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From symptoms to diagnosis of sarcoma – revealing the diagnostic pathway

PhD dissertation

Heidi Buvarp Dyrop

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Preface

The work presented in this thesis was performed during my employment at the Department of Experimental Clinical Oncology, Aarhus University Hospital, Denmark.
The thesis is based on the following articles:

I. *Dyrop HB, Safwat A, Vedsted P, Maretty-Nielsen K, Hansen BH, Jørgensen PH, Baad-Hansen T, Bünger C, Keller J.*
Cancer Patient Pathways shortens waiting times and accelerates the diagnostic process of suspected sarcoma patients in Denmark
Health Policy 2013 Nov;113(1-2):110-7.

II. *Dyrop HB, Vedsted P, Safwat A, Maretty-Nielsen K, Hansen BH, Jørgensen PH, Baad-Hansen T, Keller J.*
Alarm symptoms of soft tissue and bone sarcoma among patients referred to a specialist center
Acta Orthopaedica 2014; Dec;85(6):657-62

III. *Dyrop HB, Safwat A, Vedsted P, Maretty-Kongstad K, Hansen BH, Jørgensen PH, Baad-Hansen T, Keller J.*
Characteristics of 64 sarcoma patients referred to a sarcoma center after unplanned excision
Journal of Surgical Oncology 2016; Feb;113(2):235-239

IV. *Dyrop HB, Vedsted P, Rædkjær M, Safwat A, Keller J.*
Routes to diagnosis for suspected sarcoma – the impact of symptoms and clinical findings on the diagnostic process
Submitted

V. *Dyrop HB, Vedsted P, Rædkjær M, Safwat A, Keller J.*
Imaging investigations before referral to a sarcoma center delays the final diagnosis
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This thesis was carried out during my employment as a research year student and later as a Ph.d.-student at the Department of Experimental Clinical Oncology, Aarhus University Hospital from 2011 to 2016.

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Heidi Buvarp Dyrop, November 2016

Contents

Abbreviations

2WW	Two-Week Wait
ASC	Aarhus Sarcoma Centre
AUH	Aarhus University Hospital
CT	Computed Tomography
CPP	Cancer Patient Pathway
GP	General Practitioner
IQI	Interquartile Interval
MRI	Magnetic Resonance Imaging
NICE	National Institute for Health and Care Excellence
NPV	Negative Predictive Value
PET-CT	Positron Emission Tomography-Computed Tomography
PPV	Positive Predictive Value

Introduction

This thesis focuses on the diagnostic journey of patients suspected of having a sarcoma in Denmark. Sarcoma patients are often subject to a long and complicated diagnostic process with significant delays before they are diagnosed at a sarcoma centre. This is in great part due to the rarity and subtle symptom development of the disease. Patients with sarcomas are seldom encountered by physicians, and the disease does not attract great interest for research in environments outside specialised sarcoma centres. The story of these patients' journey through the health care system outside sarcoma centres is thus to a large extent untold.

The problem of delays before diagnosis has also been recognised for many other cancer forms, and in Denmark the issue gained special interest after studies emerged showing lower cancer survival in Denmark and England compared to similar European countries [1,2]. It was concluded that cancer patients in Denmark had a higher malignancy grade at diagnosis compared to other countries [2,3], and this was presumed to be caused by waiting time before diagnosis. This initiated the work on the four national cancer plans, hereunder the development of standardised Cancer Patient Pathways [4,5].

It is the hope that these fast-track referral pathways will reduce delay before diagnosis and hereby improve cancer survival in Denmark. This initiative is unique in its massive political and financial backing enabling implementation on a national scale, and its success is highly anticipated. However, it is not given that such a broad initiative tailored to fit all cancer forms will succeed in reducing waiting time for sarcoma patients. After CPP implementation, the effect on waiting times has been investigated in other studies, but as the incidence of sarcoma is extremely low, all audits exclude this disease entity and only report on the larger cancer forms such as colorectal, breast, lung, melanoma and urinary tract cancer. Apart from the immediate effect on time intervals, the contents of the CPP for sarcoma should also be evaluated after implementation to ensure that the initiative works as intended with regard to inclusion of patients and organisational functionality.

Several questions arise in the aftermath of the Danish sarcoma CPP implementation. First and foremost: Has it solved the problems of delay for Danish sarcoma patients? Does it catch all the sarcomas and if not, why? Can we further improve the diagnostic process for sarcoma patients? And where do we go from here?

To gain some evidence for answering these questions, the overall aim of this thesis was to describe the immediate effects of the Danish CPP for sarcomas on the diagnostic process for suspected sarcoma patients. Further, the diagnostic journey of patients suspected of having a sarcoma in the new steady state after CPP implementation is described to highlight possible areas for improvement.

Background

Sarcomas

Epidemiology and aetiology

Sarcomas are a rare form of cancer that represent 1% of all new malignancies, amounting to approximately 300 new cases per year in Denmark [6,7]. The tumours arise from mesenchymal tissue and can be separated after tissue of origin into soft tissue sarcomas and bone sarcomas, with soft tissue sarcomas being the most common type. These groups can further be divided into more than 50 histological subtypes with different growth patterns and aggressiveness [8]. A sarcoma can also contain several different subtypes within the same tumour, making the correct diagnosis and treatment of these tumours challenging. Most sarcomas occur randomly without any known aetiology, and only a few subtypes are associated with previous irradiation or certain genetic mutations (Li-Fraumeni syndrome, familial retinoblastoma and familial neurofibromatosis) [8]. Sarcomas can arise in any age group, but most commonly in the middle-aged adult population. However, certain subtypes such as rhabdomyosarcoma, osteosarcoma and Ewing sarcoma are more frequent among children and sarcomas constitute 7–10% of all childhood cancers [6]. Metastasis is mainly haematogenous and the lungs are the predominant location for distant metastases.

Presenting symptoms

Bone sarcomas usually start out as an ache in the affected area, which gradually worsens and becomes more persistent. Especially nightly pain is common among bone sarcomas and should cause concern. Many patients associate the onset of pain with a trauma or excessive strenuous exercise, which often confuses physicians and delays the diagnosis. A swelling may develop over time, especially if the affected bone is superficial and located in the extremities. A palpable bone growth can also be the only symptom. For some patients, a pathological fracture through the tumour area due to weakening of the bone may be the first disease presentation [9-14].

Soft tissue sarcomas usually present as an indolent lump and pain in soft tissue sarcomas is more likely to arise from pressure on adjacent structures than from the tumour itself. Aggressive sarcomas can grow rapidly, whereas benign soft tissue tumours often have a slow growth pattern extending over years. Sarcomas are usually larger in size than benign tumours, and size over five centimetres is used as a cut-off point for malignancy suspicion [15]. Finally, tumour depth is important because malignant soft tissue sarcomas most often occur below the deep muscle fascia [11,12,16-20]. This deep location unfortunately also makes the tumour difficult to discover, and deeply situated tumours can attain a large volume before being noticed. General symptoms such as

loss of appetite, fever, anaemia, weight loss, nausea and malaise are usually only seen in the late stages of the disease and most newly diagnosed sarcoma patients are healthy and feel well.

Diagnostic workup

The initial investigation of a patient suspected of having a sarcoma should be a thorough physical examination where especially tumour size, consistency, mobility and depth relative to the deep muscle fascia are evaluated. The patient's medical history should be taken with special emphasis on tumour growth, presence of pain and any history of previous trauma.

If a sarcoma is still suspected after this, proper imaging of the tumour should be obtained. Magnetic Resonance Imaging (MRI) is considered the gold standard for imaging of musculoskeletal tumours because it achieves a high sensitivity and accuracy in separating benign from malignant tumours [12,21,22]. If access to MRI is limited, ultrasonography can be used to ascertain the necessity of an MRI [23]. A plain x-ray image should always be obtained if a bone tumour is suspected as it is a good indicator of malignancy and forms the basis for subsequent investigations [9]. The MRI should be performed with intravenous contrast injection to portray any heterogeneity or signal enhancement within the tumour or surrounding tissue. Computed tomography (CT) can be of relevance for tumours of the abdomen and retroperitoneal space and also for bone tumours to evaluate cortical involvement. However, MRI is superior to CT in showing the tumour's relation to adjacent structures. A chest CT should be obtained for evaluation of distant metastases and either a bone scintigraphy or a positron emission tomography-CT (PET-CT) can be used to further assess disease dissemination [9,16,17,24,25].

The precise histological diagnosis can only be achieved by a tissue biopsy, either performed as an image-guided needle biopsy or open surgical biopsy. Biopsy of suspected sarcomas is a hazardous procedure and should only be performed by experienced sarcoma experts [26]. A poorly performed biopsy may result in tumour seeding along the biopsy tract, with contamination of initially tumour-free anatomical structures, which may complicate later excision. Further, the tissue sample may be taken in the wrong part of the tumour, resulting in a falsely benign diagnosis or a non-representative sample. The interpretation of the histological specimen may also be erroneous if investigated by pathologists inexperienced with sarcomas [27].

When all imaging and histological material are available, the diagnosis should be discussed at a multidisciplinary team meeting between surgeons, oncologists, radiologists and pathologists specialised in sarcoma management.

Treatment

The treatment for both soft tissue and bone sarcomas is often multimodal, but surgical excision with a wide margin of normal tissue surrounding the tumour is considered the main treatment [9,16,17,24,25]. The tumour should be removed *in toto* without any leakage of tumour cells to surrounding tissue and, if present, the biopsy tract should also be excised. It is preferable that the surgeon performing the biopsy also performs the later surgical removal of the tumour. In the past, the amputation rate for sarcoma patients was high but with more advanced prosthesis technology limb salvage can be achieved in most cases [28,29]. Some paediatric sarcomas (rhabdomyosarcoma, osteosarcoma and Ewing sarcoma) are treated with initial chemotherapy, followed by subsequent final surgery and post-operative chemotherapy. Adult-type sarcomas have a low sensitivity to chemotherapy and radiation, and these treatment modalities are only used in an adjuvant or palliative setting for this patient group. Radiotherapy is often used postoperatively to ensure removal of any viable tumour cells in the excision cavity, especially if the margins are inadequate. If the tumour is unresectable, initial chemotherapy or radiation may be attempted in the aim of downsizing the tumour and hereby enabling surgery or a reduction of symptoms related to tumour size. The role of adjuvant chemotherapy after surgery is debated and is not used as a standard treatment [24].

Prognosis

The overall five-year survival for sarcoma patients is around 65% [7], but this depends on the subtype and dissemination of the disease. Several factors have been shown to affect the prognosis of sarcoma patients. The most important is malignancy grade [30-35], where high-grade tumours have a poorer prognosis than low-grade tumours. Further, tumour size is an important prognosticator and large tumour size has consistently been associated with worse outcomes [15,30,33-39]. Tumour depth also affects prognosis [31,33-35], possibly due to the larger size of deeply situated tumours. The effect of symptom duration is more complex and will be discussed later in the thesis. Finally, free tumour margins after excision [32,34,40,41], anatomical location [30,32,34], age [30,32,34,38,40], presence of comorbidity [42,43] and use of radiotherapy [32] have also been shown to affect prognosis.

Delay before diagnosis

Sarcoma patients often experience great delays before diagnosis due to the rarity and low awareness of the disease and the subtle symptom presentation described earlier [10,44-52]. Delay before diagnosis is a recognised problem for many cancer forms [53-56] and is often the focal point of political debates and complaints from disgruntled patients. For sarcoma patients it is the most frequent cause of patient lawsuits [57].

Effect of delay on outcomes

It is commonly perceived that an earlier cancer diagnosis must result in better outcomes. This association seems logical in the case of sarcomas as size is the most important prognostic factor and longer symptom duration has been associated with tumour growth in cancer patients [53,58,59]. However, the effect of delay on cancer survival is much debated, and there is no clear evidence of a consistent relationship. Reviews have concluded that delays in cancer diagnosis matter, but this varies between cancer forms, and the effect on prognosis is difficult to quantify [60-64]. The problems of establishing an association can be related to the unavoidable lack of trial evidence and confounding caused by the waiting time paradox, which refers to the phenomenon where both short and long waiting times before diagnosis result in decreased survival. This has been reported in studies on several other cancer forms showing a U-shaped association between symptom duration and survival [65-69]. This may confound statistical analyses that use the median or mean symptom duration as a cut-off point to separate patients into two groups for comparison of survival between patients with long and short waiting times. If the waiting time paradox is not taken into consideration, the results will show no difference in survival between the two waiting time groups and give evidence against the benefit of expedited diagnosis. This may also be the case for sarcomas as most studies dichotomize symptom duration in analyses. Some studies find that long symptom duration increases survival [40,70-73], others find poorer survival with longer symptom duration [36,39,74], and some find no difference [30,37,38,47,51,75]. However, when symptom duration is analysed as a continuous variable it has been shown to be an important prognostic factor for sarcoma patients, but the association follows a J-shaped curve [32]. The direction of the association has also been reported to vary depending on the type of sarcoma [76]. This may explain the difficulties in proving scientifically that long waiting times before diagnosis worsens the prognosis for sarcoma patients.

Apart from the effect of delay on survival, other outcomes such as patient distress and surgical outcome should be taken into consideration as well. Delays can affect patients psychologically [45,77], both in the form of anticipatory anxiety and uncertainty before diagnosis, and later contemplations of whether the delay had affected their prognosis. Increasing tumour size

may affect the surgical options for the patient and necessitate more extensive surgery with a potentially greater loss of function [15,45]. Survival time is a relatively long term outcome, and may seem distant to patients at the time of diagnosis, whereas the experience of distress and the cosmetic appearance after surgery are more short-term outcomes affecting the patient on a daily basis in the time before and after diagnosis. These consequences of delay are more easily understandable for patients and policy makers and may explain the great focus on reducing delay regardless of the lack of clear evidence of an association between delay and survival.

Initiatives to reduce delay

The largest and most well-described initiative for reducing delay before cancer diagnosis is the two-week wait (2WW) referrals implemented in the UK in the year 2000. This gave GPs the opportunity to make urgent referrals for patients suspected of cancer, ensuring the patient a specialist consultation within two weeks [78]. This referral rule is accompanied by the National Institute for Health and Care Excellence (NICE) guidelines for referral, which contain recommendations on alarm symptoms qualifying for a 2WW referral, proper diagnostics and treatment [79]. A similar initiative has also been implemented in Spain, although not as extensive as the British 2WW referral [80-82]. Within the sarcoma area, guidelines for referral have been described in other countries, but the contents and scope of these vary greatly. In the Netherlands, national guidelines for diagnostics and treatment of sarcomas have been described, but no time limits for referral are included [83,84]. Spanish fast-track programmes differ between regions, but some of these include alarm symptoms as referral criteria, direct access to specialist consultations and a 30-day target for time from suspicion to treatment [50,80,81]. In Sweden, simple guidelines for referral of sarcomas based on alarm symptoms have been used for many years, and an open-access outpatient clinic is available for referral from GPs, but no limits for time expenditure are defined [85]. Finally, a managed clinical network for sarcomas was established in Scotland in 2004, containing alarm symptom-based referral guidelines but no defined time limits [86].

The idea for the Danish CPPs came from the 2WW pathways implemented in the UK, and the CPPs thus contain some of the same components such as alarm symptom referral criteria and timeframes. The overall aim of ensuring timely diagnosis is also the same; however, the Danish CPPs include a larger part of the diagnostic process than the 2WW pathway.

Danish Cancer Patient Pathways

Concept

Cancer Patient Pathways (CPPs) were implemented in Denmark during the years 2007–2008. The intent of the CPPs was to increase the cancer survival by reducing system delay before diagnosis. Other goals were to increase patient satisfaction and patient health status by providing rapid treatment, decrease patient distress due to unnecessary waiting time and ensure continuity of care [5]. The implementation followed after a political decision made by the Danish Health Authority in August 2007 to treat cancer as an acute illness. The CPPs are cancer specific and CPPs for 32 cancer forms were developed in cooperation between medical experts, health administrators and politicians. They describe the ideal pathway for a standard patient through the Danish health system. A CPP consists of guidelines for referral to specialist care and includes a cancer site-specific description of the alarm symptoms and signs that should raise cancer suspicion. A general practitioner (GP) or any other physician may refer to a CPP when they have a suspicion of cancer based on these alarm symptoms. Further, the CPP describes the appropriate diagnostic procedures and final treatment of the cancer form, and also guidelines for the follow-up and rehabilitation after treatment. A set time frame for each phase of the diagnostic process is defined, and all hospitals are required to comply with these time limits for diagnostics and treatment [5].

The Cancer Patient Pathway for sarcoma

The CPP for sarcomas was implemented on the 1st of January 2009. The defined alarm symptoms and clinical signs were as follows [87]:

- Soft tissue tumour > 5 cm in diameter (relative assessment in children).
- Soft tissue tumour situated on or below the deep muscle fascia.
- Rapidly growing soft tissue tumour
- Palpable bone tumour
- Deep persistent bone pains without other obvious orthopaedic explanation
- Suspected recurrence of previous sarcoma

The CPP for sarcoma is arranged differently than most other Danish CPPs when it comes to referral because GPs may not refer directly to the CPP at a sarcoma centre based on these findings alone. The patient should be referred to a local orthopaedic hospital department for clinical examination and imaging (preferably an MRI and also an x-ray for bone tumours). It is only when the suspicion is justified based on imaging material that the patient may be referred to a sarcoma centre, and the CPP for sarcoma thus starts when the referral is received at the sarcoma centre, not when the GP

discovers the symptoms. When the referral is received at the sarcoma centre, the following time limits apply:

Table 1: Time limits for the diagnostic process of sarcomas as defined in the CPP for sarcoma.

Time limits		2009-edition	2012-edition
From date of referral to first appointment in the tumour centre (A–B)		5 workdays	8 calendar days
From first appointment in the tumour centre to decision of treatment (B–C)	Sarcoma in soft tissue	9 workdays	13 calendar days
	Sarcoma in bone	18 workdays	25 calendar days
From the decision of treatment to start of treatment (C–E)	Operation	10 workdays	14 calendar days
	Radiation therapy	11 workdays	15 calendar days
	Chemotherapy	8 workdays	11 calendar days
From date of referral to start of treatment (A–E)	Operation	24–33 workdays	35–47 calendar days
	Radiation therapy	25–34 workdays	36–48 calendar days
	Chemotherapy	22–31 workdays	32–44 calendar days

NOTE: In the initial CPP published in 2009, time intervals were measured as number of work days (excluding weekends and national holidays). In the updated 2012 edition, time limits are measured in calendar days, not work days.

The effects of the Danish Cancer Patient Pathways have been reported for other cancer forms [88-95], but the consequences of this massive political initiative have not yet been investigated within the sarcoma patient group.

Alarm symptoms as criteria for referral to Cancer Patient Pathways

Contrary to some other cancer forms there is no clinical test that can screen for the possibility of a sarcoma and standard blood tests routinely performed in cancer diagnostics are usually within normal ranges in the early stages of the disease. The initial discovery of the disease is thus based mainly on presenting symptoms. The concept of defining “alarm symptoms” or “red flags” as a diagnostic tool is frequently used to aid GPs and other physicians in detecting patients with cancer, and the symptoms defined in the sarcoma CPP were also used as guidelines for referral before CPP implementation. However, most patients presenting with alarm symptoms in general practice do not have cancer [96], and this is also the case for patients presenting with sarcoma symptoms because benign soft tissue lumps far outnumber sarcomas [17,97]. Although the sarcoma symptoms may seem specific when listed altogether in the CPP, they are unfortunately also the hallmark of many benign conditions more frequently encountered in a general population. The positive predictive value (PPV) of any cancer alarm symptom among patients seen in a GPs office rarely reaches above 5% [98-100], and for sarcomas the value is probably extremely low. The predictive value of specific sarcoma symptoms has not been investigated in a primary care setting, but in studies on alarm symptoms in a Norwegian population the presence of a lump was found to have a PPV of 1.1%–1.3% for any cancer form [101,102]. The use of alarm symptoms as criteria for referral to or inclusion in fast-track referral programmes entails a risk of both too narrow criteria and too wide

criteria. Too narrow criteria may result in exclusion of patients without alarm symptoms, whereas too wide criteria may overburden the system with unnecessary referrals [103]. Referral guidelines for sarcoma differ between countries with regard to the symptoms included as referral criteria, with size and subfascial location being the most consistent, whereas growth and pain are less consistently used [19,85,104]. Tumour growth is difficult to assess as most patients will state that the tumour has grown after they became aware of its presence. This can be due to manipulation of the tumour or an imagined growth due to worry, and not necessarily an actual increase in tumour volume. For a GP to be certain of growth, the GP must see the patient several times, which does not harmonise well with the demand for rapid referral. The use of pain as a referral criterion is debated and has been removed from some guidelines [19,85,105]. Pain is an unspecific symptom often seen in general practice, and although the sensitivity of this symptom may be high, the PPV in a general population is very low. This may explain the inconsistent use of pain as an alarm symptom for sarcoma. As the consensus on which criteria to include in a referral programme is not uniform between countries, the choice of alarm symptoms for the Danish CPP for sarcoma should be evaluated to ensure that the inclusion criteria function as intended.

Unplanned excision – patients treated outside Cancer Patient Pathways

The concept of standardised guidelines for diagnosis and treatment of sarcoma is not new, as most countries have had guidelines for sarcoma management for years. However, in spite of guidelines some sarcoma patients are still diagnosed and treated outside sarcoma centres. Unplanned excision is a well-described phenomenon for sarcoma patients [27,106-116], and may also be known as whoops-surgery or inadvertent excision [117,118]. Unplanned excision means that a sarcoma diagnosis is found unexpectedly after surgical removal of a tumour presumed to be something else, most often a misdiagnosed benign condition. The reasons for such an occurrence may be lack of awareness of sarcoma symptoms on the surgeon's part, atypical presentation with vague symptoms, inadequate pre-surgery diagnostics, false negative investigations or simply disregard for referral rules. It is widely agreed that biopsy and surgical treatment of sarcoma should be centralised to specialised sarcoma centres, and patients with suspected sarcomas should preferably be referred with their tumour untouched [10,24,31,40,119-122]. Still, approximately one third of all patients treated at a sarcoma centre are referred after surgery [29,32], with some improvement seen in later years for extremity tumours [28]. This can have severe consequences for the patient. The standard treatment for patients referred after unplanned excisions is a re-excision with a more extensive removal of the tumour bed and possibly adjuvant radiotherapy [106,117,122-125]. The rationale behind this approach is several studies showing that more than 50% of unplanned excisions are inadequate, with residual tumour tissue left in the operating field [109,110,116,117,123,125].

Positive surgical margins are associated with later local recurrences [32,34,41,122,126], and even though the survival after re-excisions is comparable to that in patients with planned surgeries [106,108,121], a later local recurrence may affect survival [33]. Apart from the effect on prognosis, unplanned excisions often require larger and more mutilating repeated surgery [107,110,111,116-118,122,123,127,128]. This can affect the patients' functional and cosmetic outcome, and in worst case scenarios necessitate an amputation not initially needed [127]. The patients are also subject to the psychological burden of repeated surgeries and may experience mistrust towards the hospital system after the initial misdiagnosis. Many studies describe the extent of unplanned excisions among patients referred to sarcoma centres and report on the surgical outcome of re-excisions, but few investigate who these patients are, where they are referred from and why they were initially misdiagnosed. The existence of this patient group is the evidence of a flaw in our diagnostic system, and valuable lessons could be learned from their diagnostic pathway.

