diseases can be difficult, particularly in a small country like Norway. The accumulation of sufficient numbers to perform legitimate scientific evaluation can take decades. Our advantage in the Nordic countries however, is that we are highly organized and regulated and have solid public institutions for care of the whole population, irrespective of means and limited migration. There is also high level of trust and compliance from both the population and within the health care system regarding the treatment of rare diseases in designated centres which gives treatment volumes comparable to much larger countries. The Cancer Registry of Norway (CRN) was established in 1952 and reporting of all cancer to the registry is mandatory by law. It has documented high levels of completeness and a quality control charter which obligates them to work towards and document the quality of data registered. My affiliation with CRN has had this same purpose; to quality control CS data at the registry and use this as a basis for a PhD on CS epidemiology.

To have a clear understanding of the articles on which this thesis is written and the thesis itself there is a need to define terms and concepts clearly. This may seem simplistic for a thesis, but it is my experience that these are terms that are misinterpreted and unclear even to seasoned sarcoma specialists. This limits the precision and value of the academic discussion. Core to the understanding of CS epidemiology are a basic understanding of the skeleton, the structure and nomenclature of bone, the growth plate as well as the terminology and definition of CS subtypes, their benign counterparts and syndromes predisposing to CS development.

Location in the skeleton.

The skeleton is in a descriptive anatomic manner divided into the axial and appendicular skeleton. The axial skeleton comprises the skull, the rib cage and vertebral column while the appendicular is as the name implies (appendix), that which attaches onto the axial. This includes the scapula, clavicle and upper extremity as well as the pelvic bones and lower extremity. (https://www.merriam-webster.com/dictionary/axial%20skeleton)

In the world of chondrosarcoma these terms are at times used incorrectly. In the 5th edition WHO book the term appendicular is commonly used but with brackets defining this as long bones of limb, thereby excluding the scapula and pelvis[2]. The distinction is as such correct, but the term appendicular is incorrect and confusing. The term “extremity”, would have been more concise.

In other work, including my own, the term “axial skeleton” is misused. This is because the behaviour and treatment of chondrosarcoma in the pelvic and pectoral girdles resembles that of the rest of the axial skeleton and are therefore grouped in company with rib cage and vertebral column. We have used this same distinction in this thesis and the articles on which it is based. That is, the glenohumeral and the hip joints define axial and extremity locations. During the course of this project I have concluded that the terms extremity/ non-extremity would likely be the most concise, but we have chosen to use the same terminology as in the included papers to avoid confusion. The most important factor is to clearly define the terms used.

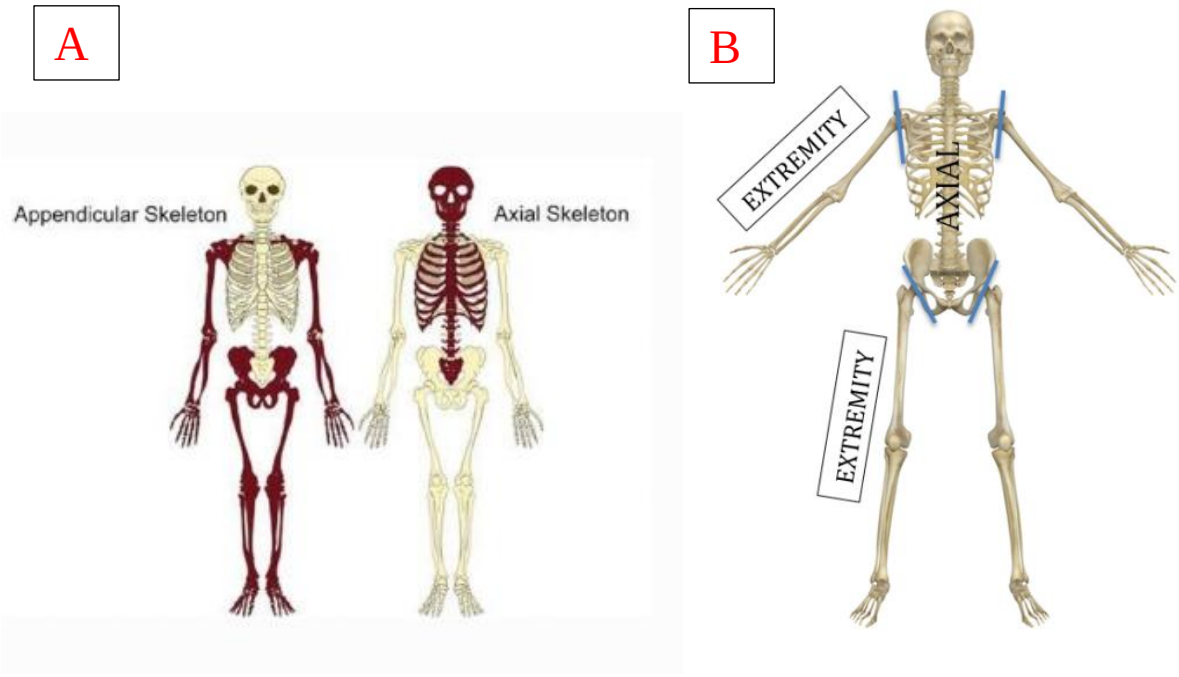


Figure 1A) Anatomical definition of axial and appendicular skeleton; B) Definition of axial and extremity skeleton as used in the thesis. Pictures from Wikipedia.

Benign bone tumours

An enchondroma is a benign cartilage tumour located in the intramedullary space of a bone. It has limited growth potential, minimal signs of aggressive behaviour and no metastatic potential. It is most common in the hands and feet as well as the end of the distal femur and proximal humerus. On performing Magnetic Resonance Imaging (MRI) of the knee for all reasons, about 3% have an incidental finding of an enchondroma in the end of the thigh bone[6] and for the shoulder about 2% [7].

An osteochondroma (synonym exostosis) is a benign bone and cartilage outgrowth from the bone in the metaphyseal region[8]. It has a common bone marrow with the underlying bone and is caused by a part of the growth plate changing direction[9]. In similar fashion to a functioning growth plate it lays down cartilage which differentiates into bone as it extends, but now at an angle to the bone, generally away from the epiphysis. It can be considered a displaced and functioning growth plate. It has limited growth potential and stops at the same time as the other growth plates of the skeleton towards the end of puberty.

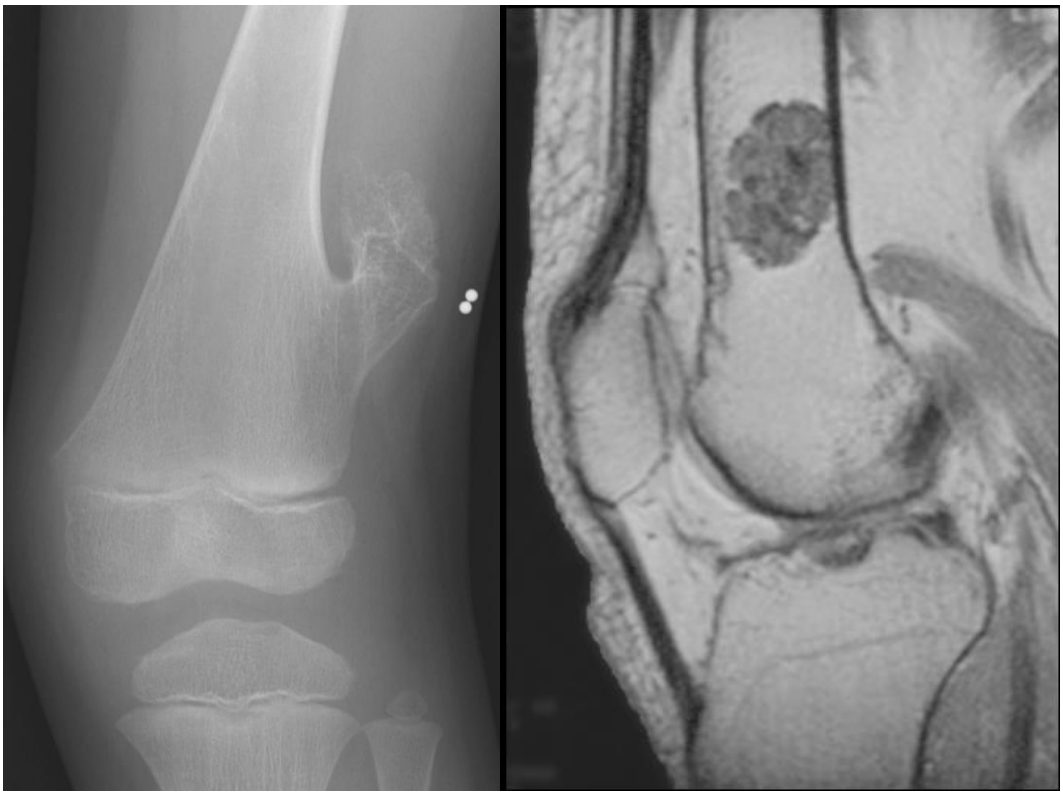


Figure 2 X-ray of typical osteochondroma distal femur to the left and sagittal T1 MRI of an enchondroma with cortical contact on the right. Pictures from Wikipedia.

Chondrosarcoma subtypes and terminology

Chondrosarcoma of bone as a general term consists of several subtypes and it is important to understand their definitions. This terminology is used interchangeably and inconsistently in the CS literature which has a tradition for analysis of mixed subtype cohorts, sometimes without definition. The terminology is based on where in the bone the tumour has arisen (in cross section) as well as morphology (how it appears in the microscope).

The most common subtype is called *central conventional CS (CCCS)* and arises intramedullary. It has its name "central" from the fact that it originates and grows from within the center of the bone, that is, in the bone marrow.

Peripheral CS is a CS arising on the surface of a benign bony protrusion called an osteochondroma. The term peripheral refers to that fact that it originates from the periphery (as seen on cross section) of bone.

Periosteal CS arises on the cortical surface in relation with the periosteum, without evidence of an osteochondroma.

Peripheral and periosteal subtypes together are often termed *juxtacortical CS*.

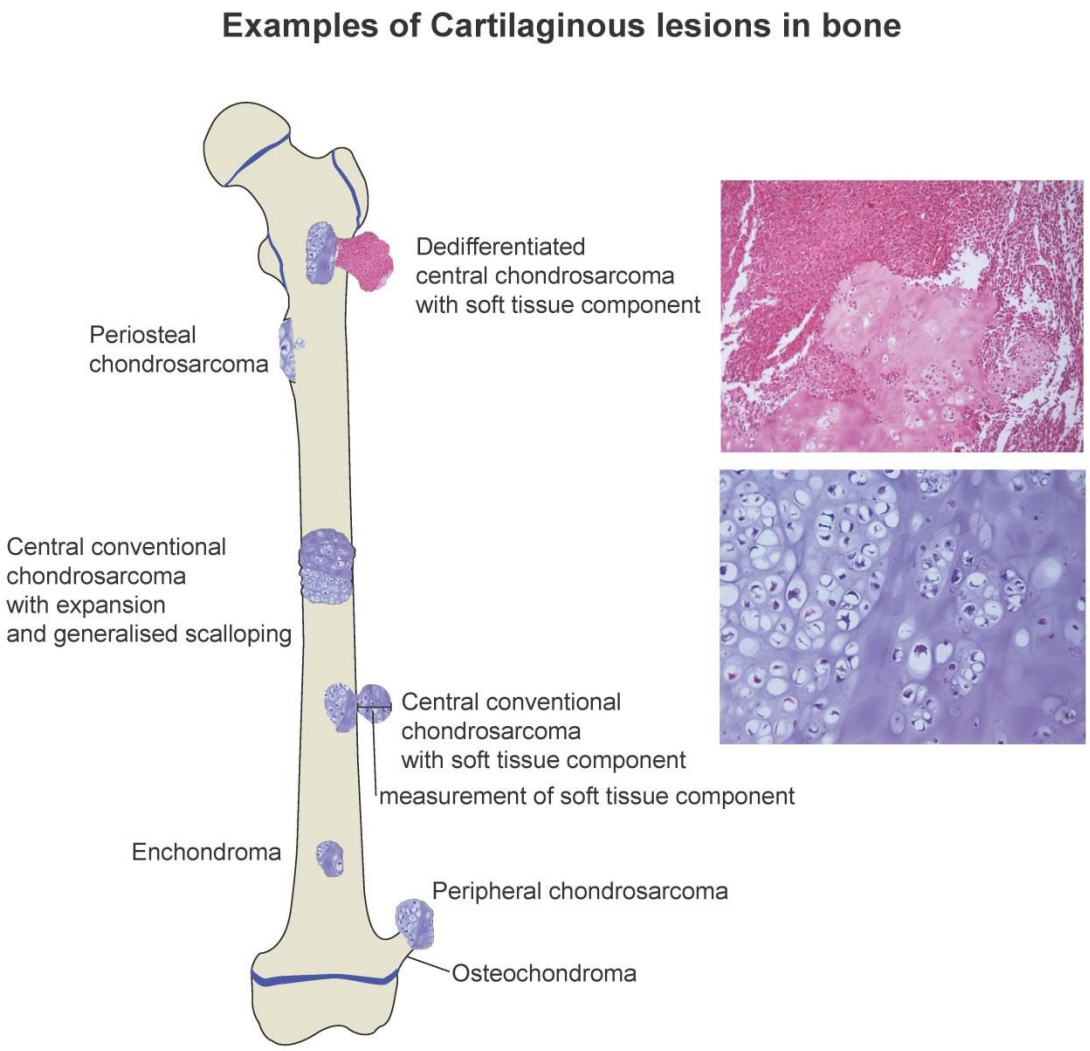


Figure 3 Illustration of cartilaginous lesions of bone by Ine Eriksen ©, University of Oslo. Used with permission.

Conventional CS most often includes central conventional and peripheral subtypes together, sometimes also with periosteal subtypes. This term is used interchangeably and should always be defined.

Conventional CS are according to the WHO nomenclature termed primary or secondary depending upon whether they arise on the background of a benign precursor lesion such as an enchondroma or osteochondroma. This entails that all peripheral CS are secondary, while central conventional CS can be both. Most often, one does not have radiological imagery of the affected site before diagnosis, and as such one can not truly know if it is primary or secondary. This distinction does not have any practical consequence for either treatment or prognosis and as such it is not used in the thesis and has not either been used in the containing articles. Rather we have chosen to include demographic data on those CS patients with a

predisposing syndrome such as Multiple Osteochoromatosis (MO), Olliers disease or Maffucci syndrome which have been associated with a worse prognosis, at least for MO and peripheral CS [10,11].

For both central and peripheral conventional subtypes the WHO has in 2013 introduced the term A*typical Cartilaginous Tumour (ACT)* as a synonym for grade I disease. This is meant to better convey the indolent course of this disease. In the new 2020 edition published during the course of writing this thesis, ACT is further defined as a direct translation of ACT in extremity location only. This term has not been used in Norway during the study period and it has therefore not been introduced into the cohort. Where the term ACT is used in the thesis or manuscripts, this is used as a synonym for grade I CS as per the 2013 WHO definitions.

CS can also arise from cartilage. It can arise from the costochondral or costosternal cartilage in the thorax and in this instance is often presented based on location together with other CS of the thorax and chest wall [12-15]. We have chosen to treat them as central conventional CS without further specification since their treatment and prognosis is not known to differ, but further study should in fact investigate whether their behaviour is similar or not.

CS that arises in nasal and laryngeal cartilage are extremely rare tumours, expanding in anatomically very confined spaces, close to many critical structures. Their investigation and treatment is highly specialized [16-20] and their behaviour difficult to predict, but mostly indolent. They are registered in the CRN and form part of the initial investigation into incidence. They are grouped together with skull base CS as "Head & neck CS" with rates of LR, Met and DSS in paper 1, but are not addressed with regards to prognostics or discussed further in the text or this thesis.

The same challenge of anatomical location and critical structures is even more pertinent in the skull base and upper cervical spine. Again extremely rare, they are surgically even more difficult to access than nasal/ laryngeal CS. This has led to the increasing treatment of these lesions with radiotherapy [21-25], originally as an adjunct to incomplete surgery and now increasingly as sole primary treatment. Proton radiotherapy is not yet available as a service in Norway, but patients are referred to providing centres in both Europe and the USA. They have been grouped together with nasal/ laryngeal CS as "Head & neck CS" and are presented with rates of LR, Met and DSS in paper 1, but are not analysed prognostically.

The term dedifferentiation involves change into a new subtype or completely new disease. *Dedifferentiated CS* exists when part of a CS undergoes a radical change in morphology, most often of a more aggressive manner and coexists with the cartilaginous component. This can occur for both CCCS and peripheral CS. It is the dedifferentiated tissue which is thought to predict prognosis in this disease, rather than the cartilaginous component. It has a notoriously poor prognosis and challenging multimodal management though with some evidence for a better prognosis in peripheral dedifferentiated CS[26] than for the central dedifferentiated disease [27] for unknown reasons.

The term *upgrading* however describes the situation in which a central or peripheral conventional CS recurs with a higher histological grade than it had previously. For example a

grade I CCCS from the primary setting has a local recurrence with histology showing grade II or III. This is distinct and separate from dedifferentiation as described above.

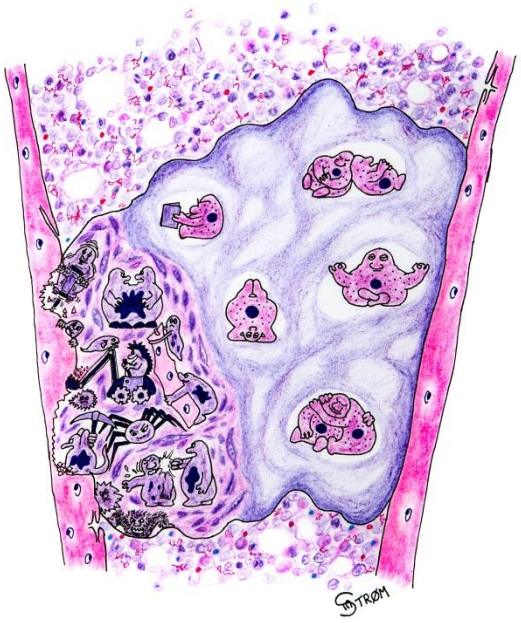


Figure 4 Histological drawing of dedifferentiated central chondrosarcoma. © Thale Asp Strøm. Used with permission.

Clear cell CS and Mesenchymal CS are even rarer subtypes of CS not included in the project directly. They are defined according to predilection for specific anatomical sites and histological appearance. Mesenchymal CS of bone from the South Eastern health area have been included in a separate European collaboration publication not included in the thesis [28].

There are sparse publications of an extremely rare subtype called myxoid chondrosarcoma or chordoid sarcoma of bone [29]. In SEER's publications, this can include up to 10% of CS cases [30,31] but the likelihood that these are wrongly registered extra skeletal myxoid CS of the soft tissues is large and findings should be interpreted with caution. Myxoid chondrosarcoma of bone is not a separate subtype in the current WHO ICD-10 categorisation, but rather myxoid change is part of routine histological grading and these lesions are included in the central conventional CS group. It remains a separate diagnosis in ICD-03 morphology codes used by pathologists.

Origin of benign and malignant cartilage tumours

There is much that is not known about the origin of CS. The most current thinking is that cartilage tumours develop from pluripotent mesenchymal stem cells and likely with a step wise progression from benign to malignant to highly malignant [1,32]. Attempts to understand the origin of CS has been driven by knowledge of normal bone and growth plate development as well as changes occurring during the development of the benign cartilage tumours enchondroma and osteochondroma.

The epiphyseal plate, physis or growth plate is a specialized region of hyaline cartilage in the metaphysis of a long bone. It occurs at each end of the bone and is the area in which the bone grows lengthwise or longitudinally and is covered by a thick connective tissue layer called perichondrium. It contains chondrocytes that undergo a coordinated process of differentiation to provide the framework for new bone formation and growth. This differentiation occurs from resting chondrocytes or pro-chondrogenic cells to proliferating chondrocytes to pre-hypertrophic chondrocytes, hypertrophic chondrocytes and finally towards bone cells (osteoblasts and osteoclasts). It becomes closed or fused towards the end of puberty.

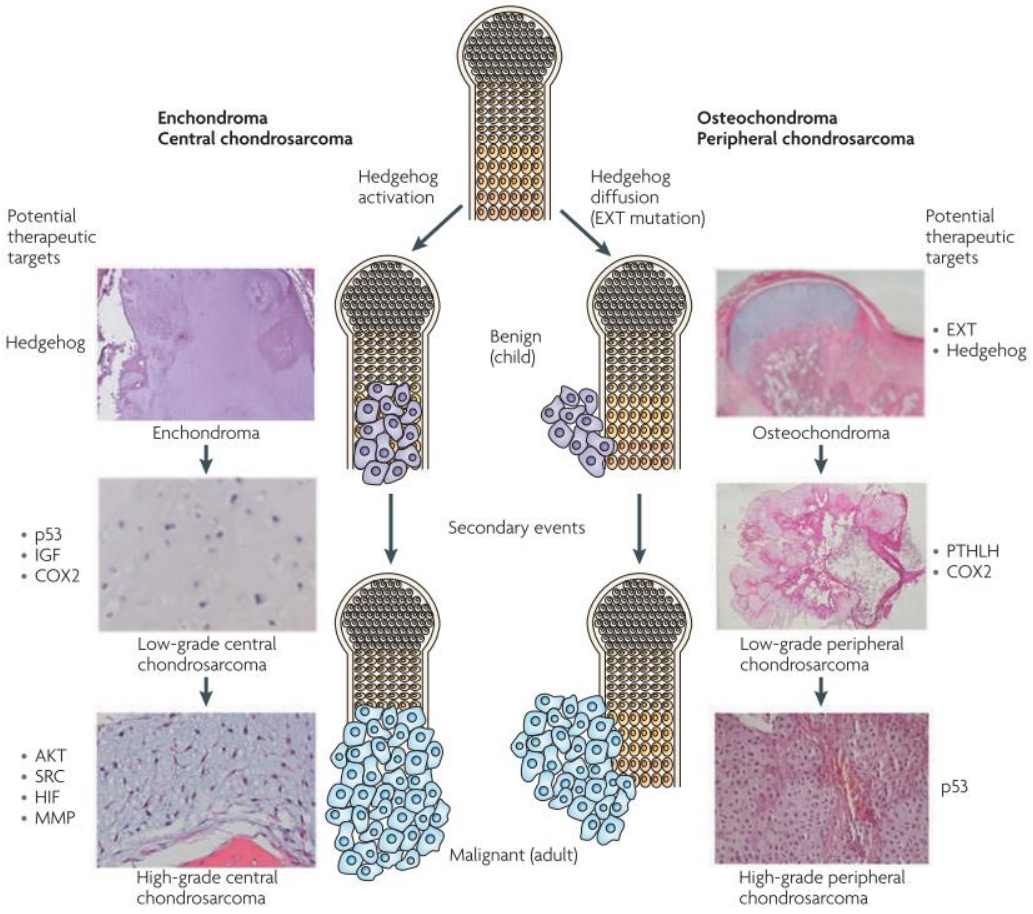


Figure 5 Development of benign cartilaginous tumours from growth plate and their progression to low-grade and high grade chondrosarcoma, with associated signaling and genetic events as potential therapeutic targets. Bovee et al.[8]. With permission from Springer Nature.

Indian Hedgehog (IHH) expressed by pre hypertrophic chondrocytes and parathyroid hormone-like hormone (PTHLH) produced by perichondrial cells function in a negative feedback loop to regulate this process.

For osteochondromas it is thought that mutations in genes encoding exostosin 1(EXT1) or exostonsin 2 (EXT2) are vital. This mutation leads to dysfunction of heparan sulphate

processing which in turn is thought to lead to loss of polar organization in an area of the growth plate leading to proliferation in another, non functional direction.

The origin and evolution of central chondroid lesions is less clearly understood. One theory to explain enchondroma formation is that they can be the result of a failure of terminal differentiation in the growth plate chondrocytes. Enchondromas display active IHH signaling which inhibits normal growth plate chondrocyte differentiation [8]. Douis et al attempted to display displaced areas of cartilage from growth plates by MRI imaging without success [33].

Others believe central cartilage tumours to result from mesenchymal stem and progenitor cells located in the bone marrow [1,34], but also present in other tissue of the body. We know that the differentiation path from precursor stem cell to chondroprogenitor, differentiated, hypertrophic and post hypertrophic chondrocyte similar to that observed in the growth plate is also evident in fracture callus formation, primary chondrogenesis by enchondroal ossification and secondary chondrogenesis during degenerative cartilage disease. It is thought that enchondromas are the result of this same differentiation pathway from stem cells in the bone marrow.

Aigner et al has studied the biochemistry and cell biology of CS subtypes with particular attention to collagen gene expression of the extracellular matrix. They found similarities between the differing subtypes and points of stem cell/ chondrocyte differentiation as illustrated below. The mesenchymal subtype is thought to be a neoplastic mesenchymal precursor, while enchondromas, osteochondromas and conventional CS are thought to be neoplastic differentiated chondrocytes and clear cell CS neoplastic hypertrophic chondrocytes. The marked heterogeneity of the extracellular matrix between and within different CS tumours is well established, but poorly understood.

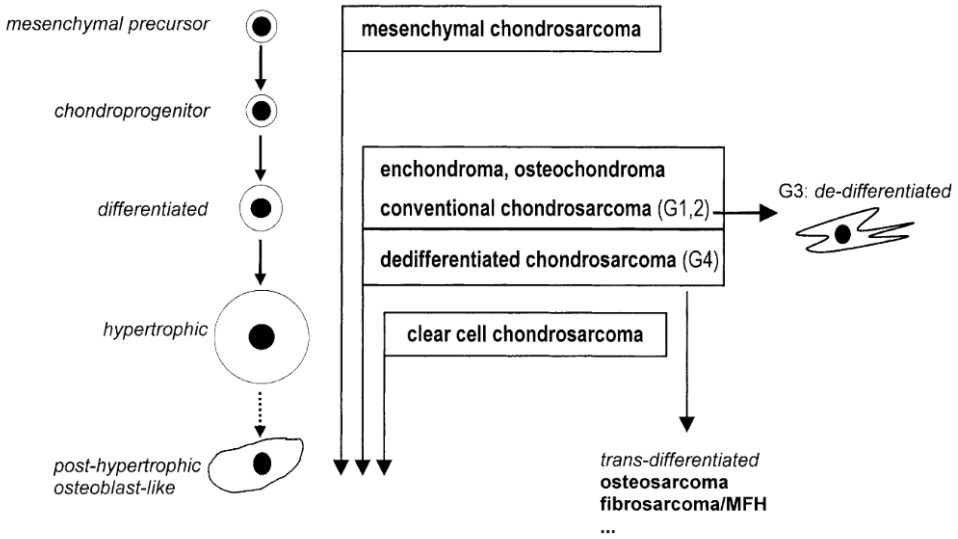


Figure 6 Categorisation of chondrogenic neoplasms according to their cellular differentiation pattern. From Aigner et al[34]. With permission from Springer Nature.

It is unclear whether central conventional CS always develop from a benign counterpart or whether they also can arise de novo. The finding of enchondroma tissue in 40% of central conventional CS cases can either support at theory of progression or underline the heterogeneity of cartilaginous tumours[35]. Most believe however that CS develop in the setting of step wise progression rather than a single change giving rise to a single biological potential[32]. This in my mind, supports the theory that they develop via an enchondroma, but the truth of this is yet undiscovered.

This is a complicated area of evolving technological study and the paragraphs above are very simplified. It has not been a focus of this PhD investigation, but understanding the origin of chondroid lesions is clearly highly significant to both predicting behaviour and understanding potential non surgical treatments in the future.

Chondrosarcoma precursor syndromes

There are inborn syndromes which have an important role in this thesis. In particular Multiple Osteochondromatosis (MO) and Olliers disease have been important models for understanding the aetiology and progression of benign and malignant chondroid lesions [9,36-38] as well as the fact that they are both predisposed to developing CS.

Multiple Osteochondromatosis

MO, also previously termed MHE- Multiple Hereditary Exostosis or HME- Hereditary Multiple Exostosis is as the name implies a hereditary (autosomal dominant) syndrome in which a number of benign bony outgrowths known as exostosis or osteochondromas develop, primarily from the long bones. The birth prevalence is estimated to be 1:50 000 [39]. It is defined by the presence of two or more osteochondromas while the number may vary greatly within and between families, but the mean number is 15-18 [40]. The most common location is the distal femur or proximal tibia (around the knee) while they can occur in any bone that develops from enchondral ossification. An osteochondroma has been described earlier as a growth plate that extends in the wrong direction, usually away from the adjacent joint. For the most part they are asymptomatic and grow until late puberty. They can however cause discomfort and pain directly or by impingement on nearby structures requiring surgical removal. The cartilage cap of these osteochondromas can develop into peripheral CS with a lifetime risk of 0,5-5% in MO patients [41]. Patients with MO need in adult age instruction and education with regards to CS surveillance, but there is no clear evidence as to the best regime for this internationally [42]. In Norway we have together with a wide array of specialities agreed on the recommendation of a specialist consultation in a sarcoma unit in early adulthood with imaging to create a full overview of disease as well as direct education about frequency of CS, signs, symptoms, management and prognosis of CS. They are also provided with contact information to their regional sarcoma centre if needed in the future. A further aim of this visit is to transfer care formally to the general practitioner with written advice regarding the risk of CS and initiation of yearly consultations to discuss changes that may elicit imaging.

In almost 90% of MO patients, germ line mutations in the tumour suppressor genes EXT1 and EXT2 are found which can be used in diagnostics. Further, there is some evidence to suggest that those with EXT1 mutations might have more severe disease [43,44] and possibly increased risk of developing peripheral CS [44].

MO has many more features than osteochondromas and many suffer pain not explained by osteochondromas. Other skeletal abnormalities including short stature, widened metaphysis, bowing of the radius and short ulnas, knee and ankle valgus deformities as well as scoliosis. They also suffer from reduced quality of life[45] and fatigue[46] amongst others afflictions.

Ollier disease

Enchodromatosis or Olliers disease is an inborn disease where multiple benign cartilage lesions (enchondromas) develop intraosseously (centrally) in the bone in the first decade of life. The prevalence is estimated at 1:100 000 and it is non-hereditary and either caused by a single gene defect or by combinations of mutations [39,47]. The distribution of enchondromas is asymmetrical and extremely variable in terms of number, size and location and evolution. As such the clinical consequence is also very variable with surgical management aimed at treating pathological fractures, growth disturbance, axial deviations and malignant transformation. One group has suggested a prognostic model based on location [48].

The lifetime risk of developing a central CS is as high as 25-40% [48,49] and patients are therefore advised follow a plan of education and follow-up in Norway as for MO. Patients with Olliers disease also appear to have a slightly raised risk of developing glioma, leukemia and juvenile granulosa cell tumours[48].

A challenge to clinicians is that patients with Olliers disease can have more aggressive radiological and pathological tumour features without malignancy, making accurate CS diagnostics and prognostics even more challenging[50].

Chondrosarcoma investigation and management

Generally

The true clinical presentation of CS patients has not been assessed prospectively. In our prognostic cohort of 306 cases, we have retrospective data on 303 cases. Of these 56% present with pain without correlation for other causes of this. 22% present with a lump or mass and 13% are truly incidental findings. 9% present with some sort of compression of another structure (neurological, vascular, respiratory and so on).

The incidence of chondrosarcoma increases with age. Reports looking at age as categorical variable have shown that above 40 years of age, CS is statistically more frequent than enchondromas. However, enchondromas exist in the elderly and CS is also rarely reported in the paediatric population. As such, it is a difficult criterion to use diagnostically.

The mainstay of investigation of chondroid tumours is radiological. Rather than to address each modality in relation to each separate CS subtype, I think it more worthwhile to address the clinical setting and discuss the different methods contributions to clarifying this setting in the sections that follow.

The purpose of investigation is:

- To confirm that the bone lesion under investigation is a cartilage tumour.
- To determine subtype of chondroid tumour.
- To differentiate a benign cartilage tumour (enchondroma/ osteochondroma) from malignant (central grade I chondrosarcoma/ peripheral CS).
- To define those CS which appear to be of higher malignancy grade or dedifferentiation.
- To define tumour extension

Primarily ,plain X-rays or CT are used to assess the destructive and reparative processes influencing the cortical bone and patterns of calcifications, while MRI is used to assess tumour signal, extension and growth pattern.

Cartilagenous tumours are characterized by a lobulated pattern and high signal intensity in T2- weighted MRI images. A juxtaposed area of different signal can be indicative of dedifferentiation.

A radiological description of a central cartilaginous lesion should include anatomical location, comment on MR signal and CT density and measurement of the longest axis or size of the tumour. Further it should comment on its contact and influence on cortical bone from a scale of no contact-contact-thinning/scalloping with quantification of depth- breakthrough (i.e. cortical hole), proceeding on to the presence or absence of a soft tissue component. Some define scalloping with regards to its depth of penetration ><2/3 of the depth of the cortical bone, while others as focal or generalised. The relationship of a soft tissue component to the periosteum and its size are important issues. Other features of note are expansion, cortical thickening or destruction, active periostitis, reactive bone marrow oedema or presence of

fracture. Also important is assessment of growth pattern with regards to trapped fat and the availability of earlier radiological assessment to allow for quantification of growth.

Precise anatomical detailing is vital in planning the correct surgical procedure with safe margins and minimal morbidity.

Some have a practice driven by biopsy estimated grade while others use biopsies only as a confirmation of a CS diagnosis and use anatomical location and the presence/ absence of a soft tissue component to guide treatment. The role of biopsies is discussed separately below.

Distinction of enchondroma from central conventional CS

Being able to distinguish an enchondroma from grade I central CS/ ACT by reliable means is difficult for both experienced tumor radiologists and pathologists. It is also a reasonably common clinical scenario. It is the topic of many investigations without clear consensus [51-60]. This is most often a radiological conundrum since these lesions are often not biopsied and more recently, not always actively treated [61]. A challenge to methodology in this setting is the desire to describe a single feature with perfect specificity and sensitivity, while this likely is a qualitative assessment where an experienced radiologist and clinician must weigh the combination of several features. Even in this expert setting, this diagnosis is open to inter- and intraobserver interpretation by radiologist, pathologist and orthopaedic oncologist[62,63].

The research on the field is further challenged by the lack of established diagnostic criteria and most reports base their conclusion on a histological diagnosis open to interobserver variation, rather than observations of biology such as observed growth or rates of metastasis [56,57,60,64].

In the axial skeleton any cartilaginous tumour should be carefully assessed and followed, since enchondromas are thought to be extremely rare in the axial skeleton.[52] Any growth, significant cortical destruction or expansion is considered indicative of CS.

A current review on the topic [52]for the appendicular skeleton (likely anatomic definition) states that “the finding on conventional radiographs of a cartilaginous tumour with popcorn calcifications, no cortical influence, a diameter less than 2cm and a location in the small bones of the hand or feet or distal metaphysis (They probably mean femur) can be interpreted as an enchondroma without further attention or follow-up.” This is fairly uncontroversial. An important premise is that the authors are partly the same as those of a national epidemiological study with a large increased incidence of CS driven by a tremendous increase in ACT’s.

Furthermore; “within the small bones or a diaphyseal location, slight expansion, superficial scalloping and septonodular enhancement on MRI, a size <5cm in long bones, and even some increase in size are consistent with enchondroma”. Others, (myself included) would exercise caution in the presence of expansion [59] or growth which have by many been considered reliable (though not documented) predictors of malignancy. Interestingly one small study recently showed that 50% of central cartilaginous tumours (enchondroma and ACT) actually regress [65].

Indicative of grade I CS or ACT are size > 5cm combined with cortical remodeling, deep scalloping, a metaphyseal location and fast enhancement on dynamic gadolinium chelate-enhanced MRI [64]. The validity of dynamic contrast enhancement to differentiate enchondroma from ACT/ grade I CS is however uncertain [57], and since these are often incidental findings contrast series are often not taken.

Size>5cm and presence of pain are frequently used diagnostic criteria in both radiology and pathology reports while both should be interpreted with caution.

It is important to note that research supporting 5cm as indicative of CS [55] is an example of categorizing a continuous variable [66,67]. More specifically, the chosen measure of 5cm is one chosen at random without a clear rationale other than that size in general is an expression of growth potential. There is statistically more CS than enchondroma if the lesion is >5cm compared to<5cm, but CS and enchondroma are present in both groups as illustrated in my box plot below (figure 7), inspired by Geirnaerdt et al. Furthermore, the outcome variable of CS/enchondrom is reported by an imprecise standard (pathological definition). This rather than biological variables, like rate of metastasis or local growth potential. These considerations together make the clinical use of this finding difficult.

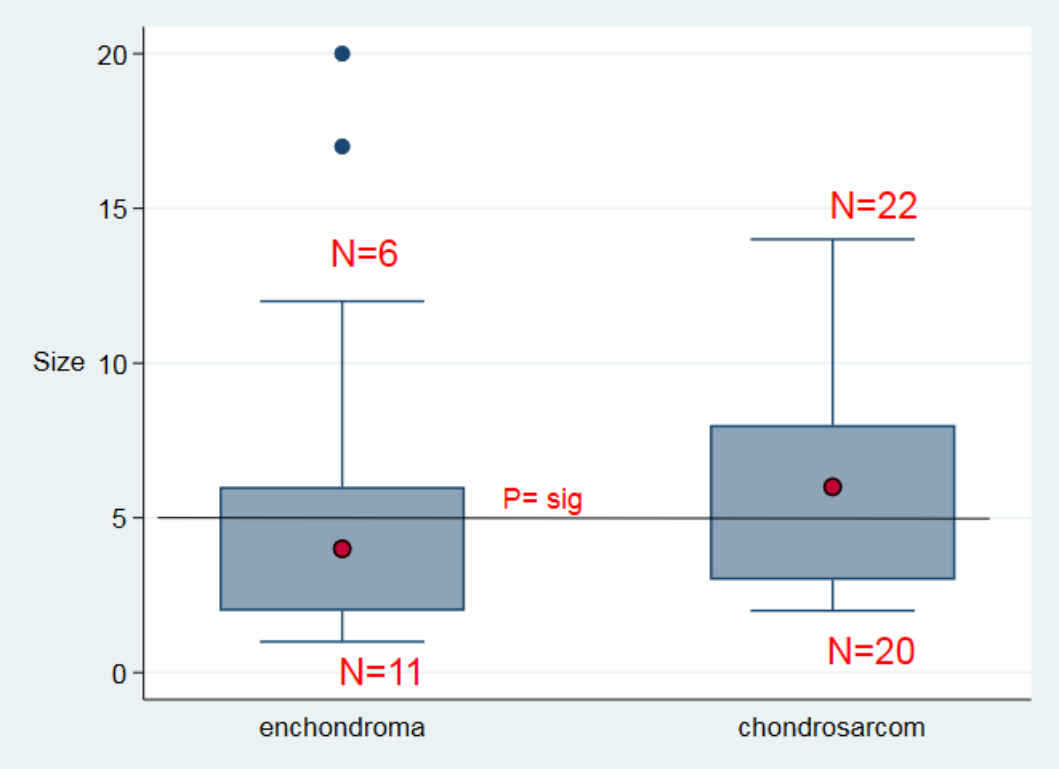


Figure 7 Box plot interpretation of scatter plot of size versus malignancy status inspired by Geirnaerdt et al[55].

In the same manner, the presence of pain has been reported to be an indicator of CS over enchondroma. The reporting of pain retrospectively is clearly a difficult variable to interpret qualitatively. Pain is present in patients with both enchondroma and CS and clinical examinations ability to predict the cause of pain is fairly unreliable. One series looking at

patients with pain and presumed incidental findings of enchondroma in the proximal humerus found that 82% (47of 57 patients) had MRI and clinical findings that suggested other disease was present and could explain the pain [68].

Diffusion-weighted MRI and PET-CT have both been shown to *NOT* reliably differentiate enchondromas from grade I CS [69,70].

An important part of investigation in this setting is to know when to refer to a tumour centre. This has been studied for assessment of solitary central cartilaginous lesions and is a common dilemma. The Birmingham Atypical Cartilage Tumour Imaging Protocol (BACTIP) as shown below was published with retrospective validation for the proximal humerus , distal femur and proximal tibia in 2019 [71]:

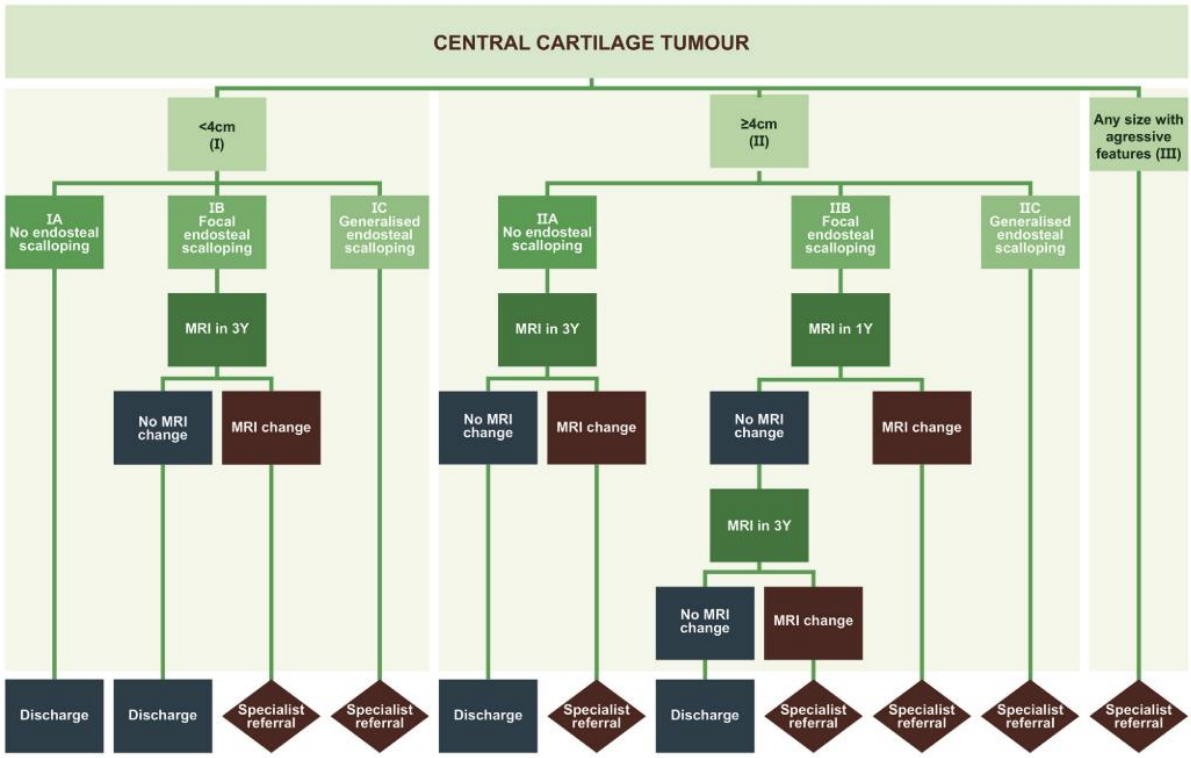


Figure 8 Birmingham Atypical Cartilaginous Tumour Imaging Protocol (BACTIP). Algorithm for the MRI differentiation of central cartilaginous tumours (CCT) in the proximal humerus, distal femur and proximal tibia. Key aggressive features = bone expansion and/ or cortical thickening, periostitis, cortical destruction and soft tissue mass. No aggressive features = absence of above criteria +/- endosteal scalloping. MRI change = increase in longitudinal length of CCT>1cm, progression of scalloping and/or development of aggressive features. Davies et al[71]. With permission from Elsevier publishing.

The Birmingham group use presence or increase of endosteal scalloping, growth in longitudinal axis size, expansion, cortical thickening, periostitis, cortical destruction and presence of soft tissue component to direct cases into one of 7 groups which then can be either discharged, observed or assessed by an orthopaedic oncologist. Validating its use in 387 patients over a 10 year period they found that incidence of CS increases with increasing

BACTIP group status. The final histologic or radiological diagnosis was enchondroma in 100%in group IA and IB, 96% in IIA and 83% in IIB. 57% of type IIC and 97% of type III were diagnosed as CS. They experienced a 5 month delay in diagnosis of a single case.

The length of follow-up for lesions with no aggressive features is much debated. Our practice in Oslo has been to discharge these without observation (Appendix A) as I know to be practiced in a similar fashion in other institutions. Other authors recommend lifelong follow up schemes for all enchondromas but without any real debate as to the gain/ cost of this[72]. For lesions with limited signs of aggression the observation must be tailored to the specific case with aim to reveal progression of the lesion, but avoidance of over treatment. Observation has been recommended for 1-3 years without evidence for a superior regime [61,71,72].

For central cartilaginous tumours in phalangeal locations, eccentric extremity location or in the presence of Ollier disease / enchondromatosis it is common to accept more aggressive radiological features before qualifying for CS diagnosis, but this has not been quantified [50,73]. Core features in this case are presence of soft tissue components and or growth after skeletal maturity.

Distinction of grade I from grade II/III disease for the central subtype

Imaging findings suggestive of higher grade disease are expansion, widespread lysis, bone destruction, periosteal reaction and most importantly a soft tissue component [60]. The presence of a soft tissue component is the single feature that on its own best predicts more aggressive behavior and is therefore also cited in treatment guidelines. PETCT is being investigated and has shown more promise in depicting more aggressive lesions, but is not in routine clinical use [70,74]. It has primarily been studied in its ability to predict malignancy grade rather than directly to rate of metastasis.

Distinction of osteochondroma from peripheral chondrosarcoma

The final diagnosis of peripheral CS must be based on both radiological and pathological assessment combined, but the decision to treat a lesion as a peripheral CS must in general be based on radiological assessment alone. This is explained further in "the role of biopsies".

Bernard et al published in 2010 a standardized measurement of the cartilage cap at CT and MRI imaging [75]. This has become the core method for distinguishing peripheral CS from osteochondroma pre operatively. Their described method entails measuring the cartilage thickness as illustrated below in figure 9, excluding the crevasses. For diagnosing peripheral CS, using 2cm as a cut off has sensitivity of 100%, specificity of 98%, positive predictive value of 96% and negative predictive value of 100%. This is correlated to a pathological diagnosis, but not presented with follow up. Essentially this represents the authors' ability to agree within their own pathological conclusion. From 101 osteochondromas and peripheral CS they found however that 18% of osteochondromas had cartilage caps of >1cm and 7% >1.5cm. I would argue that this be interpreted with caution in the skeletally mature and that a significant cartilage cap in this situation is in essence pathological. The size of a cartilage cap is analogous to the measuring of tumour size in this setting. In the skeletally immature the

presence of a cartilage cap can be seen as a displaced growth plate or alternatively the osteochondroma's growth plate and is essentially normal. In adults however, the presence of a cartilage cap (growth plate) is by definition pathological. We have cases of peripheral CS in the CRN CS cohort which have presented as recurrence of intralesionally removed osteochondromas with original cartilage caps of 1-2cm and benign histology, but this is a rare occurrence.

It is important to remember that the osteochondroma stalk at times can be eroded by the tumour, but remnants can typically be identified radiologically. This can be important for correct distinction of subtype.

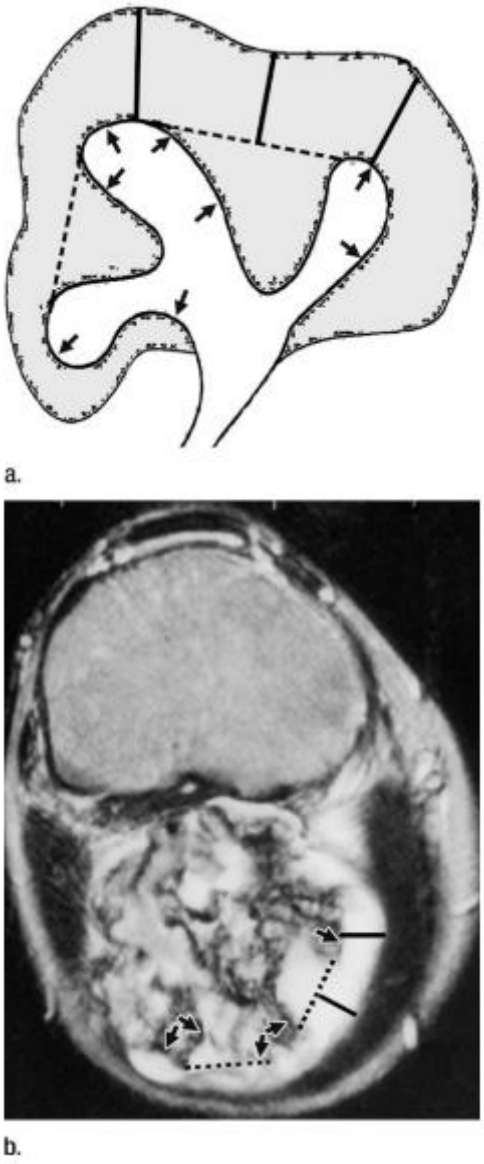


Figure 9 Drawing and MRI slide illustrating method of measurement of cartilage cap thickness on an osteochondroma. Note importance of not measuring the crypts or crevasses, but perpendicular from the tidemark (dotted line)[75]. With permission from Radiology.

Imaging for metastases

Primary metastatic disease is quite a rare event for all CS, but risk varies with subtype. The primary mode of investigation to check for metastatic disease is a CT scan of the chest since this is clearly the most common site of metastatic disease. Although NCCN and ESMO guidelines do not differentiate investigation of CS from other bone sarcoma and thereby advocate the use of a bone scan looking for skeletal metastasis , a recent discussion does not support the benefits of this[76-78], but rather proposes that it be reserved for those with lung metastases.

An institutional look at 454 cases of mixed CS finds that 22% have pulmonary nodules on initial or follow-up CT of the thorax, of which 8.1% were pulmonary metastases [79]. Histological grade of the original CS, size and margin of the nodule and presence of subtle/ irregular calcification are used to predict whether they represent metastases or not. Of the 52 cases where nodules measured <1cm, 40 (77%) showed no progression or resolved on subsequent imaging and were designated as non-metastatic.

The need for chest imaging in those with a diagnosis of grade I CS/ ACT has not been studied to my knowledge. With the inclusion of extremity location in the definition of ACT in the 2020 WHO reference book[2] along with the intended communication of limited metastatic risk, it would be natural to conclude that chest imaging was unnecessary.

The role of biopsies

The British NICE guidelines[80], the European ESMO[81] guidelines and American NCCN guidelines all recommend biopsies in the investigation of bone sarcomas, but do not comment specifically on its use for chondrosarcoma. Histological distinction between enchondroma and CCCS is open to significant inter and intra observer variation and chondroid lesions are known to be significantly heterogenous. There is therefore a clear risk of sampling error in assessment of chondroid tumour biopsies.

Jennings et al studied the correlation between needle biopsies and final histological grade in 78 long bone CS of undisclosed subtype [82]. They found correlation for 86% and correct distinction between low and high grade in 94%. They conclude that needle biopsy was "critical in determining treatment plan" and that all cases received an appropriate surgical intervention. They no not compare their practice to one where biopsies are not performed and do comment that "when diagnosis and management are not in doubt, biopsy may be avoided."

The ability of biopsies to predict final histological grade in central chondroid lesions varies along with various conclusions as to its usefulness [82-85]. Reports on direct curettage for radiologically presumed low grade intramedullary CS [86,87] without biopsy conclude that it is a safe practice. The same reports advise biopsies for suspected high grade disease before performing resection[60]. None however, propose a clear argument for this recommendation or have studied it scientifically. The CRN CS cohort shows biopsies in 72% of cases. In Oslo, our informal practice has increasingly been to not perform biopsies in the extremity where treatment is directed by intra/ extracompartmental status and radiological signs of aggressiveness. We have also increasingly negated biopsies in the axial location and have no

negative experiences from this. When a biopsy is performed, its purpose is to confirm chondroid tissue rather than predict grade. In the case of suspected dedifferentiation, biopsy has been directed to the area of suspected dedifferentiation. A wide (R0) resection is however indicated in both high grade conventional and dedifferentiated CS and as such a biopsy result does not influence management as long as radiology securely confirms chondroid tumour with sufficient features warranting resection rather than curettage.

In the setting of Peripheral CS biopsies are clearly confusing. From a modern report of 51 cases all undergoing needle biopsies, only 48% showed malignant cells and final histological grade was correct in only 27%[10]. Histological grade does not alter management in this setting. As such, the indication for biopsies for peripheral CS appears limited.

Chondroid tissue is known to be able to survive in avascular conditions due to the cartilage cells' nutrition via diffusion and not vascularisation. It is therefore commonly believed that biopsy tract seeding is a particular challenge for CS patients. There are a limited number of reports describing this in the literature [88,89] but there is no evidence that this is more common for CS than for other sarcoma [88] and a very rare event when using image guided core needle biopsies. Although needle biopsies have significantly less complications than open biopsies [90-92], in the setting of a patient needing surgical management, any complication carries the risk of delay.

Biopsy is an interventional procedure: Advocates of this have an obligation to document and publish its advantages. The notion that this is important because it has been performed historically, or is vital in the investigation of other sarcoma is not strong enough in my mind.

Surgical management of chondrosarcoma

Surgical removal is the mainstay for management of all CS of bone, according to all modern guidelines [80,93]however surgical strategy regarding the required surgical margins is still a matter of debate. In cornerstone text books such as Dahlins's 6 eth Edition Bone Tumours from 2010, an aggressive approach to surgery is advocated, stating "surgeons with much experience in the treatment of bone tumours have learned that the optimal treatment for chondrosarcoma is early radical removal with as wide a margin of uninvolved tissue as possible.[94]" The study of magnitude, quality and setting of surgical margins is complex and much debated. For CS, there has luckily been an evolution of this understanding towards both lesser margins, as well as curettage for selected cases. This does not appear to have compromised oncological outcome, but lessened the morbidity of treatment.

For CCCS, treatment guidelines are based on anatomical location in an extremity versus axial skeleton and the presence or absence of soft tissue components. The use of a controlled curettage with adjuvants has been established as a safe and reliable procedure for intramedullary grade I CS of the extremities in numerous publications [95-100]. Curettage is a lesser surgical intervention and thereby associated with less morbidity and better function than resection and reconstruction [101]. The use of an adjuvant such as a high speed burr, phenol, bone cement or even liquid nitrogen is advocated by many to secure local control [102-106], but one method has not been found to be superior to the other. Formally, using an

adjuvant in this setting has not been compared to not using one and only performing curettage.

Many centres perform curettage without a pre-operative biopsy when the radiological signs of aggressiveness do not indicate high grade or dedifferentiated disease [86]. When histological examination of the curettage specimen is grade II or III, many centres would advocate performing a re-resection of the operative cavity [107] and show that outcome in this situation is at the same level as primary resection. This is of course associated with significant morbidity. The need for this second procedure has been transferred from other sarcoma practice using grade to guide treatment. The necessity of such a re-resection has however not been documented and series of cases with this treatment scenario and follow-up without re-resection are sorely needed. The limits of curettage also need further study. The upper level of radiological signs of aggressiveness of intramedullary confined tumours with regards to cortical destruction and size for a safe curettage has not yet been established. Although this is a procedure not recommended for axially located tumours, a single publication with strict selection has advocated curettage for the very rare enchondromas or ACT's in the pelvis [108] while others comment that this selection is very difficult [109]. The role of observation only is not discussed.

The surgical margins required to achieve local control at resection are not entirely clear. Guidelines recommend R0/negative margins or descriptively "a covering of normal tissue[80,81]". The true measure of a margin is of course a local recurrence. The extent of a surgical margin in distance in cancellous bone or as quality of barrier has not been extensively studied at a subtype level. Stevenson et al looked at the millimetre distance of a clear margin of a mixed CS cohort (88% central conventional CS) reported by grade [110]. They found that for grade I disease >1mm was sufficient, while for grade II or III disease, >4mm was recommended to achieve local control.

A swiss group studying margins in a smaller mixed CS cohort have found that a wide (>10mm) margin was associated with improved DSS compared to marginal (1-10mm) or intralesional margin, but also that an intact anatomical barrier (intact fascia, periosteum, cortical bone) gave a similar DSS as a wide (>10mm) margin [83].

Two studies address margins for central conventional CS as an isolated group. Both define adequate margins as wide or radical and inadequate as intralesional or marginal and exclude curettage patients. Fiorenza et al find a significant relationship with adequate/ inadequate margins and rates of LR [111], while Andreou et al study a combined event free survival variable and found no clear association [112]. Neither group found a clear relationship between margin categories and survival. Also a central subtype specific review article, did not find a relationship between margins and survival [113].

The tendency in recent guidelines for treatment of peripheral CS is to carefully recommend the need for lesser margins. Both European and UK guidelines state "…aiming to excise the tumour with a covering of normal tissue over it", as opposed to a "wide" margin recommended for other tumours. A multicentre study looking at 50 peripheral CS of pelvic

location found that no cases suffered local recurrence, metastasis or disease related death when the surgical margin was ≥1mm [114] which supports this new recommendation.

The role of radiotherapy

The role of radiotherapy for CS of bone is limited for most cases since it is known as a relatively radio- resistant malignancy. Its use has mainly been studied in the setting of skull base, spinal and sacral/pelvic CS where adequate surgical margins can be either impossible or difficult to achieve technically or associated with such morbidity that it is not acceptable to patients. Local recurrence for skull base CS treated by surgery alone has been reported at 44% while the addition of radiotherapy to an incomplete surgical procedure has been shown to be associated with significantly improved local control at 9% LR [115]. Radiotherapy in this setting has often been studied in mixed cohorts of CS with chordoma and other sarcoma, showing local control rates of 80% over 10 years with a mixed photon/ proton regimen to high radiation dosages with median 76.6 Gy [22]. Three reports of proton therapy in the same situation for CS/ chordoma cohorts report local control rates of 58-89% for regimens with median 70 Gy or more [21,23,24,116] and 89% local control at 10 years for a single institution proton therapy of skull base CS alone . The Heidelberg group studied the efficacy of carbon ion therapy versus proton therapy in 101 patients with grade I or II skull base CS and found that there were high rates of local control for both regimes (≥90% over 10 years), without a significant difference [117].

Radiotherapy has also been studied as an adjunct to surgery in a mixed "high-risk" CS of bone and soft tissue cohort (N=60). High risk was defined as "lesions at complex locations where complete resection was an anticipated problem and/or resection with close/involved margins and or high grade lesions". In this trial 36 patients received post-operative RT with a median dose of 60 Gy while 24 received preoperative RT to median dose 50 Gy. The crude local control rate in this cohort was 90%, primarily driven by excellent outcome for those in whom an R0 or R1 resection was achieved [118]. A French comparative analysis of post-operative RT with various regimes found support for better local control and disease related survival for those with R1 or R2 margins after both resection and piecemeal operations [119].

The role of chemotherapy

The topic of chemoresistance in the setting of conventional CS is complex and beyond the scope of this PhD. Clinical studies devoted to chemotherapy effect are primarily carried out in the setting of end stage disease where the clinical indication is palliative and with the aim of delay of progression and relieve of symptoms, but interpretation is challenged by low numbers and many different regimes being used in different stages of disease for different subtypes. A review article of 31 studies primarily concluded as to the need for more studies at all levels and that effort to increase the number of studies was urgently needed [120].

A multicenter retrospective report of 50 patients with unresectable conventional CS of bone analysed outcome for first line systemic treatment. The most promising results came from a small group (N=7) treated with antihormonal therapy, with mean progression free survival of 6.7 months. This compared to 3.1 months for those treated with chemotherapy in the same report[121].

A similar multicenter report of chemotherapy in the advanced setting showed response according to RECIST criteria for conventional CS (N=113) of only 11.5% [122]. 73% received anthracyline-containing regimes.

Most recently, a prospective study of tyrosine kinase inhibitor Panzopanib has been studied for (N=47) patients with unresectable or metastatic conventional CS. They found evidence of positive drug activity with 43% local control at 4 months and a median progression free survival of 7.9 months. Response according to RECIST criteria were as follows:

TABLE 2. Week 16 DCR and Best RECIST Tumor Responses (n = 47)

Tumor Response	All Patients, No. (%)
DCR at week 16	20 (43)[a]
Best RECIST response	
CR	0
PR	1 (2)
SD	30 (64)
PD	11 (23)
Not evaluable	5 (11)

Abbreviations: CR, complete response; DCR, disease control rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.
[a]*P* = .09 versus null hypothesis of DCR = 30% (2-sided Fisher exact test).

Table 1 RECIST criteria response for trial of Panzopanib. Chow et al[123]. Permission from Wiley publishing.

There are currently12 drug interventional trials actively recruiting for chondrosarcoma patients at http://clinicaltrials.gov. (accessed 06.11.20). 10 of these are observational trials and two are randomised placebo controlled trials looking at the effect of oral Regorafenib.

Epidemiology

Epidemiology is the study of distribution, patterns and determinants of health and disease conditions in defined populations [124].

Incidence is the measure of the number of new cases of a disease during a given time period in a defined population.

$$Incidence = \frac{Number(N)\ of\ new\ cases\ with\ disease}{Total\ number\ of\ person\ years\ at\ risk}$$

Where the total number of person years is the sum of time each individual in the population is at risk. For our needs, this is approximated by the sum of the total number of people alive in Norway per year of the study. These numbers are available from the Statistics Norway/ Statistisk Sentralbyrå (www.ssb.no/en). These numbers are highly reliable in a country like Norway which has a high level of public organisation, stable socioeconomic structure.

Rates of events or rates of survival are most commonly presented by the Kaplan-Meier estimator. This was a method developed in 1958 by Edward Kaplan and Paul Meier to deal with incomplete observations[125]. This entails that one registers the number of events of the outcome of interest and relates them to the actual period of observation time from start of follow-up, eg diagnosis and until the event happens or follow-up ends without the event occurring because the study period ends or the patient is removed from follow-up for some other reason. This produces what are known as survival curves which is somewhat misleading in that they can display any event and do not necessarily portray "surviving," but rather time until any defined event such as death, death from a certain cause, metastasis, local recurrence, a complication, surgical revision of a prosthesis or even return to work. This gives rise to curves such as metastasis free survival (MFS), ie proportion observed without metastasis at any given point in time. At the start of observation everyone is event –free so the estimate is 100%, and as observation progresses and events occur (ie. metastasis) this number decreases until no further events are observed or one reaches the end of observation time. At a particular point in time (for example at 5 years) one can measure the level of the curve, giving for example at 70%. This means that 70% of patients have not had metastasis (70% 5 year MFS). The reciprocal of this is that 30% had metastasis. The Kaplan Meier curves can easily be inverted to display the frequency of the actual event we are measuring, i.e. the rate of metastasis. In this case 100%-70%= 30%. This curve will start at zero and rise in accordance with the number of observed metastasis to 30% at 5 years.

In crude percentage we divide the number of events of interest by a total persontime, implicitly assuming we had complete follow-up for each individual, despite the event having occurred early on in the observation. This will underestimate the real risk by inflating the denominator. As a very basic example we have followed 10 patients with CS for one year. We are interested in the rate of metastasis. Two patients develop metastasis after 6 months. A further patient dies of unrelated causes at 3 months and one moves overseas and is lost to follow-up after 3 months. Let us compare rate of metastasis by crude percentage and Kaplan-Meier estimator:

***For crude percentage*:**

Rate of metastasis=$\frac{Number\ of\ events}{full\ observation\ ie\ number\ og\ cases\ observed} = \frac{2}{10}$ = 20%

For Kaplan-Meier estimator of survival function [S(t)]:

Event data in years (censored data indicated by numeral+, event data by numeral only
0.25+;0.25+;0.5;0.5

Time in years (t)	Event (d)	Censor (c)	Risk set (n)	Survival factor (1-d/n)	Survival S(t)
0			10		1.0
0.25	0	2	10	1.0	1.0
0.5	2	0	8	(1-2/8) =0.75	0.75
1	0	0	6	(1-0/6) =1.0	0.75

Survival starts off as 1 at beginning of observation (where 1= 100%).

For clarification at 0.5 yrs; S= Survival factor at 0.5×Survial at 0.25 =0.75×1.0=0.75

Which means at 1 year 75% Metastasis Free Survival(MFS), or 25% rate of metastasis

Kaplan-Meier curves and logrank tests are examples of univariable tests. These describe survival according to one factor under investigation, but ignores the influence of any others. These can be used when the predictor is categorical (one category or the other).

The cox proportional hazards model was described in 1972 by British statistician Sir David Cox. It is a regression model commonly used to investigate the association between the survival time of patients and one (univariable) or more (multivariable) predictor variables often termed covariates. This works for both categorical and continuous variables. In addition the model gives an effect size for each factor as expressed by the hazard ratio (HR) which again is an expression of relative risk. Where HR=1 there is no cause of effect, HR<1 implies a negative effect, reduction in hazard, protective role or good prognostic influence. HR>1 implies a positive effect, increase in hazard, poor prognostic influence. The model assumes and should be tested for proportional hazards over time to be valid meaning that the HR is constant over time. It is of great importance that covariates to be studied are selected based on a reasonable theoretical assumption and clinical basis to be of value.

Cancer registries

Cancer Registry of Norway (CRN)

Norway was one of five countries whom in 1948 was asked by the WHO to formally study the incidence of cancer [126]. The Norwegian Ministry of Health and Social Affairs passed legislation in 1951 to commit all health care workers to report all cases of cancer to the newly established Cancer Registry of Norway from 1st January 1952.

The main objective of any cancer registry is to collect and classify information on all cancer cases in order to produce statistics on the occurrence of cancer in a defined population. This can further be used to assess the impact of cancer in the community and drive cancer research.

For a register to be able to give reliable conclusions regarding CS in Norway for example, it must first be able to demonstrate acceptable degrees of completeness. More precisely; what proportion of diagnosed cases in the given population are actually reported and present in the register. It is the duty of any registry to seek and publish such key figures. The CRN reports greater than 95% overall completeness and 97% for primary bone malignancies in the period 2001-05 [127].

Other registries

While the CRN covers all of the Norwegian population, other registries like the SEERS covers a proportion of the population (approx. 30%) and by demonstrating that this population is representative of the whole, they can thereby extrapolate their findings.

Another method is to merge reporting from a number of registries, on various levels, like the English National Cancer Data Repository [128] , the combined Nordic cancer statistics database (NORDCAN) or at an international level [4]. For each step removed from reporting from a single complete register with a single set of rules and practice one introduces new possibilities of error. All the Nordic cancer registries score high on data quality and completeness for example, but analysis of NORDCAN concluded that they are best used to assess overview of trends [129]. For epidemiological study of a single cancer type, the differences in registration, screening and coding should be taken into account and the authors recommend use of national statistics supplemented with other national data.

For rare cancers there are further challenges to the use of register data. The variables registered are generally limited in number. If the report form for a given cancer is too long it increases the chance of the same form never being filled out. The registered variables are often driven by the larger cancer groups. The reporting form used (Norwegian only) through the study period of this thesis (Appendix 2) includes patient details, icd-10 code with text and location, morphological diagnosis, basis of the diagnosis (radiology?/biopsy?/ Other?), TNM stage at diagnosis as well as primary treatment details.

This covers the very hard core of CS prognostication such as ICD code and metastatic status at diagnosis. However, primary tumour details at diagnosis are sparse and need to be reported or attained by other means. In Norway the full pathology report for both biopsies and operative specimens has been sent attached to the formal CRN report which improves the

number of variables greatly (eg tumour subtype, size, soft tissue extension, grade, margin). This however requires interpretation and pathology reports are not standardised. The CRN is currently working in close cooperation with the hospital tumour boards and the Norwegian National Advisory Unit for Sarcoma to implement full electronic reporting as part of the "national quality control register" which will increase the number of variables still in a more formal prospective manner.

Although the struggle with any rare disease is to attain a large enough number of cases to draw meaningful conclusions, this must be balanced by the quality of data for these cases. The SEERS data base has given publications with up to nearly 3000 patients [30] and re-examined with machine learning in up to 1500 cases [130] but without real new findings. This is likely due to a mixture of limited variables and data quality [131-133]. In an attempt to critically review the 8th version of AJCC staging system for CS, Compton et al tried to use the SEER database for model validation. They found however that up to 40% of skeletal CS entries in the database lacked essential pathological annotation such as size, grade or tumour extent [134].

Chondrosarcoma prognostication

Central conventional chondrosarcoma

The most common subtype of CS has an equal distribution among the sexes and mean age of presentation 55 years of age. It has been documented from late adolescence to the very elderly. It occurs equally in the extremity and axial skeleton and has a 10 year survival of approx. 75% for all locations together.

A recent review article focusing on prognostic factors in CCCS of bone, found that high grade tumours and axial/ pelvic location were indicators of a poor prognosis in relation to overall survival [113]. They warn of heterogeneity of cohorts, treatments as well as outcome variables and wisely call for prospective and comparative studies to increase the evidence base for CS management. The heterogeneity they describe makes interpretation and comparison of CS literature troublesome.

Grading

In 1977 Harry L. Evans MD authored what is probably the most important CS paper of the last 50 years, entitled "prognostic factors in chondrosarcoma of bone"[135] in the journal Cancer. It was a retrospective analysis of 81 cases of CS treated at the M.D. Anderson Hospital and Tumour Institute from 1948-74. He states "this study was undertaken in an effort to formulate a method for histologic grading of chondrosarcomas which would utilize objective, reproducible criteria and which would show significant relationships with tumour behaviour, particularly metastatic potential, and prognosis." His work was based on observations by other prominent sarcoma personalities such as Lichtenstein and Jaffe(ref*), O'Neal & Ackerman [136], Dahlin & Henderson(ref*) as well as Lindbom[137]

Histological slides were available for 71 of the 81 cases of unspecified subtype. He assessed the following:

- Character of the intercellular background as chondroid or myxoid
- nuclear size as small and dark- staining, moderate with visible intranuclear detail or large and pleomorphic.
- cellularity
- mitotic rate by counting mitotic figures in the most cellular areas of 10 or more high power (x40) fields
- frequency og lacunae containing multiple nuclei

He highlights that they are highly heterogeneous tumours and states that the areas of highest grade are to be used. This finding has been rediscovered in a modern cohort[138]. He then divides them into grade 1-3 as follows:

> Grade 1; Small and densely strained nuclei, background varies from chondroid to myxoid. Multiple (≥2) nuclei within one lacunae, absence of mitotic figures or moderate/ large nuclei

Grade 2; moderate sized nuclei but low mitotic rate per field (<2). Increased cellularity, nuclei are paler staining and have visible intranuclear detail. Background is more cellular and tends to be myxoid rather than chondroid

Grade 3; ≥2 mitosis per 10 high power fields in the most active areas, more cellular and often non-visible matrix. He also included 4 cases of 18 with a clear spindle cell pattern and a mitotic rate well in excess of the minimum criteria described as a fibrosarcoma like picture. One can only speculate as to whether these in fact were cases of dedifferentiated CS.

The authors found significantly different rates of overall survival between grade III (N=18) as compared to grade I (N=32) and II (N=21), and a tendency but not statistical significance between grade I and II. The findings as related to rate of metastasis were more "striking" with 0% for grade I, 10% for grade II and 71% as grade III. This gave a highly significant difference for grade III as compared to I and II. Further they conclude that rate of LR is "primarily dependent on the adequacy of surgical therapy rather than histological grade."