The diagnostic journey before referral to Cancer Patient Pathways

As sarcomas are a rare disease entity, diagnostics and treatment have been centralised. Sarcoma research is thus almost exclusively conducted in highly selected populations of sarcoma patients seen in specialised centres. The focus of most studies is either orthopaedic treatment in terms of improving surgical techniques, prostheses, wound healing and functional outcome after surgery, or oncological treatment investigating new chemotherapy regimens, adjuvants, biological therapy, radiotherapy regimes and dose planning. The diagnostic pathway before a referral is received at the sarcoma centre is sparsely described in the literature, and little attention is given to this part of sarcoma management.

Selection of patient populations for research

The selected populations for sarcoma research usually only include patients with a confirmed sarcoma, leaving out the population of benign tumours who are unavoidably referred to a sarcoma centre. It is only after the diagnosis has been made that these two populations differ because they have been one during the entire process leading up to the diagnosis. They must have presented with similar symptoms, generated the same degree of malignancy suspicion in our health system and been through the same investigations as they all end up at a sarcoma centre. The obviously benign tumours have been weeded out along the diagnostic pathway and the patients who have been found to have a benign tumour after a sarcoma centre investigation are thus just as selected and interesting as the sarcoma patients. Of course, this population should not be a part of clinical trials investigating sarcoma treatment, but when investigating the diagnostic challenges of sarcomas, they should be included to get the full impression of the diagnostic pathway.

Limitations in reporting of time intervals

When reporting on delay in sarcoma studies, the time interval is usually reported as the total time elapsed from first symptom to diagnosis in a sarcoma centre. However, this time period can and should be separated into different subcomponents, such as patient interval, primary care interval, local hospital interval and diagnostic interval according to the Aarhus Statement for uniform reporting on waiting times [129]. This enables identification of the time interval that holds the most potential for improvement, and efforts to reduce delay can be more specifically directed based on such evidence. The different subcomponents of delay have been described for other cancer forms [56,130-133], whereas few studies separating delay into subcomponents exist for sarcoma populations [50,134]. Furthermore, the time spent in each specific time interval varies greatly depending on the organisational structure of the health system, and reports on waiting time before diagnosis are thus rarely generalisable to other countries. Detailed time intervals for Danish cancer patients have been reported for other cancer forms [89,91,135], but no such studies in patients referred to a Danish sarcoma centre exist. It is thus essentially unknown how these patients fare in the Danish health system and where any waiting time occurs.

Time intervals and presenting symptoms

A fast-track referral programme based on alarm symptoms can be a disadvantage for patients presenting without alarm symptom criteria [103,136-138]. The scope of this issue may be wide as only 50% of cancer patients present to a GP with alarm symptoms, the rest have vague and unspecific symptoms [136,139,140]. If patients fall outside alarm symptom criteria and are referred as non-urgent referrals, they may in fact have longer delays than patients with alarm symptoms because most resources are allocated to the fast-track referral programme [137,138]. The problem of cancer patients being diagnosed outside the fast-track referral programmes has been reported from other countries [81,82,132,141,142], and in the UK most sarcomas are diagnosed outside the 2WW [143]. Apart from the possibility of increased waiting time, this may also result in unplanned excisions, as discussed previously. Danish studies on other cancer forms performed after CPP implementation have indicated that patients presenting without alarm symptoms have longer waiting times [89,139,144], but this has not been investigated for sarcoma patients.

Local investigations vs direct referral to a sarcoma centre

While there is a wide consensus that suspected sarcoma patients should be investigated properly with use of imaging such as MRI, CT and x-ray the question of where these investigations should be performed is more debated. In the Danish CPP for sarcoma there is a requirement for imaging

performed locally before referral to a sarcoma centre [87]. GPs may not refer directly to an MRI or CT for soft tissue or bone tumours, but have to refer to a local hospital department specialist who can order these scans. In the initially implemented 2WW pathways in the UK there was no requirement of imaging prior to referral, and patients could be referred based solely on the presence of alarm symptoms. In the years following implementation, several reports emerged indicating that the proportion of referrals resulting in a diagnosis of malignancy (conversion rate) was low, and specialist centres were flooded with patients with benign conditions, with no accompanying increase in malignancies being detected [141,142,145,146]. This is the major concern when designing a referral programme based on alarm symptoms, and it has been shown that early imaging can help in the prioritisation of onward referral of suspected sarcoma patients to reduce the amount of benign conditions referred [147,148]. However, in Sweden the referral guidelines for sarcoma are also based on clinical alarm symptoms alone, with no requirement for pre-referral investigations, and direct referral is encouraged to save time [49,85]. The reported benign/malignant ratio is three to one, indicating that the extreme excess referral of benign tumours has not happened in Sweden. Direct referral of patients suspected of having a sarcoma has also been advocated on the basis of poor imaging quality in scans performed locally, necessitating repetition of scans at the sarcoma centre [52,85]. Another argument against local imaging is the potentially increased time expenditure at local hospitals before a referral can be made to a sarcoma centre, which has been shown in some studies [52,85,149,150]. The extent of this problem will depend on the organisational structure of the health system in terms of access to imaging and waiting time for specialist consultations. The excess time expenditure and difference in conversion rate between patients referred after local investigations and patients referred directly have not been investigated in a Danish setting, and the consequences of the CPP requirement for pre-referral investigations has not yet been evaluated.

Aims and hypotheses

Based on evidence and issues outlined above, the specific aims and hypotheses of this thesis were as follows:

I: To evaluate the effects of implementation of the CPP for sarcomas on time intervals of the diagnostic process at the Aarhus Sarcoma Centre
Hypothesis: The introduction of cancer patient pathways has shortened the duration of the diagnostic process of sarcomas.

II: To investigate the presence of alarm symptoms in patients referred to a sarcoma centre
Hypothesis: Symptoms and signs defined as CPP inclusion criteria are prevalent among patients suspected of having a sarcoma and predictive of malignancy.

III: To describe patient and tumour characteristics, initial symptoms, initial and final diagnosis, and explore reasons for unplanned excision among sarcoma patients referred after unplanned excision.
Hypothesis: Sarcoma patients referred after unplanned excisions present atypically, causing initial misdiagnosis.

IV: To examine time intervals, symptom presentation and routes to diagnosis from first perceived symptom to diagnosis at a specialist centre, among patients referred to the Cancer Patient Pathway for sarcomas.
Hypothesis: The time to diagnosis and treatment for suspected sarcoma patients depend on the presenting signs and symptoms.

V: To describe differences in time intervals and proportion of malignant diagnoses between patients referred after initial investigations and imaging at local hospitals and patients referred directly to a specialist sarcoma centre on clinical suspicion alone.
Hypothesis: Pre-referral investigation at local hospitals lengthens the diagnostic process and increases the proportion of malignant diagnoses for suspected sarcoma patients compared to direct referral to a sarcoma centre.

Materials and methods

Setting

The health care system in Denmark is publicly funded by taxes. Health care services are thus free of charge and access to hospital care is equal for all patients. The national health insurance covers all residents and apart from hospital care also includes treatment in the primary health care sector and treatment from private specialists holding a health insurance agreement. Nearly all Danish citizens (more than 98%) are registered with a specific general practice and must consult this practice for all medical advice except emergencies. The GPs act as gatekeepers to secondary care services, and hospital specialists cannot be accessed directly by patients. All residents in Denmark are assigned a unique 10-digit identification number (the CPR number), with which all contacts to the health system are registered. This enables the tracking of a patient across different health care providers [151].

Aarhus Sarcoma Centre

Sarcoma diagnostics and treatment have been centralised to two national centres in Denmark, one in Copenhagen and one in Aarhus. The Aarhus Sarcoma Centre (ASC) handles all referrals from Western Denmark, with an uptake population of approximately 2.5 million inhabitants. The ASC is organised as a subdivision of the orthopaedic department at Aarhus University Hospital (AUH) that collaborates with relevant experts from other specialties such as oncologists, pathologists, radiologists and paediatricians. The ASC has two functions in the CPP for sarcomas. First and foremost, it serves as a highly specialised sarcoma department responsible for the final diagnostic work-up and treatment of patients referred to the sarcoma CPP from hospitals outside AUH. Secondly, it serves as the local orthopaedic department for patients suspected of having a sarcoma residing in the uptake area of AUH. These latter patients can be referred directly to ASC without the required clinical investigation and MRI at a local orthopaedic department outlined in the sarcoma CPP. The standard diagnostic programme at ASC consists of an initial clinical examination, a tissue biopsy, imaging investigations such as PET-CT, bone scintigraphy and thoracic x-ray/CT for staging purposes, and a multidisciplinary team meeting. For patients who have not had an MRI performed before referral, this is also a part of the diagnostic workup.

Study design

Studies I, II and III were designed as retrospective observational studies of medical record data. Studies IV and V were designed as a mixed-methods study entailing both a retrospective review of

medical records and the use of GP questionnaires and patient questionnaires for reviewing the diagnostic journey before first appointment at the ASC.

Study population

The selection of study populations are also described in the published articles for studies I, II and III [152-154] and in the submitted manuscripts for studies IV and V.

Patients with retroperitoneal or gynaecological tumours are managed at other departments in consultative collaboration with ASC and do not enter the CPP at the orthopaedic department at ASC. They are thus not included in any of the study populations in this thesis. Children enter the CPP and are seen at ASC for clinical examination and tissue biopsy in the same way as adult patients and are thus included.

Studies I and II

We aimed to include all patients referred from other hospitals outside AUH to the ASC with a suspicion of malignancy in the period from January 1st 2007 and December 31st (two years before and two years after CPP implementation on January 1st 2009). The selection of our patient population started by identifying all patients referred to ASC in the defined time period through an extraction from the hospital administrative system (4726 patients total), and afterwards excluding all patients coded as referred directly from a GP or from within AUH (2957 patients excluded). This left 1769 patients referred from hospitals outside AUH. To identify patients referred with a suspicion of malignancy we used the following definitions:

Referrals were considered to be with suspicion if:

- The referral mentioned a suspicion of malignancy, cancer or sarcoma and the MRI description confirmed the suspicion.
- The referring physician had a strong clinical suspicion of malignancy, cancer or sarcoma in spite of MRI describing the condition as benign.
- The referral contained a histology report of a confirmed or possible sarcoma.
- A suspicion of malignancy, cancer or sarcoma was mentioned in the MRI-description.

Referrals were considered to be without suspicion if:

- The referral mentioned no suspicion of malignancy, cancer or sarcoma and the MRI description confirmed this.

- The referral concerned treatment of a histologically verified type of cancer different from sarcoma, such as metastases and lymphomas.
- The referral concerned assistance in treatment of other conditions already diagnosed elsewhere, such as prosthesis implantation, infectious diseases and wound treatment.
- The referral concerned histologically verified borderline tumours, referred for follow up purposes.

This definition was used equally for all four years, and the presence or absence of CPP referral coding in the years 2009 and 2010 was not used as a selection criterion. The medical records of the remaining 1769 patients were retrieved and reviewed according to the above mentioned definition, and a further 643 patients were excluded due to reasons described in Figure 1. The final study population for studies I and II thus consisted of 1126 patients.

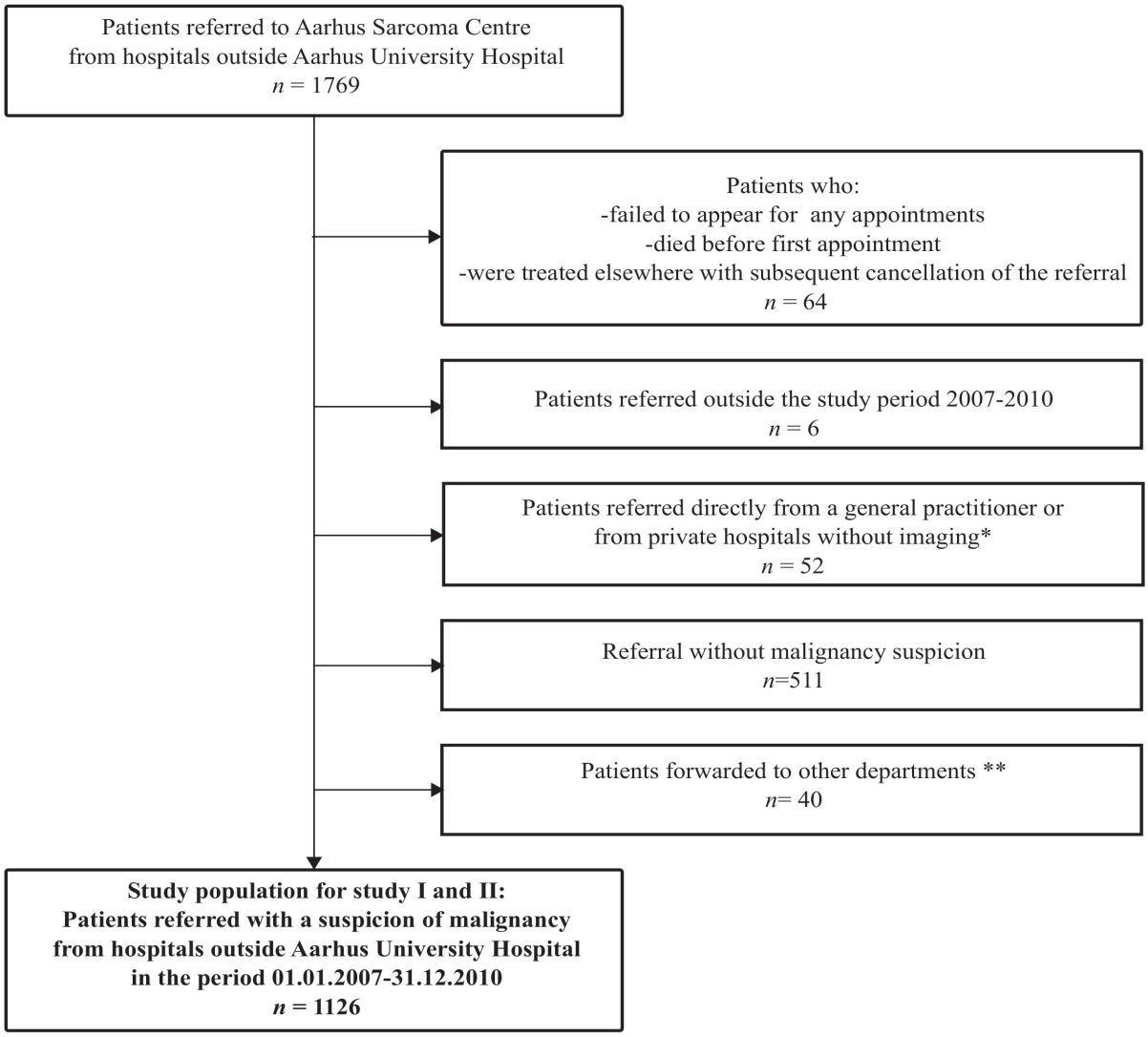
Study III

The study population used in study III was 64 sarcoma patients found in studies I and II to have been referred after an excision or biopsy performed outside ASC. The rest of the 258 sarcomas in the study population for studies I and II were referred with untouched tumours.

Studies IV and V

We invited all consecutive patients referred to the CPP for sarcoma at ASC in the period between September 1st 2014 and August 31st 2015 to participate in a questionnaire study on their diagnostic process leading up to referral to the sarcoma centre. A total of 607 patients were referred in the study period of which 545 (89.8%) accepted participation. 62 patients declined participation for reasons described in Figure 2.

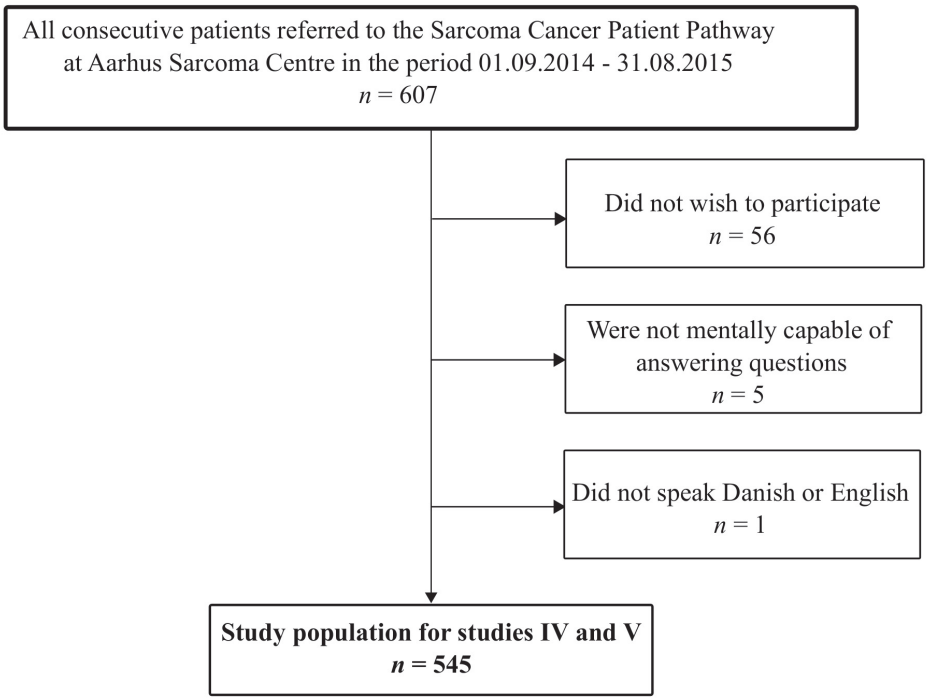
Figure 1: Flowchart for selection of patients for studies I and II



* Patients referred directly from a GP but not coded as such in the patient administrative system, and patients referred from private hospitals without MRI or a histology report confirming sarcoma suspicion.

** Referrals concerning tumours not handled by the sarcoma centre (retroperitoneal, gynaecological, neurological tumours), resulting in a direct onwards referral to the appropriate department.

Figure 2: Flowchart for selection of patients for studies IV and V



Data collection

The data collection is also described in the published articles for studies I, II and III [152-154] and in the submitted manuscripts for studies IV and V.

Studies I and II

A registration form was developed to register information from the medical records (Appendix 1). After creating the registration form it was tested on a random sample of patient medical records from the years 2007–2010 (25 patients referred in 2007, 23 in 2008, 26 in 2009 and 21 in 2010) to ensure usability before start-up of data collection. Data collected on the paper registration form were also registered in an electronic data base. Registration of data was thus done twice for each patient (first on paper and then in the electronical database) and these registrations were checked against each other to ensure correct registration. For patients with more than one referral during the four-year study period, only the first referral was registered. Patients with a previous diagnosis of sarcoma were only included if they had finished both their treatment and the full follow up time of five years.

Study III

In addition to the data collection for studies I and II, the referral papers of the 64 patients referred after excision/biopsy performed outside ASC were reviewed again for information on the referring institution, registered symptoms and imaging investigations before surgery, and initially suspected diagnosis.

Studies IV and V

Both a patient (Appendix 2) and a GP questionnaire (Appendix 3) were developed specifically for this data collection, as no available questionnaires suitable for the purpose of our studies could be identified. The question formulations and contents were based on similar Danish questionnaires used for research on other cancer forms [155], and adjusted to fit patients suspected of having a sarcoma incorporating experiences from both sarcoma and questionnaire experts. After development, the patient questionnaire was tested on a pilot group of patients to ensure understanding of the wording and question setup. The pilot group consisted of 15 consecutive patients referred to the sarcoma CPP seen over two outpatient clinic days. The GP questionnaire was initially evaluated by a group of experienced questionnaire researchers and later pilot tested among five practicing GPs to ensure understanding of questions and explanatory text. After the pilot studies, small adjustments were made in questionnaires based on the feedback from GPs, patients and their accompanying relatives.

The patient questionnaire was sent out by mail before the first appointment at ASC, and patients were encouraged to fill out the questionnaire in advance. If participation was accepted and informed consent was given the patient was interviewed after the appointment based on the questionnaire, thus ensuring correct and complete answering of questions. If the patient or the medical records stated that the GP had been involved in the diagnostic route, the GP questionnaire was sent to the patient's GP. No remuneration was given for the GP questionnaire. A new questionnaire was sent out as a reminder after 4–5 weeks with a subsequent telephone reminder after a further 3 weeks if no answer was received. By tracking the patient route backwards the local hospitals and private hospitals involved were identified and data on the diagnostic route was collected from electronic medical records or via telephone contact to the hospital. Data on the investigations performed at ASC, final diagnosis and treatment were collected from electronical medical records. Questionnaire answers were coded and read electronically into an Access database, where data from local hospitals, private hospitals and ASC were also registered.

Definition of variables

The definition of variables is also described in the published articles for studies I, II and III [152-154] and in the submitted manuscripts for studies IV and V.

Studies I, II and III

Tumour characteristics

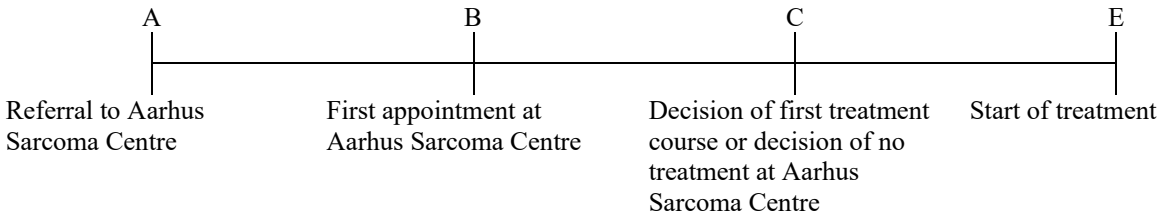
Symptom duration was defined as time between the patient's first recollection of symptoms being present to the first appointment at ASC. **Tumour size** was measured in millimetres at the largest diameter and was found in the histological report if the tumour had been surgically removed and in the MRI/CT-report if the tumour had not been removed, in accordance with rules for registration of tumour size in the Danish Sarcoma Database at that time. **Tumour depth** for soft tissue tumours was defined as subcutaneous/superficial if the tumour was located superficially to the deep muscle fascia, and as subfascial/deep if the tumour was located on or below the deep muscle fascia. **Malignancy grade** was only registered for sarcomas, and was done after the Trojani classification [156]. For analyses, Trojani grade 1 tumours were considered as low-grade malignancies and grade 2 and 3 tumours as high-grade malignancies. **Final diagnosis** was found in the pathology report if the tumour had been surgically removed, or a tissue biopsy had been performed. If no histology report existed, the consensus-based diagnosis decided at the multidisciplinary meeting was registered as the final diagnosis.

Dates and time intervals

For calculation of time intervals for study I, the date of referral, date of first appointment, date of treatment decision and date of treatment start were used, as these were the time points defined in the 2009-edition of the sarcoma CPP (Figure 3). **Date of referral (Time point A)** was defined as the day where the complete referral and all imaging material were received at ASC. **Date of first appointment (Time point B)** was the first date the patient had been seen at ASC. The **date of treatment decision (Time point C)** was the date where a decision of first treatment course was made based on the clinical investigation, imaging analyses and histology report (for benign conditions and other malignancies the decision was no treatment or treatment elsewhere). This date is thus not synonymous with date of final diagnosis, which often lies after the date of treatment as it is usually based on the pathology specimen from the final surgery. **Date of treatment start (Time point E)** was the date when the first surgery was performed, the first series of chemotherapy was given or the first radiation treatment was given (depending on the chosen primary treatment modality). Based on these dates, the four time intervals defined in the 2009-edition of the sarcoma CPP were calculated: phase A–B (from referral to first appointment), phase B–C (from first

appointment to treatment decision), phase C–E (from treatment decision to start of treatment), and phase A–E (from referral to start of treatment). Time intervals were measured in working days, thus excluding weekend days and Danish national holidays.