The WHO criteria used in Norway during this study period are as follows[50]:

Grade I: Moderately cellular, abundant hyaline cartilage matrix. Small, round nuclei that are occasionally binucleate. Mitoses are absent.

Grade II: More cellular and less chondroid matrix than grade I. Mitoses are present, but widely scattered. Nuclei are enlarged and either vesicular or hyperchromatic.

Grade III: Highly cellular, nuclear pleomorphism and easily detected mitoses. Chondroid matrix is sparse or absent.

The WHO states that dedifferentiated CS is by definition to be denoted as grade IV.

Although Evans et al stated that their aim was for an objective and reproducible method only their mitotic criteria is a non-qualitative variable. It took however many years before studies emerged looking at inter- and intra- observer variability of histological grading.

The whole world has for generations been dazzled by the power of the microscope such that all forms of cancer until recently have been categorized by their microscopic appearance. It is important to remember that there is no direct causality in these findings but rather that we discuss a statistical association between subjective microscopic features and behaviour. The sum of these microscopic features, expressed as histological grade serves as an intermediate variable to predict for example risk of metastasis.

Interobserver variation has been studied by two groups in the setting of a central cartilaginous tumour [62,139]. The Skeletal Lesions Interobserver Correlation among Expert Diagnosticians (SLICED) study group found a low level of agreement both in distinguishing benign enchondroma from CS and between "low grade" and "high grade" CS in the long bones. This was the case both between pathologists and radiologists. A dutch study group also found low reliability of the diagnosis and grading of central CS [139], most difficult in distinguishing

between enchondroma and grade I disease, while improved at distinguishing more aggressive disease.

The clinicians deciding treatment together with their patients for this surgically managed disease are the surgical oncologists. Zamora et al [63] therefore importantly studied this same observer variation between orthopaedic oncologists, in the appendicular (anatomical definition) skeleton in distinguishing enchondroma from low grade, intermediate grade and high grade central CS based on clinical and imaging information as a clinical scenario. The inter- and intraobserver agreements were only fair to good, while agreement for the proposed initial treatment strategy after diagnosis was also poor.

This has further been studied in the setting of Peripheral CS with a finding of good agreement. The authors found 78% agreement and concluded that this was substantial, but that multidisciplinary approach integrating clinical and radiological features were crucial [140].

Evolution of grading in practice

Histological grade has been central to the treatment strategy and follow-up of CS since Evans et al's original work, but has been through an evolution. Initially, management was based on clinical findings and plain x- rays. An open biopsy was performed to secure diagnosis and then surgery planned with the aim of resection with wide or even radical margins. The final histological examination then gave the true histological grade and thus an indication of risk of metastasis and death. Over the years one noted that the analysis of grade did not always coincide between the biopsy and operative specimen and studies have shown this to be true in various scenarios, but with differing impact [82-84,138]. The introduction of routine use of CT and MRI has indeed revolutionized CS care both with regards to information available to make diagnosis (tissue signal and density) and the level of planning and accuracy (extension of disease) during surgery. Next, came the introduction of curettage and adjuncts as treatment for low grade disease. Concurrent research addressed the rates of metastasis for scapular and pelvic disease as well as for those with soft tissue extension[141,142]. Most now accept that curettage is appropriate only for extremity intramedullary disease, perhaps with the exception for a few carefully selected cases[109] [98]. Curettage was only initially deemed appropriate for grade I disease while the final grade was only available after surgery. A number of patients with operative specimen histological grade II or more then underwent further surgery by resection. At the same time a number of patients who underwent resection initially due to a biopsy grade II had a final operative grade I, and appeared to be over treated.

Along with the documentation of safety of CS management without biopsy [86,87], management guidelines have changed to be driven by anatomical location and soft tissue extension [93] (NCCN - https://www.nccn.org/professionals/physician_gls/default.aspx#bone). The histological grade available after treatment either with curettage or resection still poses the question of over and under treatment. There is evidence for a step wise understanding of CS progression [32]from benign to low grade malignant to high grade malignant which supports differing levels of intervention according stage of disease. This in contrast to a diagnosis of Ewing sarcoma, where the diagnosis by mutation in itself represents a certain

potential for metastasis. Thus, ewing sarcoma should not be graded and a lesser form of surgery would be deemed inappropriate.

The role of histological grade has been examined in many articles though often in cohorts of mixed subtypes of CS, including different locations of disease and therefore with different findings [111-113,143-148]. In modern cohorts of the most common subtype (central conventional CS) it is however clear that grade is a significant predictor of survival in univariate analyses [112,148,149]. This does not include the influence of anatomical location or soft tissue extension and is therefore imprecise. One may argue that no patient has just grade I disease. Rather, patients with grade I disease of the extremity/ axial skeleton with and without soft tissue extension have different risks of metastasis and survival giving 4 groups per grade (as below exemplified for grade I). Then, for all grades I-III, in total 12 groups overall.

*Grade I extremity intramedullary

*Grade I extremity with soft tissue component

*Grade I axial intramedullary

*Grade I axial with soft tissue component etc.

Outcome data on all these subgroups do however not exist from a single cohort, but rather data on grade combined with location is as detailed as there is for now [112,150]. Most publications have statistically different outcomes for grade III disease against grade I +II, although there is often also a non-significant tendency for difference between grades I and II. Although Evans studied metastatic risk, prognostication has in more modern times been studied in relation to survival or combined event free survival outcome variables.

Size

Size has commonly been stated to predict behaviour and is part of TNM reporting. Tumour size has however in most part been studied as dichotomized variables either as<>5cm in distinguishing enchondroma from CS or as<>8cm (or similar) in predicting CS behaviour, at a univariate level [147,149,151] or as part of AJCC stage [112] . Dichotomizing continuous variables can be highly problematic [66,67] and should be avoided where possible. Two multivariate analyses of size as continuous variables (including our own) both conclude *WITHOUT* evidence of influence [134,150]. So it is in fact unlikely, that size is prognostically important for predicting systemic risk for CCCS. In the setting of CCCS, size is most often a measure of the intramedullary extent which as we have described does not appear to drive metastatic risk. It has not been investigated in this study, but a larger tumor logically entails the resection of a larger area and as such it might be a better reflection of local morbidity.

Age

Age has also been found to have a clear association to survival [134,147,151]. Risk of death does however inescapably increase with age. Furthermore we demonstrated that the CRN CS cohort includes 66 cases of second/ third and fourth cancer diagnosis while Compton et al state “that patient age was the most powerful indicator of risk of death in this cohort which suggests that most patients have died of other unrelated causes” [134].This is difficult to use

clinically and this finding's consequence is probably to highlight that prognostic analysis should be adjusted for age where possible. The effect of age on survival is nicely visualised by including a comparison with age matched controls in Kaplan-Meier curves as below. Even though patients studied with grade I CS of long bones have gradually declining survival during observation, it does not appear to be statistically different from an age matched population.

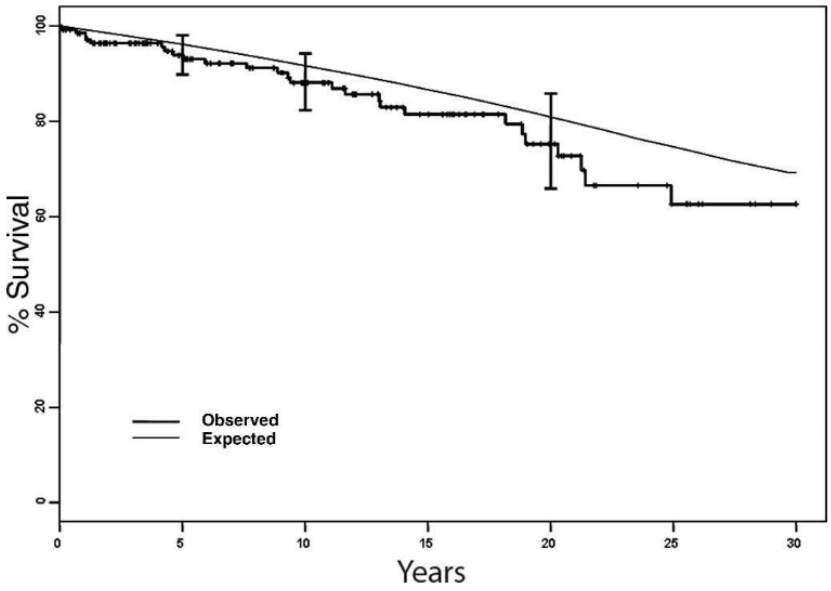


Figure 10 Kaplan-Meier survival curve (Bars=95% confidence interval) for overall survival of 164 patients treated for grade I chondrosarcoma of long bones compared with an aged-matched US population. Schwab et al. With permission from Walters Kluver publishing.

Sex

The prognostic power of gender type has been studied specifically by Laitinen et al in a cohort of undisclosed CS subtypes, but including dedifferentiated disease. The authors found that females have improved survival during their age of fertility for grade II and III disease, when compared to men of similar age. This effect diminished after menopause (>55 years of age). Others have studied the effect of sex without age restrictions in relation to survival and found no evidence for central subtype [112,149] or mixed cohorts [30].

Location

There is little doubt that the bone that CS develops within as defined by skeletal location, is an important factor, but it has been difficult to establish its exact pattern. There is widespread acceptance that central CS of the phalanges has a more benign course and one accepts a more aggressive histological picture in its grading. This is a qualitiative assessment which does not allow for a clear definition or restriction. Similarly, due the confined anatomic space as described in the introduction, CS of the head and neck are generally always analysed as a separate entity.

The importance of location is in fact accepted anecdotally to the point where it forms the foundation of treatment guidelines for CS. The definition or distinction of location varies making comparison difficult. We have discussed earlier the different meanings of the term "appendicular" and "axial"skeleton (see introduction), but this is often not appropriately defined in many reports. Others exclude, for example thoracic cases, since they as orthopaedic surgeons are not involved in their management[111] or spinal and vertebral cases for various practical reasons[134]. Furthermore, in the SEER database the reporting of location has been described to be unreliable [134,152].

The most concrete evidence supporting the influence of location is the rate of metastasis from tumours of specific locations. In this respect, articles reporting CS of isolated location can be of great value. An historic cohort of 47 conventional (Central and Peripheral subtype) scapular CS states a 21% rate of metastasis [142], another 24% [153]. Another study of chest wall CS (Central and Peripheral subtype) reports 20% rate of metastasis[13] while a Scandinavian study of 106 chest wall CS also reports 20% of metastasis [15]. For series with spinal CS, the rate of metastasis is sometimes not reported [154-156], except in a small series (21 cases) in a tertiary referral center of 43%[157] or a larger series of 98 cases; 24%. All results from these reports are in crude percentage rates.

When it comes to the pelvis, Donati et al report 124 conventional (63 Central and 61 Peripheral) pelvic CS [158]. They report an 8% rate of metastasis overall, but 96% survival for Peripheral CS group and 73% for the CCCS group. As such the metastatic events likely derive from the central subgroup and are near doubled in reality. Another two-centre series of grade I+II conventional primary central CS reports a 79% MFS at 10 years or 21% rate of metastasis by Kaplan-Meier estimator [159]. A multi-center retrospective assessment of CCCS in the pelvis of all grades reports a crude rate of metastasis of 30% [160]. Other series include dedifferentiated CS which makes interpretation difficult [141,161-163].

In a modern central subtype specific institutional series, Andreou et al report on 115 CCCS non-metastatic cases undergoing curative treatment [112] with 26% crude rate of metastasis overall, 17% for the extremity and 38% for the axial and pelvic group. They do not specify in which group the scapular lesions were included, but analyse extremity versus axial+ pelvic disease in relation to survival and find P=0.002 supporting better survival for extremity location.

From Bologna in Italy we can study the course of 296 extracranial non metastatic CCCS with different methodology [148]. They report an overall rate of metastasis (K-M rate) of 8% at 5 years and 18 % at 10 years. They do not give metastatic figures specifically for different anatomical locations, but rather related to grade. They analyse appendicular versus axial skeletal location with regards to survival, P=0.09 [OR=1.7 (CI:0.8-44.9)], but do not report rate of metastasis and they do not define their location variable precisely.

Establishing the metastatic rate of CCCS of the extremity (without pelvic or shoulder girdle) is no easy task. A historic cohort of 344 primary limb, pelvic and scapular conventional CS from the Mayo clinic [146] report 14% overall but do not distinguish on site. A Birmingham

report states 30% (crude) rate of metastasis for (N=101) long bones while 37% for (N=52) pelvis in a table. In the text however they use a different distinction with axial (N=52) and appendicular (N=101), without metastatic numbers. In a figure demonstrating the location of their tumours, they have 101 extremity tumours defined by the glenohumeral and hip joints, while 39 pelvic+4 vertebral+8 scapular+ 1 sternal = 52 axial. These numbers are difficult to interpret for our purposes, but if anything they report higher rates of metastasis than the majority of comparable studies.

Another clinical example of the importance of location is the behavior of CCCS in the phalanges of the hands and feet. In this location one accepts more advanced both radiological and pathological signs of aggressiveness in the distinction between enchondroma and CS diagnostically[2]. With regards to prognosis they are also known to follow a much more indolent course[164].

Soft tissue extension

Soft tissue extension is along with location the main factor defining CS management [80,93]. It has been said in a recent evidence based assessment of CS staging that "the transgression of the cortical bone has never been shown to be prognostically important" [134], but even before our work this is in fact not true. It has however mostly been studied as related to local control or overall survival rather than metastatic risk as shown by Fiorenza et al[111].

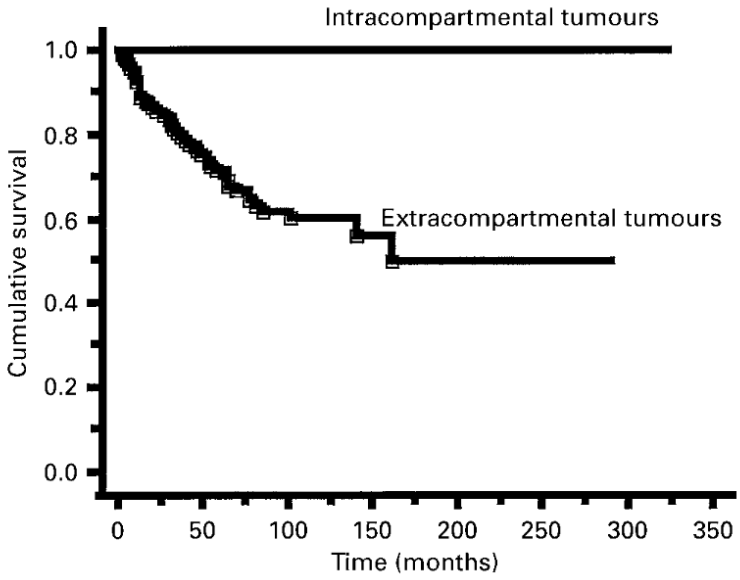


Figure 11 Kaplan-Meier curve for overall survival according to intra-extra compartmental status for central CS. Fiorenza et al[111] with permission from The Journal of Bone& Joint Surgery (Br)

Immunohistology

Immunohistological staining with Ki67 as an expression of proliferative cell activity is widely used in the study of lymphoma, breast and lung cancer. It has also been studied in the setting of chondroid skeletal lesions. Firstly it has been established that its expression is low or absent in enchondromas/ chondroblastomas or grade I central CS [165]. It has however also

been studied in relation to disease free survival in a conventional CS cohort of both peripheral (7 cases) and central subtypes (22 cases) [166]. Nawa et al found a highly significant relationship between high levels of staining (≥10% of tumour cell nuclei) with 0% 5 year disease free survival versus low levels of Ki67 staining (<10%) at 69.3%. Since the survival for peripheral CS cases was 100%, all these high staining cases were likely central subtypes although it is not directly stated. Ki67 staining has not been studied directly in relation to metastatic activity for CS to my knowledge.

CD44 has an established role in tumour growth, invasion and metastasis development for other cancer types, but also for the metabolism and proliferation for cartilage cells. Overexpression of CD44 staining, again defined as >10% was studied in relation to metastasis free survival for a mixed CS cohort of 36 cases [167]. Heyse et al found a significant relationship between CD44 overexpression and both a poor metastasis free and overall survival. Of 12 cases who developed metastasis, 8 were conventional. I have not found further studies to validate these findings.

Surgical margins

This is a complex field with challenging interpretation. The field is troubled by analysis often of limited locations or in mixed cohorts [110,144,145,168] meaning that even if the methodology otherwise is precise, the implications are limited. In mixed cohorts with for example central and peripheral conventional CS together, the stud of metastatic risk will underestimate findings due to the very low rate of metastasis in Peripheral CS. Surgical margins are however primarily a study of local recurrence, in which case Peripheral CS is known to have quite high rates of LR; and over a long time period and will likely contribute to an overestimation of frequency and time period compared to CCCS alone.

Andreou et al studied margins in CCCS, but found no significance between margins and their chosen OS and EFS variables. Bjørnsson et al found a significant increased rate of LR at 5 years for intralesional (44.5%) versus wide or radical margins (11%) in 341 primary CS of long bones and limb girdles [146]. Fiorenza et al found significantly increased rates of LR with "inadequate margins = intralesional, marginal or contamined" in 153 primary conventional CS. In a multivariate cox model containing margins, size, compartment, site of tumour and grade they found that inadequate margins independently predicted increased rate of LR with HR=8.0 (95%CI:3.0-20.9) and LR again predicted worsened survival HR=3.4(95% CI:1.6-7.1) in a similar model. Similar findings have been found using UICC (Residual tumour) margins R0 versus R1 [169]. These studies look at overall groups of CCCS, but we do not know if this is applicable to all subgroups or driven and limited to those of a higher level of aggressiveness.

Local recurrence

There is widespread discussion with regards to the impact of LR on rate of metastasis and survival which is the focus of paper 3 in this thesis. There is an acceptance that LR is associated with an increased risk of metastasis and death overall, though the methodology behind this has been challenged by the lack of accounting for immortal time bias and analysis in mixed subtype cohorts.

In CS literature, most authors have presented descriptive statistics or Kaplan-Meier estimators for groups experiencing an event against those who have not, without accounting for this potential bias [111,138,143,145]. Some evade the issue by including only patients with LR events [170-173], starting observation at the point of the LR event. They cannot directly compare the impact of LR to those without LR of course since those without are excluded. Immortal time bias has been accounted for in one study looking at the association between LR and survival, but they do not include metastasis in their analysis [112].

There appears to be an acceptance that LR is associated with worsened risk of survival overall [112], for high grade disease [111,143,171,172] and for axial location [171], which are more aggressive tumours in the primary setting. In the setting of grade 1 extremity tumours however Schwab et al conclude that although the cohort overall has similar survival to that of an age matched cohort, those experiencing LR have decreased OS, evident first after 5 years (P=0.03) [174]. This however, was contradicted by Streitbuerger et al in their analysis with 94% 10 year survival.

The exact association between LR and risk of metastasis is as such unclear. The question also remains as to whether the association is valid for only specific locations, grades or subgroups.

Metastasis

At presentation approximately 5% of CS cases have proven metastatic disease, primarily in the lungs. A metastatic event is a significant predictor of death in CCCS [111,112,146], such that most cohorts already report prognostic analysis of non-metastatic/ metastatic cases separately.

Although an extremely rare event a SEER's study of the importance of verified lymph node metastasis in the primary treatment setting gives evidence of this being a poor prognostic indicator [175], even after adjustment for other factors including subtype. On the other hand, Compton et al studied the importance of skip metastasis which is another area of tumour within the same medullary cavity interspaced by apparently healthy bone marrow [134]. This is an important notion in prognostication of osteo- and Ewing sarcoma, but they did not find any evidence for this predicting a poor prognosis for CS.

Algorithms

In 2018 Thio et al asked the question "whether machine-learning techniques can be used for 5 year survival prediction of patients with chondrosarcoma?" They used data from 1554 patients with conventional or dedifferentiated CS of extracranial location who underwent surgical treatment from the SEER registry from 2000-2010 to try to predict overall survival [130]. The variables they used were age, sex (female/ male), race (white, black, asian and other), subtype (conventional/ dedifferentiated), grade (well, moderate or poorly differentiated, tumour size (cm), tumour extension (localized/ local invasion/ distant metastasis), and location (extremitities, spine, pelvic bones and sacrum, and rib, sternum and clavicle). They developed this to a web based application which is freely available online and called it the Skeletal Oncology Research Group (SORG) algorithm. The same year Bongers et al provided external validation by examining its use in a US institutional cohort and found that it retained good discriminitative ability and performance, but overestimated 5 year

survival [131] possibly because the validation cohort represented a tertiary referral center with larger tumours. It has also been internationally validated in a CS cohort from Italy. Again the discriminative ability and performance are good but in this cohort the SORG algorithm underestimated survival for those cases with predicted probabilities from 0-0.8 at 5 years [176]. The international cohort had significant differences in subtype composition, grade and extension which are all core variable for outcome.

This algorithm is challenged by the fact that they are not subtype specific and do not report events directly related to diagnosis and treatment such as local recurrence and metastasis. Overall survival is of course an important end point for observation, but is very difficult to interpret while lacking tumour related events directly.

Peripheral chondrosarcoma prognostication

Peripheral CS commonly effects a younger age group (mean age 38 years) both in people with a solitary ostechondroma and MO but presents more commonly in the extremity (90%) than the axial skeleton (10%).

Prognostic research concerning peripheral CS also called secondary CS with osteochondroma is a very limited field. In the literature we can find mostly descriptive statistics and some univariate analysis, but not multivariate analysis. This is partly due to the rarity of disease with an incidence of 0.4 / million/ yr. (95%CI:0.3-0.5). It is also a result of being grouped together with central CS under the term conventional CS of bone in much of the literature. There is an increasing recognition and understanding however that peripheral CS has a different aetiology, prognosis and management than the central subtype (CCCS) in addition to occupying a completely different anatomical space and as such should clearly be analysed separately. It appears clear that peripheral CS is most common in the pelvis, trunk and extremities and that metastatic disease is very infrequent (approx. 2-8%) [10,11,177].

Although the mortality overall is very good with 90% 10 year survival, the most frequent cause of death is in fact from local disease or other unrelated causes [10,11]. Tsuda et al studied retrospectively peripheral CS over a 34 year period from the tumour database at the Royal Orthopaedic Hospital in Birmingham, UK. They found as demonstrated by their K-M curve of disease specific survival below that tumours in a pelvic location had a worse prognosis, due to higher rates and consequence of LR on OS. Ahmed et al also report that 15 of 18 deaths from their cohort of 107 cases were attributable to local recurrence [11].

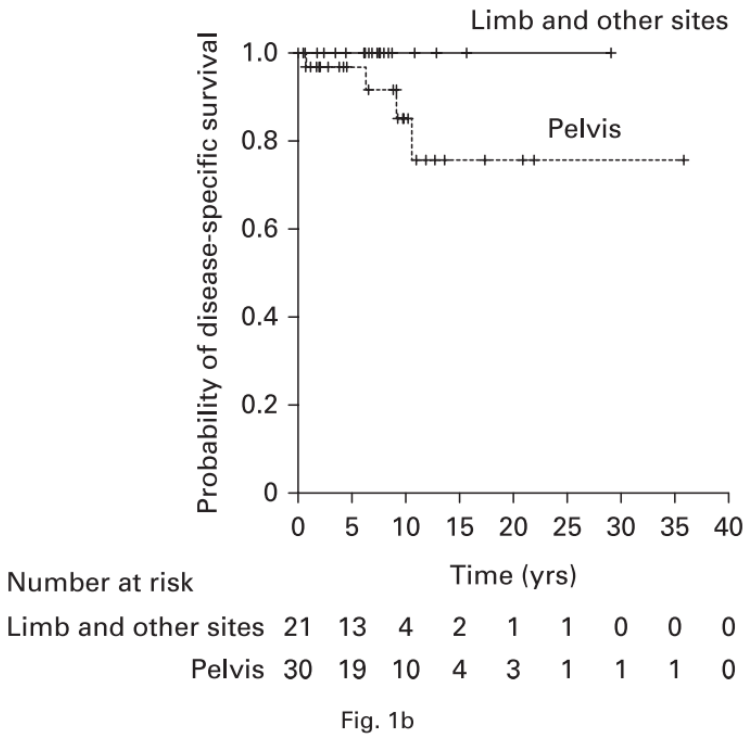


Figure 12 Kaplan-Meier curve illustrating disease specific survival for peripheral chondrosarcoma according to anatomic site of origin[10]With permission from the Bone and Joint Journal..

The role of pre operative biopsy has been studied and correlates with findings in the operative specimen in only 27% of cases and as such is of little use in planning.

There is a tradition to carry out histological grading, but the role of grading for peripheral CS in the literature is unclear. This is considered a low grade disease and in fact nearly always presents as grade I or II disease. Tsuda et al found univariate significance among 51 cases for a association between grade II disease and worsened Local Recurrence Free Survival (LRFS) as compared to grad I disease [10] as illustrated below, but no multivariate analysis was performed. There is no evidence that grade predicts risk of metastasis or in fact survival [10,11,178] though Tsuda comments that they saw a single case of metastasis for 35 cases of grade I tumours, while 3 from 13 for grade II tumours. The role of grading in Perpheral CS needs evaluation with in larger numbers and multivariate analysis.

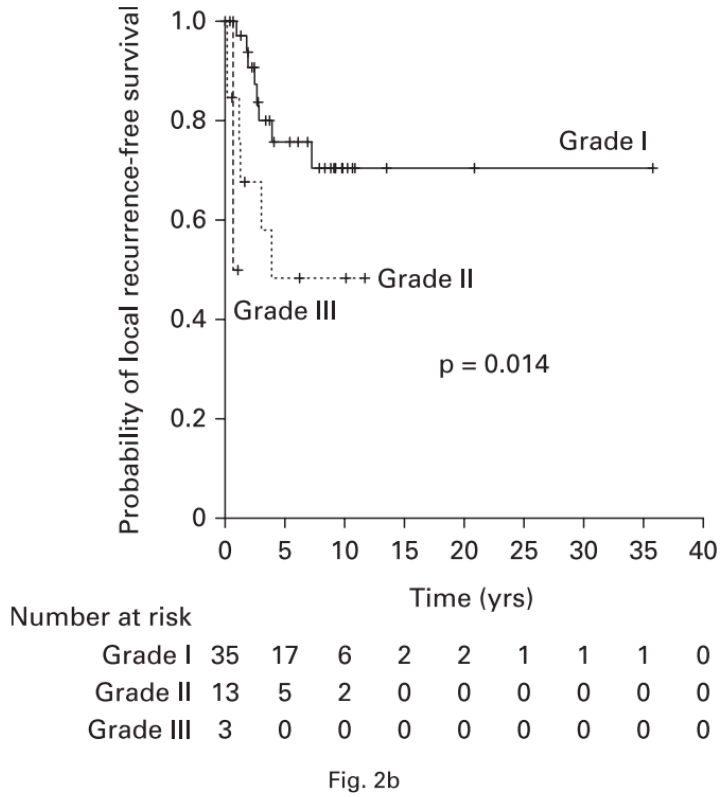


Figure 13 Kaplan-Meier curve illustrating probability of local recurrence free survival according to histological grade for peripheral chondrosarcoma[10]. With permission from the Bone and Joint Journal.

Peripheral CS in the setting of MO is associated with a significant worse rate of both LR and OS in the two main studies [10,11].

Surgery is the mainstay of management and margins with a clear margin ≥1 mm appear to be sufficient in a study in a modern setting of pelvic tumour location [114].

Thesis aims

The overall aim of this thesis is to contribute to a better understanding of the behaviour of CS. With this to give better advice and information to patients, as well as to guide decisions about the need and level of treatment and follow-up for patients and clinicians together. Furthermore we hope that this can form the foundation for new directions in CS prognostication and research.

Paper 1 aimed to uncover the true incidence of CS in a modern era in Norway. It aimed to present rates of local recurrence, metastasis and survival as well as analyse which features best predict outcome in the most common subtype; CCCS.

Paper 2 aimed to further analyse the influence of the size of the soft tissue component and other features in predicting behaviour of CCCS and to use these findings to present the cohort by risk groups accordingly.

Paper 3 aimed to establish the true patterns and impact of LR in CCCS.

Synopsis of papers

Paper 1

Paper 1was the initial work in establishing the CRN CS of bone cohort, allowing analysis of 311 histology confirmed CS of bone diagnosed between 1990 and 2013. We could then show that the total incidence of CS of bone during the study period was 2.85 /million/year, rising from 2.39/million/year in the first 5 year period to 3.45 /million/year in the last 5 year period. There was an increase during the study period, stronger for females than for males so that the incidence at the end of the period was similar for both sexes. The increase in incidence follows the pattern for the most common subtype (CCCS) which increases during the study period and with age. The increase was most clear for grade II disease.

Incidence over time by grade, all subtypes in CRN chondrosarcoma cohort			
	rate per million(95% CI)		Change between first/ last period
Time period	**1990-1994**	**2004-2013**	
Grade I	0.58 (0.37-0.85)	0.63(0.42-0.89)	+0.05
Grade II	0.76(0.52-1,07))	0.90(0.65-1.21)	+0.14
Grade III	0.42(0.25-0.66)	0.44(0.27-0.67)	+0.02

Table 2 Incidence over time by grade for all subtypes. Adapted from Thorkildsen et al[150] With permission from Taylor Francis publishing .

Overall disease specific survival in the cohort was 75% at 10 years.

For the most common subtype CCCS we found 10-15% rates of local recurrence, all evident by 5 years while metastasis rate increased with location and grade ranging from 0% rate of metastasis for extremity grade I disease at 10 years to 56% for axial grade III disease. Axial grade III disease was the only central subgroup with local or metastatic events after 5 years and particularly high rates of LR (47% at both 5 and 10 years).

The Peripheral CS subtype showed very low levels of metastasis at 2% over 10 years, but developed LR also after 5 years (10%) until 10 years (13%).

We analysed prognostic factors for the CCCS subtype and found that the presence of a soft tissue component independently predicted adverse outcomes of LR, metastasis and decreased survival. Male sex was associated with an increased risk of LR compared to females and grade III disease independently predicted increased risk of metastasis. DSS was independently predicted by age and strongly by metastasis at diagnosis.

Paper 2

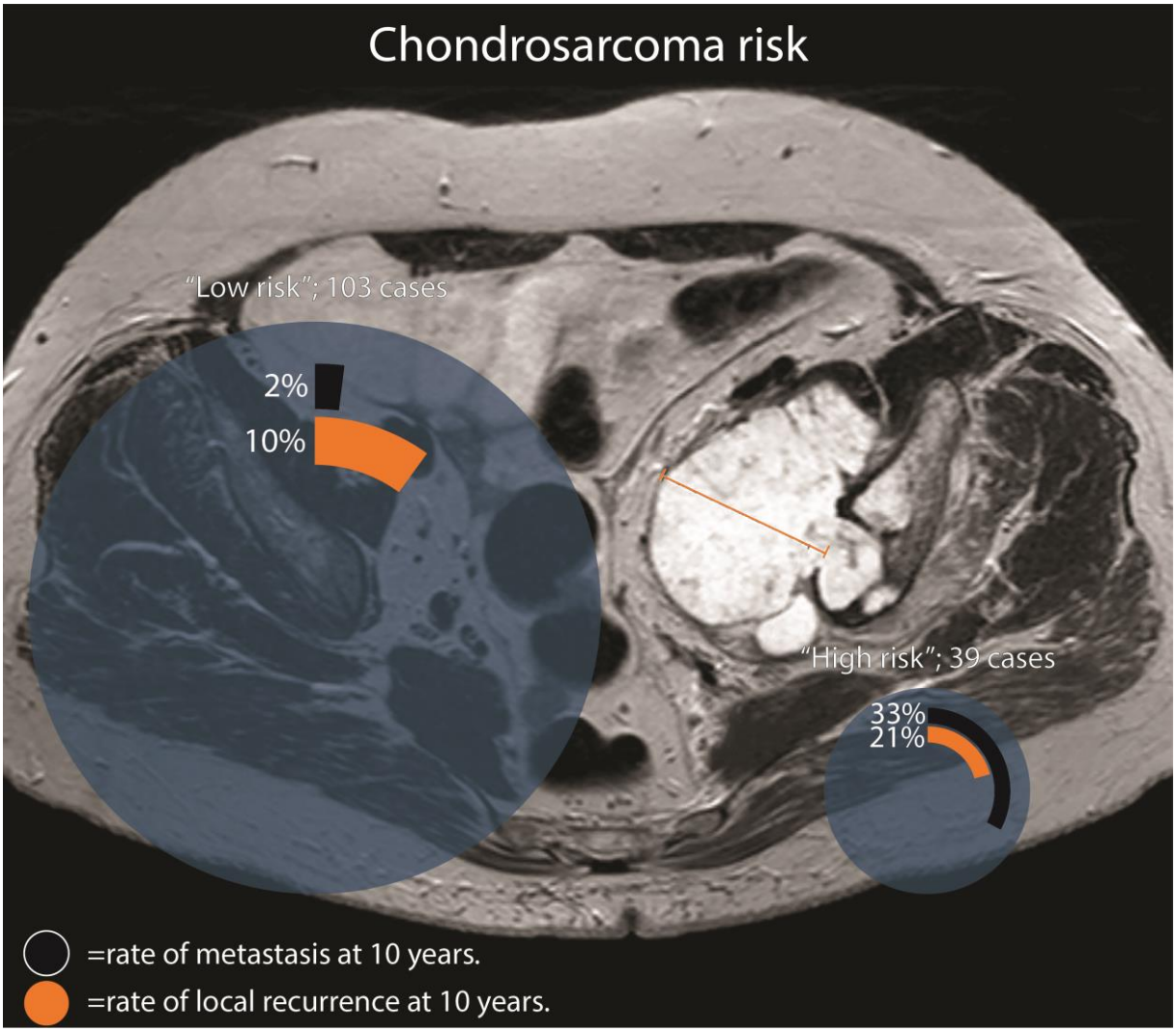


Figure 14 Illustration of chondrosarcoma risk by Oslo risk group. Cover Image JSO. Thorkildsen et al[179], with permission from Wiley publishing.

Paper 2 is a further prognostic analysis of CCCS. We have assessed traditional predictors of outcome like location, grade, age, sex and soft tissue extension together with the size of the soft tissue component assessed by standardized radiological measurement.

By combining axial location with ≥1 cm sized soft tissue component we found an independent predictor of risk of metastasis and death without the use of histological grade.

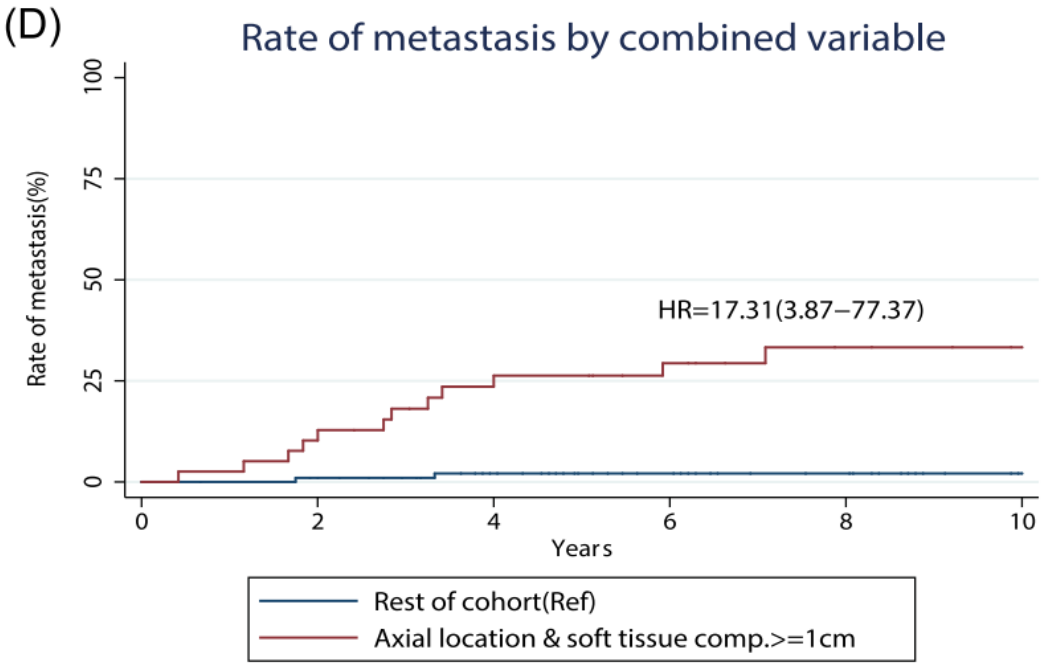


Figure 15 Kaplan-Meier curve for risk of metastasis by Oslo risk group. Oslo high risk(red line) =axial location & soft tissue component≥1cm, Oslo low risk(blue line) = rest of cohort. Thorkildsen et al[179], with permission from Wiley publishing.

Along with primary metastatic status this can be used to create a risk stratification model for CCCS as follows:

	NAME OF GROUP	DEFINTION
Low risk	Low risk I	Extremity cases, intramedullary, or with a soft tissue component < 1cm
	Low risk II	Extremity cases with a soft tissue component ≥1cm
	Low risk III	Axial cases with a soft tissue component<1cm
High risk	High risk	Axial cases with a soft tissue component≥1cm
Primary metastatic	Primary metastatic disease	Primary metastatic disease

Table 3 Definition of Oslo risk groups. Thorkildsen et al, with permission from Wiley publishing.

This creates a small high risk cohort of 39 patients with a 10 year local recurrence rate of 21%, rate of metastasis of 33% and 70% survival. The low risk cohort was larger with 103 cases and a 10 year rate of local recurrence of 10%, rate of metastasis of 2% and 91 % survival.

The low risk group had no further local or metastatic events after 5 years while the high risk group had continued risk of metastasis between 5 and 10 years.

Paper 3

Paper 3 presents a study of local recurrence of the most common CCCS subtype (N=180) in the CRN CS of bone cohort [180]. In a question driven manuscript we had the following queries:

- **What is the true pattern and frequency of upgrading and dedifferentiation in locally recurrence CCCS?**

  We found that in 32 first LR and 40 LR overall, there were two cases that recurred as dedifferentiated central CS and a single case of upgrading where the original tumour was grade II and the LR grade III.

- **What is the impact of LR on rates of metastasis and overall survival for CCCS?**

  The 10 year risk of metastasis for those *without* LR was 11% and for those *with* LR 42% [HR=4.1 (CI:1.5-10.7)]; that is a four times higher risk of metastasis. 16 of 32 patients with a first LR also developed metastasis, 10 of which occur together with the LR. The average time to LR being discovered was 1.4 years (range 0.2-4.4), and average time to developing metastasis after this was 1.7 years (range 0.3-3.3).

  The 10 year OS for those experiencing a LR was 24%, while for those without 81% [HR=9.3(5.0-17.5)]. For those with a LR, but without metastasis the 10 year OS was 48%.

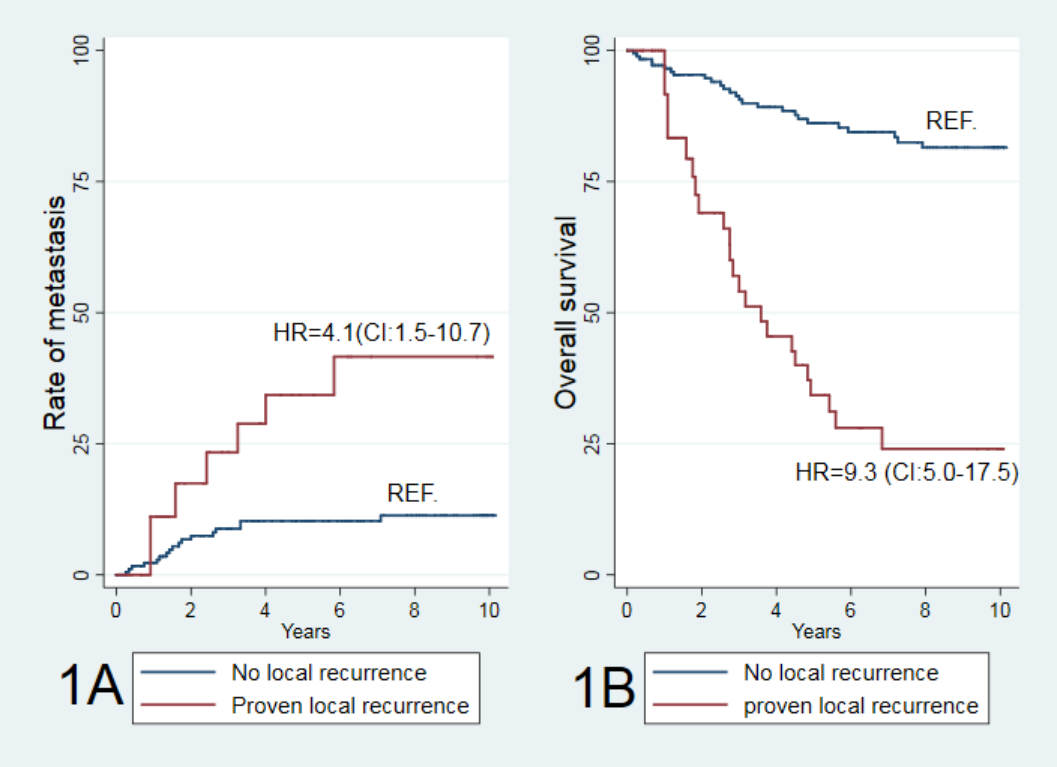


Figure 16 Kaplan-Meier curves for A) Rate of metastasis by local recurrence status and B) Overall survival by local recurrence status. Thorkildsen et al[180], with permission from Wiley publishing.

- **Does the impact of LR vary with subgroups of patients?**

We found no evidence that a LR in the setting of an appropriate curettage increased the risk of metastasis as opposed to those undergoing resection/ amputation; P=0.02. The appropriate curettage subgroup comprises only 37 cases (21% of cohort) while the resection/ amputation subgroup contains 141 (79% of cohort). It would therefore be advantageous to distinguish risk further within the latter group.

In subgroup analysis it is important to understand that there is overlap of cases in the different subgroups such as those for axial location (N=81), grade II disease (N=73) and soft tissue extension (N=106), all with a significant increase in risk of metastasis in the event of LR. These are all traditional features of a more aggressive tumour in the primary setting, but overlap among them makes precise interpretation a challenge in the clinical setting.

Interestingly, there was within Oslo low risk definitions (N=103) no evidence of any increased risk of metastasis or death, while the Oslo high risk group had a clearly increased risk of death [HR=8.9(CI: 1.8-42.7)]. The high risk group did not statistically have a significant increased rate of metastasis, but descriptively of 8 LR cases, 6 developed metastasis. This distinction is clinically more useful since the two groups are clearly defined without overlap and results in 74% of cases without increased risk of systemic disease and only 26% with increased risk.

- **How does locally recurrent CCCS present and is routine surveillance helpful in discovering it?**

50% of LR were asymptomatic, but discovered by routine surveillance, while the rest were uncovered by the patient themselves as pain or a palpable mass.

General discussion

Methods

CRN chondrosarcoma of bone cohort

The quality control charter of the CRN obligates them to perform quality enhancement work at the CRN. This includes the recovery of clinical files as well as radiological and pathological material where necessary. The construction of the CRN CS of bone cohort and its analysis is a part of this quality control work at the CRN.

We searched the CRN for all ICD-10 codes C40, 41, 30-32 and co-existant ICD-03 morphology codes 9220/3, 9221/3, 9231/3 and 9243/3. This resulted in 327 cases. 18 cases at the CRN were registered with incorrect morphology or topography codes. These were identified by the same search in tumour databases of the 4 regional tumour treatment providers at Oslo University Hospital (N=251), Haukeland University Hospital (N=58), St Olav's University Hospital (N=30) and University Hospital of Northern Norway (N=9). A number of cases were identified at more than one center. In total this gave 348 eligible cases. The NCR search gave 38 cases not found in the hospital databases while in the hospital search we found only three cases not registered at the CRN. All data for these 348 cases was quality controlled from information in the CRN, in the hospital databases, as well as the clinical files by the main author based on definitions agreed on in advance in a group setting.

The radiology was reviewed (N=223) for all those cases were radiology was available for the cases from Oslo and Bergen by senior sarcoma radiologist Dr I. Taksdal. A number of cases from Trondheim and Tromsø also had radiology in Oslo or Bergen since there had been communication about the case during the clinical management. It is an increasing challenge to this type of research that radiological files either on film or digital file are destroyed after a period of time due to storage issues. This is particularly the case for a slowly progressive disease like CS known to have late recurrences and should be used as a further motivation for prospective registration.

Histopathological review (N=112) was performed on slides from the operative specimen with indication as illustrated by table below.

Reason for pathological review	**Numbers. (N)**
Unclear pathological grade	46
Any doubt regarding diagnosis in clinical files	20
Missing information	20
Unspecified or unclear subtype CS	18
Unusual biology in clinical files	8
TOTAL	**112**

Table 4 Reason for pathological review in CRN CS cohort. Thorkildsen et al.

37 cases were excluded after review for the following reasons:

Reason for exclusion	**Numbers. (N)**
Borderline malignant chondroid diagnosis	11
Uncertain/ non CS diagnosis	11
Other CS diagnosis	6 (mesenchymal and clear cell CS)
Soft tissue origin	5
Foreign residency-missing information	4
TOTAL	**37**

Table 5 Reason for exclusion from cohort from CRN CS cohort. Thorkildsen et al.

311 cases were analysed for incidence and 306 for prognostication since 5 had only needle biopsies, not allowing meaningful interpretation of grade.

The pathology review (N=112) was carried out by a single pathologist for the cases from Oslo, while the rest were reviewed in a group setting at a meeting of the Norwegian mesenchymal tumour board. Ideally all cases would have been reviewed in a group setting, but resources did not allow for this. Slides of pathology specimens exist for all cases, but to limit the work we attempted to identify all those cases for review whom either had missing or unclear information, as well as those at risk of wrongful diagnosis. Examples of this are those where the distinction between benign and malignant disease appeared unclear which resulted in the exclusion of 11 cases. For these cases the radiological findings were presented at the pathological review. Another indication for review was where there was clear doubt in the clinical files as to whether this in fact were a CS. Distinguishing a chondroblastic osteosarcoma from a CS with osteosarcoma dedifferentiation can as an example be difficult.

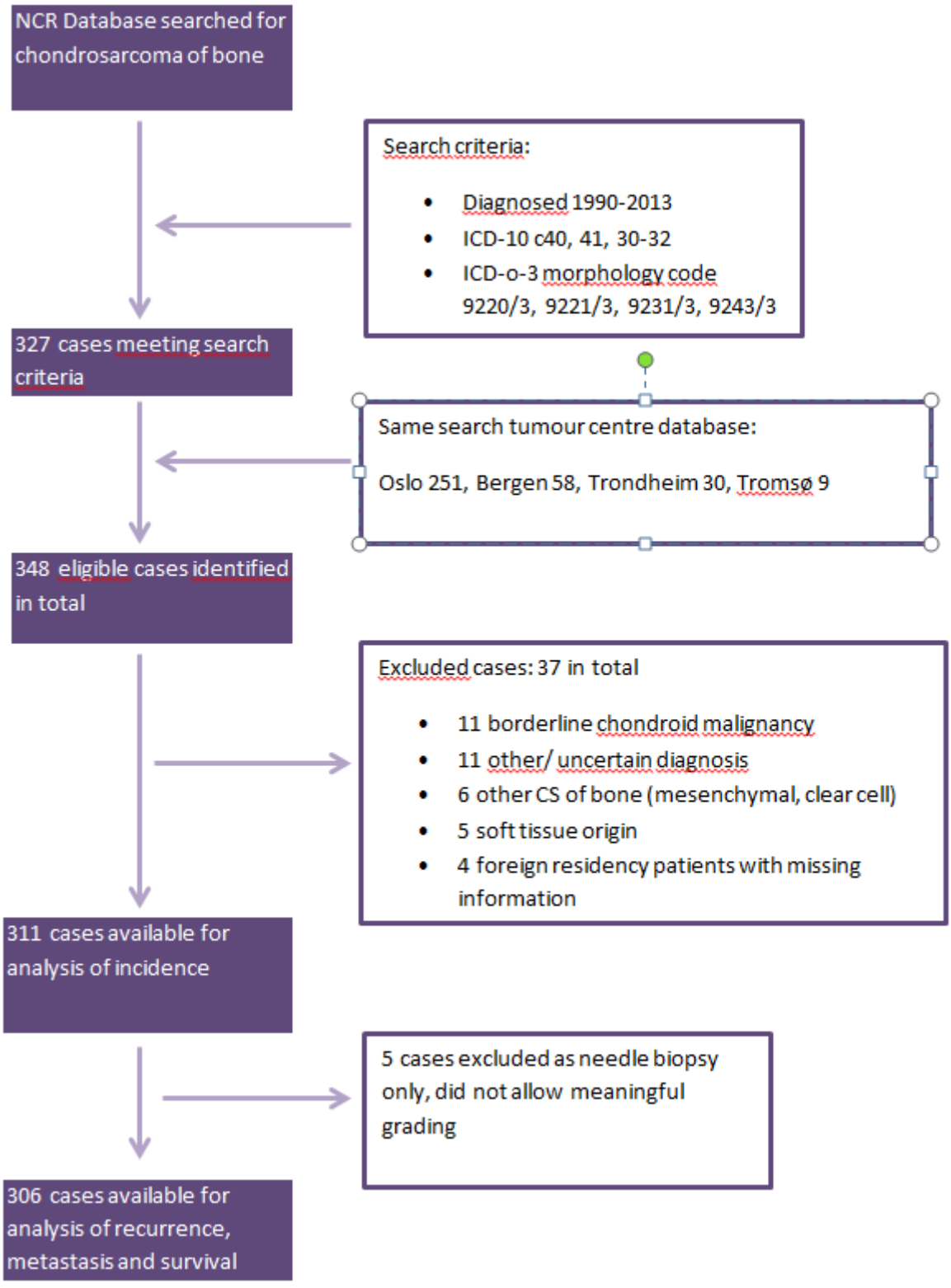


Figure 17 Flow chart illustrating methodology for inclusion/ exclusion for CRN CS cohort. NOTE changed from original publication: "same search tumour centre database ***Oslo251****, Bergen 58, Trondheim 30, Tromsø 9". Thorkildsen et al[150], with permission from Wiley.*

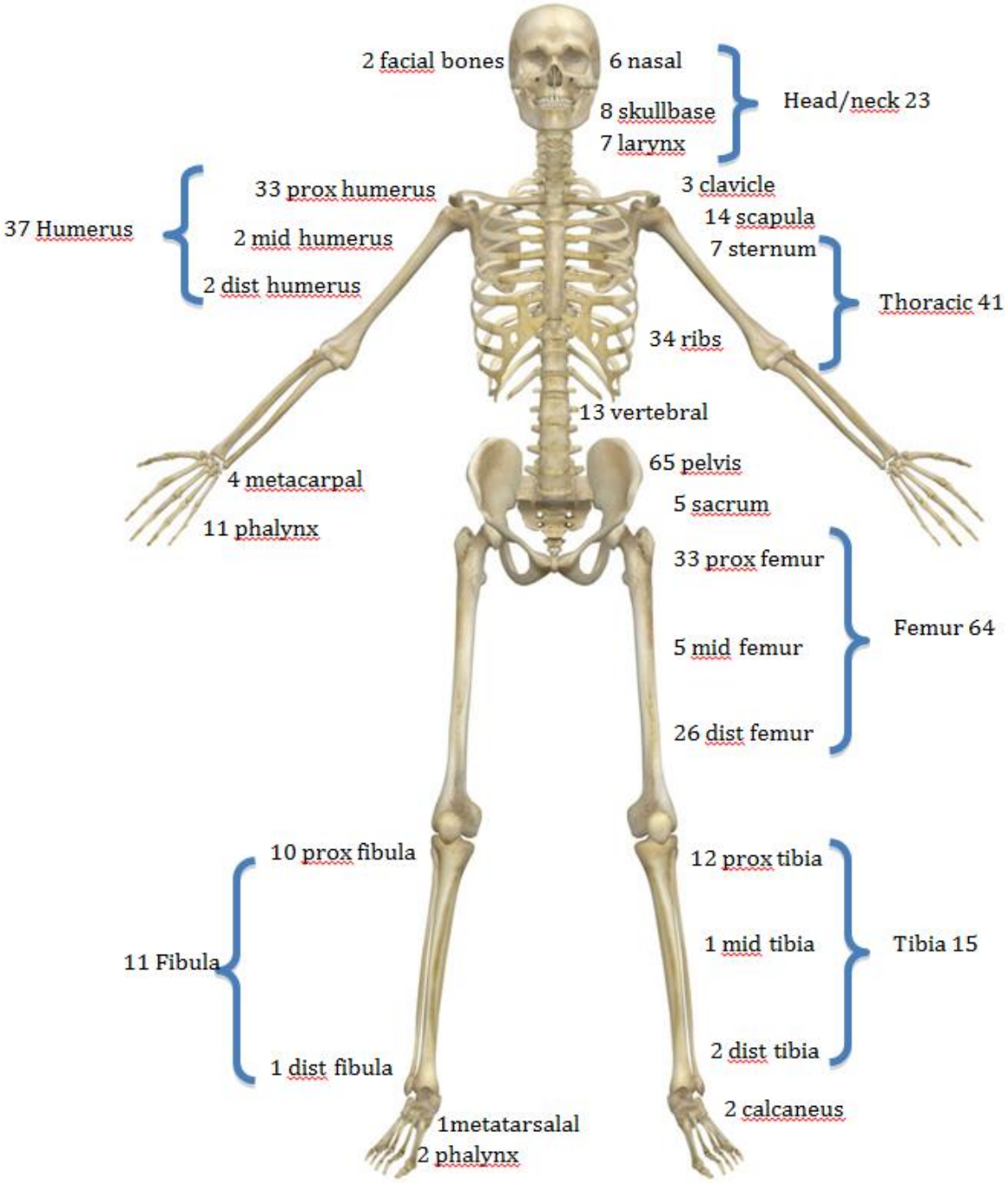


Figure 18 Anatomical location of chondrosarcoma in CRN CS cohort. Constructed by main author Thorkildsen using skeleton from Wikipedia.

On the basis of previously described quality control process, we have stated in all papers that we believe our data to have high quality. We stand by this. Common measures of data quality are the numbers of unspecified CS subtype included, numbers excluded due to missing variables or numbers excluded due to loss of follow-up [4]. Our numbers in all these categories are very low which is certainly unique.

No data were changed without a review assessment to minimize the subjective assessment by a single researcher. The review was a separate process for radiology and pathology, while we know that both are open to inter and intra observer variation. Assessment in a multidisciplinary setting is recommended and would be preferred. To establish the true subtype for example, the distinction between central and peripheral subtypes can be surprisingly difficult. In a total of 13 cases we combined the review to define this as clearly as possible.

All those involved with the review have also been involved in the primary care of many of the patients in the cohorts as well as authors of the resultant publications. This means both that they may be influenced by their own personal assessment in the past and that they subconsciously could be influenced by their inclusion in the research questions raised. The ideal scientific situation would be to have an external review of an uninvolved multidisciplinary team or at least separate radiological or pathological practitioner, but this was beyond the resources of this project.

The UICC surgical margins variable was an assessment by the main author from clinical files. Furthermore for the reporting of grade for 11 cases, the histology report concluded either "high grade" or "low grade". Practice in Norway during the study was to denote grade I or II as "low" and III or IV as "high". The high grade case had no area of dedifferentiation and was therefore denoted as grade III. The 10 cases of "low grade" disease where all denoted as grade II in line with both historic and recent literature supporting that the area of highest grade best depicts behaviour, even if this area is minimal [135,138].

We have not used the terms "primary" and "secondary" CS but rather focused on subtype specific analysis and provided details of cases with predisposing syndrome in the patient demographics. Our main argument for this is that the terms "primary" and "secondary" are imprecise, unnecessary and do not contribute to our findings. Peripheral CS are by definition "secondary" and as such the terminology does not contribute to further understanding. For the central subtype however, the most common scenario is that there are no previous radiological examinations before diagnosis and therefore we can not presume to know whether the case is "primary" or "secondary". This point was interestingly stated also in 1961 by Lindbom et al [137].

The cohort is a national database which avoids the setting of bias in referral to tertiary centres. The care of CS has been highly centralised for a long time and since 2007 practiced at only two centres. The cohort contains low levels of "untouched referrals" and contaminated referrals occur primarily in the setting of a misunderstood diagnosis rather than as local recurrence after inappropriate surgery at low volume institutions. This is an important point of context with regards to the studies external validity

Prospective versus retrospective

It is important to address whether this indeed is prospective or retrospective work since this relates directly to the level of evidence or power of our findings. Prospective studies are in general less prone to influence by bias and confounders than retrospective studies and are considered a higher level of evidence.

Paper 1 was termed an "observational study" in the title, and in the text we have described a "retrospective search". In paper 2, we have written "… it is a prospective register, but we have retrospectively quality controlled all data" and "this is a historical prospective analysis of a small national cohort, while most CS literature is retrospective." These are all observational studies in that there is no intervention being studied, but rather just an observation of the everyday real life treatment and practice in relation to CS patients.

Some authors are very clear and state that register studies are by definition restrospective [181] without further cause for debate. From the orthopaedic literature on the other hand a recent editorial describes registers as "prospective collection of outcome data" [182]. A textbook for statistics used for this thesis also defines an observational cohort study as prospective as long as the cohort is registered at the outset and follow-up occurs forward in time to a defined outcome variable[124]. Exposure is registered first and then followed to an outcome while in restrospective studies we identify the outcome and look back to register and analyse exposure. Others would argue that it is not the registration of data or follow up which decides, but rather the point in time at which the study design/ protocol or research question is established. Another way of viewing prospective versus retrospective is as illustrated below by the question "when did the researcher enter the scene?" If data and follow up are already collected prospectively in a register and you as a researcher at a later point in time establish a study protocol which assesses and uses these data, this is a retrospective design. By this definition our studies are retrospective. This same design would be called a prospective historic cohort study by others. The difference of course is whether one is describing the data gathering or the study protocol. Some of the challenges to interpretation given by prospective versus retrospective recruitment [183] apply to a lesser degree to register data since there is no active recruitment based on any treatment or patient characteristic. For the CRN, patients are registered by law and completeness documented.

Most CS literature states that patients are identified from a local tumour register or database and traditionally these are all termed retrospective in their design. These registers are primarily registers of particular disease states, but not with follow-up towards defined outcome variables which are identified retrospectively from clinical files for the selected cases.

In real life, studies are often a mixture and the important fact is to recognize and document the potential bias and confounders applicable to your chosen design and describe that design appropriately. The data at the CRN are registered prospectively, but we have quality controlled and supplemented them retrospectively. Outcome is in part registered prospectively in that CRN's survival variable is linked and checked against the national death register four

times yearly. A local recurrence and metastasis will also be registered prospectively if it generates a biopsy or operative specimen, but less likely so if no intervention or treatment occurs.

STROBE checklist

We know that the level of evidence in bone sarcoma practice and literature is low when assessed by the STROBE checklist [184] which we have used actively throughout the thesis. (https://www.strobe-statement.org). An increasing number of journals now have this as a pre-requisite for publication. It was developed between 2004-08 by methodologists, epidemiologists, statisticians, researchers and journal editors [185]. Its aim or function as the name implies was to strengthen and standardize reporting and produce accurate and complete observational studies in comparison to the CONSORT (http://www.consort-statement.org/) statement for randomized control trials. This will both increase the power of the findings in the paper and improve reproducibility and transparency. It is a 22 point checklist with explanations. In all papers, using the checklist was our initiative without requirement for the journal, but uniformly applauded by reviewers.

The evidence for the effect of using the STROBE checklist is limited, but stronger for the CONSORT checklist for randomized controlled trials. The methodology in such an evaluation is also challenging [186] , but it appears that there is an improvement found when studied in, the fields of nephrology [187]and hand surgery [188] or more generally [189] for a limited number of checklist points. There is a consensus however that the standard remains suboptimal and that endorsement and implementation by journals is important.

Missing radiology

In paper two we have selected extracranial non-metastatic CCCS of bone from the cohort. Since a vital part of our method was to measure the size of the soft tissue component, we were hampered by missing radiology. Missing radiology (N=48, 25% of cohort) was primarily an issue of time and not of any characteristic of the case itself, in that cases from the early part of the study period were more likely to be destroyed in a hospital effort to clear areas of old radiological films. We included 15 cases of proven intramedullary disease where radiology was neither available nor strictly necessary. Their inclusion could influence results. In analysis of high vs low risk it would be likely to underestimate effect size since intramedullary disease is part of the low risk or reference subgroup.

Measurement of soft tissue component

The method of measurement of the soft tissue component was predetermined and inspired by the methodology of cartilage cap measurement [75]. It was performed on preexisting images with standard planes of imaging (ie axial, coronal and sagittal). A straight line measurement was made at a 90 degree angle from the cortical surface and drawn to the edge of the soft tissue component. Where the cortical bone was absent due to destruction, an imaginary line was drawn between the ends of bone remaining and the soft tissue component was measured at 90 degrees from this line. The radiological plane considered most appropriate was used to measure the greatest thickness of the soft tissue component. This is a new method and

therefore not yet validated. The method has however consciously been held to a simple method so as to increase the chances of it being reproducible. Oedema was not measured.

The idea to measure the size of the soft tissue component came from a hypothesis that a large intramedullary tumour with a small soft tissue component was less aggressive than a small intramedullary tumour with a large soft tissue component as illustrated by my drawing "Dilemma" below. Interestingly if assessed by tumour size the tumours below would be assessed as similar, although the measurement would portray very differing features.

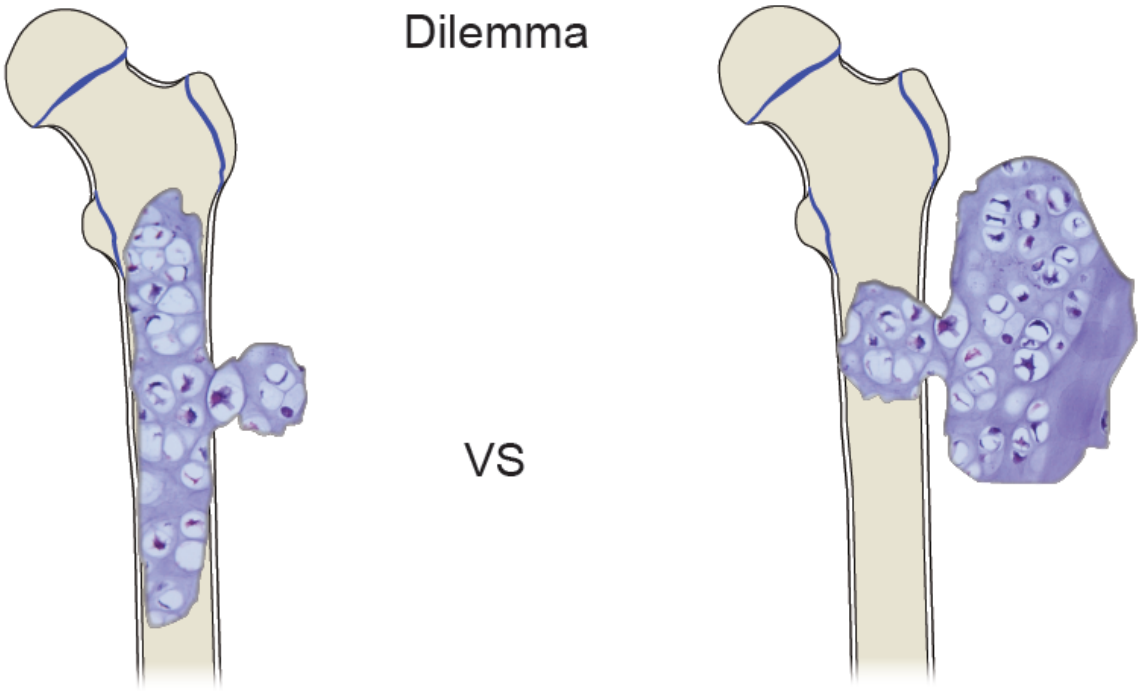
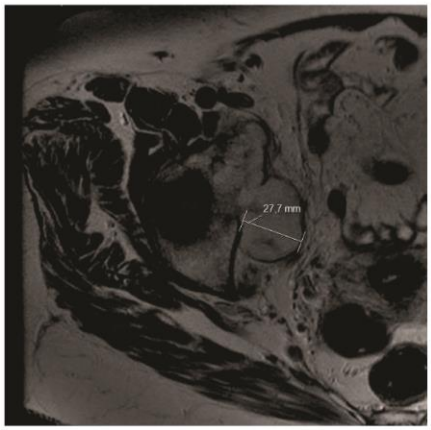
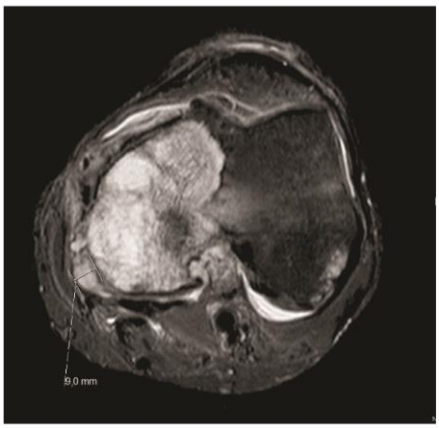


Figure 19 Illustration demonstrating hypothetical dilemma of tumour extension by Ine Eriksen ©, University of Oslo. Used with permission.

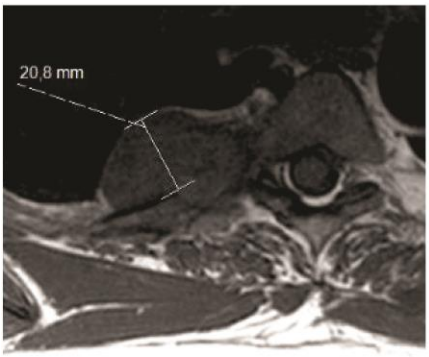
We then agreed on the standardized measurement as described above and exemplified below in figure 20. In analysis we first attempted to look at a ratio of the intramedullary component to the soft tissue component and relate this to rate of metastasis. This was however difficult to interpret which led to the exploration and analysis of whole centimeter measurements of the soft tissue component. The size of the soft tissue component is an expression of extracompartmental spread. At the same time, the intracompartmental measurement as portrayed by the measurement of the intramedullary part is likely of less interest in predicting metastatic spread, but rather more a measurement of local morbidity. In an attempt to explain how the size of the soft tissue component depicts extracompartmental spread one could hypothesize that 1cm in some way represents a critical level for penetration of tumour through periosteum rather than just breaching the cortical bone. This should be a point of investigation in the future as the periosteum is the true outer boundary of the intramedullary compartment.



Transverse T2-weighted image



Transverse STIR image



Transverse T1-weighted image

Figure 20 Examples of measurement of size of the soft tissue component. Thorkildsen et al[179], with permission from Wiley publishing.

Rate of metastasis as outcome variable

An important premise in our methodology, is that metastatic events are the most important measure of systemic biology. It is, in a way, an intermediate variable between tumour characteristics and death. Relating CS biology to death directly opens the analysis to a wide spectrum of confounding variables such as other illness or morbidities, which are difficult to adjust for in a register study and as such must be interpreted with caution. The more aggressive the disease type the less marked this distinction will be (for example central dedifferentiated CS). For epidemiological studies of conventional CS, we assess a slow growing disease with quite low levels of metastasis overall and precisely in this setting is our point pertinent.

Statistical considerations

The cohort or demographics have in all three papers been described by descriptive statistics without statistical testing. Presenting the details of the cohort is of course important for any comparison to other cohorts as well as understanding the findings in our own. It was my preference to not include formal statistical tests of the cohort demographics since I think it

distracts the reader from the actual message or information in the demographics as well as distracting the reader from the statistics performed elsewhere in the paper. When comparing two groups' demographics, seemingly insignificant differences could be both clinically and statistically relevant in later analysis. Alternatively, using significant differences as a way of determining which analyses to perform later may be misleading. Any discrepancies should be discussed in context such as our over-representation of male sex in relation to local recurrence.

We have also used rates of events estimated by Kaplan-Meier (K-M) method throughout. Many CS studies that provide information on the rate of an event of interest do so with crude percentage and this distinction is important in case of comparisons. When censoring (loss to follow-up) occurs during observation time, crude percentages give downward biased estimates of the desired proportion since it fails to account for the decrease in denominator (patients at risk) over time.

Furthermore we have chosen to use the inverted K-M curves to give the rate of specific events for LR and Met rather than report LR free and Met free survival curves. We believe this to be simpler and clearer, but this is a question of taste. In my mind when I hear that the MFS is 80% I have to translate this to a rate of metastasis of 20% which is a term my patients can understand. It is no large feat, but distracts the reader from other points of interest, particularly if presenting many figures. We have also chosen not to assess a combined event free survival (combined LR and Met) such as Andreou et al, since the factors that influence these two outcome variables are different.

The quality of any multivariate model is of course open to debate. Our model in paper 1 was established after a detailed review of CCCS literature, but there is always a degree of interpretation in such a process and the model must be assessed on its own terms. We included age and sex because they are important baseline features. Otherwise we have chosen patient and tumour characteristics understood to influence CCCS behaviour such as size, soft tissue extension, location and grade. We have not included surgical margins and treatment related outcomes because these are not features available at diagnosis and are primarily features directed at local control. Furthermore the assessment of surgical margins is highly complex, requires a lot of space and as such must be part of future work.

It would have been ideal to incorporate a morbidity score in our model predicting survival. This has been done by using the Charlson-Deyo Score in the National Cancer Database and is a smart way of adjusting for comorbid status in the study of a cohort with high mean age and an overall indolent course. No such morbidity score exists at the CRN.

We analysed size as a categorical variable (<>8cm). Our primary reason for this was to allow for comparison to other papers, but the creation of categorical variables from continuous is a practice that should be avoided[66,67] since it can result in residual confounding, loss of power and introduction of bias. I was not fully aware of this during the early phase of my research, but repeat analysis with size as a continuous variable showed unchanged results as mentioned in the manuscript.

In paper 2 we measured and analysed the size of the soft tissue component. This is a continuous variable which we have converted to a categorical. The reasons for this was as previously explained one of practicality and simplicity after first attempting to assess a more complex ratio of size. We have used a method which I now understand has been termed "optimal cutpoint" approach. The conflict in this is between what is statistically correct and what is clinically useful. Ideally a finding should be both, but in reality the clinical use of a continuous variable that is significant, but without a practical "cutpoint" of some form makes it at best much less useful or possibly not at all.

In paper 2, 48 cases of CCCS with a soft tissue component were excluded since radiology was missing and we therefore could not measure the size of the soft tissue component by our chosen method. This increases the size of the reference group since intramedullary cases were included even without radiology (15 cases) and may underestimate the effect of soft tissue components in analysis. In theory, the distribution of sizes of soft tissue components of those 48 excluded may not be the same as the 149 which were measured and included for analysis, although there is no specific reason why this should be the case.

In paper 3, we introduced the concept of immortal time bias. This is the statistical concept of observational time where an event cannot occur. LR is said to be a time dependent covariate since it can occur at differing times during observation. Time from surgery to date of local recurrence is time where a LR cannot influence risk of metastasis. This time is considered immortal time and is illustrated below in the setting of a pharmacological trial. For our purposes, "start of follow-up" is the date of surgery, "First prescription" in our setting is synonymous with LR and "outcome of interest" is rate of metastasis and death [190].