Figure 3: Time points used for calculation of time intervals in study I



Delay

In study I, a patient was classified as delayed when they exceeded the time limits defined in the 2009-edition of the sarcoma CPP. Delay was further classified as either being caused by passive waiting time or by a need for clinically justified supplementary diagnostics not included in the standard diagnostic programme at ASC. The standard diagnostic programme at ASC was defined to include a chest x-ray and/or a chest CT, a PET-CT, a bone scintigraphy and a biopsy. An MRI was considered to be a part of the standard diagnostic programme only for patients referred with a histologically verified diagnosis of sarcoma after surgery/biopsy elsewhere. Clinically justified supplementary diagnostics included a CT of the tumour area (not registered as supplementary if part of the biopsy procedure), repeated PET-CT, MRI, ultrasound (not registered as supplementary if part of the biopsy procedure), repeated bone scintigraphy, repeated biopsy, extended histopathological evaluation, second opinions from external experts, patient-requested time-out, production of a custom-made prosthesis. If none of these reasons for delay was present, the delay was classified as caused by passive waiting time.

Presenting symptoms

For registration of symptoms causing the referral to the ASC in study II, the following categories were used: soft tissue tumour > 5 cm, deep seated soft tissue tumour, fast growing soft tissue tumour, palpable bone tumour, deep persisting bone pain, incidental finding during imaging of the area, referral with a confirmed histological sarcoma diagnosis, suspected recurrence of known sarcoma and other symptoms. Patients could thus have more than one symptom causing the referral. When defining the presence or absence of a symptom, only tumour symptoms/clinical findings mentioned before the tumour was removed were considered as a presenting symptom. In study III, the medical record annotations made before excision/biopsy at hospitals outside ASC were reviewed for any mention of the presence of one or more of the five alarm symptoms/signs defined

in the sarcoma CPP (soft tissue tumour > 5 cm, deep seated soft tissue tumour, fast growing soft tissue tumour, palpable bone tumour and deep persisting bone pain).

Studies IV and V

Tumour characteristics

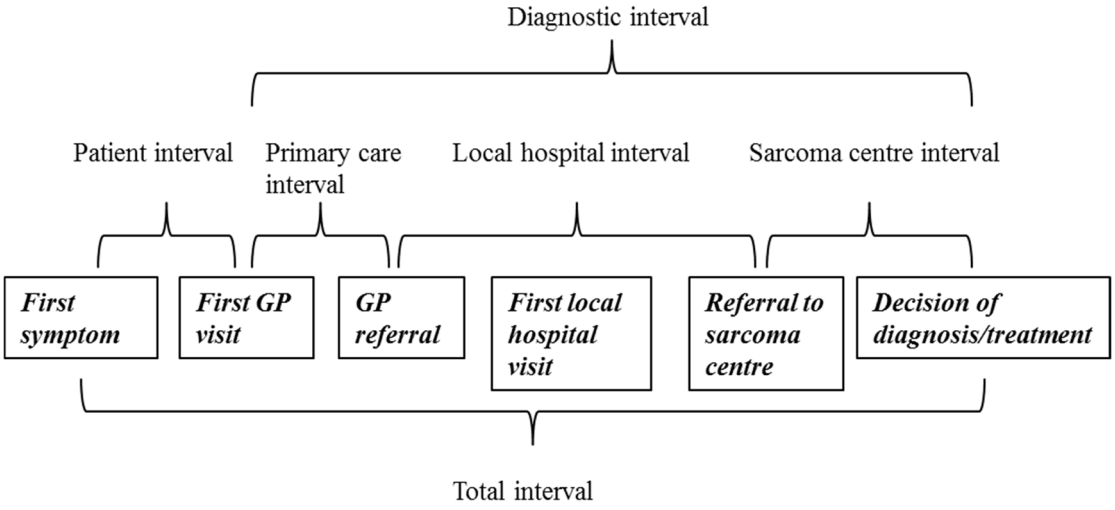
The definitions of malignancy grade, tumour depth and source of final diagnosis described for studies I, II and III were also used in studies IV and V. However, in studies IV and V **tumour size** was measured in centimetres at the largest diameter on the diagnostic MRI or CT. If none of these scans had been performed, size was taken from the pathology report if the tumour had been removed and from ultrasound, x-ray or clinical measurement if the tumour had not been removed. This change in measurement technique from the pathology specimen being the primary source in studies I, II and III to the MRI being the primary source in studies IV and V was due to a change in the definition of gold standard for tumour size measurement in the national Danish Sarcoma database happening between the two data collections. To accommodate any later comparability between datasets we made the same change in our registration method.

Dates and time intervals

In studies IV and V, we defined time points and time intervals in accordance with the Aarhus statement on uniform reporting of time intervals [129]. Time points were collected from several sources. In the patient questionnaire, patients reported date of symptom debut and date of their first visit to a doctor. In the GP questionnaire, GPs also reported the date of first visit along with the date of referral for further investigation at hospitals. The date of first appointment and date of onward referral for each local hospital department visited was collected from medical records. From ASC records the date of received referral and date of decision of initial treatment were collected. If patients or GPs had only stated a month and year, but no specific date, the 15th of that month was registered. If only a year had been stated, with no specific date or month, the 1st of July that year was registered. The patient-reported date for first visit to a doctor was used to calculate patient interval only if the GP had not responded, otherwise the GP-reported date was used. If the patient had not visited the GP the first hospital department visit was used as first visit to a doctor. Six time intervals were defined and calculated: patient interval, primary care interval, local hospital interval, sarcoma centre interval, diagnostic interval and total interval (Figure 4). Patient interval was calculated as time from first symptom to first visit to a doctor. Primary care interval was calculated as time from first GP visit to referral to hospital. Local hospital interval was calculated as time from referral to the first local hospital to final referral to the ASC. The sarcoma centre interval was calculated as time from received referral at ASC to the date where a decision of initial treatment

was made. This decision was either a decision of no treatment/treatment elsewhere or a decision of one of the final treatment modalities in the CPP (surgery, chemotherapy or radiation). This decision date was also the end point of the diagnostic and total interval. The starting points of the diagnostic interval and total interval were the first visit to a doctor and the date of first symptom, respectively. The decision date was chosen as the end point instead of the date of diagnosis or date of first treatment to ensure comparativeness of time intervals between patients regardless of final diagnosis because these time points are highly dependent on the diagnosis and chosen treatment. The treatment interval from decision of treatment to start of treatment for patients receiving treatment at ASC is thus not included in any of the time intervals.

Figure 4: Time points and calculated time intervals used in studies IV and V, based on the Aarhus Statement [129]



Presenting symptoms and GP suspicion

Questions about initial symptoms and development in symptoms over time were answered by the patients in free text fields. Each symptom reported was coded with a unique number, and no category grouping of symptoms was done during the initial data recording. The recorded numbers could then later be collected into groups for analyses. We did not use validated coding systems such as the International Classification of Primary Care (ICPC) or ICD-10 as these systems are very organ specific. Sarcomas can arise in any anatomical location and thus do not fit into regular symptom coding systems based on organ of origin. The same approach was used for the patient-reported reason for seeking medical care, presenting symptoms reported from GPs, and for the tentative diagnosis reported by GPs. For analyses, all tentative diagnosis codes corresponding to a suspicion of malignancy were classified as GP suspicion being present.

Statistical analyses

Data analyses for studies I, II and III were performed using Stata® statistical software, version 11. For studies IV and V, version 13 was used. P-values below 5% were considered statistically significant in all analyses.

Studies I, II and III

Descriptive statistics were applied to describe the patient population. Continuous variables such as time intervals, age, symptom duration and tumour size were reported as medians with interquartile intervals (IQI) as the data were non-normally distributed with right-skewed outliers. Differences in age, tumour size and symptom duration between two groups were tested with the Wilcoxon Rank Sum Test. To test whether the development in time intervals over the four-year period in study I was significant, we used a non-parametric test for trend across ordered groups (Stata-command: *nptrend*), which is an extension of the Wilcoxon Rank Sum Test. The test shows whether a systematic increase or decrease in rank sums over the four years is statistically significant, and does not compare specific years against each other. For the symptom analyses in study II, patients were separated into two groups according to tumour tissue type (bone and soft tissue). In the soft tissue tumour group, the predictive values for symptoms of soft tissue sarcoma were analysed. In the bone tumour group, the predictive values for symptoms of bone sarcoma were analysed. Positive exposure was the presence of a symptom or symptom combination; positive outcome was a final diagnosis of sarcoma. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for sarcoma were calculated for each single symptom and symptom combinations.

Studies IV and V

Descriptive statistics were used to portray questionnaire response rates and patient demographics. Differences in gender distribution and age distribution between participants and non-participants were tested with the chi-squared test (gender) and Wilcoxon Rank Sum Test (age). The Wilcoxon Rank Sum Test was also used for comparing the number of local hospital departments visited and number of GP consultations between patient groups. In study V, the comparison of malignancy proportions was done with the chi-squared test. Only the two groups following the official referral pathways described in the CPP were compared in study V, the remaining two groups were left out of the statistical tests comparing time intervals and malignancy proportions. Time interval data used for both study IV and study V were right-skewed, and are thus reported as medians with IQIs. For the estimation of differences in time intervals at different quantiles, we applied quantile regression

analyses on the smoothed quantiles using the "QCOUNT" procedure for Stata® written by Miranda [157]. The procedure calculates the estimated difference in number of days between two groups at specific percentiles and calculates 95% confidence intervals for the found difference using standard errors estimated by bootstrapping techniques with 1000 repetitions. We estimated differences at the 50^{th} and 75^{th} percentiles to portray both the difference in central tendency and differences in the size of the right-skewed tail inherit to waiting time data. Age distribution differed between groups, and the regression analyses were thus adjusted for age as a categorical variable (separated into four groups; < 20, 20–39, 40–59 and ≥ 60 years). Gender distribution was found to be equal in all groups, and was not adjusted for. The regression analyses were also repeated with adjustment for both gender and age to evaluate the effect of gender on estimated differences. The inclusion of gender had no or little effect on point estimates and only widened confidence intervals and thus reduced the statistical precision. Considering our fairly small study population, we chose to only include age as a confounder in the final model.

Results

Results presented here are also included in the published papers for studies I, II and III [152-154], and the submitted manuscripts for studies IV and V.

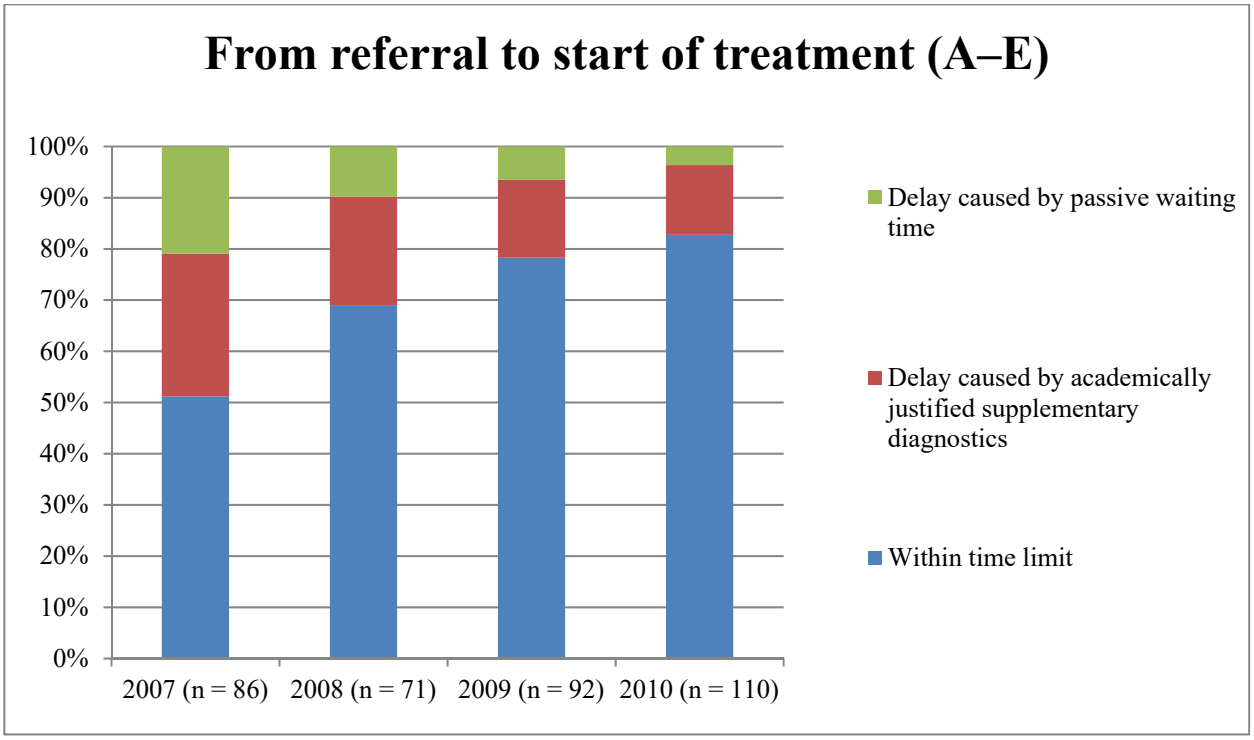
Study I

Of the 1126 patients included in study I 258 (22.9%) patients were diagnosed with a sarcoma, 743 (66.0%) were diagnosed with benign conditions, and 125 (11.1%) were diagnosed with other malignancies. The proportion of sarcomas diagnosed per year was 21.6% in 2007, 25.5% in 2008, 21.8% in 2009 and 23.2% in 2010. As seen in Table 2, median time intervals decreased in all defined phases of the diagnostic process, with the most significant decrease happening in the phase from received referral first appointment (Phase A–B). The 75th percentile was also decreased in most phases, indicating an overall shift towards shorter processing times. The proportion of patients exceeding CPP time limits was reduced over the four-year period, and the larger part of the delays in 2010 was caused by academically justified supplementary diagnostics, not passive waiting time (Figure 5). As a secondary outcome, we found a statistically significant reduction in tumour size for soft tissue sarcomas from a median diameter of 70 (IQI: 40–100) millimetres in 2007 to 49 (IQI: 30–70) millimetres in 2010 ($p = 0.044$). No such statistically significant change was found for bone sarcomas or non-sarcomas of soft tissue or bone type. There was no significant change in symptom duration during the four year period for any patient groups.

Table 2: Median and interquartile intervals of time spent in each phase measured in work days, and non-parametric test for trend across the period 2007–2010 for patients diagnosed with sarcomas, benign conditions and other malignancies

		From referral to first appointment in centre (A–B)	From first appointment in centre to final decision of treatment (B–C)	From final decision of treatment to start of treatment (C–E)	From referral to start of treatment (A–E)
Soft tissue sarcoma	**2007**	7 (5–10.5)	10.5 (1–21)	6 (4–11)	28 (18–38)
	2008	8 (6–11)	6 (1–16)	8 (5–10)	23 (16–33)
	2009	3 (4–6)	8 (1–13)	8 (6–11,5)	21 (14.5–29.5)
	2010	3 (4–6)	8 (1–11.5)	7 (4–10)	18 (13–25)
	p-value	< 0.001	0.236	0.827	< 0.001
Bone sarcoma	**2007**	4 (5–11)	11 (3–35)	7 (6–8)	31 (18–40)
	2008	5 (3–9)	12.5 (5–24)	6 (3,5–7)	16,5 (13.5–29.5)
	2009	4 (1–7)	13 (6–17)	7 (3–10)	23 (12–31)
	2010	2 (1–5)	5 (2–8)	7 (6–8)	14 (10–20)
	p-value	0.004	0.046	0.145	0.503
Benign soft tissue tumours	**2007**	9 (6–12)	8.5 (1–18)	10 (8–15)	24 (18–36)
	2008	9 (6–12)	5 (1–13)	4 (4–10)	19 (15–24)
	2009	5.5 (4–7)	7 (1–13)	6.5 (3–12)	18 (9–20.5)
	2010	4 (3–5)	5 (1–10.5)	6 (3–9)	12 (10–15)
	p-value	< 0.001	0.054	0.402	0.605
Benign bone tumours	**2007**	9 (6–11)	17.5 (5–23)	13.5 (13–16)	24.5 (23–25)
	2008	9 (4–12)	12 (1–18)	18 (18–18)	29 (29–29)
	2009	5 (3–7)	12 (3–16)	13 (3–22.5)	20 (9–30)
	2010	4 (3–6)	12 (7.5–18.5)	10 (6–11)	18 (16–23)
	p-value	< 0.001	0.437	0.577	0.553
Other malignant soft tissue tumours	**2007**	9 (4–12)	10 (7–23)	-	-
	2008	7 (3–12)	10 (7–15)	-	-
	2009	5 (4–8)	8 (7–13)	-	-
	2010	3 (3–5)	9 (8–13)	-	-
	p-value	0.024	0.850	-	-
Other malignant bone tumours	**2007**	7 (5–7)	15.5 (9–25)	-	-
	2008	6 (4–7)	8 (5.5–10)	-	-
	2009	5 (4–6)	11 (7–15)	-	-
	2010	3 (2–5)	9 (5–12)	-	-
	p-value	< 0.001	0.237	-	-

Figure 5: Proportion and type of delay among all patients who went through the phase from date of referral to start of treatment (A–E)



n = number of patients who went through this phase per year.

Study II

Of the 258 sarcomas, there were 174 soft tissue sarcomas and 84 bone sarcomas. For soft tissue tumours, "Tumour over 5 cm in diameter" was the alarm symptom/clinical finding with the highest sensitivity (45%) and PPV (25%) for predicting a sarcoma diagnosis. For bone tumours, "deep persisting bone pain" yielded the highest sensitivity (82%) and PPV (23%). The symptom combination with the highest sensitivity (21%) was a deep-seated soft tissue tumour over 5 cm. Sensitivity, specificity, NPV and PPV for all symptoms and symptom combinations are presented in Tables 3 and 4.

Table 3: Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for sarcoma of single symptoms and combinations of the symptoms and signs defined as inclusion criteria for soft tissue tumours in the Cancer Patient Pathway, in suspected sarcoma patients

	Soft tissue tumours (*n* = 706)							
Symptom[a]	Sarcoma (*n* = 174)		Non-sarcoma (*n* = 532)		Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Present	+	-	+	-				
1	78	96	233	299	45 (37–53)	56 (52–61)	25 (20–30)	76 (71–80)
2	76	98	293	239	44 (36–51)	45 (41–49)	21 (17–25)	71 (66–76)
3	50	124	164	368	29 (22–36)	69 (65–73)	23 (18–30)	75 (71–79)
1+2	36	138	91	441	21 (15–28)	83 (79–86)	28 (21–37)	76 (73–80)
2+3	5	169	34	498	3 (1–7)	94 (91–96)	13 (4–27)	75 (71–78)
1+3	6	168	31	501	3 (1–7)	94 (92–96)	16 (6–32)	75 (71–78)
1+2+3	26	148	37	495	15 (10–21)	93 (91–95)	41 (29–54)	77 (74–80)

[a] Symptom 1: soft tissue tumour > 5 cm; symptom 2: soft tissue tumour on or profound of the fascia; symptom 3: fast growing soft tissue tumour.

Table 4: Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for sarcoma of single symptoms and combinations of the symptoms and signs defined as inclusion criteria for bone tumours in the Cancer Patient Pathway, in suspected sarcoma patients

	Bone tumours (*n* = 420)							
Symptom[a]	Sarcoma (*n* = 84)		Non-sarcoma (*n* = 336)		Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Present	+	-	+	-				
4	12	72	44	292	14 (8–24)	87 (83–90)	21 (12–34)	80 (76–84)
5	69	15	237	99	82 (72–90)	30 (25–35)	23 (18–28)	87 (79–92)
4+5	8	76	14	322	9 (4–18)	96 (93–98)	36 (17–59)	81 (77–85)

[a] Symptom 4: palpable bone tumour; symptom 5: deep persisting bone pains

Seventy-nine (31%) of the 258 sarcoma patients were not referred due to any of the five CPP alarm symptoms/clinical findings. Seven of these patients were referred after an incidental finding on imaging of the area performed for other purposes. Sixty-four patients were referred with a confirmed histological sarcoma diagnosis after excision/biopsy elsewhere. Five patients were referred due to a suspected recurrence of a previous sarcoma. The last three patients did not have any of the defined alarm symptoms nor any of the above described referral reasons. One had haemoptysis, one had weight loss and fatigue, and one had a subcutaneous soft tissue tumour under 5 cm in diameter.

Study III

Of the 64 sarcoma patients referred after excision/biopsy performed outside ASC, 26 (40.6%) were females. Median patient age was 58.2 years (IQI = 42.5–70.7). The median symptom duration for the entire group was 87 days (IQI = 27.5–120), females had a median duration of 180 days (IQI=60–731), males had 46.5 days (IQI = 27.5–120)). The difference in symptom duration between genders was statistically significant ($p = 0.046$). Soft tissue sarcomas were most frequent (61 patients, 95.3%), and median tumour size was 35 mm (IQI = 20–50). In the total study population 32 (50%) of the 64 sarcomas were superficial tumours smaller than 5 cm. There were 27 (42.2%) low-grade tumours and 37 (57.8%) high-grade tumours. As seen in Table 5, 36 (56.3%) patients were referred from surgical public hospital departments, the rest from various other hospital departments and private specialists. Thirty-nine (60.9%) patients had received no imaging investigations before surgery was performed. The most frequent patient reported symptom was a lump (58 of 64 patients (90.6%)), and pain (18 of 64 patients (28.1%)). Twelve (18.8%) patients reported that it was the second removal of the tumour after it had grown back. Five patients (7.8%) reported that the tumour had started changing after being present for years. In 25 (39.1%) of the 64 patients, one or more of the five CPP criteria had been detected and annotated by the referring hospital in medical records before surgery. The remaining 39 (60.9%) patients fell outside of defined CPP criteria or the presence of alarm symptoms had not been detected by the referring hospital.

Table 5: Distribution of the referring hospital for 64 sarcoma patients referred after unplanned excision

Operating physician/department	*n*	%
Surgical department, public hospital	17	26.6
Orthopaedic department, public hospital	13	20.3
Private surgeon	7	10.9
Private orthopaedic surgeon	6	9.4
Private dermatologist	5	7.8
General practitioner	4	6.3
Urology department, public hospital	4	6.3
Private hospital	2	3.1
Medical department, public hospital	2	3.1
Department of plastic surgery, public hospital	1	1.6
Private ear/nose/throat-specialist	1	1.6
Private plastic surgeon	1	1.6
Department of thoracic surgery, public hospital	1	1.6
Total	**64**	**100**

Study IV

In study IV, 545 patients suspected of having a sarcoma were included, of which 102 (18.7%) were diagnosed with a sarcoma and 68 (12.5%) with other malignancies, resulting in a total proportion of malignancies of 31.2%. The most frequent reasons for seeking medical care were pain, wanting to know what it was, consulting for something else, being urged by others and incidental findings on imaging, and 83.7% of patients had presented to their GP first. Sarcoma patients had visited significantly more hospital departments compared to patients with benign conditions ($p = 0.001$) and also had a higher number of GP consultations than patients with benign conditions ($p = 0.051$). As presented in Table 6, the patient interval and the local hospital interval were the longest, contributing to a median total interval of 155 days from first symptom to diagnosis. Sarcoma patients tended to have longer time intervals than patients with benign conditions, whereas patients with other malignancies had shorter time intervals compared to patients with benign conditions. The median total interval was significantly shorter for patients with high-grade sarcomas compared to sarcoma patients with low-grade sarcomas. This was due to a shorter patient interval in patients with high-grade sarcomas, as the diagnostic interval was longer for high grade sarcomas. Presenting signs and symptoms modified some of the intervals (Table 7). The presence of pain significantly prolonged time intervals and initial GP suspicion of malignancy shortened time intervals. Patients presenting with a lump tended to have a longer patient interval than patients without a lump, whereas the primary care interval and sarcoma centre intervals were significantly shortened. The patient interval and thus the total interval were significantly longer for patients with large tumours over 5 cm compared to patients with smaller tumours; however the local hospital interval was significantly shorter for patients with tumours over 5 cm. Patients with deep-seated soft tissue tumours had a significantly shorter patient interval than patients with subcutaneous tumours.

Table 6: Median number of days (interquartile intervals) spent in each interval of the diagnostic process from first symptom to decision of treatment

	Patient Interval	Primary Care Interval	Local Hospital Interval	Sarcoma Centre Interval	Diagnostic Interval	Total Interval
	Median (IQI) *n* = 545	Median (IQI) *n* = 416	Median (IQI) *n* = 386	Median (IQI) *n* = 545	Median (IQI) *n* = 545	Median (IQI) *n* = 545
All patients	54 (12:241)	8 (1:36.5)	26.5 (13:58)	15 (9:22)	50 (30:98)	155 (61:423)
Gender						
Female	48.5 (9:182)	11 (1:39.5)	23 (13:60)	16 (11:23)	52 (31:98)	144.5 (60:341)
Male	59 (13:319)	4 (1:35)	28 (13:54)	15 (8:22)	50 (29:99)	158 (62:507)
Age						
< 20	31 (15:84)	22 (2:73)	21 (11:58)	15 (8:20)	55 (30:139)	118 (47:259)
20–39	76 (21:539)	12 (1:49)	36.5 (18.5:102)	17 (11:25)	57 (33:148)	184 (77:924)
40–59	110 (17:349)	7.5 (1:36)	32.5 (16:72)	15 (8:22)	62 (31:106)	225 (78:591)
≥ 60	36.5 (4:134)	3.5 (1:33)	21 (11:43)	15 (9:23)	42.5 (27:78)	99 (46:240)
Pt had or developed lump						
No	38.5 (1:215)	22 (4:58)	24 (9:67)	19 (11:28)	57.5 (35:116.5)	147 (49.5:342.5)
Yes	59 (17:251)	3 (1:31)	28 (15:54)	15 (9:21)	49 (28:98)	156 (63:507)
Patient had or developed pain						
No	33.5 (3:236.5)	1 (1:31)	23.5 (12:47)	15 (9:21.5)	41 (26:84)	95 (43.5:389.5)
Yes	76 (20:241)	13 (1:44)	29 (14:65.5)	16 (9:22)	58 (34:134)	182 (77:465)
Tumour size[1]						
Under 5 cm	46 (11:194)	8 (1:35)	29 (14:59)	15 (8:21.5)	50.5 (29.5:92)	140.5 (54:374.5)
Over 5 cm	65 (15:353.5)	8 (1:37)	23 (12:52)	16 (10:23)	52 (31:104)	180 (70.5:605.5)
Tumour depth[2]						
Subcutaneous	86 (15:528)	1 (1:36)	28 (15:54)	13 (8:20)	42 (28:91)	181 (60:734)
Subfascial	58.5 (14:234)	7 (1:29)	29 (15:56)	15 (9:21)	55 (31.5:100.5)	147 (65:416)
GP suspected malignancy at initial referral[3]						
No	81 (22:319)	9 (1:45)	38 (20:78)	15 (9:22)	63 (38:139)	197 (90:690)
Yes	45 (11:141)	4 (1:25)	18 (9.5:28)	15 (8:21)	34 (21:58)	94 (45:215)
Referred from Aarhus local uptake area						
No	55 (11:227)	8 (1:40)	28 (15:58)	15 (9:22)	35 (21:88)	158 (63:401)
Yes	43 (13:323)	3 (1:28)	18 (6:47)	16 (9:25)	56 (33:106)	135 (51:469)
Diagnosis						
Sarcomas	77 (11:261)	17 (1:56)	29 (15:56)	17 (10:24)	65 (42:133)	176 (83:673)
Other malignancies	38 (6:97)	12.5 (1:25)	15 (7:32)	20 (14:26)	44 (27.5:68)	103 (49.5:202.5)
Benign	54 (13:296)	4 (1:35)	28 (16:62)	15 (8:21)	48 (29:91)	158 (59:507)
Malignancy grade[4]						
Low-grade	213 (26:963)	21.5 (1:50)	29 (19:47)	17 (8:23)	60 (43:103)	250 (108:1665)
High-grade	41 (8:154)	17 (1:57)	29 (13:58)	17 (13:25)	71 (42:140)	164 (69:376)

n = total number of patients with available dates for calculation of this interval.
[1]Anaysis included only patients with data, 33 patients with missing data on tumour size excluded.
[2]Analysis included only patients with soft tissue tumours.
[3]Analysis included only patients with data available for this variable. Patients who were not seen by the GP and patients where the GP had not answered the question were excluded from the analysis.
[4]Analysis included only sarcoma patients.

Table 7: Estimated differences in time intervals at the 50th and 75th percentiles, Measured as difference in calendar days with 95% confidence intervals (CI), calculated by quantile regression.

	Patient Interval	**Primary Care Interval**	**Local Hospital Interval**	**Sarcoma Centre Interval**	**Diagnostic Interval**	**Total Interval**
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
Sarcoma patients vs patients with benign conditions						
50th percentile	16 (-37:69)	**10 (4:15)**	0 (-9:10)	0 (-9:10)	**19 (10:28)**	26 (-34:86)
75th percentile	-7 (-18:5)	**24 (9:39)**	-2 (-12:9)	-2 (-12:9)	**30 (14:45)**	**206 (145:267)**
Patients with other malignancies vs patients with benign conditions						
50th percentile	**-21 (-30:-12)**	9 (-3:22)	**-13 (-18:-8)**	**5 (3:8)**	-2 (-9:6)	**-47 (-60:-34)**
75th percentile	**-211 (-226:-196)**	**-6 (-11:-2)**	**-27 (-36:-17)**	**4 (0:7)**	-15 (-43:13)	**-285 (-296:-274)**
Patients presenting with a lump vs patients presenting without a lump						
50th percentile	26 (-3:56)	**-19 (-26:-12)**	4 (-2:10)	**-4 (-7:-1)**	-9 (-22:3)	-4 (-40:31)
75th percentile	**39 (11:67)**	**-30 (-42:-17)**	**-21 (-28:-14)**	**-7 (-10:-3)**	-11 (-52:29)	**121 (75:167)**
Patients presenting with pain vs patients presenting without pain						
50th percentile	**40 (18:61)**	**12 (1:23)**	5 (-3:13)	1 (0:3)	**17 (12:21)**	**78 (60:96)**
75th percentile	19 (-10:47)	**14 (5:23)**	**16 (7:26)**	1 (-2:4)	**37 (23:51)**	**82 (58:105)**
Patients where GP initially suspected malignancy vs patients where GP did not suspect malignancy[1]						
50th percentile	**-41 (-54:-28)**	-1(-12:10)	**-20 (-29:-11)**	-1 (-2:1)	-31 (-68:7)	**-104 (-117:-91)**
75th percentile	**-187 (-202:-171)**	**-21 (-28:-15)**	**-50 (-62:-38)**	-2 (-5:2)	**-74 (-112:-35)**	**-480 (-516:-445)**
Tumour size over 5 cm vs tumour size under 5 cm[2]						
50th percentile	**26 (7:45)**	0 (-4:4)	**-5 (-9:-2)**	1 (0:3)	2 (-12:15)	**51 (34:69)**
75th percentile	**117 (86:147)**	6 (-7:19)	-6 (-20:8)	2 (-1:4)	15 (-9:39)	**232 (216:249)**
Subfascial depth vs subcutaneous depth[3]						
50th percentile	**-31 (-49:-12)**	2 (-2:5)	3 (-8:14)	1 (-1:3)	**9 (2:16)**	-34 (-81:13)
75th percentile	**-306 (-319:-293)**	-2 (-17:13)	-4 (-16:7)	2 (0:4)	5 (-9:19)	**-296 (-309:-283)**
High-grade tumours vs low-grade tumours[4]						
50th percentile	**-160 (-191:-129)**	-1 (-11:8)	0 (-5:5)	0 (-4:4)	**21 (11:31)**	**-104 (-110:-98)**
75th percentile	**-1195 (-1281:-1110)**	7 (-2:16)	**20 (11:28)**	**4 (1:7)**	**38 (29:46)**	**-1270 (-1288:-1253)**

All estimates are adjusted for age. Bold numbers indicate statistical significance at the 5% level.

[1]Analysis included only patients with soft tissue tumours.

[2]Anaysis included only patients with data, 33 patients with missing data on tumour size excluded.

[3]Analysis included only patients with data available for this variable. Patients who were not seen by the GP and patients where the GP had not answered the question were excluded from the analysis.

[4]Analysis included only sarcoma patients.

Study V

Of the 545 included patients, 143 (26.2%) were referred from the local uptake area of Aarhus University Hospital. Ninety-one patients (16.7%) were referred from the local uptake area without pre-referral MRI and/or CT and/or histology, and 357 (65.5%) were referred from outside the local uptake area after pre-referral MRI and/or CT and/or histology. The primary care, local hospital, diagnostic and total interval were all significantly longer in the outside group referred after pre-referral MRI and/or CT and/or histology compared to patients referred from the local uptake area without MRI/CT/histology (Table 8). Both the proportion of malignancies and the proportion of sarcomas was significantly higher in the outside group referred after pre-referral MRI and/or CT and/or histology when compared to the group referred from the local uptake area without pre-referral MRI and/or CT and/or histology ($p < 0.001$) (Table 9). Twelve (3.5%) of the 345 MRI-scans performed locally before referral had to be repeated at the sarcoma centre before a decision of diagnosis/treatment could be made; none of the CT scans were repeated.

Table 8: Estimated difference in time intervals between patients referred from outside the Aarhus Local uptake area after MRI and/or CT and/or histology performed locally vs patients referred from Aarhus local uptake area without MRI and/or CT and/or histology performed locally. Measured as difference in calendar days at the 50th percentile and 75th percentile with 95% confidence intervals (CI), calculated by quantile regression.

Percentile	Patient Interval	Primary care Interval	Local Hospital Interval	Sarcoma Centre Interval	Diagnostic Interval	Total Interval
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
50th percentile*	13 (0:27)	**14 (9:19)**	**27 (16:38)**	-3 (-7:1)	**41 (30:51)**	**91 (76:106)**
75th percentile*	**-47 (-61:-32)**	**37 (27:48)**	**51 (36:65)**	**-6 (-8:-4)**	**61 (29:94)**	**110 (95:124)**

*All analyses adjusted for age

Bold numbers indicate statistical significance at the 5% level.

Table 9: Proportion of malignancies and sarcomas, by referral pathway

Referral pathway (*n*)	Proportion of malignancies (*n* (%))*	Proportion of sarcomas (*n* (%))
Referred from Aarhus local uptake area		
With MRI or CT or histology (*n* = 52)	13 (25.0)	9 (17.3)
Without MRI or CT or histology (*n* = 91)	13 (14.3)	6 (6.6)
Referred from outside Aarhus uptake area		
With MRI or CT or histology (*n* = 357)	134 (37.5)	84 (23.5)
Without MRI or CT or histology (*n* = 45)	10 (22.2)	3 (6.7)

*Includes all sarcomas and other malignancies

Discussion

Methodological considerations

Study design

All studies in this thesis were designed as retrospective observational studies. This approach is not comparable to a randomised study for evaluating the effects of CPPs, but Danish CPPs were implemented nationally with mandatory compliance for all hospitals, thus eliminating the possibility of randomisation. Further, it would be unethical to offer a rapid diagnostic process only to a selected patient group when the absence of adverse effects of delay on prognosis is unproven. The retrospective observational approach is therefore the best available method to study the effect of CPPs in Denmark. However, the observational design limits the possibility of inferring absolute causality from observed associations, and our results should be interpreted with this in mind.

Selection bias

Selection bias means a systematic error in results due to a selected study population that is not representative of the population intended to be analysed.

In **studies I and II,** we sought to investigate the development in time intervals and presence of alarm symptoms in the patient group for which the sarcoma CPP was intended, namely patients referred to ASC for final diagnostics and possible treatment of a suspected sarcoma after investigations at other hospitals outside AUH. As described earlier, the local population of AUH is in a special position because the ASC is their local orthopaedic department, and they enter the sarcoma CPP through a backdoor without any requirements for pre-referral investigations. In these patients, there is a lower degree of suspicion, which necessitates additional imaging investigations not accounted for in the CPP-defined time limits. They are thus not representative of the patient population for whom the CPP should improve the diagnostic trajectory. This is also the case for the few patients referred directly from a GP outside the Aarhus local area. We therefore excluded all patients referred directly from a GP or from other departments within AUH. The exclusion process was based on codes extracted from the hospital administrative system, and it may be possible that some patients who were referred from hospitals outside AUH, and thus should have been included in our study population, were miscoded as being referred from a GP or from other departments at AUH. This could result in selection bias if the miscoding happened in a non-random fashion linked to both the exposure and outcome studied, for example, if it was only patients with exceptionally long time intervals referred in the year 2010 or only sarcoma patients with alarm symptoms present. Such a selective miscoding is unlikely, as the diagnostic process at ASC begins after the code is registered in the administrative system, and coding is performed by several different secretaries

unrelated to the content of the referral or later diagnosis. We thus believe the selected population for studies I and II is representative for the purposes of the studies.

The same considerations apply for **study III** as the population for this study derives from the study population used in studies I and II. Patients referred after unplanned excisions at the GPs' offices or other departments at AUH are not included in the study, and we cannot know whether these excluded patients differ from the included patients with respect to tumour size and depth and presence of alarm symptoms before removal.

In **studies IV and V,** all consecutive patients referred to the CPP for sarcoma in a confined time period were invited to participate without exclusion of any patient groups. The only patient drop-out was the 62 patients who declined to participate. The non-participants did not differ in age or gender distribution from the included patients, but we do not have any information on the time intervals and malignancy proportion of this excluded patient group. Patients did not know specifically which exposures and outcomes would be linked together in analyses, and they were not aware of their diagnosis at the time of the interview. It is therefore unlikely that the drop-out was associated with both the exposure and the outcome used in analyses, and any bias will thus only be towards the null hypothesis. Further, the small number of non-participants limits the effect of any bias. Regarding GP participation, it is plausible that GPs of patients with long primary care intervals would decline to participate. Depending on the postal time and length of investigations at ASC, the GP may have received notice of the patient's diagnosis before making the decision to decline participation. The GP dropout may thus be associated with both the exposure and outcome for the analysis on waiting times among different diagnosis groups. Overall, the participation rate in studies IV and V was high with regard to both patients and GPs, and included all consecutive patients referred from a large geographical area (Jutland, approx. 2.5 million inhabitants). Thus, we consider the patient group included to be representative of patients referred to a Danish Sarcoma CPP.

Information bias

Information bias means a systematic error that arises due to misclassification of either exposure data and/or outcome data. The misclassification can be non-differential or differential. Non-differential misclassification means that the misclassification of the exposure is independent of the outcome or that the misclassification of outcome is independent of the exposure. This misclassification can only cause bias towards the null hypothesis of no difference. Differential misclassification means that the misclassification of exposure is dependent on the outcome or that the misclassification of outcome is dependent on the exposure. Differential misclassification can cause bias of an association in any direction. Data used in studies I, II and III were collected exclusively from patient medical records. The registration was done by one person, thus limiting any inter-person variability in recording.

In study I, the dates of received referral, first appointment, date of decision and date of treatment were registered in the medical record at the time of the event, and thus hold little uncertainty. For the registration of supplementary diagnostics and other circumstances causing delay some events may not have been registered in the medical records. During the four-year study period, all registration in the medical records at the ASC was done by the same four surgeons, with no known changes in registration methods. Any misclassification of supplementary diagnostics is expected to be equal in all four years, and should not bias the found changes in passive and active waiting time across the four-year study period.

In study II, the final diagnosis was taken from the histology report or the consensus based decision made at ASC, and the outcome thus holds little potential for misclassification. Regarding the symptoms causing the referral, it is possible that some symptoms were not recorded in the medical records. If this misclassification happened differently depending on whether the patient had a sarcoma or not, the results of study II could be biased. The recording of symptoms was done by the referring physician in the referral text and by the surgeons at the ASC immediately after the first appointment at the centre before the final diagnosis had been made. Further, all patients were referred with a suspicion of malignancy and the same attentiveness to describing symptoms was presumably observed in the referral and at the first ASC appointment. We therefore assume that any misclassification of symptoms in study II was non-differential, which may only cause an underestimation of associations.

Study III was more of a descriptive nature, with no definitive exposure and outcome analysed. The same considerations regarding registration of alarm symptoms also apply in this study because it is possible that patients found to have presented initially without alarm symptoms actually had the symptoms, but this was not registered. Further, some patients may also have had imaging investigations performed before surgery that were not registered in the medical records.

In questionnaire studies on time to diagnosis, like **studies IV and V,** there may be problems associated with the measurement of time and dates retrospectively as there is a risk of recall bias. We tried to minimise this problem as much as possible by collecting most dates from the medical records, and not from patient questionnaires. However, the date of first symptom was given solely by the patient and the patient interval and the total interval may thus be misclassified. The direction of any bias resulting from this depends on whether the misclassification is different in the groups analysed, for example, whether patients with a malignant diagnosis recalls the date more accurately than patients with benign conditions. Most patients were unaware of their diagnosis at the time of answering the questionnaire, so this should not be a major problem. A more likely differentiation in misclassification would be that patients presenting with a lump have a better recollection of symptom debut than patients with more diffuse symptoms. For the primary care, local hospital,

sarcoma centre and diagnostic interval, the dates were taken from medical records and GP electronic patient systems, and we consider these data accurate. There were however some non-responding GPs. If, as mentioned earlier, there was a selective drop out of GPs of patients having long primary care intervals, our results could be biased. We used the patient-reported dates of first GP appointment to estimate patient and diagnostic intervals for patients with a missing GP response to abate this problem. However, the primary care interval could not be calculated for patients with missing GP response, and this interval may thus be underestimated. The information on presenting symptoms used in study IV stems from both patient and GP questionnaire data combined with an interview to achieve a detailed and correct registration of all symptoms. It was thus not affected by the previously described problems regarding retrospective registration of symptoms from the medical records. There is however a possibility of recall bias because patients may not remember all the symptoms they have had related to the present condition. If the difficulty of recalling symptoms increases with the length of the patient interval, the misclassification would be differential and bias our results.

Confounding

A confounding factor is a factor associated with both the exposure and the outcome that is unevenly distributed between exposure groups and not a part of the causal pathway between exposure and outcome. As all our studies were designed as observational studies the interpretation of results should be done with the possibility of confounding in mind as our estimates may be affected by unknown, unmeasured or residual confounding.

In **Study I** we found that the time intervals of the diagnostic process at ASC had been reduced in the four-year study period. The most likely explanation is the implementation of the sarcoma CPP in the middle of the study period. However, we cannot conclude this with absolute certainty as causality cannot be inferred from an observational study. The reduction in time intervals may be caused by some unknown factor coinciding with CPP implementation. To our knowledge there were no other initiatives aimed at reducing time intervals for sarcoma patients in the study period, and there were no other changes in diagnostics and treatment at ASC apart from the CPP-related organisational changes. The non-parametric test used for evaluating the development in time intervals across years did not permit any adjustment for confounding factors, and this was not relevant for the purposes of the study.

The quantile regression used in **studies IV and V** was adjusted for age because this factor varied significantly between analysed groups and affected the time intervals. This is expected as sarcomas are more prevalent in certain age groups, which affects the degree of suspicion and timeliness of referral. Age was entered into analyses as a categorical variable, which may introduce

residual confounding of age. Gender was left out in the final analyses, as this factor did not differ between the exposure groups. Further, sarcoma is not a gender-specific disease and gender should thus not affect the diagnostic pathway within the health system. There are several possible confounders not adjusted for, such as comorbidity and socioeconomic status, which may affect time intervals. Data on these confounders were not collected. When repeating the quantile regression analyses with adjustment both for age and gender, the addition of gender did not change the point estimates but widened confidence intervals considerably, indicating that the addition of this possible confounder only lowered the statistical precision of the analyses. This is probably due to the fairly small sample size, and inclusion of further confounders in the analyses could jeopardise the validity and stability of the regression model. However, these unmeasured confounders and other unknown confounders should be kept in mind when interpreting results.

Statistical precision and choice of analyses

It is not advisable to rely solely on *p*-values to define significance, especially with small sample sizes. We therefore report the statistical precision as 95% CIs when appropriate. All medians are also supplied with IQIs to reflect the spread of data. We used strictly non-parametric methods for all analyses of time intervals. Time interval data are known to be right skewed, with a long tail of outliers. This affects the calculation of the mean, which, as a consequence, will be misleadingly high and not representative of the central tendency of the population. The median is less affected by outliers and is thus a better measurement of central tendency. However, the non-normal distribution of the data limits the available methods for comparisons between groups. For comparison of time intervals between two groups, the Wilcoxon Rank Sum Test would be an appropriate choice. However, in study I we wanted to examine whether the development in time intervals seen across the four years was significant, not compare two years against each other. We therefore chose to use a non-parametric test for trend across ordered groups, as this is an extension of the Wilcoxon Rank Sum Test suitable for comparison of more than two groups with a natural ordering. In studies IV and V, we compared two groups against each other which could be done with the Wilcoxon Rank Sum Test, but this test does not compare medians against each other, only ranks, and cannot be adjusted for confounders. As we were interested in the difference in median and the 75th percentile between the groups, quantile regression was chosen. This method is more robust against outliers and is thus appropriate for non-normally distributed data. Further, the method allows adjustment for confounders. The STATA procedure for quantile regression written by Miranda was used as this is designed specifically for use on discrete count data with many ties by applying jittering methods [157]. Quantile regression was chosen over logistic regression as this method would require categorisation of time intervals, with a resulting loss of information and risk of confounding.

Further, logistic regression would only provide odds ratios, which can be difficult to interpret.

Generalisability

Our results with regard to the effect of CPPs, symptoms and pre-referral imaging on time intervals are highly dependent on the organisation of the Danish health system, and generalisation of time intervals to other countries should be done with caution. Our results give a strong input on how waiting time can be reduced, but the success of implementing similar initiatives elsewhere will depend on the available hospital resources, financing and cultural differences. These considerations also apply for study III as reasons for unplanned excision will differ depending on the organisational structure of the diagnostic pathway. The predictive values of alarm symptoms found in study II are only representative of a population seen at a highly specialised sarcoma centre, and they may not be transferred to patients in general practice or any other population in which the prevalence of the disease is lower. However, if the prevalence of the disease is the same, for example in populations seen at foreign sarcoma centres, our numbers may be used for comparison.