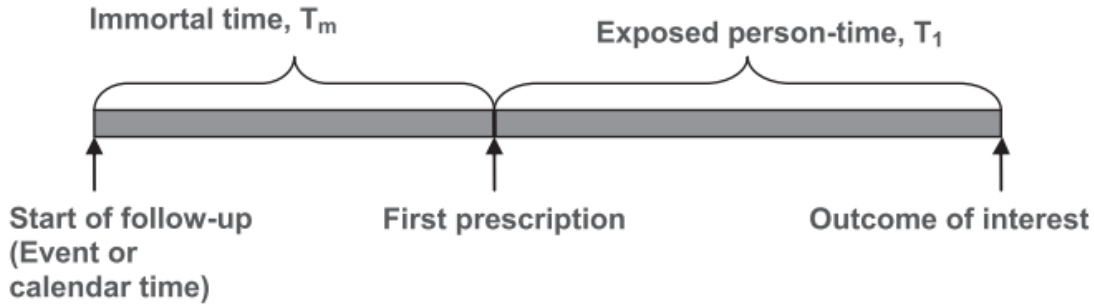


Figure 21Illustration of observation time for time dependent variables, Liang et al[190], with permission from Elsevier publishing

If LR is not handled as a time dependent covariate it will lead to misclassified person time. That is, observation time from start observation until LR will be included in the LR group and thereby falsely increasing its denominator while it will be compared to non LR group with a falsely low observation time or denominator. In total, this will underestimate the effect of LR on the outcome, but can give divergent results by different mechanisms [190].

We use Cox analysis in the subgroup analysis. In this setting it is also important to highlight a negative finding where there are too few events for analysis (denoted NA). This is naturally

also an important finding supporting low risk. The larger number of cases (size of N), the more valuable it is. For example, curettage (N=38) in table 2 "influence of LR on Met" is "NA". For resection/ amputation, HR =3.4(1.1-10.7) which is significant. The latter tells us of the influence within the resection/amputation group without comparison, though the additive value of a positive finding in resection/amputation (there is an influence) and a negative finding in curettage (no evidence of influence) strengthens our findings. For influence on overall survival we found for curettage HR=2.5(0.6-10.2) which again is a negative finding or "no evidence of influence". In this situation we can perform a likelihood ratio-test (lr-test) which gives us the statistical comparison of the influence between the two groups. The findings and pattern in both of these settings are important and should be assessed together and in context. An example of the latter is the sum of evidence in this table for Oslo risk group. There was no evidence for influence of LR on Met and survival for Oslo low risk, but for Oslo high risk there is a non-significant, but clear descriptive support for influence of Met and significant evidence for survival. Likelihood ratio-test gives P=0.068 which is not significant, but a value often referred to as "borderline significant". The total value of these findings, together lend support to the statement that LR does influence Met and survival in the high risk group, but not low risk.

CS is a rare illness and both LR and Met are rare occurrences. The size of our cohort (size of N) is decided by the basic incidence of the disease. Care should always be taken when interpreting findings with low N-value. There is also a fine line between the appropriate level of N-values for using descriptive statistics only as opposed to statistical testing. In either case, the sum of findings should be interpreted together and validation sought in other cohorts where available. Some compensate for low number by increasing their inclusion period, including patients back to the early 1900's, but this introduces new biases and limitations.

Discussion of Results

Chondrosarcoma incidence

We have found an incidence of CS of bone in Norway during the study period 1990-2013 of 2.85/ million/yr. overall. We found an increase during the period, rising to 3.45/ million/ yr. in the most recent 5 year period. This increase was larger for women than for men such that the incidence was equal among the sexes in the final period.

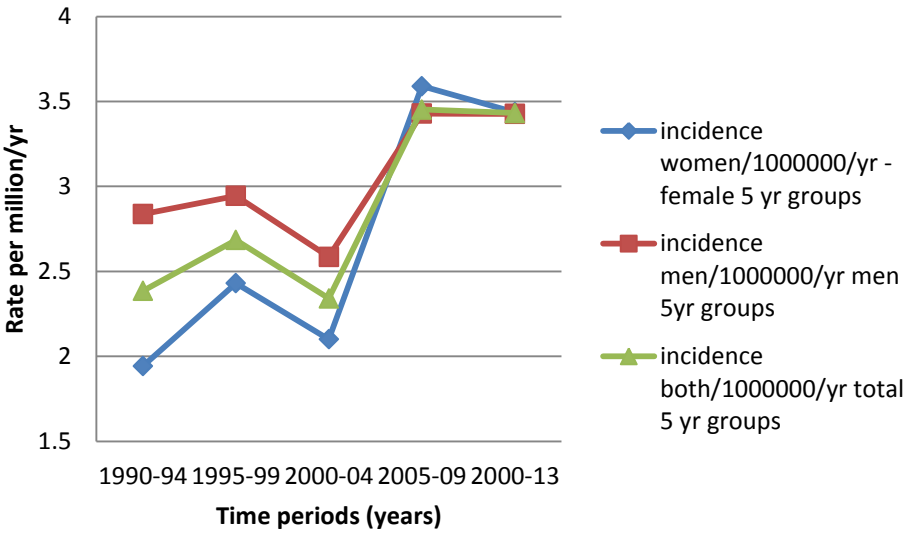
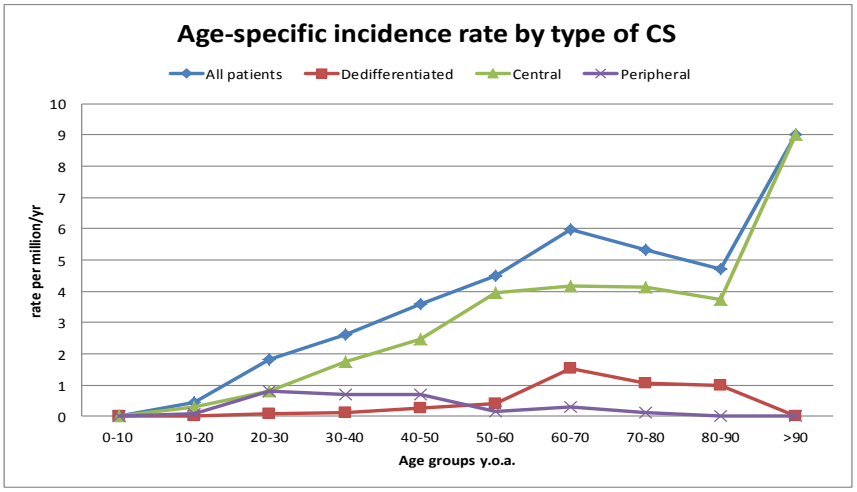


Figure 22 Incidence of CS by sex and combined, 5 year age groups. Thorkildsen et al[150], with permission from Taylor Francis publishing.

This is driven by the increase in the most common central CS subtype.

There is also an increased incidence with age (age-specific incidence), again driven by the trend for the most common central CS subtype.



Age	All Patients(95% CI)	Dediff. (95% CI)	Central (95% CI)	Peripheral (95% CI)
0-10	0	0	0	0
10-20	0.4(0.2-0.9)	0	0.3(0.1-0.7)	0.1(0.0-0.4)
20-30	1.8(1.2-2.6)	0.1(0.0-0.4)	0.8(0.4-1.4)	0.8(0.4-1.4)
30-40	2.6(1.9-3.5)	0.1(0.0-0.5)	1.7(1.2-2.5)	0.7(0.3-1.2)
40-50	3.6(2.7-4.7)	0.3(0.1-0.7)	2.5(1.7-3.4)	0.7(0.4-1.3)
50-60	4.5(3.4-5.8)	0.4(0.1-0.9)	3.9(2.9-5.2)	0.2(0.0-0.6)
60-70	6(4.6-7.7)	1.5(0.9-2.5)	4.2(3.0-5.6)	0.3(0.1-0.9)
70-80	5.3(3.8-7.3)	1.1(0.5-2.1)	4.1(2.8-5.9)	0.1(0.0-0.8)
80-90	4.7(2.8-7.4)	1.0(0.3-2.5)	3.7(2.1-6.1)	0
>90	9.0(3.3-19.6)	0	9.0(3.3-19.6)	0
Total	**2.8(2.5-3.2)**	**0.4(0.3-0.5)**	**2.1(1.8-2.3)**	**0.4(0.3-0.5)**

Figure 23 Age specific incidence rate by subtype of CS. Thorkildsen et al[150], with permission from Taylor Francis publishing.

The increase is largest for grade 2 disease.

The most natural comparison can be made to the work of Van Praag et al. [149] with a national registry cohort from 1989-2013 published just before our own work. From the Cancer Registry of Netherlands they report an incidence of 2.88/ million/ yr. between 1989-'96 rising to 4.15 between '96-'04 and 8.78/ million/ yr. between '05-'13. This vast increase is driven by an increase in the incidence of atypical cartilaginous tumours/ grade I chondrosarcoma (2013 definition) which they again relate to the number of diagnostic radiological examinations performed in the period. Their increase in ACT/ grade I CS from 1995 to 2012 is 10 fold or 1000% (1/million/yr. in 1995 to 10/ million/yr. in 2012). They report an increase for all grades.

Our cohorts differ in some clear aspects. Van Praag et al have considered 2186 cases and excluded 571(26%) in total; 274 (13%) due to missing values despite supplementation from clinical files, 162 (7%) for not having curative treatment intent and 104 (5%) due to being non conventional morphology code. Review of pathology or radiology is not described.

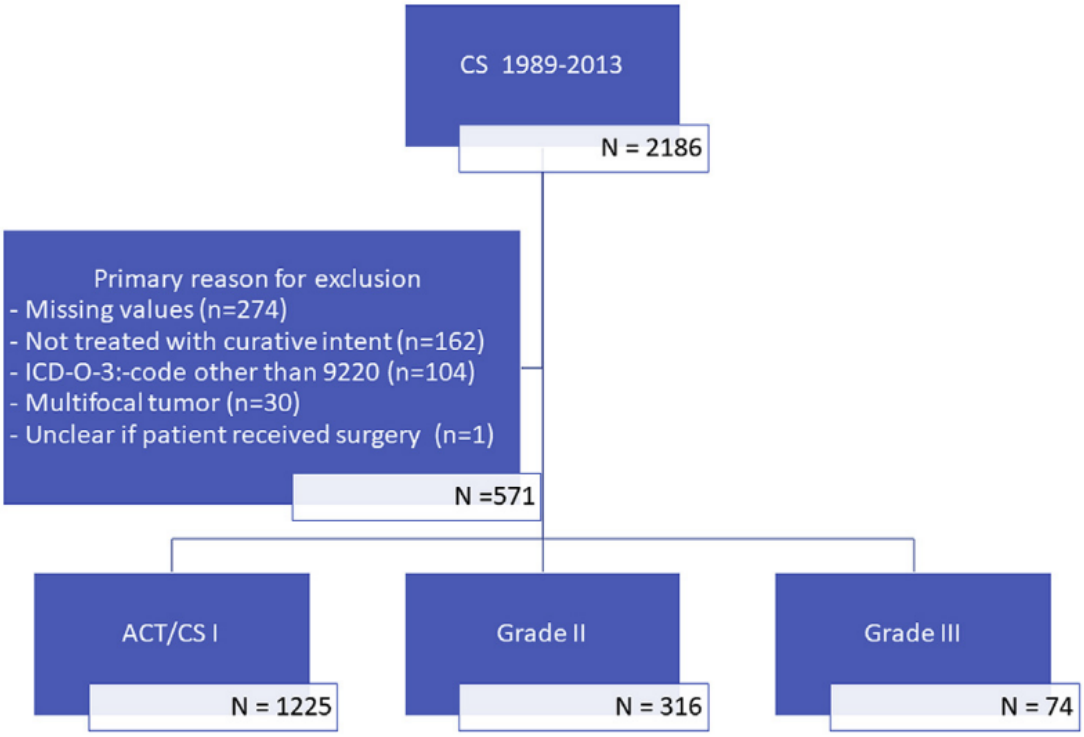


Figure 24 Flow chart illustrating selection process, van Praag et al[149], permission from Wiley publishing

We have assessed 348 cases from the registry and performed 223 radiological and 112 pathological reviews to select 311 cases of central, peripheral, periosteal and dedifferentiated verified subtypes of all locations with review of all variables from clinical files and a complete data set. It is probable that our review results in an improved data quality.

The clear difference in the numbers is fascinating since our populations and societies are more similar than most. The incidence presented by Van Praag et al is clearly the highest in the world [4]. The Dutch have been a leader in defining CS terminology including ACT's as synonyms for CS grade I, first suggested in the 2013.[50] The intention of introducing the ACT terminology is, to my understanding, to better communicate the limited metastatic potential of the entity and burden of a CS diagnosis. The 2020 definition incorporates the differences in behaviour according to anatomical location (axial/ extremity) by stating that ACT is only to be used in the extremity[2], but it does not include the presence/ absence of a soft tissue component in its definition which is somewhat problematic. At the same time there have been no clear advances in the histological or radiological distinction between a benign enchondroma and grade I CS. The Dutch numbers indicate that they have possibly introduced or altered their definitions before their formal introduction in 2013. It also indicates that the Dutch likely have a lower threshold for defining CS at its lower limits of aggressiveness, than in Norway. This is a natural response to the acceptance of inter-observer variation in pathological, radiological and clinical interpretation of CS [63,139,140]. Furthermore Van Praag et al describe an attempt to treat all ACT's in an attempt to decrease the incidence of dedifferentiated CS. It is unclear if this is a study question posed retrospectively or a prospective plan. If the latter is the case it would likely lower the threshold for defining an ACT. Lastly, it is of course possible that there is more CS in the Netherlands, but this seems less likely.

In England, Whelan et al report from the National Cancer Intelligence Network (NCIN), a collaboration between 8 regional cancer registries from 1979-2007, reporting age-standardised rates (ASR) per million. Whelan et al also present an increase through the period with ASR= 1.7/ million/ yr. for '79-'87, 1.9 for '88-'97 and 2.0 for '98-'07. They report a higher incidence for men (1.9 for '79-'81 and 2.6 got '05'-'07) than for women (1.2 for '79-'81 and 1.7 for '05-'07), but a larger increase for women (42%) than for men (37%). The English also report an increased incidence of CS with age as demonstrated by figure 25 below.

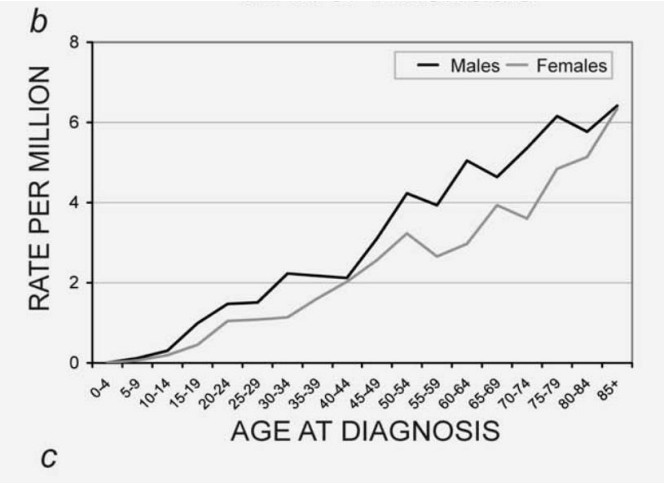


Figure 25 Incidence of CS of bone(all subtypes)in England 1979-2007-. Whelan et al[128], permission from Wiley publishing.

US data have been presented by Arnfinsen et al. They present age-specific and age-standardised rates per 100,000 from 1976-2005, by analysis from 9 registries all part of the SEER program, which covers about 30% of the US population. Arnfinsen et al again report slightly higher incidence in men than women and an increase in age-specific incidence with age at diagnosis overall. They report stable levels for men, but a 70% increase for women through the period giving ASR of 0.27/100 000 person years for both sexes from '96-'05.

I think we can conclude that there has been an increase in the incidence of registered CS in the last few decades, largely driven by an increase in women and likely by an increase in the central subtype. The age standardized rate is at a minimum 2.8/ million /yr. and possibly higher.

Whether this increase is real or not remains unclear. Arnfinsen relates the increase in age cohorts exposed to increased use of female hormonal contraception as well as hormone replacement therapy. Estrogens have been studied and been linked to CS growth in vitro, but with negative findings in vivo. Anti estrogens have been used in end stage CS disease with some evidence of effect, but at the same time Laittinen et al found that being female and hormonally active (ie age<55) gave a survival advantage as compared to men which dissipated over age > 55 years[191].

Van Praag et al demonstrate nicely that an increased use of radiological examinations reveals more CS. This makes complete sense intuitively, since a proportion of CS is either an incidental finding and truly asymptomatic or alternatively indolent and produce mild symptoms. Previous reports have found that 6 % of CS is asymptomatic[146] ,while we found that for extracranial CCCS as much as 15% were categorised as incidental findings. These are of course retrospective findings without correlation for other causes or reasons to describe symptoms. One report has found that in as much as 80% of cases of the proximal humerus with a central chondroid lesion, one can find another cause or explanation for the complaints that elicited the exam [68]. Not to mention the number of conditions that can not be diagnosed by radiological examination at all. Van Praag et al present a curve with CS incidence together with a curve of the number of "diagnostic images". The scale tells us that this was at 100 000 in 1995, 200 000 in 2002 and 750 000 in 2012. The term "diagnostic images" depicts number of MRI examinations, but the source is not listed.

In Norway, the Norwegian Radiation and Nuclear Safety Authority (Statens Strålevern) produce reports assessing the radiation exposure from radiological examinations at a national level. They have reports for 2002 and 2008[192], but not annual numbers unfortunately. The 2008 report tells us that the total number of radiological examinations in total was quite steady between the two periods, but with a decrease in x- rays being met by a doubling of number of CT and MRI examinations. In total in Norway in 2008, there were 4 265 533 radiological examinations or 900/ 1000 inhabitants.

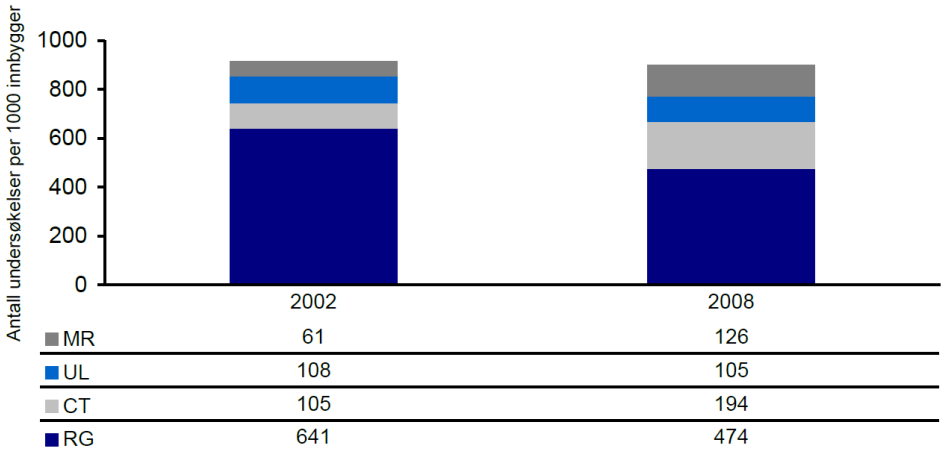


Figure 26 Number of radiological examinations per 1000 inhabitants in Norway in 2002 and 2008. Almen et al[192], with permission from Statens Strålevern.

The report also contains data that display Norway as having more frequent radiological examinations as compared to the Netherlands in 2008. This is shown below by the x-axis showing relative number of radiological examinations per 1000 inhabitants in a selection of European countries.

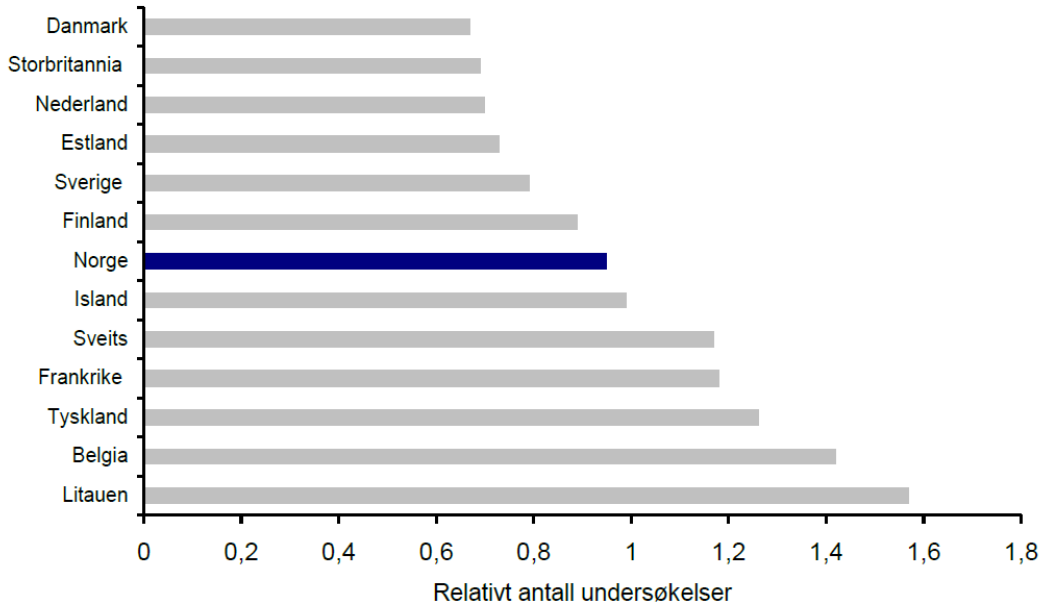


Figure 27 Relative number of examinations per 1000 inhabitants for a selection of European countries. Almen et al[192], with permission from Statens Strålevern

The number of MRI's in total can easily be calculated using population data at the time together with number of MRI per 1000 inhabitants as per figure 25 (61/1000 inhabitants in 2002 and 126/1000 inhabitants in 2008). The Norwegian numbers are illustrated as red stars in an adaption of van Praag et al's figure below. The number of MRI performed in Norway and the Netherlands is therefore very similar and as such there is little reason why one should display much more ACT's then the other.

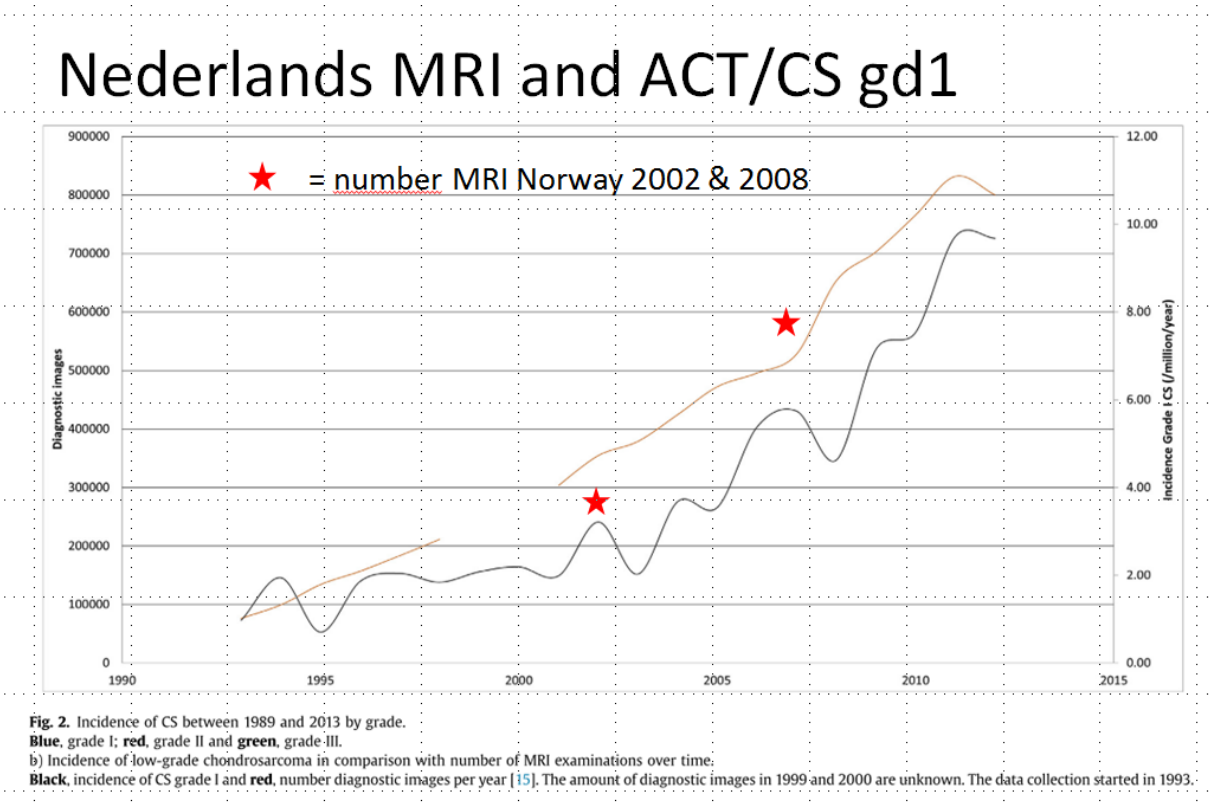


Fig. 2. Incidence of CS between 1989 and 2013 by grade.
Blue, grade I; **red**, grade II and **green**, grade III.
b) Incidence of low-grade chondrosarcoma in comparison with number of MRI examinations over time.
Black, incidence of CS grade I and **red**, number diagnostic images per year [15]. The amount of diagnostic images in 1999 and 2000 are unknown. The data collection started in 1993.

Figure 28 Incidence of ACT/CS grade 1in the Netherlands, between 1989 and 2013(grey line), number of MRI examinations over time in the Netherlands (brown line.Aadapted with red stars depicting number of MRI examinations in Norway in 2002 and 2008. Adapted from van Praag et al[149], with permission from Wiley publishing.

Van Praag et al also argue that an aging population can partly explain an increased incidence since the age specific incidence rises. In the table underneath we can look more closely at population numbers for Norway comparing 1990 to 2013 (https://www.ssb.no/en/befolkning).The absolute number of people aged over 80 has increased by over 40% in this period which is a challenge for politicians with responsibility for care of the elderly. The proportion of the population over 60 years of age has also increased 16%, but less than the population in total (19%). The proportion aged 80 and up has clearly increased in number and as proportion of the population, but the total proportion of the population is still low (4.4%). The absolute increase in numbers for those age 60 or more in the period is 185 488. This is the part of the population with highest incidence of CS.

Table 6 population changes in Norway 1990-2013			
	1990	**2013**	**% change `90-'13 (absolute number)**
Total population	4 233 116	5 051 275	+19%
60-79 years old	733 493	853 675	+16.4%(120 182)
>80 years old	156 279	221 585	+41.8%(65 306)
% >60 years old	21.0%	21.3%	
%>80 years old	3.7%	4.4%	

We can extract similar numbers from Statistics Netherlands (https://www.cbs.nl/en-gb/figures/detail/37556eng). These show that there is an increase in the proportion of the population which is both older than 65 or 80 years of age from 1990-2010. The total number for the period is 632 000. These numbers are however far too small in absolute terms to explain a 10 fold rise in incidence of grade I CS which is a rare tumour even if one accepts a high incidence of 10/million/yr.

Table 7 Population changes in Netherlands 1990-2010			
	1990	**2010**	**% change '90-'10 (absolute numbers)**
Total population	14 893 000	16 575 000	+11.3%
65-80 years old	1 478 000	1 890 000	+27.9% (412 000)
> 80 years old	428 000	648 000	51.4%(220 000)
%>65 years old	12.8%	15.3%	
%>80 years old	2.9%	3.9%	

The impact of changing definitions of ACT/ grade 1 CS versus enchondroma is the most obvious methodical consideration not discussed by van Praag et al, or indeed by her co-author in an expert opinion commentary addressing this very issue[52]. The inter-observer variation in assessment of chondroid lesions for radiology, pathology and clinical assessment combined with inappropriate use of dichotomized univariate analysis for age <>50, pain/ no pain and size <> 5cm related to an unsure gold standard has likely led to a more careful interpretation by many and thereby to a larger number of benign or borderline chondroid lesions being defined as central grade I CS or ACT. It is natural that the use of the ACT synonym increases this effect even more, since this evades the burden of a cancer diagnosis or even the necessity of treatment. It does however not better the differentiation from benign enchondroma. In essence it is the threshold for surgery which defines the incidence of CS.

It is problematic that the WHO has introduced the numbers and explanations by van Praag et al without further assessment.

Our findings likely represent a stricter definition of central grade I CS and a larger increase in grade II disease supports the hypothesis of a real increase. Even in this setting it may be that the selection between curettage for grade 1 intramedullary extremity CCCS and resection for grade II disease or those with soft tissue components has led to a selection bias or unconscious change in grading practice to comply with the surgical procedure by pathologists. That is that the pathologist could be more likely to answer grade 1 for a curettage specimen and grade 2 for a resection specimen. The incidence recorded for grade III disease is remarkably stable over time and similar in both Van Praag and our own work.

We certainly have an increase in registered CS internationally and that although this is plausibly and partially explained by some mechanisms, we can not be sure if this represents a true increase in the disease itself or merely changing definitions.

Follow-up

Evans stated in his original article of mixed CS subtypes that CS needs long follow-up (even beyond 10 years) due to the possibility of late events, but at the same time recommended caution in interpretation of his statement, as less than half of cases actually had follow-up beyond this time [135] in his material. Indeed, CS is anecdotally known for rare late recurrences. This can however not be a justification for recommending that all patients undergo near life long follow-up.

In contrast, our findings suggest that there are only two situations that require longer follow-up than 5 years in CS practice. Patients with peripheral CS need attention towards discovering local recurrence which continued to rise from 10% at 5 and 13% at 10 years. The other group is that of axial grade III disease or "Oslo high risk". Both groups show an increase in metastatic events between 5 and 10 years of follow-up. This has clear implications for both clinical follow-up and requirements for follow-up in CS studies.

Prognostics

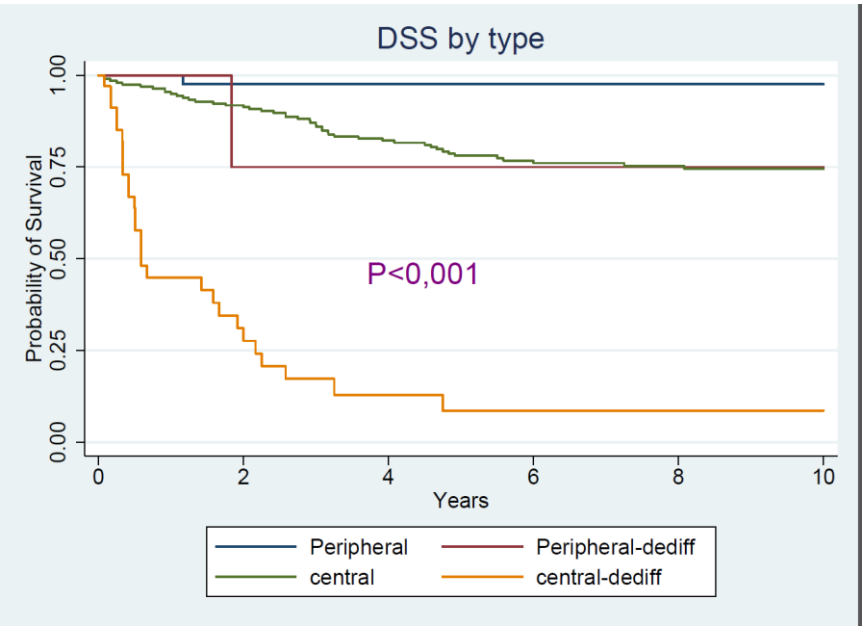


Figure 29 Kaplan-Meier curve for probability of overall survival by CS subtype in CRN CS cohort. Thorkildsen, previously unpublished.

The above curve is based on the cohort of paper 1. It shows the differing survival between the subtypes. Similar reports have published similar findings as part of a multivariate prognostic analysis of the same mixed cohort [193]. The decision to analyse these subtypes separately is of course not due to this graph, but a methodical decision since they are different diseases, with different aetiology, management and prognosis.

The Cox proportional hazard analysis must also be examined further. An important methodical consideration is that the analysis only applies to the extra-cranial central conventional CS

For clarity, the uni and multivariate findings for paper 1 are presented again in table form below:

Table 8 –Results of univariate Cox analysis; central chondrosarkoma no.197 (Supplementary table A, Thorkildsen et al[150], with permission from Taylor Francis publishing. Hasard ratios (95% confidence intervals)			
Variable	LOCAL RECURRENCE	METASTASIS	DISEASE SPECIFIC SURVIVAL
Age at diagnosis	1.00(0.98-1.02)	1.00(0.97-1.02)	1.03(1.01-1.05)
Sex female/male	3.37(1.52-7.47)	2.32(1.06-5.09)	1.43(0.83-2.45)
Extremity/axial location	1.93(0.96-3.88)	4.06(1.73-9.50)	1.89(1.10-3.26)
Soft tissue component no/yes	4.32(1.66-11.19)	11.08(2.63-46.61)	6.29(2.69-14.72)
Tumour size <>8cm	1.82(0.92-3.61)	2.16(1.04-4.49)	1.98(1.16-3.39)
Malignancy grade Grade1 Grade 2 Grade 3	 Ref 1.20(0.48-2.99) 3.14(1.32-7.51)	 Ref 3.31(0.91-12.04) 10.31(3.00-35.47)	 Ref 3.35(1.45-7.76) 6.20(2.64-14.58)
Metastasis at diagnosis	NA	NA	19.93(7.17-55.41)

LOCAL RECURRENCE	METASTATIS	DISEASE SPECIFIC SURVIVAL
Soft tissue component HR 3.20(1.07-9.57) P=0.03	*Soft tissue component* HR 5.25(1.10-25.08) P=0.02	*Soft tissue component* HR 2.82(1.09-7.28) P=0.02
Sex female/male HR 2.55(1.10-5.93) P=0.02	*Malignancy grade* Gd1 Ref Gd2 HR 2.05(0.55-7.63) Gd3 HR 5.24(1.44-19.10) P=0.01	*Age at diagnosis* HR 1.02(1.00-1,04) P=0.01
		Metastatis at diagnosis HR 13.62(4.63-40.01) P<0.01

* Variable name, Hasard ratio (95% confidence interval); P value for likelihood-ratio test. Model includes age, sex, size<>8cm, extremity/axial location, malignancy grade and presence of soft tissue component for analysis of LR and Met. For DSS metastasis at diagnosis is also included.

Table 9 Results from multivariate Cox analysis; significant findings only. No.=197 Thorkildsen et al[150], with permission from Taylor Francis publishing.

This paper is the first to give statistically sound support to the current internationally accepted treatment guidelines which recommend treatment based on anatomical location and soft tissue extension [80,93]. It is also an answer to a recent evidence based review of CS epidemiology stating that the importance of soft tissue extension has not been proven[134]. Further, it contradicts AJCC staging (8th version) by validating that size in fact does not predict

behaviour in CCCS prognostics (not significant at multivariate level as both dichotomised and continuous variable).

It is important to note that malignancy grade III also proved to predict risk of metastasis at multivariate level.

Although discussed first in Paper 2, the influence of size and soft tissue components have a direct consequence for selection of patients for curettage. This is direct support for extending the indication of curettage towards larger intramedullary extremity tumours rather than smaller tumours with a soft tissue component.

Oslo risk groups

In paper 2 we contribute towards the understanding of anatomical location in CCCS epidemiology. We highlight the important distinction between an anatomical definition of the axial skeleton and that which should be used in CS research (hip and glenohumeral joints). Secondly we incorporate this directly into a simple prognostic model predicting metastasis and death. This model is based on multivariate analysis in which histological grade becomes insignificant.

These findings need validation. The methodology for measuring the size of the soft tissue component needs assessment separately and the effect of location together with size of soft tissue component needs repeat assessment in other cohorts.

It is difficult to compare our risk model to others, but the most appropriate would perhaps be the Vanderbilt staging system developed from analysis of NCDB cohort. This system assesses a mixed CS cohort of limited anatomical locations based on 5 and 10 year mortality. It utilizes histologic type (dedifferentiated vs conventional non-dedifferentiated), histological grade and presence of metastasis.

Vanderbilt Stage	Definition	N*	5-Year OS (%)	10-Year OS (%)
Stage IA	Grade 1; M0	813	92	82
Stage IB	Grade 2; M0	625	88	77
Stage II	Grade 3; M0	201	67	54
Stage III	Dedifferentiated; M0	134	51	29
Stage II	Grade 1; M1	5	83	83
Stage III	Grade 2; M1	18	52	—
Stage IV	Grade 3; M1	11	34	—
Stage IV	Dedifferentiated; M1	35	14	—

*Estimates are adjusted for patient age. 158 cases were missing staging information.

M0 indicates no metastatic disease or skip metastasis only; M1, metastasis to lung, lymph node, or other distant site excluding discontinuous skip metastasis.

Table 10 Vanderbilt staging of CS from NCDB cohort with 5 and 10 year adjusted overall survival rates. Compton et a[134]l, with permission Walters Kluver publishing.

The Vanderbilt staging does not free us from the challenge of observer variation in grading and is based on survival rather than risk of metastasis.

The advantages of creating only two (dichotomous) groups in non metastatic CCCS are also significant. In particular when the risk, or rate of events in one of these groups is low. This provides the possibility of better exploring other markers of biology such as a proliferation marker (Ki-67) or Pet-CT signaling, previously studied in relation to 3-tiered grade (all with some risk) and limited by overlapping of findings [70,74,144].

Our combined variable is sensitive (picks up nearly all metastatic events), but not specific (also picks up a large portion without metastatic events). In the interest of identifying a group eligible for adjuvant chemotherapy one would hope to increase this specificity further and thereby decrease the burden of chemotherapy to those not actually at risk. Of 39 patients in the high risk group, 4 patients have grade I disease and none of these have metastatic events, but only future assessment of a larger cohort will be able to develop this further.

Local recurrence

The rate of dedifferentiation in LR cohorts is consistently low and rests on the accurate diagnosis and referral patterns. We had two cases from 40 LR in 181 cases. Andreou et al had two cases from 38 LR in 115 cases and Laitinen et al had three cases from 126 LR in 519 cases.

The rate of upgrading however varies significantly from our 2.5% to 22% by Laitinen et al. We can not be sure why this is, but we know that the histological grading is prone to both sampling error and inter-observer variability which are quite plausible methodological explanations. Furthermore as discussed briefly in the paper 3, Laitinen et al report in another study that on reexamination of original histological slides they found small areas containing higher grade in 30% of cases and that these areas best depict behaviour in similar fashion to Evans's original work[138]. They describe the same practice in their LR publication. No report contains details of how much of the tumour tissue actually is sectioned and assessed microscopically. The standard for this in Norway is one section per cm, up to 10 sections. A section is typically 2-3mm thick and the actual microscopic film examined per section is 0.4 micrometers thick. As such a large part of any chondroid tumour remains unexamined.

Even in the presence of upgrading microscopically, there is still no clear evidence that the tumour in fact has changed behaviour and become more aggressive. One can of course interpret a LR event as evidence for this change (ie the tumour has changed and is to blame). A LR is likely a remnant from the original tumour and is alternatively interpreted as evidence that one has underestimated the original tumour (ie we have assessed the original tumour incorrectly and our method of grading is to blame) in addition of course to the margin achieved not being adequate. It is logical that a missed area of higher grade drives the LR development. A study of 50 CS samples including 11 LR by comparative genomic hybridization failed to show any clear cytogenetic findings correlated to behaviour [194], but should ideally be studied both for the primary tumour and LR or even better sequentially in the setting of an upgraded case. Molecular genetic characterization of both components of a dedifferentiated CS gave useful information to understand its histiogenesis [195], but I am not aware that this has been published for primary CCCS and upgraded LR.

The results of subgroup analysis in LR CCCS were also somewhat divergent. While Andreou et al found a significant effect on survival irrespective of location and grade in their study of LR, Lin et al found an association between worsened OS and axial location or grade III disease. Both agree that there is an association between LR and increased metastasis and death overall. Looking only at LR, in the setting of grade I central CS of long bones from 1911- 2003, Schwab et al found an association with poorer survival after 10 years and advocate more aggressive surgery in the setting of LR. Our findings support an increased rate of metastasis and death associated with LR along the same lines that predict high risk in the primary tumour setting such as axial location, grade II disease, soft tissue extension, but not for low risk disease such as intramedullary limited disease.

For maximal clinical impact it is useful to summarize these findings by treatment groups from the primary treatment setting; curettage vs resection/ amputation or Oslo low vs high risk. The latter places 76% of cases in a subgroup without increased risk of metastasis and death in the event of LR, and 24% at risk. Numbers investigated are small and these findings need validation. We know also that prolonged survival is possible despite LR, but the addition of metastatic events renders the prognosis very poor. Some have warranted a regime of aggressive surgery for those with LR and no concurrent metastasis at diagnosis [172]. Oslo risk stratification may contribute to better selection of treatment level in the case of LR, since a LR in "Oslo low risk group" definition is unlikely to develop metastasis and should therefore be treated appropriately.

Discussion of Limitations

One could argue that the structure of society in most Northern European countries is so similar that the external validity of our findings should be high. I believe, given the same definitions this in fact would be the case. It is therefore contradictory to see that our numbers are so different from those of the Netherlands. As we have debated above, the most likely difference is one of definitions of CS in the clinical environment, at the lower level of disease aggressiveness. That is in the distinction between benign enchondroma and intramedullary grade I CS or ACT. This is a vast topic and not a focus of this PhD. The only way to truly confirm the external validity would be to carry out the same investigation in a similar country with similar definitions, for example Sweden or Denmark.

We have used the CRN outcome variable "dead from cancer" as synonymous with "disease specific survival" or DSS. A search for other cancer diagnosis in the cohort revealed 59 reported 2nd cancers, six third and even one fourth. A Swedish study of second primary malignancies of bone in patients with a primary bone sarcoma showed a Standardised Incidence Ratio (SIR) of 1.51for chondrosarcoma, but did not look at 2nd malignancies in general [196]. It will be a topic of future research to address this separately, but it is a reminder that survival variables for a slow growing disease like CS with low overall rates of metastasis should be interpreted with caution.

The accuracy of death certification in depicting correct cause of death has been studied in some populations and found to be surprisingly poor with >50% major errors and 60%

incorrect ICD-10 coding [197,198] . It is somewhat improved in the setting of a diagnosis of cancer [199], having been studied for prostate cancer. The same data found worse accuracy when there were multiple cancer diagnoses with the recommendation even in randomized trials for an independent cause of death evaluation.

Another point, briefly discussed in paper 2 was the accuracy of metastatic disease status. A recent publication by E. McLoughlin et al from Birmingham assessed the significance of pulmonary CT findings in 78 Conventional (CCCS+PCS) and dedifferentiated CS at presentation and follow-up [79]. "Indeterminate pulmonary nodules" (IPS) were defined as a pulmonary nodule<10mm in long axis diameter, with or without calcification. They classified them as false when they remained static or resolved, while as metastatic if there was evidence of progression or growth. As shown below, nearly 80% of IPS were in fact not metastasis, while nearly all nodules>10mm were metastasis. There was a marked increased specificity in the setting of dedifferentiated or grade III disease.

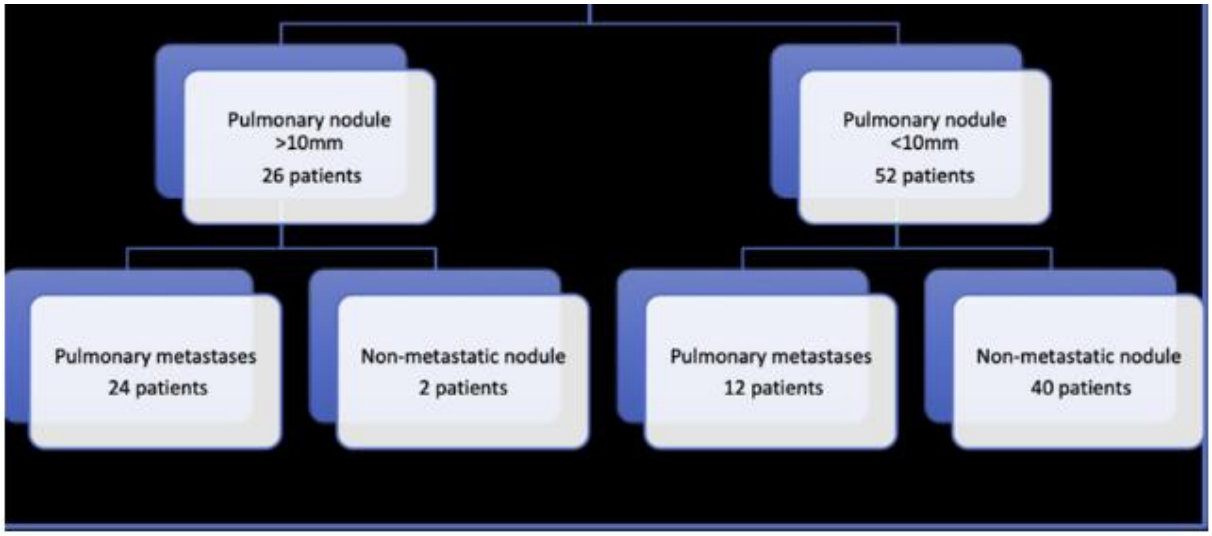


Figure 30 The diagnostic significance of pulmonary nodules on CT thorax in chondrosarcoma of bone, McLoughlin et al[79], with permission from Elsevier publishing

I have contacted the author of this publication and asked if they have survival data which would be a clear quality control of their definitions and findings, but this was unfortunately not available.

Using very similar definitions we present a cohort with 100% mortality from metastatic CS and it seems likely that our interpretation be quite strict.

We have used the same distinction between static/ resolution versus progression in the definition of metastatic disease in our cohort. I have not quantified or documented this in our cohort, but my impression is that part of those with thoracic findings at diagnosis have originally been interpreted and registered as metastatic in the CRN. I think however the paper by McLoughlin et al is an important support for the necessity of quality control of a metastatic outcome variable.

We found similar survival (76% and 67% at 10 years) between low risk II (extremity cases with a soft tissue component ≥1cm) (76% 10 year OS) and high risk cohorts (67% 10 year OS). This despite wide differences in the rate of metastasis between these two groups (0% vs 33% at 10 years). This divergence can be an expression of a significant error in our registration of the metastatic variable, but more likely a reminder that survival is a challenging outcome variable in CS epidemiology.

The main difficulty in interpretation of the findings in paper 3, were low numbers. Rare events in a rare illness are a challenge to scientific precision. We have defined a "modern cohort" by the routine use of axial imaging, but there is no doubt that CS practice in 1990 differs from 2013. This can only be overcome by improved prospective registration of well defined variables along with more multicenter collaboration.

Another challenge to interpretation is the overlap between factors studied such as soft tissue component, location and grade. This overlap between these findings makes them difficult to use in the clinical setting in addition to these features not identifying a distinct treatment cohort.

We have therefore chosen in the manuscript to focus attention on the curettage vs resection/ amputation and Oslo low vs high risk distinction which in fact do identify clear treatment groups without overlap. These also represent the subgroup analysis with clearest statistical findings.

We chose to use OS as our chosen survival outcome variable in this paper 3. This is a result of our finding that DSS continues to fall despite stable rates of LR and Met in paper one and two. The DSS variable was based on the CRN variable "death from cancer", but its accuracy in defining this has not been formally validated. It is problematic that we do not know for sure dead patients in the cohort actually died from CS and not other cancer, or unrelated disease. As such it seemed appropriate to use OS instead. Interestingly the combination of indirect evidence from LR and Met events together with information on whether local control was achieved and other cancer diagnosis give us the possibility of assessing each patients course in more details as described in the text, but in the future prospective registration will have to address this more reliably.

Ethical considerations

Data collection for this cohort is based on the quality control charter of the CRN legislature. The regional ethical committee has been consulted and support this foundation. They conclude that they do not formally have to approve the study. This means that there is no formal consent from the patients included either. All data handling is regulated strictly both by the local data protection officer as well as by CRN rules and regulations.

The data delivered from the CRN are anonymous and can only be reconnected to identifiable data at the CRN. All the same, data are often not completely anonymous. This is particularly so for rare diseases. Staff previously involved in the treatment of the cases will likely remember them when re-examining radiology or pathology slides and possibly be biased by

their knowledge of outcome for the same patient. The main author responsible for data collection has worked at the main treating hospital since 2010 and has not been involved in the care of most of these patients.

On the other hand, there is also a well functioning patient society in Norway for patients with MO, Olliers and Maffucci syndromes. Norway is a small country and some of these families may indeed recognize themselves or others from our statistics. I have presented data from part of this work at an educational meeting of MO patients and families after invitation from the National Advisory unit for MO and highlighted the "harshness" of outcome variables. This is an area difficult to avoid in rare disease research in small countries, but rather should be recognized and handled delicately and with respect.

Conclusions

- The incidence of CS in Norway from 1990-2013 is 2.85/million/yr. with an increase from 2.4/million/yr. from 1999-94 to 3.45/million/yr. during 2000-13. This increase is driven by an increase in the incidence of the most common subtype (CCCS), which is more common with increasing age. There is an increase for all grades, largest for grade II disease. The increase is larger for women than for men so that the incidence is equal for the sexes in the latter part of the study period.
- Rates of LR, met and DSS vary for different subtypes and for CCCS with extremity/ axial location and grade.
- For CCCS rates of LR at 10 yr. varies from approx. 10-20 percent except for axial grade III disease which has 47%. There were no further LR after 5 yr. follow-up in this CCCS cohort.
- For CCCS rates of metastasis varies from 0% for extremity grade I disease and 10-20% otherwise to 56% at 10 yrs for axial grade III disease. There are no further metastatic events after 5 yrs. follow-up except for axial grade 3 disease.
- For peripheral CS the rate of metastasis is only 2% at 2 years and no further events, while rate of LR increases steadily from 5-10-13% at 2, 5 and 10 yr. of follow-up.
- For CCCS, size does not appear to predict behaviour when adjusted for other variables. The presence of a soft tissue component is the one feature that predicts adverse rates of LR, Met and DSS together while malignancy grade III independently predicts increased risk of metastasis. Metastasis at diagnosis is a clear poor prognostic indicator.
- For CCCS a combined variable of axial location and a soft tissue component≥1cm significantly predicts risk of metastasis and death in a multivariate model leaving histological grade insignificant. Together with metastasis at diagnosis this can be used to create a new risk model for CS giving a large low-risk group (103 cases) with 2 % risk of metastasis and a small high-risk group (39 cases) with 33% risk of metastasis.
- LR in the setting of CCCS increases the risk of metastasis and death overall, but appears to be driven by those at high risk in the primary treatment setting (resection/amputation, soft tissue component, grade II disease, axial location or Oslo high risk definitions). There is no evidence in this cohort for increased risk of metastasis if LR occurs in the setting of an appropriate curettage or Oslo low-risk group. Upgrading and dedifferentiation are rare events in LR CCCS and routine surveillance is effective in uncovering asymptomatic LR.

Implication for the future

Paper 1- Establishes both real incidence and likely increase in incidence of CS while future work must better define definitions of CS at the lower levels of aggressiveness to allow meaningful comparisons. Further it presents rates of LR, met and DSS in a complete national cohort at subtype level in a modern setting as a reference for future work. This also allows tailoring of follow-up regimes. The prognostic work highlights the importance of soft tissue extension which already drives management, but which is largely not registered or analysed in much CS prognostics to date. It also supports the investigation of an extension of curettage towards larger intramedullary extremity tumours.

Paper 2- Provides a new and simple method of assessing risk in CCCS cohorts free from the constraints of histological grade. It must naturally be validated in other cohorts and its methodology studied for inter-observer variation. The high risk cohort must be examined in larger numbers together with other observation of behaviour to see if an even more specific subgroup of high risk can be established. Other markers of biology studied in relation to histological grade should be re –examined along this axis of high/ low risk and within the high risk cohort.

Paper 3- Contributes to evidence that a LR in CCCS is associated with an increased risk of metastasis for some patients, but not others. It ca be a useful tool for informing patients in a vulnerable time and tailoring the level of intervention to their situation according to risk group.

Legend of tables and figures

Future planned projects

Second cancers in CRN CS of bone cohort

Clinical and radiological presentation of Oslo risk cohort

Multicentre prognostic analysis of peripheral chondrosarcoma

Interobserver variation in Oslo risk assessment

Validation of Oslo risk in other cohort

Prospective registration of CS in Norway with CS specific variables

Prospective observation of untreated ACT

Multicenter observational study of curettage treated intramedullary grade 2 disease.

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Appendices

Appendix A: Central cartilaginous lesions at the radiology demonstration OUS-HF

Translated from "Enchondromer på røntgenmøte"- OUS e-handbook by J. Thorkildsen..

Most enchondromas are incidental findings. Radiologist should decide whether available files are adequate for appropriate assessment. Normal differential diagnoses include central chondrosarcoma, bone infarct, fibrous dysplasia, low-grade osteosarcoma amongst others.

Generally:

- Plain x-ray can be sufficient if typical features and no cortical influence.
- In the case of suspicion of cortical influence, CT is the best modality
- In the case of suspicion of soft tissue component or need for more precise definition of extension, MR is the best modality.

Signs of malignancy: If there is any sign of malignancy the case should be investigated at referral centre as possible chondrosarcoma. These include growth, remodeling (expansion or cortical thickening), active periostitis, cortical defect, soft tissue component or oedema.

Size can not be used as a risk factor for chondosarcoma alone

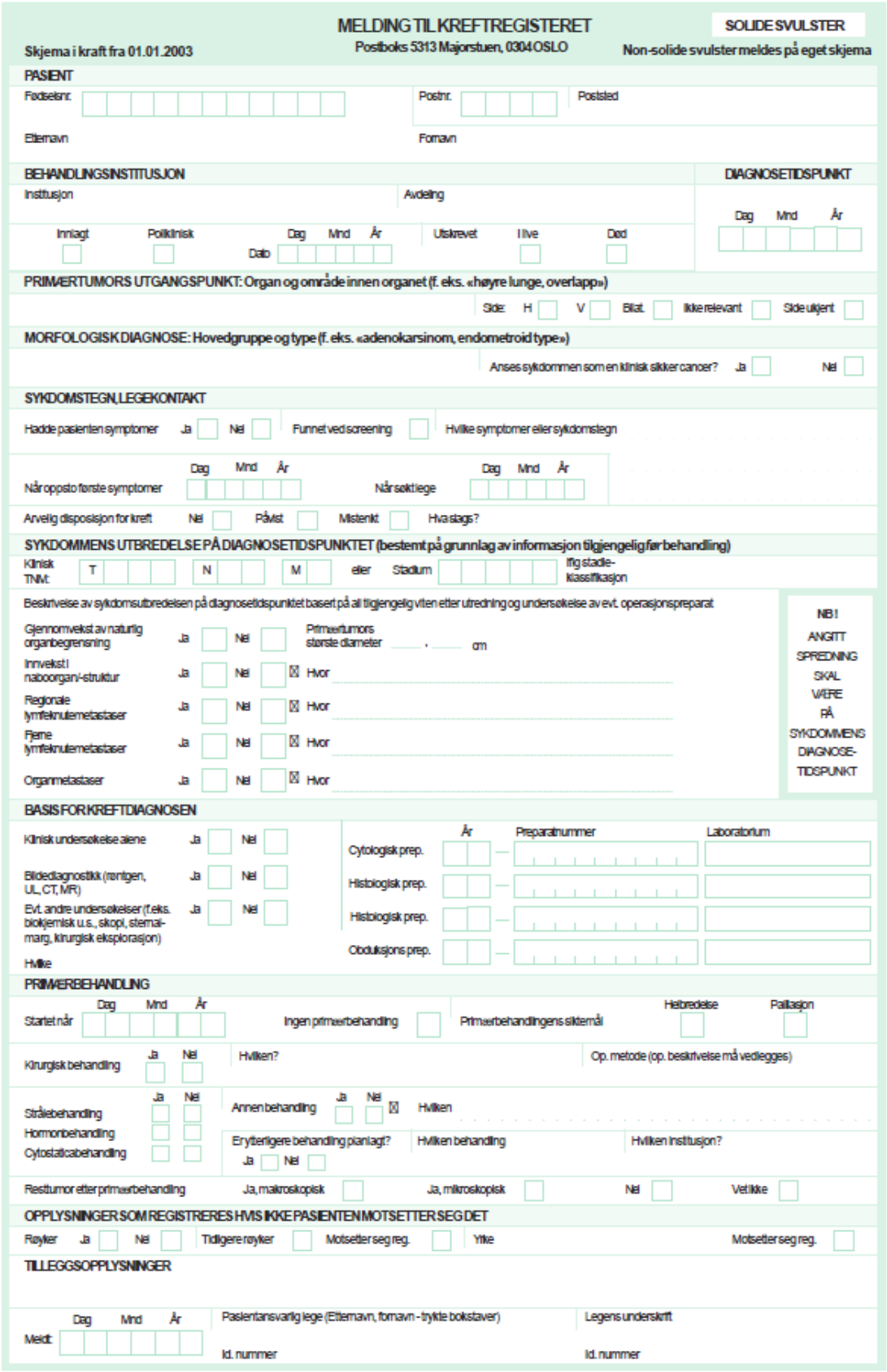
Pain can not be used as a risk factor for chondrosarcoma alone. Patients with pain have a higher need for information. Patients with pain should be referred to local appropriate clinician for further investigation.

Location probably has little influence for risk of malignancy when enchondromas are in typical locations like the femur, tibia or humerus. Enchondromas in the phalanges can look more aggressive radiologically and pathologically with out increased risk of malignancy. Enchondromas in non-extremity location, ie pelvis, scapula, spine, thorax are very rare and should be investigated with follow-up at a referral centre.

Recommended follow-up for enchondromas:

- With any signs of malignancy as listed above, the patient should be investigated with MR and CT and assessed at referral centre.
- Enchondromas in the non-extremity location should also be fully assessed, informed and followed at a referral centre.
- Enchondromas of the extremity without cortical contact do not need follow-up
- Enchondromas with cortical contact or possible other sign of malignancy should be followed at minimum 12 months. Patients can be informed by study nurse or orthopaedic surgeon about the situation. We recommend which modality is to be used and where they are to be taken. If this shows no change then follow up can be ended, if growth or any sign of malignancy they should be assessed again at referral centre.

Appendix B: Cancer Registry of Norway register form



MELDING TIL KREFTREGISTERET

SOLIDE SVULSTER

Skjema i kraft fra 01.01.2003

Postboks 5313 Majorstuen, 0304 OSLO

Non-solide svulster meldes på eget skjema

PASIENT

Fødselsnr. | Postnr. | Poststed

Etternavn | Fornavn

BEHANDLINGSINSTITUSJON

Institusjon | Avdeling

Innlagt | Poliklinisk | Dag Mnd År | Utskrevet i live | Død

Dato

DIAGNOSETIDSPUNKT

Dag Mnd År

PRIMÆRTUMORS UTGANGSPUNKT: Organ og område innen organet (f. eks. «høyre lunge, overlapp»)

Side: H | V | Bilat. | Ikke relevant | Side ukjent

MORFOLOGISK DIAGNOSE: Hovedgruppe og type (f. eks. «adenokarsinom, endometroid type»)

Anses sykdommen som en klinisk sikker cancer? Ja | Nei

SYKDOMSTEGN, LEGEKONTAKT

Hadde pasienten symptomer Ja | Nei | Funnet ved screening | Hvilke symptomer eller sykdomstegn

Når oppsto første symptomer Dag Mnd År | Når søkt lege Dag Mnd År

Arvelig disposisjon for kreft Nei | Påvist | Mistenkt | Hva slags?

SYKDOMMENS UTBREDELSE PÅ DIAGNOSETIDSPUNKTET (bestemt på grunnlag av informasjon tilgjengelig før behandling)

Klinisk TNM: T N M eller Stadium ifg stadie-klassifikasjon

Beskrivelse av sykdomsutbredelsen på diagnosetidspunktet basert på all tilgjengelig viten etter utredning og undersøkelse av evt. operasjonspreparat

NB! ANGITT SPREDNING SKAL VÆRE PÅ SYKDOMMENS DIAGNOSE-TIDSPUNKT

Gjennomvekst av naturlig organbegrensning	Ja	Nei	Primærtumors største diameter ___,___ cm	
Invekst i naboorgan/-struktur	Ja	Nei	☒ Hvor	
Regionale lymfeknutemetastaser	Ja	Nei	☒ Hvor	
Fjerne lymfeknutemetastaser	Ja	Nei	☒ Hvor	
Organmetastaser	Ja	Nei	☒ Hvor	

BASIS FOR KREFTDIAGNOSEN

				År	Preparatnummer	Laboratorium
Klinisk undersøkelse alene	Ja	Nei	Cytologisk prep.			
Blidediagnostikk (røntgen, UL, CT, MR)	Ja	Nei	Histologisk prep.			
Evt. andre undersøkelser (f.eks. biokjemisk u.s., skopi, sternal-marg, kirurgisk eksplorasjon)	Ja	Nei	Histologisk prep.			
Hvilke			Obduksjons prep.			

PRIMÆRBEHANDLING

Startet når Dag Mnd År | Ingen primærbehandling | Primærbehandlingens siktemål: Helbredelse | Palliasjon

Kirurgisk behandling	Ja	Nei	Hvilken?	Op. metode (op. beskrivelse må vedlegges)	
Strålebehandling	Ja	Nei	Annen behandling	Ja	Nei ☒ Hvilken
Hormonbehandling			Ytterligere behandling planlagt? Ja Nei	Hvilken behandling	Hvilken institusjon?
Cytostatikabehandling					

Resttumor etter primærbehandling | Ja, makroskopisk | Ja, mikroskopisk | Nei | Vet ikke

OPPLYSNINGER SOM REGISTRERES HVIS IKKE PASIENTEN MOTSETTER SEG DET

Røyker Ja | Nei | Tidligere røyker | Motsetter seg reg. | Yrke | Motsetter seg reg.

TILLEGGSOPPLYSNINGER

Meldt: Dag Mnd År | Pasientansvarlig lege (Etternavn, fornavn - trykte bokstaver) | Id. nummer | Legens underskrift | Id. nummer

Appendix C: Data management license Oslo University hospital

Oslo universitetssykehus

Oslo universitetssykehus HF

Postadresse:
Trondheimsveien 235
0514 Oslo

Sentralbord:
02770

Org.nr:
NO 993 467 049 MVA

www.oslo-universitetssykehus.no

PERSONVERNOMBUDETS TILRÅDING

Til:	Joachim Thorkildsen
Kopi:	
Fra:	Personvernombudet ved Oslo universitetssykehus
Saksbehandler:	Stein Vetland
Dato:	24. oktober 2013
Offentlighet:	Ikke unntatt offentlighet
Sak:	Personvernombudets tilråding til innsamling og databehandling av personopplysninger
Saksnummer/ ePhortenummer:	2013/14989

Personvernombudets tilråding til innsamling og behandling av personopplysninger for prosjektet "Chondrosarkom"

Viser til innsendt melding om behandling av personopplysninger / helseopplysninger. Det følgende er personvernombudets tilråding av prosjektet.

Med hjemmel i Personopplysningsforskriftens § 7-12 jf. Helseregisterlovens § 36 har Datatilsynet, ved oppnevning av personvernombud ved Oslo Universitetssykehus (OUS), fritatt sykehuset fra meldeplikten til Datatilsynet. Behandling og utlevering av person-/helseopplysninger meldes derfor til sykehusets personvernombud.

Databehandlingen tilfredsstiller forutsetningene for melding gitt i personopplysnings-forskriften § 7-27 og er derfor unntatt konsesjon.

Personvernombudet tilrår at prosjektet gjennomføres under forutsetning av følgende:

1. Databehandlingsansvarlig er Oslo universitetssykehus HF ved adm. dir.
2. Avdelingsleder eller klinikkleder ved OUS har godkjent studien.
3. Behandling av personopplysningene / helseopplysninger i prosjektet skjer i samsvar med og innenfor det formål som er oppgitt i meldingen.
4. Data lagres som oppgitt i meldingen (vedlagt). Annen lagringsform forutsetter gjennomføring av en risikovurdering som må godkjennes av Personvernombudet.
5. Pasientene har allerede undertegnet samtykke som dekker denne studien.
6. Dersom formålet eller databehandlingen endres må personvernombudet informeres om dette.
7. Kontaktperson for prosjektet skal hvert tredje år sende personvernombudet ny melding som bekrefter at databehandlingen skjer i overensstemmelse med opprinnelig formål og helseregisterlovens regler.
8. Data slettes eller anonymiseres ved prosjektslutt 1.november 2019 ved at krysslisten slettes og eventuelle andre identifikasjonsmuligheter i databasen fjernes. Når

formålet med registeret er oppfylt sendes melding om bekreftet sletting til personvernombudet.

Prosjektet er registrert i sykehusets offentlig tilgjengelig database over forsknings- og kvalitetsstudier.

Lykke til med prosjektet!

Med vennlig hilsen
for Personvernombudet

Stein Vetland, personvernrådgiver
Oslo universitetssykehus HF
Stab pasientsikkerhet og kvalitet
Seksjon for personvern og informasjonssikkerhet

Epost: personvern@oslo-universitetssykehus.no
Web: www.oslo-universitetssykehus.no/personvern

Reprint of papers 1-3

Paper 2

Thorkildsen J, Taksdal I, Bjerkehagen B, Norum OJ, Myklebust TA, Zaikova O. Risk stratification for central conventional chondrosarcoma of bone: A novel system predicting risk of metastasis and death in the Cancer Registry of Norway cohort. *J. Surg. Oncol.* 2020

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RESEARCH ARTICLE

Journal of SURGICAL ONCOLOGY WILEY

Risk stratification for central conventional chondrosarcoma of bone: A novel system predicting risk of metastasis and death in the Cancer Registry of Norway cohort

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Funding information
Norwegian National Advisory Unit for Sarcoma

Abstract

Background and Objectives: Interobserver variability in histological grading of central conventional chondrosarcoma (CCCS) limits the quality of patient information and research progression. We aim to quantify known and new prognostic variables and propose a risk stratification model.

Method: We selected 149 cases from the Cancer Registry of Norway. Cox proportional hazard models were estimated. Based on these results a dichotomous risk classification was proposed and presented by Kaplan-Meier estimates for rates of local recurrence, metastasis, and disease-specific survival.

Results: The influence of axial skeletal location (Hazard ratio [HR] = 19.06), a soft tissue component ≥1 cm (HR = 13.45), and histological grade 3 (HR = 16.46) are all significant in predicting the rate of metastasis. The creation of a variable combining axial skeletal location and a soft tissue component ≥1 cm strongly predicts the risk of metastasis (HR = 14.02; $P < .001$) and death (HR = 2.74; $P = .030$) at multivariate analysis, making the histological grade insignificant. Together with metastasis at diagnosis (HR = 285.65; $P < .001$), this forms the basis of our proposed risk stratification, producing a small high-risk group (39 cases with 33% risk of metastasis) and a large low-risk group (103 cases with 2% risk of metastasis) without a histological grade.

Conclusion: Axial skeletal location and a soft tissue component ≥1 cm combined divides a CCCS cohort into low- and high-risk groups without a histological grade.

KEYWORDS

chondrosarcoma, classification, prognosis, risk

1 | INTRODUCTION

The role of histological grading in the prognosis of chondrosarcoma (CS) of bone was first described over 50 years ago.[1] During the last 10 years, the inter-observer variability of grading between expert pathologists, radiologists, and orthopedic oncologists and its clinical and research implications has been well documented.[2-5]

Despite this, the scientific literature presents results for CS of bone by histological grade.[1,6-12] These results are generally in mixed cohorts, and include central, peripheral, and often dedifferentiated CS subtypes[1,8-13] together. Though these subtypes have similar features on microscopic examination,[14-16] they are now recognized as different diseases with varying biology and treatment[17] and as such, the prognostic work should also be performed at a subtype level.

Many cohorts with central conventional chondrosarcoma (CCCS) alone are limited to specific anatomical locations or with multivariate analyses for limited variables in institutional cohorts.[6,7,18] Histological grade significantly predicts survival at univariate analysis in two national CCCS cohorts,[14,19] but has not been proven in multivariate models. Neither does it convey the established importance of anatomical location and soft tissue extension which drives treatment of CCCS.[17]

A new system of risk stratification for CS of bone is needed.[20] It should ideally depict differing risk groups with regard to both local and systemic control in as few categories as possible[21] and must be specifically validated for each subtype. The methodology should be simple to ensure low inter-observer variability, thereby establishing common definitions to allow for the pooling of cases vital to rare disease research.

We have previously shown the prognostic importance of a soft tissue component in CCCS of bone.[14] We, therefore, chose to look at whether the soft tissue components' size by standardized measurement was associated with prognosis.

Our primary aim was to use prognostic analysis from a complete national cohort of CCCS of bone[14] to quantify the influence of anatomical location, presence, and size of a soft tissue component, as well as malignancy grade.

The secondary aim was to propose a risk stratification model for CCCS based on the above and to present results from our cohort by this stratification.

2 | MATERIALS AND METHOD

The Cancer Registry of Norway (CRN) cohort of CS of bone from 1990 to 2013 has been previously described, and the same definitions were applied to this study[14] (Supporting Information Material). It is a prospective register, but we have retrospectively quality controlled all data. There were 197 eligible cases of CCCS in the cohort for all anatomical locations excluding head and neck. Radiology was reviewed for 134 cases. Radiology was missing in 63 cases due to the hospitals deleting the images 10 years after diagnosis. Of the 63 cases, 48 had histologically proven soft tissue components. These 48 were therefore excluded since we had no means of measuring the soft tissue component, while the other 15 cases were intramedullary cases and were included in the study. This resulted in 149 cases eligible for analysis (Figure 1).

Thirty-eight of the 149 cases were selected for histological review by set criteria to complement missing or unclear data. All 149 cases are histologically confirmed and have complete data sets and documented follow-up. All information in the register for all cases was quality controlled by the main author from the clinical notes.

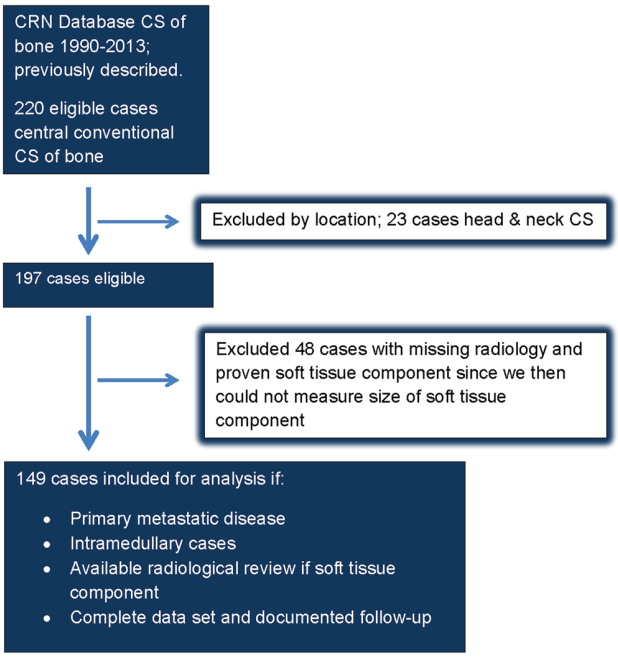

FIGURE 1 Flowchart illustrating methodology for inclusion/exclusion of cohort [Color figure can be viewed at wileyonlinelibrary.com]

Borderline malignant lesions have intentionally been excluded under the selection of the original cohort (11 cases).[14]

The size of the soft tissue component was measured using radiology software to the nearest mm, perpendicular to the stipulated outer cortex in the plane that best allowed the greatest measurement by coauthor IT, a senior sarcoma radiologist. Examples are illustrated in Figure 2. Edema was not measured. In the case of circumferential tumor, measurement was made where the largest.