Discussion of results

Effects of the Cancer Patient Pathways

We saw in our first study that the time intervals of the diagnostic process at ASC were reduced over the four-year period. We believe that a great part of this drop in time expenditure can be attributed to the CPP implementation, although no direct causality can be inferred, as discussed previously. The changes started already in 2008, which can be explained by the implementation of CPPs for more common cancer forms that started already from the beginning of 2008. The CPPs for rarer cancer forms such as sarcoma were postponed to 2009; however the implementation was anticipated and prepared for and the changes in the diagnostic process probably happened gradually during 2008. This gradual decrease in time intervals was also seen for other cancer forms during the implementation of CPPs [5]. Our study is the first to report the effects of the Danish CPP implementation for suspected sarcoma patients, and the literature on comparable initiatives for suspected sarcoma patients in other countries is limited. The initiatives that are most similar are the 2WW pathways and NICE guidelines in the UK, which have encountered several challenges. Firstly, the adherence to these guidelines has been reported to be low, and great delays for sarcoma patients persisted after implementation [44,45,145,158]. Further, it has been indicated that the 2WW pathways and NICE guidelines have not reduced time intervals for sarcoma patients [48,146,158,159], although it has reduced the diagnostic interval for other cancer forms [136]. On the contrary, the waiting time has been reported to increase because many sarcoma patients fall outside referral criteria and are diagnosed outside the 2WW [145,146]. Finally, the 2WW has not resulted in the diagnosis of more sarcomas, only an increase in patients referred with benign conditions taking up valuable sarcoma specialist capacity [145,146,158]. The problem of low adherence to guidelines for sarcoma management has also been reported from the Netherlands [120], but adherence improved after the guidelines were made more standardised [83]. These studies do not report time intervals or proportion of benign referrals. Sweden has had guidelines for referral of sarcoma patients for many years, with good adherence [85], although results have only been reported for a small geographical area of Sweden. No comparison of time intervals before and after implementation of guidelines is given in this study, but the authors report that there has been no great increase in referrals of patients with benign conditions. Fast-track programmes have also been implemented in Spain, but only in selected geographical regions. Reports on other cancer forms state that the time to diagnosis has been reduced after the Spanish implementation [80-82]; however, no data on time intervals before the implementation are provided, and thus any improvement cannot be evaluated. Another Spanish study from a different region has reported great delays for sarcoma patients, although guidelines for referral of patients exist [50]. Finally, guidelines for referral of sarcomas have also been adopted in Scotland, and good adherence and a

reduction in processing time at a sarcoma centre are reported, but no information on the proportion of patients with benign conditions has been provided [86].

The success of Danish Cancer Patient Pathways in reducing time to diagnosis has been reported for several other cancer forms [88-91,93,94], in accordance with our findings. This good compliance to the aim of reducing waiting time is to a large extent due to the top-down implementation following a unique cooperation between politicians and health professionals in designing the diagnostic pathways. Further, and most importantly, the implementation was backed by a large financial investment for the procurement of necessary staff and medical equipment to carry out the diagnostic programmes within time limits. This financial interest also ensures continued compliance because waiting times are monitored by the government, and if the proportion of patients breaching the time limits becomes too high, the responsible department may be subject to sanctions or withdrawal of financial support. Our results showed that the proportion of patients being diagnosed and treated within the time limits increased after implementation. However, 17% of the patients going through the entire sarcoma programme from referral to treatment in 2010 breached the time limits, but most of these patients were delayed because of supplementary diagnostics. No other studies on Danish CPPs have differentiated between patients following the standard diagnostic programme and patients undergoing supplementary diagnostic procedures, and we have demonstrated that the compliance to CPP time limits is vulnerable to patients stepping outside of the ideal pathway described in the CPP.

The effects of CPPs on more long-term outcomes, such as survival and tumour stage, have not been investigated specifically for sarcoma patients, and these outcomes were not part of our studies. However, CPPs have been found to be an independent prognostic factor for survival in colorectal cancer [92]. For head and neck cancer, the tumour grade was found to be higher after the CPP implementation compared to before [91], whereas another Danish study investigating several cancer forms found that there was no difference in tumour stage distribution before and after CPP implementation and that patients referred in a CPP were less likely to have a localised tumour compared to patients referred outside a CPP [95]. This difference in results is most likely due to confounding by severity, and this has been shown in other studies as well [160]. Overall, the survival of Danish cancer patients continues to increase and it has been argued that this can be attributed to the Danish Cancer plans, and especially the CPPs [161]. Whether this is also the case for sarcomas remains to be seen.

A concern related to the implementation of Cancer Patient pathways is that patients may react negatively to the expedited diagnostic process, which leaves little time for reflection and adjustment. Our impression after patient interviews was that most patients handled this acceptably and preferred to have answers and clarification quickly to relieve their anticipatory anxiety. This is

also supported by another Danish study showing that patients referred to the CPP for head and neck cancer tolerated it well, and although they experienced it as chaotic and overwhelming, they would not have wanted extra time [162].

The predictive value of alarm symptoms

After establishing that the CPP for sarcoma has streamlined the diagnostic process at the ASC, it is important to ensure that the correct patients are selected for the pathway. It has been shown for other cancer forms in Denmark that the reduction in time intervals is far smaller among the patients not referred to a CPP, suggesting that the benefits of CPP implementation require correct referral [93]. For patients to be referred correctly the referring physician must be aware of referral guidelines and be provided with clear and sufficient criteria to select patients for referral. However, a system based solely on alarm symptoms favours only the symptomatic patients, not the ones with vague symptoms [103], although these patients may be the ones who would benefit from being detected because they are in the early stages of their cancer [137]. The selection of alarm symptoms for the sarcoma CPP should thus ideally identify all sarcoma patients to ensure timely diagnosis and treatment, without including too many patients with benign conditions. We found in study I that such an overburdening did not happen because the proportion of sarcomas referred in all four years remained stable and there was a manageable increase in total number of referrals. In study II, we found that the alarm symptoms/signs defined in the sarcoma CPP were predictive of sarcoma, with PPVs in the range of 21–25% and sensitivities ranging from 29% to 82% for each single symptom. Higher sensitivities and PPVs for the same alarm symptoms have been reported in other studies [11,18-20]; however, these studies had a higher prevalence of malignancies in their study populations making comparison difficult. It has been reported from the UK that GPs have difficulties applying 2WW referral criteria because the PPVs are too low [163] and the 2WW criteria only capture a small proportion of patients [132]. This may also be a problem for Danish GPs. PPVs are highly dependent on the prevalence of the disease in the population, and this is what makes the task of spotting cancer patients in a general population so challenging. Cancer symptoms are prevalent in an unselected Danish population [164], and the positive predictive values of alarm symptoms are low [98]. When sarcoma-specific symptoms only reach a PPV of around 20% in a highly selected population seen at our sarcoma centre, one can only imagine how low the PPVs of sarcoma symptoms are in a Danish general practice setting. None of the alarm symptoms were present in all sarcoma patients in study II, and the highest PPVs were seen for combinations of symptoms. The use of symptom combinations has also been suggested by others as a way of increasing the PPV of referral criteria [100]. To our knowledge, no studies on the prevalence of specific sarcoma alarm symptoms in general practice exist, and the sarcoma CPP is thus based on

the symptom presentation seen at specialised sarcoma centres. Although we have shown that the selected symptoms are prevalent among the referred patients and predictive of sarcoma, further studies on symptom presentation in primary care is needed to ensure optimal and effective referral criteria. In a UK sarcoma centre study, it was suggested to reduce the tumour size limit of suspicion from 5 to 4 centimetres as this would increase the sensitivity considerably [19], and the size of a golf ball (4.27 centimetres) has also been advocated as the critical size for sarcoma suspicion [15,20]. However, no considerations are made as to how many extra referrals of patients with benign conditions this change would generate. Future estimates on the relationship between the increase in referral rate versus the increase in referred sarcomas would have to form the basis of such a change in referral policy in Denmark.

Patients falling outside Cancer Patient Pathway referral criteria

The significance of choosing the right inclusion criteria becomes evident when looking at the findings from study III. The proportion of sarcoma patients in studies I and II that were not referred due to alarm symptoms, but after unplanned excisions was quite high (25%). Studies from other countries report that many of the patients referred after unplanned excisions had presented with alarm symptoms before surgery (ranging from 50% to 90%), indicating that the problem can be attributed to disregard of referral criteria [107,109,115]. This does not seem to be the main cause in our study population as 61% of the patients had in fact fallen outside of the alarm symptom criteria. Half of our patients referred after unplanned excisions had a small subcutaneous tumour, which is consistent with findings in other studies [109,110]. Subcutaneous sarcomas are usually smaller and of a lower malignancy grade than deep-seated sarcomas and thus often have a more favourable prognosis [165]. These sarcomas can, however, also be highly malignant with metastatic potential and should be treated in specialist centres [166]. Our findings show that many sarcoma patients simply do not fit into the sarcoma CPP, and alarm symptom referral criteria cannot be trusted blindly. Other indications of malignancy such as regrowth of a previously removed tumour or changes in a tumour that has been present for years should be taken into consideration as well. A strict definition of referral criteria for inclusion in a fast-track pathway does not accommodate for patients without alarm symptoms, and sarcoma patients with atypical presentation may thus be disadvantaged and undergo unplanned excisions.

The problem of patients falling outside of CPP criteria has also been recognised for other cancer forms and a recent development in Denmark after the initial CPP implementation is the introduction of a three-legged strategy for cancer diagnosis [167]. In addition to the cancer-specific CPPs, a CPP for unspecific symptoms has been added to accommodate patients with atypical presentations, and yes-no-clinics with easy access to imaging for GPs are provided for swift

clarification of suspicion. This strategy may also aid in the reduction of unplanned excision for sarcoma patients.

Effect of symptom presentation on time intervals

The importance of alarm symptoms was further underlined when we examined the associations between presenting symptoms/signs and waiting times in study IV. The presence of a visible lump shortened time intervals, especially at the GPs' office, and large tumour size shortened the local hospital time. Presence of alarm symptoms has also been shown to reduce waiting times for other cancer forms in both Denmark [139], and the UK [136]. Further, cancer patients presenting without alarm symptoms have been shown to have a higher mortality compared to patients presenting with alarm symptoms [168]. Sarcoma patients in the UK presenting with 2WW guideline features were found to have shorter waiting times before diagnosis [104], and it seems that this side-lining of patients with atypical presentation may also be happening in Denmark. The presence of pain, which is a more unspecific symptom often encountered in general practice, significantly lengthened time intervals. Pain has been found to be a poor predictor of malignancy in suspected sarcoma patients [15,19,20,48,74], and it has been suggested to remove this feature from referral guidelines for sarcomas as it may confuse physicians [105]. However, these reports are on the predictive value of this symptom for soft tissue sarcomas. Pain is only included in the Danish CPP as a referral criterion for bone sarcomas, and as shown in study II this feature had the highest sensitivity in identifying a bone sarcoma. We believe this separation to be crucial because long lasting pain is often the only symptom of bone sarcomas. Apart from affecting time intervals, pain was also the most frequent reason for seeking medical care for sarcoma patients, and 50% of the soft tissue sarcoma patients in study III had pain related to the tumour. It would thus be faulty to convey to GPs that soft tissue sarcomas should not cause pain. Nielsen et al. also found that pain was the most frequently reported initial symptom at first GP contact among cancer patients, and only 49% presented with alarm symptoms in primary care [140]. However, inclusion of pain as an independent referral criterion for soft tissue sarcoma could result in a great increase in referral of painful benign tumours with none of the other malignancy signs, inconveniencing both patients and sarcoma specialists. Further research into the use of pain as a predictor of soft tissue sarcoma in a primary care setting is needed to clarify this issue.

We found in study IV that the GP plays a large role in expediting the diagnosis of suspected sarcoma patients as an initial presence of GP suspicion of malignancy considerably shortened the diagnostic interval, in accordance with studies on other cancer forms [89,139,144]. The GP was the first health provider contacted by more than 80% of the referred patients in study IV, and owing to the organisational structure of the Danish health system, they act as gatekeepers to the rest of the

diagnostic pathway. A Danish study showed that the number of GP consultations start to increase as early as three months before a cancer diagnosis is made [169], which indicates a potential for spotting cancer patients earlier. However, the GP had only suspected malignancy in about one third of our sarcoma patients, which is lower than the 48% reported by Jensen et al. in a study on GP suspicion of other cancer forms in Denmark [139]. This, along with the finding that sarcoma patients visit significantly more hospital departments and have longer time intervals than patients with benign conditions indicates that sarcomas are difficult tumours to diagnose and may go unnoticed in primary care for a long time. This was also the conclusion in English studies showing that sarcoma patients were more likely to be referred outside the 2WW as non-urgent referrals [143], and had more GP consultations before diagnosis than other cancer forms [170]. The considerations of whether such delay affects the prognosis of sarcoma patients has been discussed previously in this thesis, but attention should be drawn to our finding of a longer diagnostic interval for patients with high-grade malignancies. These patients had a much shorter patient interval and thus also a shorter total interval than patients with low-grade sarcomas, probably due to more severe symptoms causing the patients to seek help earlier. However, the diagnostic interval indicates that high-grade sarcoma patients waited longer in the later stages of their diagnostic journey, and we cannot know whether the high tumour grade was present before this waiting time happened or developed during this period. The retrospective observational design of our study is not suitable for investigating this concern, but the issue should be examined in later studies.

Waiting time before referral to a sarcoma centre

Although successful in reducing the time spent at a sarcoma centre, the sarcoma CPP does not provide time limits for the referral pathway before a patient is seen at the ASC, and our study is the first to provide detailed information on waiting times occurring before the CPP referral for suspected sarcoma patients in Denmark. Other studies have indicated that the waiting time for sarcoma patients does not occur at the end of the diagnostic journey [50], and the blame for delay is often placed on the GPs [45,46]. In our study the greatest part of waiting time for suspected sarcoma patients consisted of the patient interval, followed by the local hospital interval, however the GP interval was the shortest interval with a median of 13 days for sarcoma patients. The patient interval for Danish sarcoma patients of median 77 days is somewhat longer than that reported in most other sarcoma studies, although results range from a median of 13 days to 3 months [11,36,44,50,134]. Only a few other studies have reported on the separate parts of the diagnostic interval [50,134], making comparison difficult as most studies report some kind of combination of the patient, primary care, local hospital and sarcoma centre intervals [11,38,40,44,45,48,52,72,85,86,104]. Ramos-Pasqua et al. reported a primary care interval of

median 31 days which is higher than our finding of approximately one week for the entire patient cohort and 13 days for sarcoma patients [50]. In the study by Lyratzopoulos et al., a median primary care interval of seven days is reported, which is more similar to our numbers. The local hospital interval reported by Ramos-Pasqua et al. is also far longer (51–67 days depending on definition) than our finding of 26 days for sarcoma patients [50]. However, a median waiting time of 26 days at a local hospital is still long, bearing in mind that the time interval data are right skewed, meaning that 50% of patients wait considerably longer. This waiting time at local hospitals for suspected sarcoma patients does not comply with the concept of expedited diagnosis outlined in the overall aim for CPPs, and the diagnostic interval found in our study is longer than that of other cancer forms after CPP implementation [93]. The explanation for this difference can be found in the organisation of the entry to the sarcoma CPP. As described earlier the GP may not refer directly to the ASC when they suspect a sarcoma based on clinical symptom presentation. The patient must be referred to a local orthopaedic hospital for MRI and clinical investigation, and only when this is confirmed at local hospitals may the patient be referred on to the ASC. The CPP does not start until the referral is received at the ASC and there are no time limits described for the diagnostic pathway leading up to the referral. This is contrary to CPPs for other cancer forms where the CPP is initiated by the GP, and all investigations are included as a part of the fast-track pathway. In study V, we were able to evaluate the consequences of this organisation on time intervals, by using the population of patients residing in the uptake area of AUH where the ASC acts as the local orthopaedic department. As these patients may be referred directly to ASC without initial investigations at local hospitals they have their entire diagnostic process performed as a part of the fast-track programme at the ASC. Our results show that investigations at local hospitals with MRI and/or CT and/or histology increased the median diagnostic interval by 41 days and the median total interval by 91 days (adjusted for age). This is in accordance with reports from other countries showing that local investigations lengthen waiting time for suspected cancer patients [52,85,149,150], and direct referral for suspected sarcoma patient has been advocated elsewhere [49,52,85]. Direct referral of suspected sarcoma patients without imaging would significantly lower the proportion of referrals resulting in a diagnosis of malignancy, as seen both in our results in study V and also in studies on sarcoma patients referred under the 2WW pathway in the UK [145,146]. In Sweden, the proportion of malignancies among patients referred to a sarcoma centre is similar to ours although there is no requirement for pre-referral imaging [85]. However, many patients in this study had been investigated with imaging before referral and the conclusions regarding the effect of direct referral on malignancy proportion from this study should be used with caution. Imaging in the early phases of the diagnostic process for sarcoma patients can aid in the prioritisation of onwards referral [147,148], and the practice of direct referral based on symptoms has also been changed in

the UK in 2015. New NICE guidelines now state that suspected sarcoma patients should be investigated with ultrasound before referral [79,171], and this can be a valuable tool in the selection of patients in need of more advanced imaging studies such as an MRI [23,172,173]. Pre-referral imaging definitely has a place in the future diagnostic process of suspected sarcoma patients in Denmark; however, the questions of when and where should be discussed. The time spent on local investigations in Denmark is long, and this is probably due to the serial manner in which investigations are performed. The major organisational change at the ASC after CPP implementation was a shift from serial to parallel investigations where all investigations are initiated at once, thus reducing the waiting time between events. This has not happened at local hospitals outside the ASC and the booking of imaging investigations and doctor appointments are done in accordance with the same waiting time regulations and limited access to imaging as before the CPP. This organisation and the resulting waiting time should be addressed, either by including the local hospital investigations in the fast-track programme and defining recommended time limits, or providing GPs with easier access to fast track imaging. This latter option has also been suggested by other authors as the way forward for cancer diagnostics in Denmark [139,174,175], and should be explored for suspected sarcoma patients.

Conclusions

Study I

We found that the time intervals of the diagnostic process at the ASC were reduced in the period 2007–2010, which was most likely caused by the implementation of CPPs in the beginning of 2009. Further, we showed that the time limits defined in the CPP are vulnerable to deviations from the standard diagnostic programme, and most delays in 2010 were caused by a need for supplementary diagnostics.

Study II

We found that the alarm symptoms/signs defined in the sarcoma CPP were prevalent among patients referred with a suspicion of sarcoma, and predictive of a sarcoma diagnosis. However, no single symptom could identify all sarcomas, and alarm symptoms were also frequently seen among patients with benign conditions. About one third of the sarcoma patients were not referred because of alarm symptoms, but because of an incidental finding after surgery or imaging.

Study III

Among patients referred after unplanned excisions outside the sarcoma centre, 50% had small, superficial tumours and 61% fell outside of referral guidelines and had not presented with alarm symptoms before surgery. Further, 61% of the patients had not received any imaging before surgery was performed. CPPs are not a guarantee for identifying all sarcoma patients and careful review of the diagnosis should be made before removing a tumour.

Study IV

We described the diagnostic journey for sarcoma patients from first symptom to diagnosis, and identified that the largest part of waiting time before referral to a sarcoma centre can be attributed to the patient and the local hospital. Further, the presence of clear symptoms, such as a visible lump and large tumour size, and an initial GP suspicion of malignancy expedited the diagnostic process, whereas the presence of pain increased waiting time.

Study V

We showed that investigation with MRI and/or/CT and/or histology at local hospitals before referral to a sarcoma centre increased waiting times significantly compared to direct referral, but the proportion of malignancies (conversion rate) was more than doubled in the group referred after imaging.

Future aspects

After the development and successful implementation of a sarcoma CPP, it is important to distribute the knowledge of referral rules and the possibility of fast-track referral for this patient group to GPs and other referring physicians. This may be achieved by information campaigns aimed at GPs and other specialists handling potential sarcoma patients, and inclusion of the sarcoma CPP in ongoing education of medical students and specialists in training. Public awareness campaigns on the importance of recognising alarm symptoms and seeking medical care could aid in reducing the patient interval, which constituted the greatest part of the waiting time.

To ensure the correct selection of patients for fast-track referral, more research into symptom presentation and the prevalence of musculoskeletal tumours in a primary care setting is needed. Such studies would provide evidence on the usability of defined alarm symptom criteria for GPs and form the basis for estimates of the potentially increased patient load related to changes in CPP referral criteria.

Continued vigilance to time limits and adherence to referral guidelines will be necessary to sustain the success of the Danish CPPs. Further, the effect of the CPP implementation on more long term outcomes, such as survival, should be investigated to justify the continued efforts to reduce waiting time before diagnosis. The time expenditure at the ASC has now been reduced to a minimum, and future attention should be focused on the time expenditure outside the ASC. The time spent at local hospitals is the next focal point for reducing waiting time for sarcoma patients, and various possibilities should be considered. The requirement for pre-referral investigation with MRI could be removed thus allowing direct referral from GPs to the ASC. This decision would have to be based on estimates of scanner capacity at the sarcoma centre and the increased number of referrals such an initiative would generate. If this option is found to be unrealistic, a consensus on reasonable waiting time for investigations at local hospitals should be reached between sarcoma specialists and local hospital administrators. Hereafter, the defined time limits may be included in the fast-track description and the CPP extended to include the work-up at local hospitals. This would not affect the ASC scanner capacity and the time spent at local hospitals could be shortened as there is a nation-wide consensus on compliance with CPP guidelines and the local hospital time interval would be included in national monitoring. This would also enable GPs to initiate the CPP promptly when alarm symptoms are identified. Finally, Danish GPs could be given better access to imaging investigations. If the GPs could book the necessary investigations to justify the suspicion and hereafter react to this by prompt referral to a sarcoma centre, the entire local hospital waiting time would be spared. The feasibility of this latter initiative should be investigated in a randomised clinical trial to evaluate MRI use and increase in number of referrals to the ASC.

English summary

Sarcoma patients often experience delay before a diagnosis is made, which may affect patient experience, prognosis and treatment outcome. Delay before diagnosis has also been reported for many other cancer forms, and the problem has received increased attention in recent years. Denmark implemented Cancer Patient Pathways (CPPs) in 2008/09 to abate the problem, and these pathways describe the ideal diagnostic pathway for suspected cancer patients, hereunder criteria for referral, suggested diagnostic work-up and time limits for each phase. The effects of this implementation for patients suspected of a sarcoma have not been investigated, and the diagnostic journey leading up to referral to a specialised sarcoma centre is sparsely described. To ensure timely diagnosis and optimal management of sarcoma patients it is important to identify where waiting time happens and possible areas of improvement. Overall, this thesis sought to investigate the immediate effects of the Danish CPP for sarcomas and describe the diagnostic journey of suspected sarcoma patients in the new steady state after CPP implementation.