Extremity location was defined by the glenohumeral and hip joints, meaning that the pelvis and scapula are denoted as part of the axial skeletal location group.

Grading has been practiced in accordance with WHO criteria[22] in a four-grade system. CCCS is graded 1 to 3, while dedifferentiated CS as grade 4 was not included in this study.

The term "Atypical Cartilaginous Tumor (ACT)" has not been adopted in Norway during the study period and as such was not introduced into the manuscript.

The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) checklist was used as far as the methodology allowed.[23]

2.1 | Clinical setting

Investigation, treatment, and follow-up of chondrosarcoma in Norway during the period was highly centralized. Ninety-one percent were referred to as untouched cases, 3% had a biopsy outside a referral center, and 6% had contaminated surgeries. In the early1990s treatment was driven by grade on open biopsy, but this

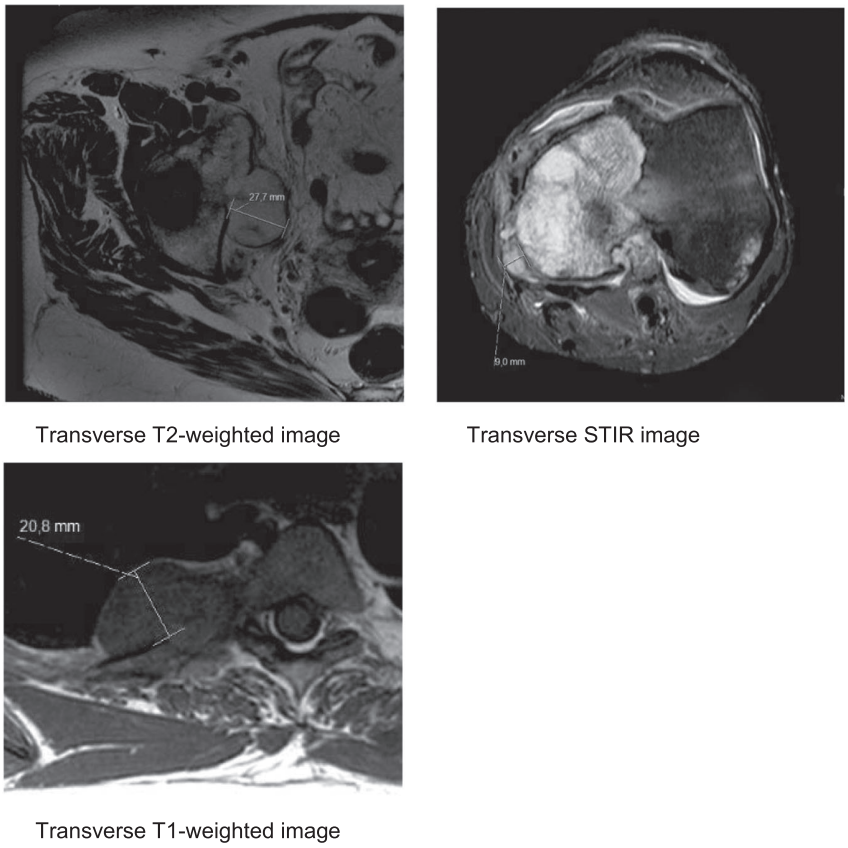

FIGURE 2 Examples of MR measurement of the size of soft tissue components in the pelvis, distal femur, and thorax [Color figure can be viewed at wileyonlinelibrary.com]

changed in the mid-90s with the acceptance of skeletal location and soft tissue components role in depicting biology together with the awareness of challenges involved in defining accurate histological grade on biopsy. Since then, curettage has been performed on extremity intramedullary lesions with limited signs of radiological aggressiveness, while all others have been resected. Similarly, needle biopsy has primarily been performed to confirm a radiological chondrosarcoma diagnosis before more extensive surgery (ie resection) and increasingly not at all, in the latter part of the study period. Reporting to the CRN was mandatory by law throughout the period.

2.1.1 | Bias

Possible bias has been addressed by the use of multiple sources. Review of both radiology and pathology where available, or by set criteria, including all cases at risk of wrongful diagnosis or with missing data. The review was partly in a group setting. The cohort is population-based, which should control for random patterns in local or regional referral practices.

There exists a possibility for selection bias since cases with a soft tissue component and missing radiology were excluded (48/197 cases = 25%). Thus, the influence of the soft tissue component on our findings may be underestimated in magnitude in prognostic analysis when compared to intramedullary disease. We have reason to believe that our national cohort is complete.[24] A recent national Dutch cohort[19] report an overall CS incidence nearly twice that of Norway and clearly highest in the world.[25] Their documented incidence increase is driven by ACT's while ours is for grade 2 disease and as such it seems likely that they define ACT at a lower level of aggressiveness in the Netherlands as opposed to Norway. Since ACT's are by definition tumor with limited or no metastatic potential this should not effect our results.

2.1.2 | Statistics

Stata 14 software was used for statistical analysis. Significance was set at $P < .05$ and was tested using two-tailed tests.

Descriptive statistics are presented as mean values with range for continuous variables and frequencies and relative frequencies for categorical variables. The Kaplan-Meier estimator was used to establish rates of local recurrence (LR), rate of metastasis (Met), and disease-specific survival (DSS) at 2, 5, and 10 years of follow-up. The log-rank test was used to test for differences in survival curves. Patients were followed from the date of diagnosis to the date of the event of interest, death, or end of clinical follow-up, whichever came first. Death was treated as a censoring mechanism in analyses of LR and Met, but as an event in DSS. We have used the CRN definition "dead from cancer" as depicting DSS with censor date 30 October 2016, linked to the national death registry.

Uni- and multi-variate Cox proportional hazard models were estimated. The following covariates were included in the multivariate model: age (continuous), sex (female/male), size (<>8 cm), and histological grade (grade 1-3), and a constructed variable combining axial location with a soft tissue component measuring ≥1 cm against the rest of the cohort. The latter was based on the findings of the univariate analysis of anatomical location (Figure 3A) and size of the soft tissue component (Figure 3B) on rates of metastasis. Metastasis at diagnosis was included in DSS analysis only. Hazard ratios (HR) are reported with 95% confidence intervals. The assumption of proportional hazards was tested by Schoenfeld residuals for all models. The likelihood-ratio test was used to test the significance of each variable.

2.1.3 | Ethics

Retrieval and handling of data is in accordance with the Helsinki declaration. The project is based at the CRN and data retrieval is based on the quality control charter of the cancer registry act of 1967/2014. The regional ethics board (REK) has been consulted and accepts this foundation.

3 | RESULTS

3.1 | Follow-up

Median follow-up based on observed follow-up from diagnosis to death or end follow-up at 10 years was 8.29 years (range, 0.08-10 years). In all, 61 patients completed 10 years of follow-up while 32 died from any cause.

3.2 | Prognostic analysis

Figure 3A-D shows that for Met, the influence of extremity versus axial location was large (Figure 3A). The presence of a soft tissue component ≥1 cm was also statistically significant (Figure 3B), with an influence similar in magnitude to that of histological grade 3 (Figure 3C). Creating a variable with axial location and a soft tissue component ≥1 cm combined against the rest of the cohort identified a high- and a low-risk group with a narrowed confidence interval (Figure 3D).

Multivariate analysis (Tables 1A, 1B, 1C) showed that male sex HR = 3.77 (1.18-12.02) remained a significant independent predictor of LR in this cohort together with Residual tumor classification of

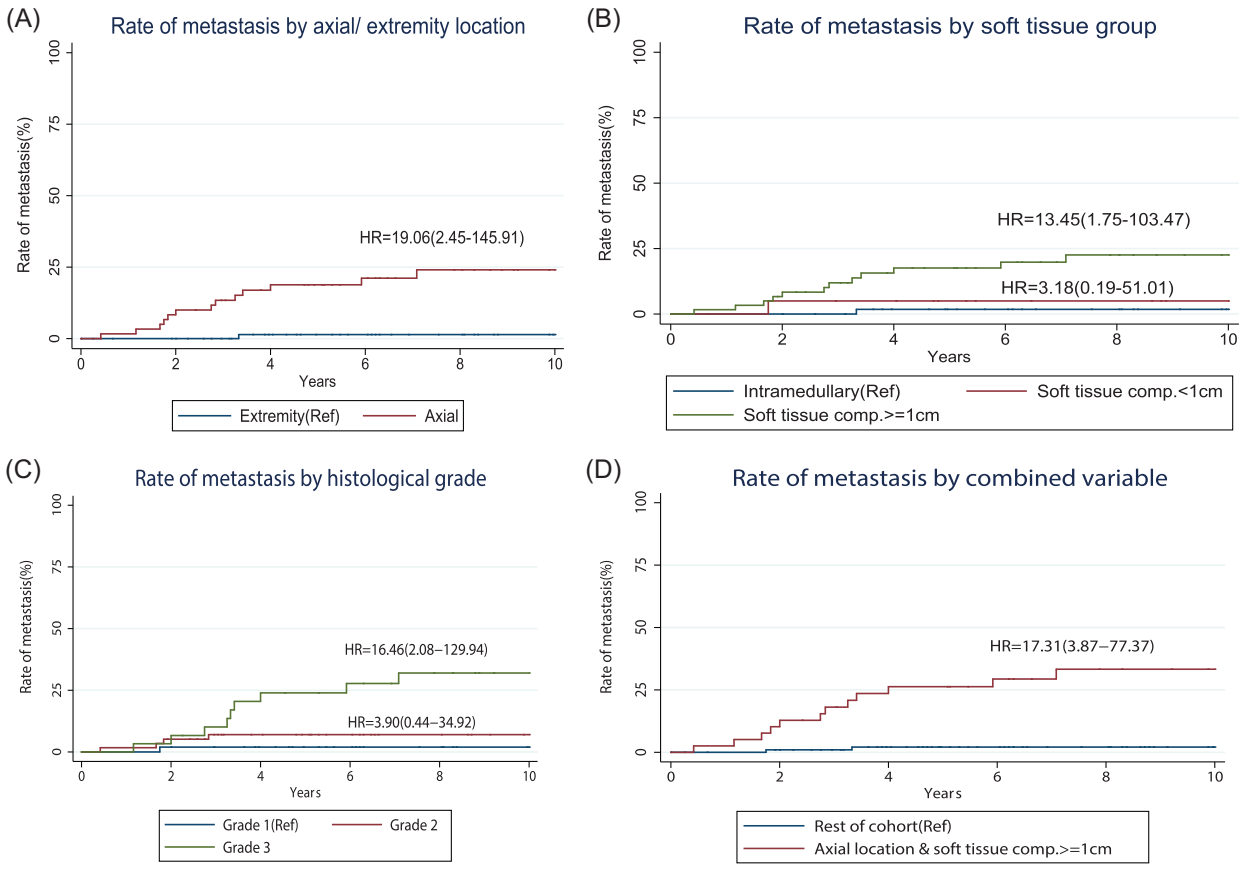

FIGURE 3 A, B, C, D, Kaplan-Meier curves for rate of metastasis; tested for location (A), soft tissue group (B), histological grade (C), and combined axial location with soft tissue component ≥1 cm vs rest of cohort (D). Hazard ratios (HR) with 95% confidence intervals [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1A Cox analysis for local recurrence no.141

Variable name	Univariate HR (95%CI)	Multivariate HR (95% CI) *P* value by lr test if significant
Age at diagnosis	1.02 (0.99-1.05)	1.01 (0.98-1.04)
Sex female/male	3.78 (1.25-11.52)	3.77 (1.18-12.02) ***P* = .015**
Size <>8 cm by AJCC	1.04 (0.40-2.69)	0.51 (0.16-1.63)
Rest of cohort/axial location with soft tissue comp. >1 cm	2.29 (0.90-5.81)	1.93 (0.67-5.56)
Malignancy grade		
Grade 1	Ref	Ref
Grade 2	0.57 (0.16-2.02)	0.80 (0.19-3.30)
Grade 3	2.40 (0.83-6.90)	3.71 (0.84-16.45)
Residual tumor margin R1 vs R0	2.97(1.17-7.54)	3.83(1.32-11.13) ***P* = .016**

Note: Hazard ratio (HR) and 95% confidence interval. Likelihood ratio (lr) test for testing of multivariate significance. *P* values given only for significant findings.
Abbreviation: AJCC, American Joint Committee on Cancer.

margin (R1vs R0); HR = 3.83 (1.32-11.13). The combined variable did not reach significance at multivariate level.

The combined axial location with ≥1 cm sized soft tissue component variable remained strongly statistically significant for rate of metastasis ($P < .001$) when corrected for age at diagnosis, size of tumor, sex, and histological grade (Table 1B), while histological grade became insignificant.

The same combined variable remained a significant independent predictor of DSS ($P = .03$), while histological grade became insignificant at multivariate analysis (Table 1C). In addition, DSS was independently influenced by age ($P = .004$) and metastasis at diagnosis ($P < .001$).

Referral status (biopsy or surgery outside a sarcoma center) did not to a significant degree effect either LR; HR = 2.3 (0.7-7.9), Met; HR = 0.8 (1.0-5.9) or DSS; HR = 1.9 (0.6-5.5) in our cohort.

3.3 | Stratification system

We propose a risk stratification model for CCCS of bone based on axial versus extremity skeletal location and a size of soft tissue component <≥1 cm together with primary metastatic status.

*Low risk = Type I + II + III

Type I = Extremity cases, intramedullary, or with a soft tissue component <1 cm

Type II = Extremity cases with a soft tissue component ≥1 cm

Type III = Axial cases, intramedullary, or with a soft tissue component <1 cm

*High risk = Axial cases with a soft tissue component ≥1 cm

*Primary metastatic disease

We analyzed the low-risk I group for the extremity and the low-risk III group for axial locations for intramedullary disease only against those with a soft tissue component <1 cm as a function of rates of LR, Met, and death. As supported by Cox analysis, this showed no significant statistical difference and thereby supported their being grouped together for both locations.

3.4 | Cohort by risk stratification

The demographic data and tumor characteristics by risk group are presented in Table 2. There was an even distribution by sex with the exception of a higher proportion of female cases in the low-risk type I

TABLE 1B Cox analysis for metastasis no. 142

Variable name	Univariate HR (95%CI)	Multivariate HR (95% CI) *P* value by lr test if significant
Age at diagnosis	1.01 (0.97-1.04)	1.01 (0.97-1.04)
Sex female/male	2.67 (0.84-8.53)	1.50 (0.48-4.76)
Size <>8 cm by AJCC	3.17 (1.06-9.45)	1.43 (0.41-4.99)
Rest of cohort/axial location with soft tissue comp. >1 cm	17.31 (3.87-77.37)	14.02 (2.98-65.94) ***P* < .001**
Malignancy grade		
Grade 1	Ref	Ref
Grade 2	3.9 (0.44-34.92)	1.74 (0.18-16.43)
Grade 3	16.46 (2.08-129.94)	5.16 (0.58-46.09)

Note: Hazard ratio (HR) and 95% confidence interval. Likelihood ratio (lr) test for testing of multivariate significance. *P* values given only for significant findings.
Abbreviation: AJCC, American Joint Committee on Cancer.

TABLE 1C Cox analysis for disease-specific survival no. 149

Variable name	Univariate HR (95% CI)	Multivariate HR (95% CI) *P* value by lr test if significant
Age at diagnosis	1.04 (1.01-1.06)	1.04 (1.01-1.07) ***P* = .004**
Sex female/male	2.12 (0.91-4.95)	1.70 (0.68-4.25)
Size <>8 cm by AJCC	2.69 (1.18-6.15)	1.12 (0.41-3.06)
Rest of cohort/axial location with soft tissue comp. >1 cm	3.65 (1.62-8.23)	2.74 (1.09-6.91) ***P* = .03**
Malignancy grade		
Grade 1	Ref	Ref
Grade 2	2.84 (0.77-10.52)	1.40 (0.35-5.58)
Grade 3	6.72 (1.90-23.83)	1.90 (0.45-7.98)
Metastasis at diagnosis no/yes	49.97 (13.37-186.77)	285.65(26.34-3098.32) ***P* < .001**

Note: Hazard ratio (HR) and 95% confidence interval. Likelihood ratio (lr) test for testing of multivariate significance. *P* values given only for significant findings.
Abbreviation: AJCC, American Joint Committee on Cancer.

cohort and a higher proportion of male cases in the high-risk cohort. For both extremity and axial locations, a larger size of soft tissue component was associated with a higher mean age at diagnosis and a larger tumor size. Primary metastatic cases had the highest age, the largest tumors, and the largest soft tissue components of all groups.

Table 3 shows the diagnostic and treatment characteristics of the cohort by risk stratification. A total of 142 cases were operated; 104 (73%) by resection, 7 (5%) by primary amputation, and 31 (22%) by curettage. Of the latter, 25 curettages were performed at a tumor center aimed at treating a known CCCS, while 6 were contaminated surgeries from other hospitals. For the total cohort, the residual tumor margin[26,27] was reported as R0, R1, and R2 in 66%, 29%, and 5% of cases. A total of nine reresections were performed, primarily due to R2 margins (seven cases). Radiotherapy and chemotherapy were infrequent treatment modalities, given to only 5% and 3%, respectively.

3.5 | Rates of LR, Met, and DSS

Table 4 shows the rates of LR, Met, and DSS by risk stratification.

LR increased from 7% to 21% at 10 years from low-risk I to the high-risk group. For all groups, LR was stable from 5 years of follow-up.

Met ranged from 0% to 5% for low-risk groups and was stable from 5 years of follow-up. This encompassed 103 patients with a total rate of metastasis at 5 years of 2% or metastasis-free survival (MFS) of 98%. The high-risk cohort included 39 patients with a metastatic rate of 10%, 26%, and 33% at 2, 5, and 10 years of follow-up or MFS of 90%, 74%, and 67%, correspondingly. This was the only group with events after 5 years.

DSS for the cohort overall was 96%, 85% and 82% at 2, 5, and 10 years. For all subgroups, the DSS at 2 years was excellent ranging from 95% to 100%. Low-risk II and III had slightly lower DSS at 5 years (86% and 89%) than low-risk I (97%). The high-risk cohort clearly had lower 5-year DSS at 76%. DSS for the high-risk group continued to fall from 76% to 70% from 5 years to 10 years of follow-up, in line with continued metastatic events in this group.

Figure 4A-D shows the Kaplan-Meier curves for rates of LR, Met, and DSS, as well as overall survival by risk stratification with log-rank testing. All patients with primary metastatic disease died. Overall survival at 5 and 10 years was similar for low-risk II (72% and 66%) and high-risk cohorts (76% and 67%), despite wide differences in the rates of metastasis between these two groups (0% vs 33% at 10 years).

4 | DISCUSSION

Prognostic analysis concerning the size of the soft tissue component has not been described previously. This is also the first report from a national cohort which attempts to quantify and organize prognostic analysis for CCCS related to the rate of metastasis, which is likely a more direct outcome measure as compared to survival. This results in a simple and novel tool for presenting systemic outcomes for patients with CCCS without the use of histological grade allowing for improved information of patients at the time of diagnosis before surgery and the pooling of results for the research. This cohort provides further evidence towards the safety of clinical CS management not driven by biopsy[28,29]| since the overall results are good when compared to other CCCS cohorts.[6,7]

Our most important finding is the organization of the cohort into a low- vs high-risk group. This dichotomous division creates a large low-risk group and a small high-risk group. Interobserver variability has not been studied for our proposed stratification, but is likely less, since the methodology has fewer elements and is less subjective by nature.

If our findings are confirmed, the clinical implications are numerous. First, the CS community will have a common language essential for cooperation between centers. As opposed to osteosarcoma or Ewing patients; CS patients are seldom included in prospective cohorts and numbers reported are often either small or

TABLE 2 Descriptive statistics of patient and tumor demographics by risk group

Risk group no.		Sex female/male no. (%)	Age mean years of age (range)	Size in cm mean (range)[a]	Ollier/Mafucci syndrome no.(%)	Soft tissue component present yes/no no.	Size of Soft tissue component present mean cm (range)[a]	Malignancy grade 1/2/3 no.
Low risk								
Type I	No. 59	38/21 (64/36)	49 (20-81)	7.1 (2-31)	5(8)	10/49	0.5 (0.1-0.9)	40/15/4
Type II	No. 22	12/10 (55/45)	64 (26-95)	10.4 (3-29)	0	22/0	2.8 (1-8.3)	3/10/9
Type III	No. 22	9/13 (41/59)	52 (17-80)	6.3 (2-14.5)	0	10/12	0.5 (0.2-0.7)	6/14/2
Total	No. 103	59/44 (57/43)	52 (17-95)	7.7 (2-31)	5(5)	42/61	1.6 (0.1-8.3)	49/39/15
High risk								
No.39		14/25 (36/64)	54 (15-80)	8.7 (3.6-15)	2(5)	39/0	3.5 (1-9.7)	4/19/16
Primary metastatic								
No. 7		3/4 (43/57)	63 (33-82)	11.9 (4.5-18)	0	7/0	6.1 (3.5-7.3)	0/3/4
Total								
No. 149		76/73 (51/49)	53 (15-95)	8.1 (2-31)	7(5)	88/61	2.7 (0.1-9.7)	53/61/35

[a]Rounded to nearest decimal point.

hampered by poor data quality. There is a clear need for multicenter prospective register reporting with quality data at a subtype level, but for this to occur there must first be a common language of accepted and reproducible definitions.

The low/high-risk finding also creates a division which can guide research investigations. Oncologists attempting to study adjuvant therapy should focus on the high-risk population. Researchers looking for new markers of systemic biology should re-examine findings along this clear dichotomous division into high and low risk, as well as within the high-risk group. It would also be interesting to re-examine findings for radiological and genetic studies along this axis.

In the clinical setting, our findings allow for improved decision making as regards to both level of surgical intervention as well as tailoring of follow-up regimes when based on reliable risk estimates of local and systemic disease. It also raises questions with regard to a number of treatment scenarios. First, this cohort includes four cases of curettage of an intramedullary CS in the extremity with final histological grade 2, without a re-resection and without further events. This has similarly been reported by an English group.[29] This is supported by the fact that a soft tissue component alone predicts LR, Met, and DSS at multivariate analysis for CCCS corrected for grade as well as the stepwise genetic changes involved in CS progression.[30] Larger prospective cohorts of this selected patient group should be sought out and published to clarify this important point.

It is also unclear what tumor related factors represent the upper limits for performing a safe curettage. When adjusted for the presence of a soft tissue component, tumor size does not depict risk of LR, Met, or DSS in this cohort. As such it seems natural to explore the limits of curettage for larger intramedullary tumors rather than those with soft tissue components. Since size previously has been considered a prognostic criteria, larger intramedullary CS was resected without a clear cut-off. This can naturally influence our findings.

We present a methodology based on a single measurement of the soft tissue components size by standardized means, somewhat similar to that for Peripheral CS measurement of a cartilage cap.[31] Our initial investigation sought to look at a ratio between the size of the intramedullary part and soft tissue part of the tumor based on the notion that a small intramedullary tumor with large soft tissue component appears more aggressive than a large intramedullary tumor with small soft tissue component. This was complex to interpret, and as such we chose to look at single centimeter measurements (1 cm, 2 cm, 3 cm) of the soft tissue component by standardized means. In this cohort, 1 cm appeared to be a cut off in predicting risk of metastasis. This has the appeal of simplicity, but needs to be confirmed in other cohorts.

The low-risk II group has increased rates of local recurrence and poorer survival compared to low-risk I and similar rates of overall survival as the high-risk cohort, despite a huge difference in their metastatic rates. The low-risk II group had higher age, larger tumors, and larger soft tissue components than low-risk I. Possibly, low-risk II might be a more morbid subgroup than low-risk I with later presentation, more demanding surgery, and poorer non-oncological survival, but this needs to be investigated further.

TABLE 3 Treatment summary of cohort by risk group

Risk group no.		Pre-op. biopsy no. (%)	Untouched referral no. (%)	Residual tumor margin no.				No surgery no.	Radio-therapy no.	Chemo-therapy no.
				R0	R1	R2	2nd Surgery			
Low risk										
Type I	No. 59	36 (61%)	57 (97%)	34	21	4	4	0	1	0
Type II	No. 22	14 (64%)	18 (82%)	15	6	1	2	0	0	0
Type III	No. 22	14 (64%)	17 (77%)	15	6	1	1	0	2	0
Total	No. 103	64 (62%)	92 (89%)	64	33	6	7	0	3	0
High risk										
No. 39		35 (90%)	36 (97%)	29	7	1	2	2	2	2
Primary metastatic										
No. 7		7 (100%)	5 (71%)	1	1	0	0	5	3	2
Total										
No. 149		106(71%)	128(90%)	94	41	7	9	7	8	4

Abbreviations: No Surgery, no surgery performed; Pre-op biopsy, pre-operative biopsy performed; Untouched referral, no biopsy or surgery outwith sarcoma center; 2nd surgery, Performed re-resection.

This finding underlines that a censor for metastatic events is the most important direct measure of systemic biology for CCCS. Measuring outcomes solely by survival will introduce other confounders and insecurities, particularly in a slow to intermediate growing disease like CS with an overall low rate of metastasis. The accuracy of a diagnosis of lung metastasis in this setting has not been studied to our knowledge, but there is little reason why there should be a discrepancy between the groups.

Our cohort shows increased number of men in the high-risk subcohort and women in the low-risk subcohort and as such and an increased influence of sex on risk of local recurrence. This may be random in a small cohort and rare disease, but could also represent different tumor biology or medical seeking behavior between the sexes. Our proposed system predicts LR at univariate (Figure 4A), but not at multivariate level (Table 1A) and as such should be re-examined in larger cohorts.

The surgical margin independently predicts risk of LR in line with intuitive thinking. Further subgroup analysis is needed, seeking to find whether this is valid for all CCCS or only the high risk group. Although LR has been linked to increased rates of metastasis and death in CS research,[13,32-37] this has been performed in mixed CS cohorts and without considering immortal time bias for time dependent variables.

There are no directly comparable reports. Two institutional reports on CCCS with multivariate analysis use either survival or a combined event-free survival censor for analysis and neither report on extracompartmental status.[6,7] In line with our findings, the German group[6] reports that grade 3 lesions with axial location have the worst prognosis. Another national register study[19] reports on a mixed cohort but with prognostic analysis at a subtype level. Their CCCS cohort is driven by a large and increasing proportion of ACT's and unfortunately lack information

TABLE 4 Rates of local recurrence, metastasis and disease-specific survival at 2, 5, and 10 y follow-up by Kaplan-Meier estimates according to risk groups

		Local recurrence rate % (95% CI)[a]			Metastasis rate % (95% CI)			Disease-specific survival % (95% CI)		
		2 y	5 y	10 y	2 y	5 y	10 y	2 y	5 y	10 y
Low risk										
Type I	No. 59	5 (2-15)	7 (3-18)	7 (3-18)	0	2 (0-12)	2 (0-12)	100	97 (87-99)	94 (82-98)
Type II	No. 22	10 (2-33)	15 (5-39)	15 (5-39)	0	0	0	95 (72-99)	86 (62-95)	86 (62-95)
Type III	No. 22	14 (5-38)	14 (5-38)	14 (5-38)	5 (7-29)	5 (7-29)	5 (7-29)	100	89 (60-97)	89 (60-97)
Total	No. 103	8 (4-15)	10 (6-18)	10 (6-18)	1 (0-7)	2 (1-8)	2 (1-8)	99 (93-100)	93 (85-97)	91 (83-96)
High risk										
No. 39		16 (8-33)	21 (12-39)	21 (12-39)	10 (4-25)	26 (15-43)	33 (20-52)	100	76(60-87)	70 (52-82)
Primary metastatic										
No. 7		0	Na	Na	Na	Na	Na	29 (4-61)	Na	Na
Total										
No. 149		10 (6-16)	13 (9-20)	13 (9-20)	4 (2-8)	9(5-15)	11 (7-18)	96 (91-98)	85 (78-90)	82 (74-88)

Note: Percentages rounded to nearest whole number.

[a]Seven patients not receiving surgery removed, five of which are primary metastatic.

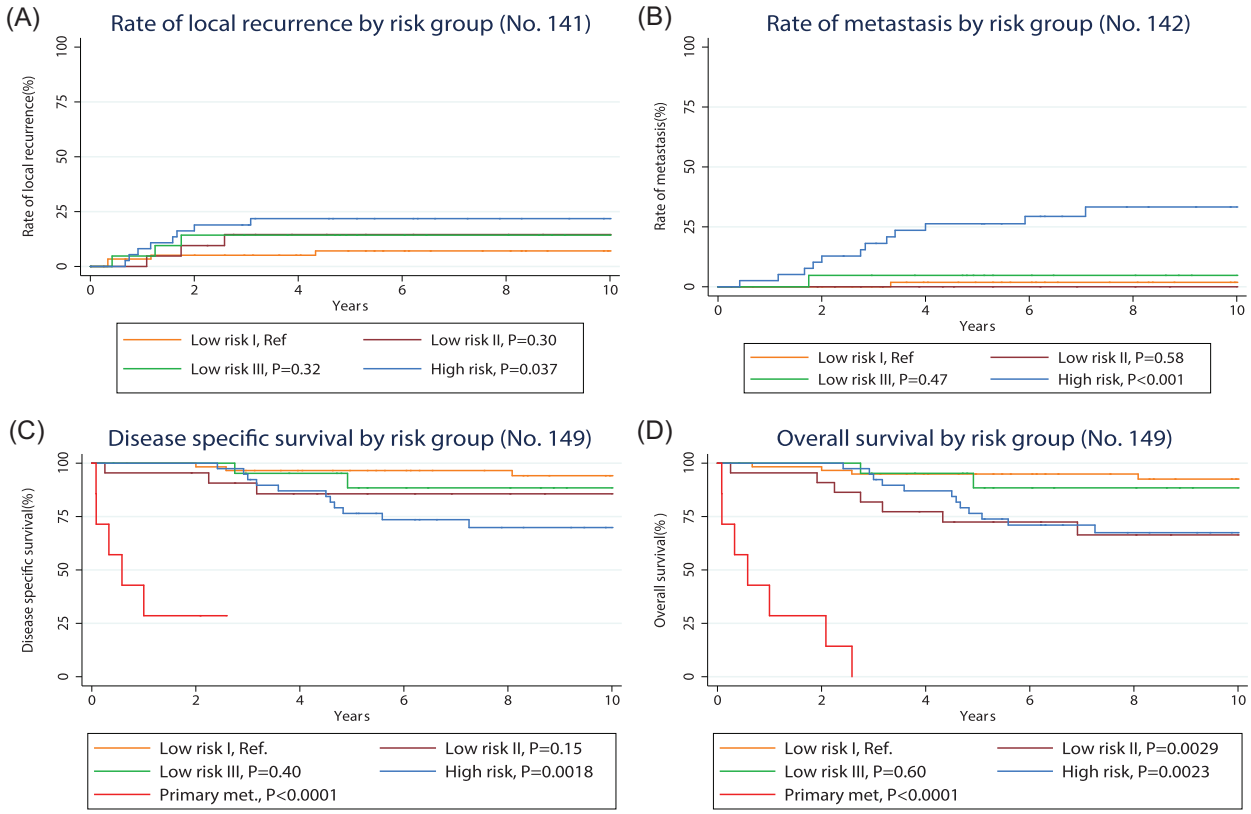

FIGURE 4 A, B, C, D, Kaplan-Meier curves for rates of local recurrence (A), rate of metastasis (B), disease-specific survival (C), and overall survival (D) by risk stratification. Log-rank testing for each curve against reference [Color figure can be viewed at wileyonlinelibrary.com]

on extracompartmental status and rate of metastasis to allow for direct comparison.

Though we present a nationwide cohort over nearly 25 years, our numbers are small and the findings should be interpreted accordingly. 25% of patients are excluded from analysis due to missing radiology and as such a degree of selection, bias may be present. It is, however, a larger cohort than Evans' original, retrospective institutional report of mixed CS subtypes (75 cases). Furthermore, large cohorts have failed to contribute significant new findings in predicting CS biology,[11,12,19] even when re-examined with machine learning,[38] likely due to limited variables and data quality.[39] We believe the quality of our data to be unique both with regard to its completeness, range of variables and quality control of every variable with a complete data set for all included at a subtype level. The CRN has a documented 97% completeness for bone sarcoma before our further quality control.[24]

This is a historical prospective analysis of a small national cohort, while most CS literature is retrospective. Only by analysis of other CCCS cohorts and multicenter prospective registration can we truly confirm the study's external validity. If validated this confers the possibility to provide a simple surrogate measure to histological grade in depicting biological CCCS activity, thereby simplifying real-life CCCS management and research.

5 | CONCLUSION

In summary, the combination of axial location and a soft tissue component ≥1 cm predicted a high risk of metastasis and death in our cohort of CCCS without the use of histological grade.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are in part available from the corresponding author. Restrictions apply to the availability of these data, which were used under license for the current study from the National Cancer Registry, and so are not publicly available. Data are however available from the corresponding author upon

reasonable request and with application to the Cancer Registry of Norway.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Paper 3

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RESEARCH ARTICLE

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Chondrosarcoma local recurrence in the Cancer Registry of Norway cohort (1990–2013): Patterns and impact

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Abstract

Background: There appears to be an association between local recurrence (LR) and risk of metastasis and death in central conventional chondrosarcoma (CCCS) of bone, but this has not been quantified in modern cohorts at a subtype level.

Methods: We identified nonmetastatic cases of CCCS ($N = 180$) from the Cancer Registry of Norway. We present prognostic analysis of LR accounting for immortal time bias by descriptive statistics and multivariable Cox models.

Results: Of 40 LR, one case demonstrated upgrading while two dedifferentiation. LR was associated with increased risk of metastasis (hazard ratio [HR] = 4.1 [confidence interval, 1.5–10.7]) and death (HR = 9.3 [5.0–17.5]) overall. LR was associated with significant increased risk of metastasis for those with a soft tissue component, axial location, malignancy grade 2, but not atypical cartilaginous tumor's, appropriately treated curettage patients, intramedullary tumors, grade 1 histology, extremity location or "Oslo low risk" group status. We found an increased risk of death for all groups except for those treated by appropriate curettage or belonging to the "Oslo low risk" group. About 50% of LR CCCS were asymptomatic and revealed by routine follow-up.

Conclusions: Upgrading of LR for CCCS was a seldom event. LR was associated with significant increased risk of metastasis and death overall, but not for appropriately treated curettage patients or "Oslo low risk" status.

KEYWORDS

chondrosarcoma, local recurrence, metastasis, prognosis

1 | BACKGROUND

There appears to be an association with chondrosarcoma (CS) local recurrence (LR) and increased rate of metastasis (Met) and death.[1-8] To date this has been assessed in mixed CS cohorts,[1-5,7,8] but we now know that different subtypes of CS have different etiology, behavior, treatment, and prognosis[9-15] and should therefore be studied at a subtype level.

Immortal time bias is the statistical concept of observational time where an event cannot occur. This occurs since LR happens at different times during the course of observation.[16] Following a case from surgery, an LR event cannot influence risk of metastasis before the LR actually occurs. LR must thus be analyzed as a time-dependent covariate to assure observation time is allocated appropriately. Failing to do so will underestimate the impact of LR on the event. Most authors have presented descriptive statistics or Kaplan–Meier estimators for groups experiencing an event against those who have not, but have not accounted for this potential bias.[1,3,5,11,17,18] Others evade the issue by including only patients with LR events[2,4,8,14] and start observation at the point of the LR, but cannot then compare its impact to those without LR.

Only one report accounts for immortal time in their methodology,[6] but their study is limited to grade 1 disease in long bone locations and a historic cohort dating from 1911 to 2003. This same cohort is a key source of knowledge in relation to the concept of CS recurring as a more aggressive grade (upgrading) in 13%–19% of LR.[6,19] The time period

predates routine use of clinical imaging and curettage for selected patients. There are also clear methodological challenges in data quality when assessed with current knowledge of CS heterogeneity and interobserver assessment. This contributes to the mythology regarding CS epidemiology and requires assessment in modern cohorts at a subtype level.

In an earlier publication from the same cohort we have found that in the primary treatment setting, we can use anatomical location (extremity vs. axial) together with the presence and size of the soft tissue component to establish a large low-risk group (Oslo low risk) and a small high-risk group (Oslo high risk) with regard to risk of metastasis and death without the use of histological grade. We plan to assess this and other prognostic subgroup divisions in the setting of LR.

A clear understanding of the impact of LR is crucial in guiding therapy and surveillance both in the primary treatment setting and for those experiencing LR.

1.1 | Study questions

1. What is the true pattern and frequency of upgrading and dedifferentiation in locally recurrent central conventional chondrosarcoma (CCCS)?
2. What is the impact of LR on rates of metastasis and overall survival for CCCS?
3. Does the impact of LR vary between subgroups of patients?
4. How does locally recurrent CCCS present and is routine surveillance helpful in discovering it?

2 | PATIENTS AND METHODS

2.1 | Study design and setting

This is a prospective observational study of a complete national cohort of chondrosarcoma of bone from the Cancer Registry of Norway (CRN). The time period for inclusion is 1990–2013. Norway has a long-standing tradition of centralization of tumor services and reporting to the CRN is mandatory by law. The Strengthening of Reporting of Observational Studies in Epidemiology checklist has been used where applicable.[20]

2.2 | Participants/study subjects

The construction of the original cohort at the CRN has been previously described,[13] but is defined again in the Supplementary Material attached. Particular focus has been to provide complete data at subtype level. All borderline malignant cases have been excluded. We selected all cases of CCCS of bone ($N = 197$) from the CRN CS cohort, except head and neck localized tumors. We have excluded cases not treated with curative treatment intent or with metastasis at diagnosis ($N = 17$). This results in180 cases, all treated at a regional tumor center (Oslo, Bergen Trondheim, and Tromsø) in Norway. Of these 180, review of pathological slides ($N = 58$) was carried out under construction of the original cohort, in the case of any missing or imprecise data (e.g., missing size, "grade 1–2" or "low grade") by sarcoma pathologist B. Bjerkehagen alone or at a meeting of the Norwegian mesenchymal tumor board. Radiological review was performed for all cases with available imaging ($N = 125$) by senior sarcoma radiologist I. Taksdal. Soft tissue components were measured to the nearest millimeter, perpendicular to the stipulated outer cortex in the plane that best allowed the greatest measurement. In addition, every variable has been quality controlled by review of clinical files giving complete data at a disease subtype level. The quality control charter of the CRN allows retrieval of clinical files, pathology slides, and radiological images for the purpose of data quality improvement. Eight patients had Ollier or Maffucci syndrome, each with only a single documented case of CS.

2.3 | Description of management

The treatment of CCCS is surgical since it is known to be radio- and chemo-resistant.[21] Surgery entails resection with wide or negative (R0) margins as a mainstay. During the study period, intralesional curettage of low-grade lesions has become increasingly popular, with gradual acceptance of this only for cases of intramedullary grade 1 disease in the extremity. In the early part of the study period, a preoperative open biopsy was performed in all cases. Recognition of the interobserver variation in the assessment of chondroid tissue[22,23] along with clarification of treatment guidelines[9,21] based on intra/extra-osseous extension and anatomical location has led to a practice where biopsies have been used less frequently, and primarily to confirm a CS diagnosis before surgery.

2.4 | Follow-up routine

Patients have been followed according to international guidelines[9,24] with clinical and radiological assessment of tumor site and lungs. For grade 1 and 2 tumors the routine for the period has been appointments every 6 months for 2 years and then annually until 10 years. For grade 3 and dedifferentiated tumors the routine has been every 3 months for 3 years, every 4 months until 5 years, and then every 6 months until 10 years. Upon the event of a LR, the follow-up has started a new according to the grade of the LR, but with a larger degree of individualization. The median follow-up in this cohort is 8.04 years (range, 0.25–10 years).

2.5 | Variables, outcome measures, data sources, and bias

The terms "primary" and "secondary" were not used as they have no practical clinical consequence in the setting of CCCS. Most patients can not precisely be denoted as one or the other since they rarely have previous imaging to exclude/confirm a pre-existing enchondroma at the same site.

"Upgrading" has been interpreted as an increase in malignancy grade from 1 to 2, 1 to 3, or 2 to 3 of a central conventional CS. This term is used distinctly from dedifferentiation as these are viewed to be differing events and open to different interpretation and bias.

Extremity location is defined by the glenohumeral and hip joints, meaning that the pelvis and scapula are denoted as part of the axial skeletal location group.

Grading has been practiced in accordance with WHO criteria in a four-grade system on the surgical specimen. CCCS is graded 1–3, while dedifferentiated CS as grade 4.

The term atypical cartilaginous tumor (ACT) as a synonym for grade 1 CS was introduced by the WHO in 2013,[25] and in 2020 revised[26] to be appropriate for only extremity locations. The term ACT was not used during the inclusion period (1990–2013) and has therefore not been introduced into the cohort definitions. Where ACT's are discussed in the manuscript they are defined as extremity located grade 1 central CS.

"Achieved local control" is defined as an obtained R0/R1 margin of a treated LR, without documentation of a further LR event.

"Oslo high risk" is defined as axial skeletal location combined with a soft tissue component more than or equal to 1 cm by standardized measurement and "Oslo low-risk" as all extremity cases together with axial lesions that are intramedullary or have a soft tissue component less than 1 cm.[27] All ACT's are therefore part of "Oslo low risk."

About 55/180 (30%) cases are missing radiology files for review since hospitals in Norway are increasingly deleting radiology films/files after 10 years of observation, with the purpose of clearing storage space. Fifteen cases are proven intramedullary and these are defined in Oslo risk group without radiology review. The 40 cases (22%) with a soft tissue component and no possibility of radiological measurement are excluded from analysis for Oslo risk. This means there is a risk of selection bias in analysis of Oslo risk groups. The radiology is, however, missing due to "time passed" and not a tumor based criteria which should limit this bias. There are 18 first LR among 140 cases with Oslo risk definitions (13%) as opposed to 32 in the whole cohort of 180 (18%).

Selection bias has otherwise been addressed by the use of multiple data sources from both a national and multicentre regional data source.

Outcome measures include rates of LR, Met, and overall survival (OS). LR is defined as a documented new chondroid tumor within the surgical cavity after obtained R0/R1 margin. Cases with residual tumor as defined by an R2 resection are only observed for LR after a further obtained R0/R1 re-resection. Metastasis is likewise a documented new chondroid lesion in regional or distant site.

2.6 | Statistical analysis

The cohort was presented by descriptive statistics using mean/median and standard deviation/interquartile range for continuous variables and frequencies and relative frequencies for categorical variables. The Kaplan–Meier method was used to estimate rate of LR, Met, and OS at 5 and 10 years of follow-up with 95% confidence intervals (CIs).

Start point for observation was the date of definitive surgery, primary surgery if R1 or R0 margin or re-resection in case of R2 margin at primary surgery. All cases were followed to the date of the event of interest, death, or end of clinical follow-up, whichever came first. Patients are censored at death in analysis for LR and Met. Death is registered at the CRN and linked to the national death registry at 30th October 2016. Death is coded at the CRN as "dead from cancer" and "death from non-cancerous cause" along with ICD-10 codes.

Multivariable Cox proportional hazard models were estimated to analyze the effect of LR on Met and OS. We adjusted for sex and age at diagnosis, and results are presented as hazard ratios (HRs) with 95% CIs. LR was analyzed as a time-dependent covariate to account for immortal time bias. We performed stratification for subgroups understood to depict prognosis (extremity/axial location, malignancy grade, soft tissue component, type of surgery, and "Oslo risk group"). Likelihood ratio test was performed to test significance of the interaction between local recurrence and the chosen subgroup. The assumption of proportional hazards was tested by Shoenfield residuals for all models.

Stata 14® software has been used for statistical analysis. Significance was set at $p < .05$ and was tested using two-tailed tests.

2.7 | Demographics

The cohort demographics are summarized in Table 1.

3 | RESULTS

The demographics, treatment, and follow-up details of those experiencing LR are summarized in Table 2.

Thirty-two patients are registered with a first LR during observation, six a second LR, and a further two developed a third LR. This totals 40 LR events. Only two cases of LR presented as dedifferentiated CS and both of these had R0 resections for their primary surgery. Of a total of 40 LR, seven cases have missing data (grade of LR) since they did not undergo further surgery. Of the rest, the LR grade is the same as that at primary diagnosis for all except one case. This single pelvic case had grade 3 histology of the LR while originally grade 2.

For the total cohort ($N = 180$), rate of first LR was 19% (CI:14–26) at 5 years with no further LR events towards 10 years. For those undergoing curettage the 5-year risk of LR was 25% (CI:14–43), while for resection/amputation combined 17% (CI:12–25) at 5 years. The risk of metastasis for the total cohort was 14% (CI: 10–21) at 10 years. The 10-year risk of metastasis for those not experiencing an LR event was 11% (CI: 7–18). For those with a first LR event the 10-year risk of metastasis was 42% (CI: 21–71).

Sixteen of those experiencing a first LR also developed metastases, 10 of which occurred together with the LR. The mean time to

TABLE 1 Demographic data of the cohort

Variable	Specification	Number of total *N* = 180 (%) or as stated
Sex	Male Female	89 (49%) 91 (51%)
Age at diagnosis	Mean Median Range	55 y.o.a. 55 y.o.a. 15–96 y.o.a.
Pre-existing syndrome	None Ollier disease Maffucci syndrome	172 7 1
Anatomical location	Axial (inc. scapula and pelvis) Extremity	81 (45%)–29 pelvis, 22 rib, 10 scapula, 10 spine, 6 sternum, 4 sacrum 99 (55%)–33 femur, 27 humerus, 12 tibia, 12 phalynx, 10 fibula, 4 metacarpal, and 1 clavicle
Pathological fracture	Present Not	11 (6%) 169 (94%)
Preoperative biopsy	None Fine needle aspiration cytology Core needle biopsy Open biopsy	59 (33%) 10 (5%) 70 (39%) 41 (23%)
Tumor size	Mean Range	8.37 cm 2–35 cm
Malignancy grade	grade 1 grade 2 grade 3	63 (35%) 73 (41%) 44 (24%)
Presence of soft tissue component	Yes No	106 (59%) 74 (41%)
MSTS stage	Ia Ib IIa IIb	69 (38%) 67 (38%) 4 (2%) 40 (22%)
Oslo risk group (*N* = 140)	Low risk High risk	103/140 (74%) 37/140 (26%)
Treatment Primary Surgery details	Curettage Resection (marginal and wide) Amputation	39 (22%) 126 (70%) 15 (8%)
Additional treatment	Re-resection(after R2) Radiotherapy Chemotherapy	15 (8%) 7 (4%) 5 (3%)
Margin as assessed by residual tumor system UICC after primary surgery- successful curettage is denoted as R1	RO R1 R2	112 (62%) 53 (29%) 15 (9%)

Abbreviations: MSTS stage, musculoskeletal tumor society stage; UICC, residual tumor status (R0/1/2); y.o.a, years of age.

first LR was 1.4 years (range, 0.2–4.4), while the mean time to metastasis after this LR was 1.7 years (range, 0.1–3.3).

There was a significant increased risk of metastasis for patients experiencing a first LR event (HR = 4.1 [CI:1.5–10.7]) as shown in Figure 1.

A total of 27 of 32 patients with a first LR received treatment with curative intent. Nine of these had no evidence of disease at end follow-up, while one was had persistent disease and 22 died. Three of these deaths have been coded as from "non-cancerous cause" at the CRN. Fourteen of 32 (44%) achieved local control.

TABLE 2 Demographics, treatment, and follow-up details of those experiencing LR

Patient	Age	Tumor site	grade	Soft tissue comp.	Oslo risk group	Surgical treatment	Margins (UICC)	Time to LR (months)	grade of first LR	grade of further LR	Local control achieved	Time to metastasis (months)	Outcome at end follow -up
1	52	Femur	1	No	Low	Curettage	R1	15	1		Yes		NED
2	34	Humerus	1	No	Low	Curettage	R1	5	1		Yes		NED
3	92	Meta-carpus	1	Yes	Low	Curettage	R1	15	1		Yes		Dead from cancer
4	47	Pelvis	3	Yes	NA	Resection	R0	20	NA		No	20	Dead from cancer
5	52	Pelvis	3	Yes	High	Resection	R0	14	NA		No	14	Dead from cancer
6	48	Pelvis	2	Yes	NA	Curettage	R1	6	3		Yes	13	Dead from cancer
7	33	Clavicle	2	Yes	NA	Resection	R1	16	2	2nd grade 2, 3rd grade NA	No	16	Dead from cancer
8	69	Spine	2	Yes	Low	Resection	R1	17	2		Yes		NED
9	67	Femur	3	Yes	Low	Resection	R1	18	3		Yes		Dead other
10	41	Humerus	3	Yes	NA	Resection	R1	6	3		Yes	6	Dead from cancer
11	32	Humerus	2	Yes	NA	Resection	R1	16	2		Yes		NED
12	73	Rib	3	Yes	NA	Resection	R1	9	a		No	9	Dead other
13	35	Pelvis	3	Yes	High	Resection	R0	8	3	2nd grade 3	Yes	39	Dead from cancer
14	91	Tibia	2	Yes	Low	Curettage	R1	20	2		Yes		Dead other
15	35	Rib	3	Yes	High	Resection	R0	10	3	2nd grade 3	Yes		Dead from cancer
16	25	Femur	3	Yes	NA	Resection	R0	17	3		Yes	3	Dead from cancer
17	81	Phalynx	1	Yes	Low	Resection	R1	54	NA		No		AWD
18	74	Pelvis	2	Yes	NA	Resection	R1	9	NA		No		Dead from cancer
19	61	Sternum	1	Yes	Low	Resection	R0	21	Dediff. grade 4		No	21	Dead from cancer
20	50	Scapula	3	Yes	High	Amputation	R0	20	Dediff. grade 4		No	20	Dead from cancer
21	52	Humerus	2	Yes	NA	Curettage	R1	32	2		Yes	33	Dead from cancer
22	72	Sternum	2	Yes	NA	Resection	R1	14	2		No	14	Dead from cancer
23	43	Humerus	1	No	Low	Curettage	R1	4	1		Yes		NED
24	48	Spine	2	Yes	NA	Resection	R1	46	2	2nd grade 2, 3rd grade 2	No		Dead from cancer

(Continues)

TABLE 2 (Continued)

Patient	Age	Tumor site	grade	Soft tissue comp.	Oslo risk group	Surgical treatment	Margins (UICC)	Time to LR (months)	grade of first LR	grade of further LR	Local control achieved	Time to metastasis (months)	Outcome at end follow -up
25	52	Rib	2	Yes	High	Resection	R0	18	2	2nd grade 2	No	18	Dead from cancer
26	38	Spine	1	Yes	NA	Resection	R1	18	1		Yes		NED
27	54	Rib	3	Yes	High	Resection	R0	8	3		Yes	48	Dead from cancer
28	67	Spine	3	Yes	NA	Curettage	R1	5	3		No		Dead from cancer
29	57	Spine	2	Yes	High	Resection	R1	17	NA		No		Dead from cancer
30	77	Spine	3	Yes	Low	Curettage	R1	5	3		Yes		NED
31	47	Rib	3	Yes	High	Resection	R0	36	3		Yes	70	NED
32	51	Pelvis	3	Yes	NA	Amputation	R0	11	3	2nd grade NA	No	19	Dead from cancer

Abbreviations: AWD, alive with disease; LR, local recurrence; Dead other, death from noncancerous cause; NA, not available since surgery not performed; NED, no evidence of disease; Soft tissue comp., soft tissue component present (yes/no); UICC, residual tumor status (R0/1/2).

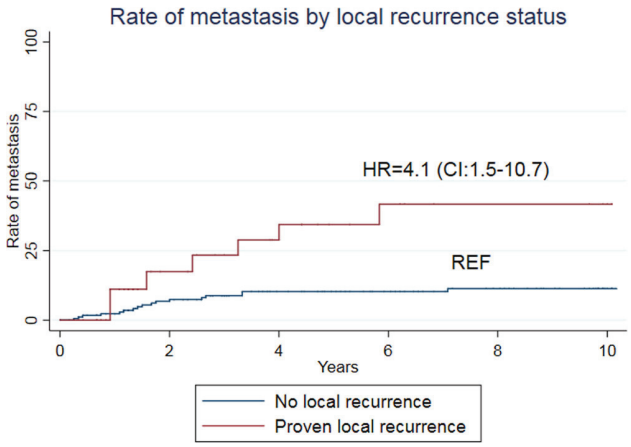

FIGURE 1 Kaplan–Meier curves for the rate of metastasis in the event of a local recurrence with hazard ratios and 95% confidence intervals [Color figure can be viewed at wileyonlinelibrary.com]

For the total cohort the rate of OS at 10 years was 72% (CI: 64–78). For those experiencing a LR, the 10 year OS was 24% (CI: 10–41) while for those without 81% (CI: 74–87). LR was associated with a significantly poorer survival rate (HR = 9.3 [5.0–17.5]) as shown in Figure 2. For those experiencing a LR, but not metastasis, the 10 year OS was 48% (CI: 18–73) while for those with both LR and metastasis, survival at 10 years was 0%.

Table 3 shows subgroup analyses adjusted for sex and age. There was a significant association between LR and increased risk of metastasis for those undergoing resection/amputation (HR = 3.4 [1.1–10.7]), those cases with soft tissue components (HR = 3.2 [CI: 1.2–8.5]), axial location (HR = 3.4 [CI: 1.1–9.4]), or malignancy grade 2 (HR = 8.8 [CI: 1.6–47.5]).

Thirty-nine patients underwent curettage as their primary surgery. There were two metastatic events in this subgroup with nine

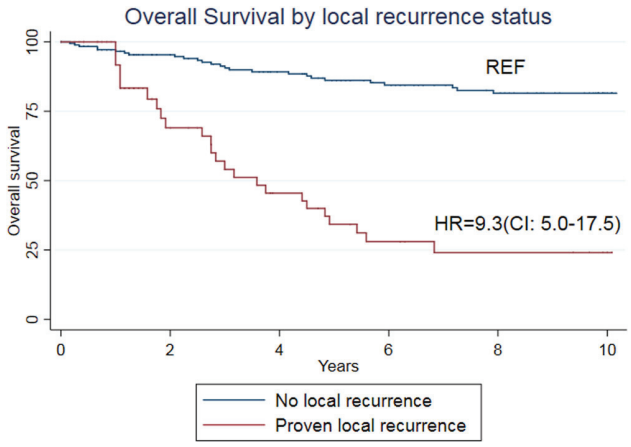

FIGURE 2 Kaplan–Meier curves for the rate of overall survival in the event of a local recurrence with hazard ratios and 95% confidence intervals [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Cox proportional hazard analysis stratified for subgroups adjusted for sex and age

Subgroup - adjusted for age and sex	Influence of local recurrence on rate of metastasisHR (95% CI)	Likelihood ratio test	Influence of local recurrence on Overall survivalHR (95% CI)	Likelihood ratio test
Total $N = 180$	4.1 (1.5–10.7)	NA	9.3 (5.0–17.5)	NA
Appropriate curettage, $N = 37$[a]	NA	NA	2.5 (0.6–10.2)	$p = .020$
Resection/amputation, $N = 141$	3.4 (1.1–10.7)		13.4 (6.0–29.7)	
Soft tissue comp.: No, $N = 74$	NA	NA	NA	NA
Soft tissue comp.: Yes, $N = 106$	3.2 (1.2–8.5)		8.9 (4.5–17.5)	
Extremity location, $N = 99$	3.3 (0.3–40.1)	$p = .814$	7.4 (2.8–19.9)	$p = .575$
Axial location, $N = 81$	3.4 (1.1–9.4)		9.5 (3.9–22.9)	
Oslo low risk, $N = 103$	NA	NA	2.6 (0.7–10.3)	$p = .068$
Oslo high risk, $N = 37$	3.0 (0.7–12.3)		8.9 (1.8–42.7)	
Malignancy grade 1, $N = 63$	NA	$p = .161$	8.0 (1.1–59.9)	$p = .827$
Malignancy grade 2, $N = 73$	8.8 (1.6–47.5)		12.4 (4.4–34.7)	
Malignancy grade 3, $N = 44$	1.8 (0.5–6.2)		8.1 (2.5–25.9)	

Note: NA, not applicable since no or too few events, for definition of Oslo low/high risk see methods section. Likelihood ratio testing for interaction between local recurrence and chosen variable.
Abbreviations: CI, confidence interval; HR, hazard ratio.
[a]Innappropriate curettage, $N = 2$ are removed from analysis.

local recurrences. Both were, however, inappropriately treated by this method based on modern knowledge. The first, an extremity tumor with soft tissue component and grade 2 histology, while the second a pelvic tumor with soft tissue component and grade 2 histology. With exclusion of these two cases ($N = 37$), there was no evidence in this cohort that a LR increased the risk of metastasis. The same is true for those lacking soft tissue component, malignancy grade 1, an extremity location or "Oslo low risk" group allocation that all had no, or too few events to allow meaningful statistical analysis.

A local recurrence was associated with a significantly increased risk of death for those undergoing primary resection/amputation (HR = 13.4 [CI: 6.0–29.7]), those cases with soft tissue components (HR = 8.9 [CI: 4.5–17.5]), both extremity (HR = 7.4 [CI: 2.8–19.9]) and axial location (HR = 9.5 [CI: 3.9–22.9]), as well as malignancy grade 1 (HR = 8.0 [CI: 1.1–59.9]), grade 2 (HR = 12.4 [CI: 4.4–34.7]), grade 3 (HR = 8.1 [CI: 2.5–25.9]), and "Oslo high risk" group (HR = 8.9 (CI: 1.8–42.7]). For curettage/resection ($p = .02$) and "Oslo low risk" groups ($p = .068$) there was evidence of interaction effects with LR for OS. For the other subgroups, no clear evidence of interactions was found.

We recorded a total of 40 LR in 180 patients. About 20 (50%) were discovered by patients themselves while 20 (50%) were asymptomatic and discovered as part of routine surveillance, nine due to a palpable mass, nine due to pain, one from a neurological compression, and one as an incidental finding at trauma.

4 | DISCUSSION

The true pattern, influence, and impact of LR in the setting of CCCS have not previously been reported. Accounting for immortal time bias we analyzed a complete modern national cohort and found that LR was associated with an increased risk of both metastasis and death overall.

4.1 | Limitations

We have earlier reported disease-specific survival (DSS) based on the CRN's "death from cancer/death from non-cancerous cause" variable.[13,27] We found that this is not as disease specific as we would like in that DSS continued to fall from 5 to 10 years of observation despite no further LR or Met events. We also reported a substantial number of second, third, and even fourth cancer diagnosis in the cohort. We chose therefore in this analysis to use OS since this appears more honestly to be what we are measuring. It has been reported that the accuracy of reported cause of death is alarmingly poor,[28,29] though somewhat improved for those with a cancer diagnosis.[30] It would be preferential to have a more accurate disease-specific outcome variable so that we could quantify precisely both the local and systemic effect of an LR event on mortality. This is likely possible only in a true prospective observational trial with predefined variables, sorely missing in CS research. In addition, we could have

presented analysis adjusted for a morbidity index as some others have done previously.[31]

The exclusion of 40 cases from "Oslo risk" analysis due to missing radiology and soft tissue component size measurement is a potential source of error as discussed in the methods section. We have in separate analysis included all extremity lesions in the low-risk group as per definition of "Oslo risk" and all axial tumors with soft tissue components in the high-risk group. This gives 121 cases (67% of cohort) for "Oslo low risk" and 59 (33% of cohort) for "Oslo high risk." For this new variable there is still a significant association between LR and risk of metastasis for "Oslo high risk" (HR = 3.2 [1.1–9.5]), but not for "Oslo low risk" (HR = 3.9 [0.4–37.6]). For overall survival, however, both groups have a significant association between LR and worse survival; HR = 13.2 (4.8–35.9) for "Oslo high risk" and HR = 6.5 (2.5–17.1) for "Oslo low risk". These data must of course be interpreted with caution. There is, however, a clear need for validation of "Oslo risk" in larger cohorts.

Assessing at a subtype level restricts numbers compared to mixed cohorts. When we assess relatively infrequent events in subgroups we must interpret our findings with caution and urge other groups to assess by similar means so as to confirm external validity. Our findings are, however, reassuringly in line with known prognostic indicators of low and high risk of behavior.

We report a median follow-up of 8.06 (0.25–10) years. 13 patients contribute observations time less than 2 years. Only two patients contribute less than 6 months observation time, one through emigration and one in an 88-year-old with a large proximal humerus grade 3 lesion successfully resected, but whom died due to an acute presentation of colon cancer shortly after. The Kaplan–Meier method was designed for the explicit purpose of people contributing differing observation times and this represents the real-life management of CS patients.[32,33]

The cohort also includes 12 cases of phalangeal CCCS (10 hand and 2 foot). This is an entity with a described indolent behavior by some[34] and as such one could debate whether they should be excluded, but reports of their behavior are somewhat divergent.[35] There are five deaths among these phalangeal CCCS with mean age at diagnosis of 80 (range, 62–96) years and as such they contribute events to OS. There is, however, only a single case of LR and no metastasis among them and this LR was managed without event. As such these cases contribute very little towards analysis of LR or Met other than observation time in the low-risk subgroups. On the other hand, the CRN CCCS cohort contains a high proportion of axial tumors. These are likely prone to higher levels of both LR and Met and the impact of LR on morbidity is likely larger than in an extremity. Our data is unique in being a complete national cohort and this case mix represents the reality of this.

4.2 | Study questions

Only one patient showed evidence of true upgrading and two LR CCCS patients presented with dedifferentiation. A single case of upgrading in a modern time period is plausibly explained by sampling error in a heterogeneous tumor rather than any change in the tumor itself.[17] Upgrading has been reported from a historic cohort dating back over 80 years by two groups at 13% and 19% previously.[6,19] They report upgrading and dedifferentiation together while these are different scenarios and should be reported separately. Compared with total number of cases the risk of upgrading in our data is 0.6% (1/180) and dedifferentiation 1.1% (2/180), while if compared with numbers of LR the rate of upgrading is 2.5% (1/40) and dedifferentiation 5% (2/40). If compared with only those where histology is available then the rate of upgrading is 3% (1/33) and dedifferentiation 6% (2/33). All methods produce low numbers when considering the rate of interobserver variation in CS assessment.[22,23,36] It is also possible that those not treated for their LR (7 of 40 cases) represent an undocumented upgraded cohort with more aggressive disease since we do not have operative specimen for grading for these patients.

Andreou et al.[11] also present two cases of dedifferentiation in 38 LR from 115 CCCS, but do not comment on upgrading. Laitinen et al.[37] report a 22% rate of increased grade from their LR CS cohort of unspecified subtype (126 cases) of extremity and pelvic locations. This includes three cases of dedifferentiation. They also present 78 LR from 343 patients, reporting upgrading from grade 1–2 or 2–3 in 10 cases (19%) of 54 with available histology.[17] This is a mixed cohort 301 central CS and 42 peripheral CS, though they do not present upgrading at subtype level. One aim of this paper is, however, to study if small areas of higher grading on histology review better depict behavior and find that when re-examining original CS resection specimens, 30% contain small areas of higher grade histology.[17] As such it is possible that their increased sampling or attention can lead to an increased level of recognition of higher grade areas in a heterogeneous tumor.

Both cases of dedifferentiation occur as first LR in axial tumors (sternal grade 1 after 21 months and scapular grade 3 after 24 months), whom both appear to be successfully treated with R0 resections. This is possibly an expression of the inaccuracy of assessment of surgical margins, but is again a different pattern than expected as one commonly believes dedifferentiation to occur after multiple LR and suboptimal surgery.

Those experiencing a LR of CCCS have four times higher risk of metastasis as compared with those that do not. The relative risk of metastasis was six times greater for patients who experienced a LR in a historic CCCS cohort excluding spine/thoracic cases, but they do not account for immortal time bias.[19] From mixed CS cohorts, we can find descriptive statistics of LR patients developing metastatic disease, but the findings are difficult to compare.[3,38]

CCCS patients are also subject to a significantly worsened rate of OS in the event of a LR. One institution looking only at grade 1 disease of the long bones also find a negative influence of LR on OS. They describe an association with metastasis but do not involve this in analysis.[6] Andreou et al.[11] present a broader CCCS cohort (115 cases), but do not account for immortal time bias in their methodology. They found an association between LR and decreased OS, in total (83 vs. 42% 10 year OS) as well as for high-grade disease and extremity location, but not for axial location or low-grade disease.

They have a different distinction of anatomical location from our study; including the pelvic girdle with axial location, but the scapula in the extremity category.

Our OS at 10 years of 24% for LR CCCS patients is low compared with some published data with 60% OS at 10 years.[2,4] Though Lin et al.[4] study 52 LR conventional CS (peripheral and central subtypes) they do not include spinal and thoracic cases where the local effect of LR on mortality is likely largest. The true difference in our results cannot, however, be elucidated from this study. The most appropriate comparison is with Andreou et al.[11] who reported 42% 10-year overall survival in the case of LR central conventional CS. They report extremity, scapular, and pelvic lesions, but only five axial (spinal and thoracic) lesions as compared with our 42 (22 ribs, 6 sternal, 10 spine, and 6 sacral). Fiorenza et al.[1] also report 40 LR in 153 localized conventional CS. They report 32% cumulative 10-year survival in the case of LR overall, while 64% cumulative 5-year survival in the case of LR without metastasis and 5% if both. They have a similar definition of axial/extremity location, but again with 35% of cases being axial as opposed to our 45%.

No patient in this cohort survived both LR and metastasis combined while for those experiencing a LR without metastasis, 48% survived 10 years of follow-up. Laitinen et al.[37] report similarly 45.5% 5-year survival in the same circumstances from a pelvic and extremity primary CS cohort.

In our data, 16 cases have LR without metastasis. Seven of these patients die. Although "death from local disease" is not a variable in the cohort we can determine this indirectly. Two patients are denoted as "death from non-cancerous cause" and both of these had local tumor control of their CS. A further case of metacarpal CS has also local control, but developed a morphology confirmed lung cancer. Four cases die without achieving local tumor control (one pelvic and three spinal cases). They fail to undergo treatment of a verified LR (two for first LR, one for second LR, and one for third LR) and have no other malignant diagnosis. Eight cases of LR without metastasis in the extremity all achieve local control, while this is only the case for 4 of 8 (50%) in the axial skeleton. The true burden of uncontrolled local tumor growth needs to be studied prospectively with predefined variables, but our data suggest that durable disease control is achievable for both extremity and axial tumors, which supports aggressive management.

LR was associated with increased risk of metastasis and death for the cohort as a whole but not for all subgroups. Groups having less aggressive disease in the primary treatment setting, such as appropriately treated curettage patients ($N = 37$), those without a soft tissue component ($N = 74$) or "Oslo low risk ($N = 103$)" group status were not at increased risk of metastasis or death in this cohort despite an LR. For extremity lesions ($N = 99$), an LR was associated with the worsened OS but not an increased rate of metastasis in line with the most comparable study.[6] The mechanism for this is unclear since a local recurrence in an extremity, as opposed to an axial location, will nearly always be amendable to further surgical treatment. There is considerable overlap amongst these variables, but the lack of influence of LR on survival for "Oslo low risk" is perhaps the most important negative finding. It comprises 74% of the cohort with available data (103/140) and includes all traditional low-risk subgroups such as ACT's, appropriate curettage cases, extremity lesion, intramedullary lesions, and means that an LR for the majority of CCCS patients has a limited consequence.

LR in the case of a primary tumor with axial location ($N = 81$), with soft tissue component ($N = 107$) or grade 2 histology ($N = 74$) were at increased risk of metastasis and poorer survival. This finding supports the notion that those with more aggressive tumors at diagnosis are also those at increased risk of a poor outcome in the event of LR.

The "Oslo high risk" cohort of 37 patients includes eight first LR events, six of which with successive metastasis; HR = 3.0 (0.7–12.3) in comparison with the low-risk group of 103 patients with 10 first LR events and one metastasis. The high-risk group had a significant association with poorer survival; HR = 8.9 (1.8–42.7) as opposed to the low risk subgroup; HR = 2.6 (0.7–10.3). Although the likelihood ratio-test for their comparison is nonsignificant ($p = .068$), we believe that the sum of evidence indicates that in the setting of LR, Oslo risk stratification from the primary treatment setting may give a useful dichotomous division of risk. If validated in larger numbers this gives us a readily available clinical tool to guide LR therapy free from the constraints of interobserver variability in both pathological grading and clinical assessment.[36] The "Oslo low risk" group represents 74% of the cohort and needs aggressive local therapy since they have a low chance of developing systemic disease and local control is achieved in 8 of 10 cases (80%). For the smaller "Oslo high risk" group (26% of cohort), however, it seems futile to pursue mutilating surgical options in the face of synchronous LR and Met, while for LR presenting alone, clinicians must attempt to balance the "cost" of therapy with the established risk of metastasis since local control is also achieved in four of eight cases (50%) in this subgroup.

The term ACT has not been used in the cohort since this was not a term in use during the inclusion period. The WHO classification of tumors (5th edition) states that ACT be used to denote grade 1 histology lesions in the extremity. By this definition, our cohort has 47 cases of ACT (26% of cohort). There are six LR, but no evidence for increased risk of metastasis (no events) or death (HR = 4.2 [0.3–59.6]) in the event of LR. Repeat analysis when excluding ACT, reveals an unchanged increased risk of metastasis (HR = 4.3 [1.6–11.3]) and death (HR = 11.2 [5.6–22.3]) for the cohort in total. Likewise, repeat analysis of "Oslo risk" without ACT's remains unchanged. The comparative literature contains these same lesions defined by location and grade without using ACT terminology, although with current knowledge of their indolent behavior it would seem appropriate to study these separately in future cohorts.

Since approximately 50% of LR are asymptomatic and discovered at routine surveillance it would seem reasonable that this surveillance be prioritized. This pattern is irrespective of grade. Conversely, 50% of LR were discovered by patients themselves due to pain or a lump and it is equally important to educate patients and be accessible to them when needed. Particularly since both our, and other's data[4] support the real possibility of attaining durable disease control.

5 | CONCLUSIONS

Upgrading and dedifferentiation in LR CCCS were seldom events. Routine clinical follow-up revealed 50% of LR which were asymptomatic. A LR was associated with a significantly increased risk of metastasis and death overall, but this did not apply low- to risk subgroups such as "Oslo low risk" cases which encompasses 74% of the cohort. Those factors depicting risk in the primary treatment setting also appeared to depict risk and outcome in the case of LR.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are in part available from the corresponding author. Restrictions apply to the availability of these data, which were used under license for the current study from the National Cancer Registry, and so are not publicly available. Data are however available from the corresponding author upon reasonable request and with application to the Cancer Registry of Norway.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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