In study I, we examined the effect of the CPP on time intervals at the Aarhus Sarcoma Centre (ASC) two years before and two years after implementation, among all patients referred because of a suspicion of malignancy from hospitals outside the catchment area of Aarhus University hospital (AUH). Further, we described reasons for delay among patients exceeding time limits. In study II, we examined the presence and predictive values of alarm symptoms/signs defined as CPP referral criteria in the same study population. In study III, we looked closer at 64 sarcoma patients found in study II that had been referred to the ASC after an unplanned excision or biopsy performed elsewhere. In study IV we described the time intervals of the entire patient journey from first symptom to diagnosis and examined whether waiting times were affected by presenting signs and symptoms. In study V, we compared time intervals and proportion of malignancies between patients referred to the CPP at the ASC after initial investigations (MRI/CT/histology) performed at local hospitals other than AUH and patients referred from the Aarhus area without these investigations. The study population for studies IV and V consisted of a prospectively collected population of all consecutive patients referred to the CPP for sarcoma during a one-year period (1st of September 2014 to 31st of August 2015).

In study I, we found that time intervals at the ASC had been reduced over the four-year period, most likely due to the CPP implementation. Most delays in 2010 were caused by a need for supplementary diagnostics, indicating that the adherence to time limits are vulnerable to deviations from the standard diagnostic programme. In study II, we showed that defined alarm symptoms were frequent among referred patients and predictive of a sarcoma; however, one third of sarcoma patients were not referred due to alarm symptoms but diagnosed incidentally after imaging or unplanned surgery. Study III showed that 50% of the patients referred after unplanned surgery in

study II had small superficial tumours, and 61% had not presented with alarm symptoms and thus fell outside of CPP referral criteria. Study IV showed that the main part of the total interval from first symptom to diagnosis for suspected sarcoma patients (median 155 days) could be attributed to the patient interval (median 54 days), followed by the local hospital interval (median 26.5 days). The presenting signs and symptoms modified some of the time intervals, with presence of alarm symptoms and GP suspicion shortening health system intervals. Study V showed that patients investigated with MRI and/or CT and/or histology at local hospitals had significantly longer median time intervals compared to patients referred without these investigations, with an estimated age-adjusted difference in median diagnostic interval of 41 days. The proportion of malignancies was significantly higher in the group referred after MRI/CT compared to the group referred directly (37.5% vs 14.3%).

In conclusion, we showed that the Danish CPP for sarcomas has accelerated the diagnostic process at the ASC and that the defined alarm symptoms are predictive of a sarcoma and prevalent among referred patients. However, a large proportion of patients fall outside of the alarm symptom referral criteria, and patients presenting with nonspecific symptoms have longer waiting times. A CPP can only benefit the patients referred to it, and initial GP suspicion of malignancy is thus crucial for an earlier diagnosis. Finally, the CPP time limits do not apply to the diagnostic process happening before referral to a CPP and performing imaging investigations at local hospitals significantly lengthens time intervals. This problem needs to be addressed, possibly by providing easier access to imaging for GPs or inclusion of the diagnostic process at local hospitals as a part of the sarcoma CPP with appurtenant time limits.

Danish summary

Sarkompatienter oplever ofte ventetid, før de får sin diagnose og dette kan påvirke patientens oplevelse af forløbet, prognosen og behandlingsresultatet. Lange ventetider før diagnose er også blevet beskrevet for andre kræftformer, og opmærksomheden på dette er øget de seneste år. I Danmark implementerede man i 2008/09 pakkeforløb på kræftområdet for at afhjælpe problemet. Pakkeforløbene beskriver det ideelle diagnostiske forløb for patienter mistænkt for at have kræft, herunder en definition af alarmsymptomer, der skal fungere som henvisningskriterier, anbefalede diagnostiske undersøgelser og tidsgrænser for hver udredningsfase. Virkningen af denne implementering for patienter mistænkt for at have et sarkom er ikke blevet undersøgt, og de udredningsforløb, der har ført til henvisningen til et højt specialiseret sarkomcenter, er kun sparsomt beskrevet. Det er vigtigt at undersøge hvor ventetid opstår, og dermed identificere mulige forbedringsområder for at sikre en rettidig diagnose og optimal håndtering af sarkompatienter. Det overordnede formål med denne afhandling var at undersøge de umiddelbare virkninger af det danske pakkeforløb for sarkomer og beskrive udredningsforløbet for patienter mistænkt for at have et sarkom i denne nye fase efter implementeringen af pakkeforløbene.

I studie I undersøges virkningen af pakkeforløbene på de forskellige tidsintervaller i udredningsprocessen ved Aarhus Sarkom Center (ASC) blandt alle patienter henvist med mistanke om sarkom fra sygehuse uden for Aarhus Universitetshospitals (AUH) optageområde, to år før og to år efter implementeringen. Endvidere bliver årsagen til forsinkelser undersøgt blandt patienter, der overskrider tidsgrænserne. I studie II undersøges tilstedeværelsen og den prædiktive værdi af alarmsymptomer og kliniske tegn, der er defineret som henvisningskriterier i pakkeforløbet, i den samme studiepopulation. I studie III kigges der nærmere på 64 sarkompatienter fra studie II, der var blevet henvist til ASC efter kirurgi eller biopsi udført andetsteds. I studie IV beskrives tidsintervallerne for hele udredningsforløbet fra første symptom til diagnose, og det undersøges, om ventetiden påvirkes af de symptomer og kliniske tegn, patienten præsenterer. I studie V sammenlignes tidsintervaller og andelen af maligne tilstande mellem henholdsvis patienter henvist til pakkeforløbet ved ASC efter indledende undersøgelser (MRI/CT/histologi) udført på lokale sygehuse uden for AUH og patienter henvist fra AUHs optageområde uden disse undersøgelser. Studiepopulationen for studie IV og V bestod af en prospektivt indsamlet patientgruppe henvist til sarkompakkeforløbet over en etårig periode (1. september 2014 til 31. august 2015).

I studie I fandt vi, at tidsintervallerne ved ASC var blevet reduceret over den fireårige periode, hvilket mest sandsynlig kan tilskrives pakkeforløbene. De fleste forsinkelser i 2010 var forårsaget af et behov for supplerende diagnostiske undersøgelser, hvilket indikerer at overholdelsen af tidsgrænserne er sårbar over for afvigelser fra det diagnostiske standardprogram. I studie II fandt vi, at de definerede alarmsymptomer og kliniske tegn er hyppige blandt de henviste patienter og

prædiktive for sarkom, men samtidig at en tredjedel af sarkompatienterne ikke blev henvist på grund af alarmsymptomer, men efter tilfældige fund på billeddiagnostik eller efter utilsigtet kirurgi. Studie III, viste at 50% af patienterne, der var blevet henvist efter utilsigtet kirurgi i studie II, havde små overfladiske tumorer, og 61% havde ikke præsenteret med alarmsymptomer før operationen og faldt dermed uden for pakkeforløbets henvisningskriterier. I studie IV fandt vi, at hovedparten af tiden fra første symptom til diagnose for patienter mistænkt for at have et sarkom (median 155 dage) bestod af patientintervallet (median 54 dage) efterfulgt af den tid der blev brugt på lokale hospitaler (median 26.5 dage). De præsenterede symptomer og kliniske tegn påvirkede nogle af tidsintervallerne, og særlig tilstedeværelsen af alarmsymptomer og den praktiserende læges mistanke om kræft forkortede tidsintervallerne indenfor sundhedssystemet. Studie V viste, at patienter undersøgt med MRI og/eller CT og/eller histologi på lokale hospitaler havde signifikant længere tidsintervaller sammenlignet med patienter henvist uden disse forudgående undersøgelser, med en estimeret aldersjusteret forskel i median diagnostisk interval på 41 dage. Andelen af maligne tilstande var signifikant højere i gruppen henvist efter MRI/CT sammenlignet med gruppen henvist direkte (37.5% vs 14.3%).

Afslutningsvis har vi vist, at det danske pakkeforløb for sarkom har accelereret udredningsforløbet ved ASC, og at de definerede alarmsymptomer er prædiktive for sarkom og samtidig prævalente blandt de henviste patienter. Der er dog en stor andel af patienterne, der falder uden for disse kriterier, og patienter, der præsenterer uspecifikke symptomer, har længere ventetid før diagnose. Et pakkeforløb kan kun gavne de patienter, der bliver henvist til det, og initial sarkommistanke ved den praktiserende læge er således afgørende for at sikre en tidlig diagnose for sarkompatienter. Pakkeforløbets tidsgrænser inkluderer ikke den udredning, der sker før henvisning til centeret, og udførelse af billeddiagnostik på lokale sygehuse forlænger ventetiden markant. Dette problem bør adresseres, for eksempel ved at give den praktiserende læge nemmere adgang til billeddiagnostik eller at inkludere udredningen ved lokale sygehuse i sarkompakkeforløbet med dertilhørende tidsgrænser.

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Appendix

Appendix 1: Registration form used for data collection in studies I, II and III

Appendix 2: Patient questionnaire used for data collection in studies IV and V

Appendix 3: General practitioner questionnaire used for data collection in studies IV and V

Appendix 1: Registration form used for data collection in studies I, II and III

Version 9 d.15/04-11

Navn:_____

CPR.nummer:_____

Mistanke om sarkom i ..... |__|
1 Bløddele
2 Knogle

Forløb forudgået af vurdering af billeder før henvisning.....|__|
1 Ja..... Dato for modtagelse af billeder|__|__|__|__|__|__|
2 Nej

Dato for modtagelse af inkomplet henvisning ..... |__|__|__|__|__|__|
Dato for modtagelse af komplet henvisning ..... |__|__|__|__|__|__|

Dato for 1. fremmøde..... |__|__|__|__|__|__|

Varighed af symptomer ..... |__|__|__| dage

SYMPTOMER (1= ja, 2= nej)

Tumor i bløddele > 5cm i diameter .....|__|
Tumor i bløddele på eller under fascien .....|__|
Palpabel tumor i knogle .....|__|
Dybe vedvarende knoglesmerter .....|__|
Tumorer i bløddele i hurtig vækst.....|__|
Tilfældigt fund ifm. billeddiagnostik i området.....|__|
Uventet fund af sarkom ved postoperativ patologivurdering .....|__|
Obs. recidiv af kendt sarkom .....|__|
Andre symptomer .....|__|
Hvilke:_____

UNDERSØGELSER

Undersøgelser udført før henvisning til centret (1 = ja, 2 = nej)
MR af tunor.....|__|
CT af tumor.....|__|

Standardundersøgelser (1 = ja, 2 = nej)
Røntgen af thorax.....|__|
CT af thorax .....|__|
PET-CT .....|__|
MR (Kun pt. som henvises med en bekræftet diagnose).....|__|
Scintigrafi.....|__|
Biopsi .....|__|__|
Dato for biopsi..... |__|__|__|__|__|__|
(2. tal ved biopsi: 1 nåle, 2 Åben, 3 Excision)

Supplerende undersøgelser (1 = ja, 2 = nej)
CT.....|__|
PET-CT .....|__|
MR.....|__|
Ultralyd.....|__|
Røntgen .....|__|
Supplerende scintigrafi.....|__|
Rebiopsi.....|__|
Udvidet histopatologisk vurdering.....|__|
Second opinion.....|__|

Følger patienten standardforløbet.....|__|
1 Ja
2 Nej

Dissemineret sygdom ..... |__|
1 Ja
2 Nej

FORSINKELSER

Patienten har ønsket time-out .....|__|
1 Ja..... |__|__|__| hverdage
2 Nej

I hvilken fase ligger timeout..... |__|
1 Fase 1
2 Fase 2
3 Fase 3

Fremstillelse af specialprotese..... |__|
1 Ja
2 Nej

Dato for afsluttet udredning ..... |__|__|__|__|__|__|

BEHANDLING

Diagnose i pakkeforløb..... |__|__|

1. tal: 1 Sarkom 2 Ikke sarkom

2. tal ved Ikke sarkom: 1 Udgået efter vurdering i centret af billeder+ sygehistorie, 2 Udgået efter afsluttet udredning, 3 Udgået efter operation.

Primær behandling .....|__|
1 Operation
2 Stråleterapi
3 Kemoterapi
4 Observation (Chondromatøse tumorer)
5 Ingen behandling

Dato for start af primær behandling ..... |__|__|__|__|__|__|
Dato for reresektion.....|__|__|__|__|__|__|

Sarkomdiagnose stillet efter pakkeforløb er afsluttet.....|__|
1 Diagnose stillet efter en observationsperiode
2 Diagnose stillet efter operation af en formodet benign tumor
3 Diagnose stillet efter fornyet udredning
4 Andet

Andet: .....

Dato for diagnose ..... |__|__|__|__|__|__|
Dato for 1. behandling.....|__|__|__|__|__|__|

TUMOR største diameter..... |__|__|__| mm

TUMOR LOKALISATION

BLØDDELE |__|__|

1 Hoved hals
2 Thorax
3 Abd/Lænd
4 Skulder
5 Overarm
6 Albue
7 Underarm
8 Håndled/hånd
9 Gluteal
10 Lår
11 Knæ
12 Underben
13 Fodled/Fod
14 Andet
17 Mamma
18 Genitalia externa

KNOGLE |__|__|

1 Hoved
2 Vertebra
3 Clavikel
4 Scapula
5 Ribben
6 Humerus
7 Ulna
8 Radius
9 Hånd
10 Sacrum
11 Pelvis
12 Femur
13 Tibia
14 Fibula
15 Fod
16 Andet

Region |__|
1 Proksimal, condyl
2 Midt, diafyse
3 Distal, condyl

Fraktur |__|
(1 Ja, 2 Nej)

UDBREDNING

BLØDDELE |__|
1 Kutan
2 Subkutan
3 Subfasciel

KNOGLE |__|
1 Intraossøs
2 Kortikal gennemvækst
3 Udbredning til bløddele

HISTOGENETISK TYPE

BLØDDELE |__|__|

Malign
1 Chondrosarcom, ekstraos.
2 Dermatofibrosarcom
3 Fibrosarcom
4 Leiomyosarcom
5 Liposarcom
6 Malignt lymfom
7 Malignt swannom
8 MFH
9 Osteosarcom, ekstraos.
10 Rhabdomyosarcom
11 Synovialt sarcom
13 Andet
14 Uklassificerbar

30 Alveolært sarcom
31 Angiosarcom
32 Malignt hæmangiopericytom
33 Clear cell sarcom
34 Desmoplastisk small round cell
35 Epiteloidt sarkom
36 Infantilt fibrosarkom
37 Solitær fibrøs tumor
39 Kaposis sarcom
40 PNET

KNOGLE |__|__|

Malign
1 Ewing sarcom
2 Chondrosarcom, klassisk
4 Kæmpecelletumor
5 Osteosarcom, klassisk
7 Malignt lymfom
8 Myelomatose
9 Kordom
10 Andet
11 Uklassificerbar
30 Ademantinom
31 Angiosarkom
32 Dedifferentieret chondrosarcom
33 Juxtacortical chondrosarcom
34 Fibrosarkom
35 Udiff. pleomorft sarcom el. MFH
36 Chondroblastisk osteosarcom
37 Teleangiektatisk osteosarcom
38 Fibroblastisk osteosarcom
39 Parostealt osteosarcom
40 Periostalt osteosarcom
41 Small cell osteosarcom

Benign	Benign
21 Desmoid	21 Aneurismatisk knoglecyste
22 Hæmangiom	22 Chondrogenetisk
23 Lipom	23 Eosinofilt granulom
24 Myxom	24 Kæmpecelletumor
25 Neurilemmon	25 Non-ossificerende fibrom
26 Nodulær fasciitis	26 Osteogenetisk
27 Andet	27 Simpel knoglecyste
15 Aggressiv fibromatose	
	28 Andet
80 Metastase	80 Metastase
90 Anden lidelse	90 Anden lidelse
Andet: _____	Andet: _____

Histologisk gradering (Trojani): |__|
1 Benign
2 Lavmalign (grad 1)
3 Højmalign (grad 2 eller 3)

MONITORERINGSINTERVALLER

Fra modtaget henvisning til 1. fremmøde ..... |__|__|__| hverdage
Fra første fremmøde til afsluttet udredning ..... |__|__|__| hverdage
Fra afsluttet udredning til start af behandling ..... |__|__|__| hverdage
Fra modtaget henvisning til start af behandling..... |__|__|__| hverdage
Fra første symptom til start af behandling ..... |__|__|__|__| dage

Appendix 2: Patient questionnaire used for data collection in studies IV and V

TIDLIG OPSPORING AF BLØDDELS- OG KNOGLESARKOMER
Samtykkeerklæring

Samtykke til indhentning af journaloplysninger

Undertegnede giver hermed Aarhus Sarkomcenter, Ortopædkirurgisk Afdeling E, Aarhus Universitetshospital, Nørrebrogade, tilladelse til på mine vegne at indhente journal oplysninger samt information fra egen læge vedrørende nuværende lidelse til brug i forskningsprojektet "Tidlig opsporing af bløddels- og knoglesarkomer".

Dit fulde navn: _____

Skriv med blokbogstaver

_____

Dit CPR-nummer: | | | | | | | - | | | | |

Dato: | | - | | | - | | | | |

Dag **Måned** **År**

Underskrift: _____

36088

SPØRGESKEMA VEDRØRENDE HOSPITALSKONTAKT, SYMPTOMER OG KLINISKE TEGN
Patientspørgeskema

Generel information

Spørgsmålene vedrører kun den problemstilling, du aktuelt er henvist til Aarhus Sarkomcenter for. Symptomer fra andre sygdomme, du lider af, og hospitalskontakt i forbindelse med disse skal ikke medregnes.

Vi gennemgår spørgeskemaet ved din ambulante aftale. Er du usikker på udfyldelsen af et spørgsmål, bedes du derfor efterlade dette spørgsmål ubesvaret. Vær opmærksom på at skemaet har flere sider.

For mindreårige patienter under 15 år udfyldes skemaet af/sammen med forældre.

Symptomer og fysiske tegn

1. **Hvilken dato blev du første gang opmærksom på tegn eller symptom(er) fra den nuværende problemstilling?** Hvis du ikke kan huske den præcise dato, kan du blot angive måned og år.

   ☐☐ - ☐☐ - ☐☐☐☐
   DAG MÅNED ÅR

2. **Hvilke fysiske tegn eller symptomer havde du den <u>første gang du blev opmærksom</u> på den nuværende problemstilling?**

   _____

   _____

   _____

   ☐ *Dette er ikke relevant for mig, da lidelsen blev fundet tilfældigt uden at jeg havde haft symptomer(i så fald, besvar herefter kun spørgsmål 6 og 8).*

3. **Hvilken dato præsenterede du første gang disse symptomer/tegn for din egen læge?** Hvis du ikke kan huske den præcise dato, kan du blot angive måned og år.

   ☐☐ - ☐☐ - ☐☐☐☐
   DAG MÅNED ÅR

4. **Er der kommet yderligere symptomer/tegn siden du oplevede det første symptom?**

   ☐ Ja ☐ Nej

   Hvis ja, da hvilke:

   _____

   _____

   _____

Forbeholdt kodning spm 2 ☐☐ ☐☐ ☐☐ ☐☐ ☐☐

Forbeholdt kodning spm 4 ☐☐ ☐☐ ☐☐ ☐☐ ☐☐

42975

Første kontakt til sundhedsvæsenet

5. Hvorfor besluttede du dig for at gå til læge?

_____

_____

Forbeholdt kodning

_____

6. Hvem var den første læge du kontaktede for nuværende problemstilling? (sæt kun et kryds)

☐ Min egen læge

☐ Privatpraktiserende speciallæge

☐ Hospitalslæge

☐ Vagtlæge

Forbeholdt kodning

☐ Anden. Noter venligst: _____

Skriv venligst lægens navn, samt evt. navnet på den private praksis eller hospitalsafdelingen:

_____

_____

_____

Behandling før første kontakt med sundhedsvæsenet

7. Har du selv forsøgt at behandle dine symptomer inden du første gang kontaktede en læge?

☐ Ja ☐ Nej

Hvis Ja, hvilken/hvilke behandlinger? (sæt gerne flere krydser)

☐ Håndkøbsmedicin (Pamol, Ipren, smertestillende gel osv.)

☐ Fysioterapi

☐ Massage

☐ Kiropraktor

Forbeholdt kodning

☐ Akupunktur

☐ Anden behandling. Noter venligst: _____

_____

_____

42975

Du bedes medbringe det udfyldte skema til din ambulante aftale.

Forløb efter første kontakt til sundhedsvæsenet

8. Hvilke læger/andre behandlere har du set i tidsrummet mellem første gang du gik til en læge med dine symptomer og dit første besøg i Aarhus Sarkomcenter?

	Kontakt 1.	2.	3.	4.	5.	6.	7.
Hospitalsafdeling	☐	☐	☐	☐	☐	☐	☐
Privat speciallæge	☐	☐	☐	☐	☐	☐	☐
Fysioterapi	☐	☐	☐	☐	☐	☐	☐
Kiropraktor	☐	☐	☐	☐	☐	☐	☐
Alternativ behandler	☐	☐	☐	☐	☐	☐	☐
Andet	☐	☐	☐	☐	☐	☐	☐

☐ Ingen kontakter mellem første lægekontakt og henvisning til Aarhus Sarkomcenter.

1. kontakt: _____

_____

2. kontakt: _____

_____

3. kontakt: _____

_____

4. kontakt: _____

_____

5. kontakt: _____

_____

6. kontakt: _____

_____

7. kontakt: _____

_____

Appendix 3: General practitioner questionnaire used for data collection in studies IV and V

SPØRGESKEMA VEDRØRENDE PATIENT HENVIST TIL PAKKEFORLØB FOR SARKOMER
Lægespørgeskema

Generel information

Spørgsmålene vedrører kun den problemstilling, patienten aktuelt er blevet henvist til Aarhus Sarkomcenter for. Skemaet bør udfyldes af den læge, der kender forløbet bedst. Vær opmærksom på, at skemaet har flere sider.

Skemaet udfyldes lettest, hvis patientens elektroniske journal er tilgængelig.

Involvering af praksis i udredningen af patienten

1. Var du/praksis ansvarlig for henvisningen af patienten til udredning af den problemstilling patienten er henvist til Sarkomcentret for?

☐ Ja → *Gå venligst videre til spørgsmål 3 og udfyld resten af skemaet*

☐ Nej → *Gå videre til spørgsmål 2*

2. Hvis du/praksis ikke var ansvarlig for henvisning af patienten til udredning, har du/praksis så på noget tidspunkt set patienten med symptomer, der kunne stamme fra den problemstilling, patienten er henvist til Aarhus Sarkomcenter for?

☐ Ja → *Besvar venligst kun spørgsmål 3 og første kolonne af spørgsmål 6*

☐ Nej → *Returner venligst spørgeskemaet til os i den frankerede svarkuvert*

Første konsultation og videre henvisning

3. Hvornår henvendte patienten sig første gang i din praksis med symptomer/tegn på den problemstilling, patienten er henvist til Sarkomcentret for?

☐☐ - ☐☐ - ☐☐☐☐
DAG MÅNED ÅR

4. Hvornår blev patienten henvist til udredning (ansvaret for det videre forløb overgivet til anden læge), og hvortil blev patienten henvist?

☐☐ - ☐☐ - ☐☐☐☐
DAG MÅNED ÅR

Forbeholdt kodning ☐

Sygehus _____ Afdeling _____

Anden institution _____

5. Hvad var den tentative diagnose ved henvisningen?

_____

_____

Forbeholdt kodning ☐☐

_____

42897

Symptomer, objektive og parakliniske fund

6. Hvilke symptomer/objektive fund præsenterede patienten ved første konsultation og ved henvisning for den nuværende problemstilling?

	Ved første konsultation	**Ved henvisning**
		Samme som ved første konsultation ☐
Patientens subjektive klager		
		Samme som ved første konsultation ☐
Evt. objektive fund		
		Samme som ved første konsultation ☐
Evt. parakliniske fund		

Forbeholdt kodning

Subj.	☐☐ ☐☐ ☐☐ ☐☐ ☐☐	Subj. ☐☐ ☐☐ ☐☐ ☐☐ ☐☐
Obj.	☐☐ ☐☐ ☐☐ ☐☐ ☐☐	Obj. ☐☐ ☐☐ ☐☐ ☐☐ ☐☐
Para.	☐☐ ☐☐ ☐☐ ☐☐ ☐☐	Para. ☐☐ ☐☐ ☐☐ ☐☐ ☐☐

Forløbet fra første konsultation i almen praksis til henvisning

7. Hvor mange konsultationer havde patienten vedrørende nuværende problemstilling før henvisningen til udredning *(overgivelse af ansvaret for det videre forløb til anden læge)***?**

☐☐☐ konsultationer

8. Hvilke diagnostiske undersøgelser, som du havde ansvaret for at følge op på, foretog du i relation til nuværende problemstilling før henvisningen til udredning? (sæt gerne flere krydser)

- ☐ Ingen
- ☐ Observation for udvikling ("wait and see")
- ☐ Blodprøver
- ☐ Røntgen
- ☐ CT-scanning
- ☐ MR-scanning
- ☐ Ultralydsscanning
- ☐ Biopsi
- ☐ Andre. Noter venligst: _____

Forbeholdt kodning ☐☐

_____

_____

9. Har patienten modtaget behandling for symptomerne nævnt i punkt 6 inden henvisningen til udredning?

☐ Ja ☐ Nej

Hvis Ja, hvilken/hvilke behandlinger? (sæt gerne flere krydser)

- ☐ Smertestillende
- ☐ Antibiotika
- ☐ Fysioterapi/kiropraktor
- ☐ Operation
- ☐ Anden behandling. Noter venligst: _____

Forbeholdt kodning ☐☐

_____

_____

Dine kommentarer

10. Har du øvrige kommentarer til patientens udredningsforløb eller til udredningen af sarkompatienter generelt?

Kontroller venligst om alle spørgsmål er besvaret.

Det udfyldte spørgeskema bedes returneret til Aarhus Sarkomcenter i den vedlagte svarkuvert.

Mange tak for din deltagelse!

Paper I

Cancer Patient Pathways shortens waiting times and accelerates the diagnostic process of suspected sarcoma patients in Denmark

Heidi Buvarp Dyrop[1,3], Akmal Safwat[1a], Peter Vedsted[2], Katja Maretty-Nielsen[1,3], Bjarne Hauge Hansen[1b], Peter Holmberg Jørgensen[1b], Thomas Baad-Hansen[1b], Cody Bünger[4], Johnny Keller[1b]

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Cancer Patient Pathways shortens waiting times and accelerates the diagnostic process of suspected sarcoma patients in Denmark

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ABSTRACT

Cancer Patient Pathways (CPPs) for suspected cancer were implemented in Denmark to reduce waiting times for cancer diagnosis and treatment. Our study describes developments in time intervals and tumour size in a natural experiment before and after implementation of the CPP for sarcomas (January 1st, 2009). Medical files for patients referred with suspected sarcoma from other hospitals to Aarhus Sarcoma Centre during 2007–2010 ($n = 1126$) were reviewed for data on milestones, time intervals, performed diagnostics, and tumour size. Results showed a statistically significant reduction in median number of work days in the phase "referral to first appointment" for all patients. For bone sarcomas, median time was significantly reduced from 11 to five work days in the phase "first appointment to decision of treatment", for soft tissue sarcomas it was reduced from 28 to 18 work days in the phase "referral to start of treatment". Passive waiting time was reduced, and delays in the fast-track programme were caused mostly by supplementary diagnostics. Median tumour size for soft tissue sarcomas was reduced from 7.0 to 4.9 cm, possibly a secondary effect of increased awareness. CPPs have accelerated the diagnostic process for sarcomas, and our results may aid international development of similar initiatives.

1. Introduction

Sarcomas are rare, representing less than 1% of all newly diagnosed cancers; in Denmark approximately 300 new cases per year [1]. Clinical experience with sarcoma is thus sparse among primary care physicians and at primary hospitals, and treatment should be centralized to specialized sarcoma centres [2,3]. Denmark has two such centres, one in Copenhagen and one in Aarhus. Diagnosing sarcomas is difficult and patients may experience delay caused by misinterpretation of symptoms and lack of awareness among doctors [4]. Delayed cancer diagnosis is heavily debated, both publicly and among medical professionals. A literature review concluded that diagnostic delays in cancer do matter, but it is hard to quantify this in terms of effects on survival or mortality [5]. Another aspect is the patients' experience of delay where no systematic knowledge can

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be found. Studies on other cancer types indicate that time from symptom presentation to diagnosis and treatment has an effect on mortality and stage at treatment [6–8]. However, for sarcomas results are mixed. Studies show that long symptom duration may be associated with better survival, due to low grade tumours [9], with increased mortality [10], or may show no association with survival [11]. Attempts to reduce the diagnostic delay with implementation of guidelines for cancer diagnosis have had varied success, and problems reported include low compliance with guidelines and low awareness of symptoms [12–15]. In Denmark, National Cancer Plans have been introduced in recent years, and a large number of reports and scientific data [16] on delays in cancer diagnosis have been heavily debated in the Danish press. This has resulted in implementation of fast-track programmes (Cancer Patient Pathways (CPPs)), with recommendations for the standard patient's ideal pathway from clinical suspicion of cancer through justified suspicion, diagnostic procedures and final treatment. The objective is to minimize passive waiting time, and only accept delays with academically justified explanations. A clinical coordinator is included in the programme to optimize logistics. Development and implementation of CPPs are described in further detail by Probst et al. [17]. Thus, the CPPs are unique translations of a political demand for faster diagnosis and treatment of cancer patients into organizational management programmes describing agreed diagnostic procedures and time intervals between defined milestones. The initiative was backed by massive political consensus and economical support. The purpose of this study was to investigate this natural experiment analysing the changes in time intervals for suspected sarcoma patients before and after implementation of CPPs. We also wished to examine whether CPPs had an indirect effect on tumour size, as a secondary outcome.

2. Materials and methods

2.1. The Cancer Patient Pathway for sarcomas

When the general practitioner has a suspicion of sarcoma, the patient should be referred immediately to the local orthopaedic hospital for a clinical examination, conventional radiographs and a Magnetic Resonance Imaging (MRI) scan of the tumour to clarify whether the suspicion can be justified by a finding of radiological changes indicative of malignancy. When a suspicion is found to be justified, the patient should be referred immediately to the CPP-programme in one of the two Danish sarcoma centres, to which all treatment of bone and soft tissue sarcomas is centralized. The CPP for sarcomas was introduced on the 1st of January 2009, and defines alarm symptoms, milestones and time limits (measured in work days) of the diagnostic programme. The following specific alarm symptoms and clinical findings of a sarcoma defined in the CPP: soft tissue tumour >5 centimetres, soft tissue tumour on or profound of the deep fascia, palpable bone tumour, deep persisting bone pains, fast growing soft tissue tumour. Milestones defined in the CPP are the day the referral is received from the local orthopaedic hospital (Time point A, see Fig. 1), the first appointment in the centre (Time point B), decision of treatment (Time point C) and start of treatment (Time point E). The day of received referral is classified as day zero. The time limit for the referral phase (A–B) is five work days, and the patient should be seen for first appointment in the centre (Time point B) on day six. The diagnostic phase (B–C) has a time limit of nine work days for soft tissue tumours, and 18 work days for bone tumours, as bone tissue biopsies have to be decalcified before microscopic evaluation. Time limits for the treatment phase (C–E) are ten work days for operation, eight work days for chemotherapy and eleven workdays for radiotherapy. Thus the time limit for the overall phase (A–E) ranges from 22 to 34 work days depending on the tissue type and choice of treatment.

2.2. Study population

Aarhus Sarcoma Centre is a subdivision of the Department of Orthopaedic Surgery, at Aarhus University Hospital (AUH) in Denmark, and handles all referrals for bone and soft tissue sarcomas (except for retroperitoneal and ear nose and throat tumours) from the area of western Denmark (approx. 2.5 million inhabitants). The Sarcoma Centre also functions as a local hospital for Aarhus County. We included all patients referred to the CPP from hospitals outside Aarhus County to the Aarhus Sarcoma Centre with a suspicion of sarcoma, in the period from 01.01.2007 to 31.12.2010. Thus, our study population includes all suspected sarcoma patients from the geographical area of Jutland (western Denmark), except for Aarhus county. Patients referred from private hospitals outside of Aarhus County without an MRI-scan do not enter the CPP and are also considered as referred from Aarhus County. A patient was considered as referred with a justified suspicion of sarcoma if malignancy, cancer or sarcoma was mentioned in the referral text, MRI-description, or both; or the referral concerned an already histologically verified sarcoma. To be sure to include all patients with a justified suspicion of sarcoma in the period we looked through all referrals from hospitals outside Aarhus County to the department and patients referred with benign conditions or histologically verified types of cancer different from sarcoma, borderline tumours, aggressive fibromatosis, or giant cell tumours of the bone were classified as non-sarcoma referrals and excluded. Patients living in Aarhus County and patients referred without MRI from private hospitals outside of Aarhus County receive the MRI-scan and clinical examination at the sarcoma centre, and the suspicion is then justified or removed. If the suspicion is justified, they follow the same diagnostic programme as patients included in the CPP.

2.3. Patient identification

We identified our study population based on an extract from the Sarcoma Centre's electronic patient administrative system containing all patients registered as referred to the centre in the period from 01.01.2007 to 31.12.2010 (two years before and two years after implementation of the CPP for sarcomas). In total, 4726 patients were identified. We excluded 1824 (38.6%) patients referred directly from their general practitioner to the Aarhus Sarcoma Centre, 773

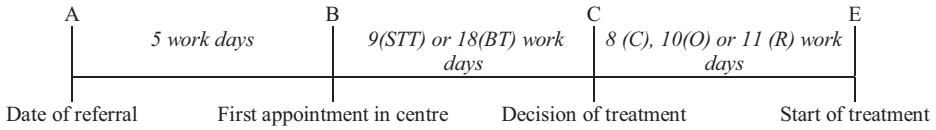

Fig. 1. The Cancer Patient Pathway for sarcomas. Milestones, phases and time limits of the patient process from date of referral from the local orthopaedic hospital to start of treatment at the Sarcoma Centre (STT = soft tissue tumour, BT = bone tumour, C = chemotherapy, O = operation, R = radiotherapy).

(16.4%) patients referred from other departments at the AUH, and 360 (7.6%) patients with a referral both from their general practitioner and from other departments at AUH. This yielded a patient population of 1769 patients referred from our defined geographical area. Medical records for all 1769 patients were retrieved, and during the review of medical files, an additional 643 (13.6%) patients were excluded; 511 were classified as non-sarcoma referrals, 6 had a referral date outside of our study period, 52 were referred from their general practitioner, from a private hospital without MRI or from other departments at the AUH but were not coded as such, 40 were referred to the Aarhus Sarcoma Centre with tumours not handled in the centre e.g. gynaecological and intra-abdominal tumours, and 34 had failed to appear at their first appointment in the Aarhus Sarcoma Centre either because they were treated elsewhere, or did not wish to be diagnosed or treated. This yielded a total study population of 1126 (23.8%) patients, included in the statistical analyses. Of the 52 patients considered as referred from the local area, 34 of them were referred from private hospitals in our chosen geographical area. The included patients, therefore, represent all patients from the well-defined geographical area of Jutland, minus Aarhus County and the 34 patients referred without an MRI-scan from private hospitals in the Jutland area.

2.4. Variables

Medical files of all 1126 patients were scrutinized for the following variables: date of referral, date of first appointment, date of treatment decision, start of treatment, tumour size, final diagnosis, and performed diagnostic procedures. The medical file review was performed by one person (HBD), and difficult cases were discussed with sarcoma experts from Aarhus Sarcoma Centre. Tumour size was registered in millimetres based on the histological report if the tumour was removed, and from the MRI-scan if tumour was not removed. For sarcomas receiving radiation or chemotherapy as primary treatment, or if the patient did not wish to be treated, tumour diameter are measured based on the MRI-scan. Thus, the main part of sarcomas where measured by the histological report. This is also the case for the larger benign tumours, and only the smaller benign tumours treated elsewhere after the CPP or not removed at all are measured by MRI-scan. A diagnostic procedure was registered as supplementary when it was not a part of the standard diagnostic programme at Aarhus Sarcoma Centre as described earlier, e.g. repeated biopsies or imaging. A patient-requested time out in the accelerated diagnostic programme was also registered as a supplementary procedure. Only procedures described in the medical files with specific dates of occurrence were registered. To ensure completeness, these data were supplemented with data from the hospital registration system and from two Danish sarcoma databases. We followed the international standard for defining milestones and intervals in cancer diagnosis [18]. Time intervals were measured in number of work days, excluding Saturdays, Sundays and the Public Danish holidays. Time intervals were calculated from dates of milestones. For the purposes of this study, a patient was classified as delayed when the time limits defined in the CPP for sarcomas (Fig. 1) were exceeded. Delay caused by clinically justified supplementary diagnostics, means that the delay was caused by the need for supplementary diagnostics in addition to the standard diagnostic programme described in the CPP. If this was not the case, and no reason for delay was described in medical files, the patient was classified as delayed because of passive waiting time.

2.5. Data analyses

Patients with a referral date after 31st of December 2008 (the day before the CPP implementation) were regarded as “after patients” and those with a referral date before this date as “before patients”. Data concerning time intervals and tumour diameter were right-skewed, non-normally distributed with outliers of very long intervals or large diameters, and therefore median and interquartile intervals (IQI) were used in the descriptive analyses. A non-parametric test for trend across ordered groups, an extension of the Wilcoxon rank sum test, was performed to test for significant changes in time intervals and tumour diameter across the four years. This test analyses whether there is a systematic increase or decrease in values over the four years analyzed as a whole, and does not compare specific years against each other. Data analyses were performed using Stata statistical software, version 11.

3. Results

3.1. Patient characteristics

Of the 1126 patients included in our study population, 258 (22.9%) patients were diagnosed with a sarcoma, 743 (66.0%) patients were diagnosed with benign tumours, and the remaining 125 (11.1%) patients were diagnosed with other malignancies such as metastases, malignant lymphomas, myelomatosis and carcinomas, and referred to other specialties for treatment. Further patient characteristics are shown in Table 1. Seventeen (6.6%) of the 258 sarcomas were diagnosed after their primary fast-track diagnostic programme was completed; five were defined as malignant after an observational period, ten were initially diagnosed as benign and malignancy was only established

Table 1
Patient and tumour characteristics.

Variables		Year	Sarcoma		Non-sarcoma		Total (%)
			Soft tissue (%)	Bone (%)	Soft tissue (%)	Bone (%)	
Referral year		2007	48 (17.3)	12 (4.3)	137 (49.3)	81 (29.1)	278 (100.0)
		2008	35 (15.7)	22 (9.9)	106 (47.5)	60 (26.9)	223 (100.0)
		2009	46 (15.7)	18 (6.1)	141 (48.1)	88 (30.0)	293 (100.0)
		2010	45 (13.6)	32 (9.6)	148 (44.6)	107 (32.2)	332 (100.0)
Gender	Male	2007	29 (20.6)	6 (4.3)	63 (44.7)	43 (30.5)	141 (100.0)
		2008	24 (20.0)	15 (12.5)	49 (40.8)	32 (26.7)	120 (100.0)
		2009	29 (17.8)	9 (5.5)	73 (44.8)	52 (31.9)	163 (100.0)
		2010	19 (12.2)	13 (8.3)	73 (46.8)	51 (32.7)	156 (100.0)
	Female	2007	19 (13.9)	6 (4.4)	74 (54.0)	38 (27.7)	137 (100.0)
		2008	11 (10.7)	7 (6.8)	57 (55.3)	28 (27.2)	103 (100.0)
		2009	17 (13.1)	9 (6.9)	68 (52.3)	36 (27.7)	130 (100.0)
		2010	26 (14.8)	19 (10.8)	75 (42.6)	56 (31.8)	176 (100.0)
Age	<20	2007	1 (2.6)	1 (2.6)	12 (30.8)	25 (64.1)	39 (100.0)
		2008	2 (5.1)	5 (12.8)	12 (30.8)	20 (51.3)	39 (100.0)
		2009	1 (2.9)	2 (5.9)	10 (29.4)	21 (61.8)	34 (100.0)
		2010	2 (4.5)	7 (15.9)	12 (27.3)	23 (52.3)	44 (100.0)
	20–39	2007	5 (11.4)	4 (9.1)	23 (52.3)	12 (27.3)	44 (100.0)
		2008	5 (15.2)	4 (12.1)	14 (42.4)	10 (30.3)	33 (100.0)
		2009	8 (14.3)	6 (10.7)	27 (48.2)	15 (26.8)	56 (100.0)
		2010	8 (12.7)	8 (12.7)	31 (49.2)	16 (25.4)	63 (100.0)
	40–59	2007	18 (18.4)	6 (6.1)	49 (50.0)	25 (25.5)	98 (100.0)
		2008	6 (10.3)	6 (10.3)	36 (62.1)	10 (17.2)	58 (100.0)
		2009	13 (14.9)	6 (6.9)	49 (56.3)	19 (21.8)	87 (100.0)
		2010	9 (9.2)	13 (13.3)	50 (51.0)	26 (26.5)	98 (100.0)
	≥60	2007	24 (24.7)	1 (1.0)	53 (54.6)	19 (19.6)	97 (100.0)
		2008	22 (23.7)	7 (7.5)	44 (47.3)	20 (21.5)	93 (100.0)
		2009	24 (20.7)	4 (3.4)	55 (47.4)	33 (28.4)	116 (100.0)
		2010	26 (20.5)	4 (3.1)	55 (43.3)	42 (33.1)	127 (100.0)
Tumour diameter	<5 cm	2007	15 (12.2)	3 (2.4)	62 (50.4)	43 (35.0)	123 (100.0)
		2008	12 (12.9)	8 (8.6)	47 (50.5)	26 (28.0)	93 (100.0)
		2009	20 (15.5)	6 (4.7)	69 (53.5)	34 (26.4)	129 (100.0)
		2010	21 (13.5)	9 (5.8)	73 (46.8)	53 (34.0)	156 (100.0)
	≥5 cm	2007	30 (22.6)	9 (6.8)	72 (54.1)	22 (16.5)	133 (100.0)
		2008	22 (19.5)	14 (12.4)	54 (47.8)	23 (20.4)	113 (100.0)
		2009	25 (17.9)	11 (7.9)	69 (49.3)	35 (25.0)	140 (100.0)
		2010	21 (14.2)	20 (13.5)	72 (48.6)	35 (23.6)	148 (100.0)
	Missing	2007	3 (13.6)	0 (0.0)	3 (13.6)	16 (72.7)	22 (100.0)
		2008	1 (5.9)	0 (0.0)	5 (29.4)	11 (64.7)	17 (100.0)
		2009	1 (4.2)	1 (4.2)	3 (12.5)	19 (79.2)	24 (100.0)
		2010	3 (10.7)	3 (10.7)	3 (10.7)	19 (67.9)	28 (100.0)
Total			174 (15.5)	84 (7.5)	532 (47.2)	336 (29.8)	1126 (100.0)

Patient and tumour characteristics of 1126 patients referred from other hospitals to Aarhus Sarcoma Centre with a suspected sarcoma in the period 2007–2010.

after removal of the presumed benign tumour, and two were diagnosed as benign and malignancy was only established after the patient had been re-referred to the CPP and undergone a new fast track diagnostic programme.

3.2. Time of exclusion from the Cancer Patient Pathway

The 258 patients diagnosed with a sarcoma went through the entire fast track diagnostic programme, and were treated and continued with follow-up appointments at the Sarcoma Centre according to the CPP. Among all patients referred each year, the proportion of sarcomas diagnosed per year was 21.6% in 2007, 25.5% in 2008, 21.8% in 2009 and 23.2% in 2010. Of the 868 non-sarcomas and the 17 sarcomas missed during the primary diagnostic process, 123 (13.9%) patients were diagnosed and excluded from the fast track diagnostic programme after evaluation of imaging and anamnesis at a multidisciplinary conference at the Aarhus Sarcoma Centre, 624 (70.5%) were excluded after a completed diagnostic programme either with a benign diagnosis or a diagnosis of another cancer form, and 138 (15.6%) were excluded after removal of the tumour. After exclusion from the fast-track diagnostic programme, patients were referred to treatment if relevant.

3.3. Tumour size

In 1035 (91.9%) of the 1126 patients' medical files the tumour size was reported. We found a statistically significant reduction in tumour size for soft tissue sarcomas from a median diameter of 70 (IQI: 40–100) millimetres in 2007 to 49 (IQI: 30–70) millimetres in 2010 ($p = 0.044$). Of the 174 soft tissue sarcomas, 154 (88.5%) were removed operatively, 1 (0.6%) received chemotherapy, 10 (5.7%) received

Table 2
Development in median time intervals in the period 2007–2010.

		From referral to first appointment in centre (A–B)	From first appointment in centre to final decision of treatment (B–C)	From final decision of treatment to start of treatment (C–E)	From referral to start of treatment (A–E)
Soft tissue sarcoma	2007	7 (5–10.5)	10.5 (1–21)	6 (4–11)	28 (18–38)
	2008	8 (6–11)	6 (1–16)	8 (5–10)	23 (16–33)
	2009	3 (4–6)	8 (1–13)	8 (6–11.5)	21 (14.5–29.5)
	2010	3 (4–6)	8 (1–11.5)	7 (4–10)	18 (13–25)
	p-Value	<0.001	0.236	0.827	<0.001
Bone sarcoma	2007	4 (5–11)	11 (3–35)	7 (6–8)	31 (18–40)
	2008	5 (3–9)	12.5 (5–24)	6 (3.5–7)	16.5 (13.5–29.5)
	2009	4 (1–7)	13 (6–17)	7 (3–10)	23 (12–31)
	2010	2 (1–5)	5 (2–8)	7 (6–8)	14 (10–20)
	p-Value	0.004	0.046	0.145	0.503
Benign soft tissue tumours	2007	9 (6–12)	8.5 (1–18)	10 (8–15)	24 (18–36)
	2008	9 (6–12)	5 (1–13)	4 (4–10)	19 (15–24)
	2009	5.5 (4–7)	7 (1–13)	6.5 (3–12)	18 (9–20.5)
	2010	4 (3–5)	5 (1–10.5)	6 (3–9)	12 (10–15)
	p-Value	<0.001	0.054	0.402	0.605
Benign bone tumours	2007	9 (6–11)	17.5 (5–23)	13.5 (13–16)	24.5 (23–25)
	2008	9 (4–12)	12 (1–18)	18 (18–18)	29 (29–29)
	2009	5 (3–7)	12 (3–16)	13 (3–22.5)	20 (9–30)
	2010	4 (3–6)	12 (7.5–18.5)	10 (6–11)	18 (16–23)
	p-Value	<0.001	0.437	0.577	0.553
Other malignant soft tissue tumours	2007	9 (4–12)	10 (7–23)	–	–
	2008	7 (3–12)	10 (7–15)	–	–
	2009	5 (4–8)	8 (7–13)	–	–
	2010	3 (3–5)	9 (8–13)	–	–
	p-Value	0.024	0.850	–	–
Other malignant bone tumours	2007	7 (5–7)	15.5 (9–25)	–	–
	2008	6 (4–7)	8 (5.5–10)	–	–
	2009	5 (4–6)	11 (7–15)	–	–
	2010	3 (2–5)	9 (5–12)	–	–
	p-Value	<0.001	0.237	–	–

Median and interquartile intervals of time spent in each phase measured in work days, and non-parametric test for trend across the period 2007–2010 for patients diagnosed with sarcomas, benign conditions and other malignancies.

radiation, 4 (2.3%) had the tumour removed before referral, and 5 (2.9%) did not wish to receive treatment. No such statistically significant change was found for bone sarcomas or non-sarcomas of soft tissue or bone type.

3.4. Time intervals

The time intervals were statistically significantly reduced in phase A–B for sarcomas, benign conditions and other malignancies, for both soft tissue and bone type (Table 2). For bone sarcomas the change was also statistically significant for the diagnostic phase (B–C). For soft tissue sarcomas the change was statistically significant in total time from referral to treatment start (A–E). The 75th-percentile decreased in most phases for all tumour types, indicating a shift towards shorter processing times (Table 2).

3.5. Delay in the specific time intervals

A total of 244 patients went through phase A–B in 2007. Of these, 59 (24.2% (95% CI: 18.9–30.1)) were within the CPP time limit of this phase, 14 (5.7% (95% CI: 3.2–9.4)) were delayed because of clinically justified supplementary diagnostics, and 171 (70.1% (95% CI: 63.9–75.8)) were delayed due to passive waiting time. In 2010, 292 patients went through the phase A–B and 217 (74.3% (95% CI: 68.9–79.2)) were within the CPP time limit, 17 (5.8% (95% CI: 3.4–9.2)) were delayed because of academically justified supplementary diagnostics, and 58 (19.9% (95% CI: 15.4–24.9)) were delayed due to passive waiting time.

A total of 244 patients went through phase B–C in 2007. Of these, 126 (51.6% (95% CI: 45.2–58.1)) were within the CPP time limit of this phase, 54 (22.1% (95% CI: 17.1–27.9)) were delayed because of clinically justified supplementary diagnostics, and 64 (26.2% (95% CI: 20.8–32.2)) were delayed due to passive waiting time. In 2010, 292 patients went through the phase B–C and 210 (71.9% (95% CI: 66.4–77.0)) were within the CPP time limit, 39 (13.4% (95% CI: 9.7–17.8)) were delayed because of clinically justified supplementary diagnostics, and 43 (14.7% (95% CI: 10.9–19.3)) were delayed due to passive waiting time.

A total of 86 patients went through phase C–E in 2007. Of these, 57 (66.3% (95% CI: 55.3–76.1)) were within the CPP time limit of this phase, five (5.8% (95% CI: 1.9–13.0)) were delayed because of clinically justified supplementary diagnostics, and 24 (27.9% (95% CI: 18.8–38.6)) were delayed due to passive waiting time. In 2010, 110 patients went through the phase C–E and 88 (80.0% (95% CI: 71.3–87.0)) were within the CPP time limit, five (4.5%

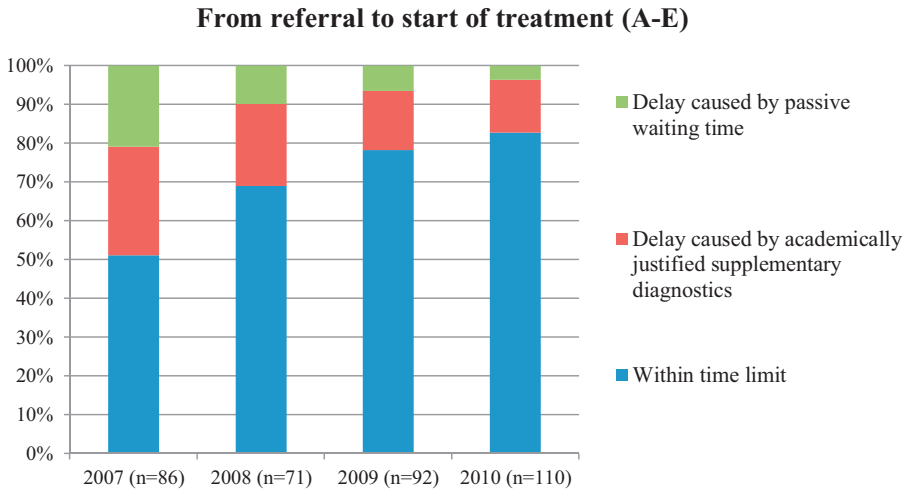

Fig. 2. Proportion and type of delay among all patients who went through the phase from date of referral to start of treatment (A–E), *n* = number of patients who went through this phase per year.

(95% CI: 1.5–10.3)) were delayed because of clinically justified supplementary diagnostics, and 17 (15.5% (95% CI: 9.3–23.6)) were delayed due to passive waiting time.

A total of 86 patients went through the overall period A–E in 2007, and 44 (51.2% (95% CI: 40.1–62.1)) were within the CPP time limit of this phase, 24 (27.9% (95% CI: 18.8–38.6)) were delayed because of clinically justified supplementary diagnostics, and 18 (20.9% (95% CI: 12.9–31.0)) were delayed due to passive waiting time. In 2010, 110 patients went through the phase A–E and 91 (82.7% (95% CI: 74.3–89.3)) were within the CPP time limit, 15 (13.6% (95% CI: 7.8–21.5)) were delayed because of clinically justified supplementary diagnostics, and four (3.6% (95% CI: 1.0–9.0)) were delayed due to passive waiting time (Fig. 2).

4. Discussion

We found a general trend of reduced median time intervals with statistically significant reduction in the referral phase for all patients, in the diagnostic phase for bone sarcomas and in the overall phase for soft tissue sarcomas. Furthermore, we found a reduction in the proportion of patients exceeding the time limits in the CPP for sarcomas. The proportion of diagnosed sarcomas was stable and relatively high at about one in five to one in four referred patients. As an additional investigation we found a significant reduction in median tumour diameter for soft tissue sarcomas.

The strengths of our study lie in our large study population and the large number of variables collected, creating a good basis for analysis of possible changes in time intervals. Data collection and registration was performed by the same person, and variables were supplemented with data from existing sarcoma databases, thereby reducing the potential for information bias. Furthermore, we presented data from before and after the implementation of CPPs, thus illustrating a natural experiment and not merely a status after an organizational change. Finally, we divided our delayed patients into subgroups depending on the reason for delay, resulting in a more nuanced interpretation of delay.

Our results may be prone to selection bias, as the study population includes only the patients referred according to the CPP for sarcomas from other hospitals outside of Aarhus County, and not patients referred from the local area of the Sarcoma Centre. Patients living in Aarhus County are referred directly to the Sarcoma Centre, and differ from our needed study population in many aspects. By excluding this geographical area, the patients under study were much more homogenous and represented patients for whom the CPP should improve the cancer trajectory. The retrospective design of the study creates the possibility of information bias. It is possible that the registration of information collected for this study from medical files has changed over the years. E.g. the introduction of CPPs could have made the registration more complete and accurate. However, there was no indication of this change when scrutinizing the files. Secondly, such a change would most likely mean that the date of referral would be registered earlier and thus result in a longer time interval after the implementation of the CPP.

Using an observational design in a natural experiment is not comparable with a randomized study where the effects of the CPP were tested. However, the implementation of CPPs in Denmark was a nationally implemented governmental initiative and compliance to the CPP was mandatory, thus eliminating the possibility of performing a randomized trial. The observational before-after study is therefore the best available research design and our results must be interpreted with this limitation in mind.

The implementation of guidelines for referral, diagnosis and treatment of sarcomas is well reported in the literature. In the United Kingdom (UK), guidelines have been implemented to achieve an earlier diagnosis of sarcomas, and there are studies describing some of the problems encountered after this initiative. Firstly, it seems that the guidelines are not well implemented, resulting in a low compliance to guidelines and a large degree of delay before referral to specialist centres [19,20]. This problem has

also been reported from the Netherlands [15], but a more recent study indicates that compliance has been improved by implementation of more standardized guidelines and increased awareness and attention to sarcoma patients as a group [14]. Secondly, an adverse effect of the referral guidelines is reported from the UK, in the form of a large number of benign tumours being redirected for diagnosis at the specialist centres, thereby overburdening the capacity and possibly delaying the diagnosis and treatment [12,21]. In our study population we found that the proportion of sarcomas diagnosed among the referred patients remained constant before and after the implementation of CPPs. This indicates that the problem observed in the UK with vast numbers of benign tumours overburdening specialist centres has not occurred in Denmark. In Sweden, the diagnosis and treatment of sarcomas have been centralized for several years and simple guidelines for referral have been implemented, with studies reporting an excellent adherence [22,23]. Furthermore, Styring et al. do not report referral of benign tumours as a problem, and they find that they diagnose three benign tumours for each malignant sarcoma [23]. This result is consistent with the findings in our study of a proportion of diagnosed sarcoma ranging from one in four to one in five. A fast-track programme for cancer has also been implemented in Spain for breast, colorectal and lung cancer, and a report indicates that the diagnostic assessment and treatment of suspected cancer patients has been accelerated and the patient pathway between primary and specialized care have been clarified [13]. However, this study only reports data from the period after implementation, and not from before, making it difficult to discern the true difference in time intervals.

The main difference between the Danish CPPs and the previously described programmes from other countries may be the political aspect of the Danish initiative. The political focus and actions behind the Danish initiative may be a particular part of why the CPPs have been so successful in Denmark. A strong political support is an important factor for making improvement of referral and treatment of cancer patients possible.

CPPs cannot directly affect tumour size, but our finding of a reduction in median tumour diameter for soft tissue sarcomas may be a sign of patients being diagnosed earlier in the natural course of tumour development. If so, this can be caused by an indirect effect on patient delay. Due to their massive political backing and press coverage, a possible side-effect of the CPPs may be an increased awareness of alarm symptoms among patients and primary physicians, changing the management of patients before referral to the sarcoma centre. Large tumour size is correlated with a poorer prognosis and reducing tumour size at treatment start is a matter of great importance [24]. It is yet too early to say whether our results also illustrates an indirect effect of the CPPs on tumour size, growth and thus survival and later studies must be initiated analysing the effects of the CPP on survival for sarcoma patients.

Our data on the development in time intervals showed that the CPP reduced the median time spent in each phase of the diagnostic process. This is consistent with results reported from Probst et al. on the Danish implementation of CPPs, which showed a general trend of reduced median waiting time for several other cancer forms [17].

The implementation of CPPs caused a change in the previous diagnostic model where investigations such as biopsies and scans were performed in a serial fashion with passive waiting time for test results before proceeding to the next investigation. The CPP is based on pre-booked appointments reserved for CPP-patients. The investigations are run in a parallel fashion to minimize waiting time. Our results show that this has been successful in reducing time intervals, but our results also show that the process is easily delayed when patients step outside of the standard diagnostic programme. Fortunately, the proportion of patients being delayed by supplementary diagnostics was also reduced over the four years. This indicates that the CPP fundamentally changed the diagnostic process of sarcomas. The CPPs are run in an accelerated pace, leaving little time for hesitations about diagnosis and treatment. This may ultimately have caused the diagnosing physicians to be more determined, and also more reluctant to order supplementary diagnostic procedures just to confirm their suspicions further. Clinical decisions in Aarhus Sarcoma Centre are made at two weekly multidisciplinary conferences, and this was also the practice before implementation of the CPP. Thus, there has been no change in the mode of decision making, but more likely a change in the team's attention to the time aspect of the diagnostic process. The clinical coordinator further insures that the time limits are observed and diagnostic procedures are booked, but takes no part in the actual clinical decisions. Such a development may also be positive from an economical point of view, as well as for the patients, as unnecessary diagnostic procedures are avoided. Patients with sarcomas are a heterogeneous group, and creating guidelines and diagnostic programmes suitable for everyone may seem impossible. However, reducing the amount of passive waiting time as we have demonstrated in our study is a great step in the right direction.

Our study demonstrates the effects on processing times for patients referred to the CPP, but whether the implementation of CPPs have caused delayed diagnosis for patients referred outside of the CPP are unknown. The sarcoma centre also specializes in wound treatment, removal of large benign tumours and bone infections, and these patients are of course not included in the CPP. Our population includes all suspected sarcoma patients from a defined geographical area, but there is a possibility that the excluded patients from Aarhus County and patients referred with benign conditions experience more delay than patients following the CPP. Further studies are needed to ensure that all patients are cared for within an acceptable timeframe.

5. Conclusion

Our study demonstrates that the Danish implementation of CPP for suspected sarcoma has been successful in shortening waiting time and accelerating the diagnostic process of sarcomas. The changes in time intervals show that patients are diagnosed more quickly and the finding of reduced median tumour diameter at referral for soft tissue sarcomas may indicate that these patients are diagnosed at

an earlier stage of tumour development. The success of the Danish Cancer Patient Pathways is a strong contribution to the international debate of diagnostic delays, and may serve as a model for similar initiatives in other countries.

Conflicts of interest

The authors report no conflicts of interest.

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Paper II

Alarm symptoms of soft tissue and bone sarcoma among patients referred to a specialist center

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Alarm symptoms of soft-tissue and bone sarcoma in patients referred to a specialist center

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Background and purpose — The Danish Cancer Patient Pathway for sarcoma defines a set of alarm symptoms as criteria for referral to a sarcoma center. This may exclude cancer patients without alarm symptoms, so we investigated the presence of alarm symptoms (defined as being indicative of a sarcoma) in patients who had been referred to the Aarhus Sarcoma Center.

Patients and methods — We reviewed the medical records of all 1,126 patients who had been referred, with suspected sarcoma, from other hospitals in the period 2007–2010 for information on symptoms, clinical findings, and diagnosis. Alarm symptoms were analyzed for predictive values in diagnosing sarcoma.

Results — 179 (69%) of 258 sarcoma patients were referred with alarm symptoms (soft-tissue tumor > 5 cm or deep-seated, fast-growing soft-tissue tumor, palpable bone tumor, or deep persisting bone pain). The remaining 79 sarcomas were found accidentally. "Size over 5 cm" for soft-tissue tumors, and "deep persisting bone pain" for bone tumors had the highest sensitivity and positive predictive value. Of the 79 sarcoma patients who were referred without alarm symptoms, 7 were found accidentally on imaging, 5 were referred with suspected recurrence of a sarcoma, 64 were referred with a confirmed histological diagnosis, and 3 were referred for other reasons.

Interpretation — Defined alarm symptoms are predictive of sarcoma, but one-third of the patients were found accidentally. Further studies on presenting symptoms in primary care are needed to assess the true value of alarm symptoms.

Rare diseases such as sarcomas should be treated in specialized sarcoma centers (Clasby et al. 1997, Nielsen et al. 2002, Skubitz and D'Adamo 2007). Biopsy or excision of sarcomas before referral to specialist centers may result in misdiagnosis, incomplete removal, and poor outcome (Randall et al. 2004, Qureshi et al. 2012). Thus, simple alarm symptoms for referral before surgery are necessary to achieve early diagnosis and proper treatment of sarcomas (Grimer and Sneath 1990, Rydholm 1998, Johnson et al. 2001, Jones et al. 2007). Defining alarm symptoms for referral to a specialist center is a fine balance between including all patients with sarcoma and preventing referral of patients with false-positive findings. A fast-track, law-based referral program (Cancer Patient Pathways (CPPs)) has been implemented in Denmark, describing a standard patient's ideal pathway through the healthcare system from clinical suspicion of cancer through diagnostics, treatment, and follow-up (Olesen et al. 2009, Probst et al. 2012). The development and implementation of CPPs was described by Probst et al. (2012). We investigated the effects of the CPP for sarcomas on the process of diagnosis of sarcomas at Aarhus Sarcoma Center in a previous study (Dyrop et al. 2013). In addition to defined time limits for diagnostic events, the CPP for sarcomas also contains specific alarm symptoms and clinical findings/signs that a patient should have to qualify for a fast-track referral from the general practitioner, for further investigation at the local orthopedic department. If the suspicion is justified, the CPP is initiated and patients are referred to a specialist sarcoma center with minimal waiting time. The purpose of this study was to investigate the presence of alarm symptoms for sarcomas in a consecutive group of patients who had been referred to our sarcoma center.

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Patients and methods

Referrals and inclusion criteria of the Cancer Patient Pathway for sarcomas

For a patient to be considered for a CPP, the presence of one or more of the following alarm symptoms or clinical findings is required: soft-tissue tumor > 5 cm, deep-seated, fast-growing soft-tissue tumor, palpable bone tumor, or deep persisting bone pain. After discovery of alarm symptoms or suspected recurrence, the general practitioner or other specialist should refer the patient to the local orthopedic hospital for further investigation—including clinical examination, conventional radiographs, and a MR-scan of the tumor area. If the suspicion is then confirmed, the patient must be referred immediately to 1 of the 2 centralized sarcoma centers in Denmark for further diagnostics and treatment. The CPP officially starts when the patient is referred from a local hospital with a justified suspicion of sarcoma. Patients living in the catchment area of Aarhus University Hospital have the Aarhus Sarcoma Center as their local orthopedic hospital, and they are therefore referred directly by their general practitioner for an MRI scan at the Sarcoma Center. The CPP for sarcomas was implemented on the January 1, 2009.

Study population

Aarhus Sarcoma Center has specialists from relevant departments and handles referrals from all over the Jutland area of Denmark, with a catchment population of approximately 2.5 million. The department also functions as the local orthopedic hospital department for patients living in Aarhus County. We included 1,126 patients who had been referred with a justified suspicion of sarcoma from local hospitals during a 4-year period, from January 1, 2007 to December 31, 2010. Firstly, we identified all the patients who had been referred to Aarhus Sarcoma Center over the 4-year study period. From this, we excluded all patients who had been referred directly by a GP or from Aarhus University Hospital. This gave 1,769 patients. Medical files of all patients were retrieved and reviewed. A justified suspicion of sarcoma was judged to be present in the referral if the patient had one of the alarm symptoms and/or an MRI-based suspicion of sarcoma, a strong clinical suspicion, or a histologically verified sarcoma diagnosis. Referrals relating to benign conditions or histologically verified types of cancer different from sarcoma, borderline tumors, aggressive fibromatosis, or benign giant cell tumors were categorized as non-sarcoma referrals and were excluded. Patients referred directly by a GP but not coded as such, and patients referred from private hospitals without an MRI scan or histological diagnosis of sarcoma were also excluded, as the suspicion was not confirmed by a local hospital. This process excluded another 643 patients, so the final study population consisted of 1,126 patients who had been referred to Aarhus Sarcoma Center from local hospitals with a justified suspicion of sarcoma.

Variables

Medical files were reviewed for the following variables: symptoms causing the referral, imaging performed before referral, tumor size, tumor depth, and final diagnosis. When we registered symptoms, these were coded as one or more of the following choices: soft-tissue tumor > 5 cm, or deep-seated or fast-growing, palpable bone tumor, deep persisting bone pain, accidental finding during imaging of the area, referral with a confirmed histological diagnosis of sarcoma, suspected recurrence of known sarcoma, and other symptoms. When defining the presence or absence of a symptom during review of the medical files, only tumor symptoms and/or clinical findings mentioned before the removal of a tumor in the Sarcoma Center were considered as a presenting symptom. Histological findings of size > 5 cm or deep-seated tumor found only in the postoperative pathology report were not considered as a positive presenting symptom. Classification of tumor size and depth was based on the tissue histology report if the tumor had been removed, or on the MRI description when the tumor had not been removed (mostly small benign tumors). Tumor size was registered as a continuous variable, measured in mm at the largest diameter of the tumor. Tumor depth for soft-tissue tumors was categorized as cutaneous, subcutaneous, or deep-seated localization. Variables collected from medical records were supplemented with information from 2 Danish sarcoma databases, ensuring completeness of data.

Data analysis

Patients were separated into 2 groups for the analysis of symptoms. The predictive values for symptoms of soft-tissue sarcoma were analyzed only in patients with soft-tissue tumors, and symptoms of bone sarcoma were analyzed only in patients with bone tumors. Positive exposure was presence of the symptom or combination of symptoms being analyzed, and positive outcome was a final diagnosis of sarcoma. Single symptoms and all possible combinations of these were tested for their ability to predict a diagnosis of sarcoma, by calculating sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Data analysis was performed using Stata statistical software version 11.

Results

Patient and tumor characteristics

Of the 1,126 patients in the study population, 258 (23%) were diagnosed with a sarcoma, 125 (11%) were diagnosed with other malignancies such as metastases, malignant lymphomas, myelomatosis, and carcinomas, and were referred to other specialties for treatment. The remaining 743 patients (66%) were diagnosed as having benign tumors. Of the 258 sarcomas, there were 174 soft-tissue sarcomas and 84 bone sarcomas. Median age of patients with soft-tissue sarcoma was 61 years. For bone sarcoma, the median age was 44 years;

Table 1. Patient and tumor characteristics for the 1,126 patients included in the study population

	Sarcoma		Other	
	Soft tissue (%)	Bone (%)	Soft tissue (%)	Bone (%)
Sex				
Male	101 (58)	43 (51)	258 (49)	178 (53)
Female	73 (42)	41 (49)	274 (52)	158 (47)
Age				
< 20	6 (3)	15 (18)	46 (9)	89 (27)
20–39	26 (15)	22 (26)	95 (18)	53 (16)
40–59	46 (26)	31 (37)	184 (35)	80 (24)
≥ 60	96 (55)	16 (19)	207 (39)	114 (34)
Referral year				
2007	48 (28)	12 (14)	137 (26)	81 (24)
2008	35 (20)	22 (26)	106 (20)	60 (18)
2009	46 (26)	18 (21)	141 (27)	88 (26)
2010	45 (26)	32 (38)	148 (28)	107 (32)
Duration of symptoms				
≤ 1 year	121 (70)	61 (73)	299 (56)	229 (68)
> 1 year	37 (21)	12 (14)	139 (26)	43 (13)
Missing data	16 (9)	11 (13)	94 (18)	64 (19)
Tumor diameter				
< 5 cm	68 (39)	26 (31)	251 (47)	156 (46)
≥ 5 cm	98 (56)	54 (64)	267 (50)	115 (34)
Missing	8 (5)	4 (5)	14 (3)	65 (19)
Histological grade [a]				
Benign	-	-	364 (68)	182 (54)
Low	57 (33)	21 (25)	-	-
High	117 (67)	63 (75)	-	-
No biopsy	-	-	168 (32)	154 (46)
Tumor depth [b]				
Superficial	63 (36)	-	182 (34)	-
Deep	109 (63)	-	350 (66)	-
Missing data	2 (1)	-	-	-
Total (100)	174 (100)	84 (100)	532 (100)	336

[a] Low: Trojani grade 1; High: Trojani grade 2–3
[b] Evaluated after imaging, clinical examination, and/or surgical removal. Not necessarily a presenting symptom.

for non-sarcoma patients with soft-tissue tumors it was 53 years, and for non-sarcoma patients with bone tumors it was 47 years. Other patient characteristics are given in Table 1. 17 (7%) of the 258 sarcomas were diagnosed after completion of the CPP; 5 were diagnosed as malignant after an observation period and 10 were diagnosed as malignant after removal of a presumed benign tumor. 2 were first diagnosed as benign and malignancy was later found after a second referral to the CPP.

Imaging before referral

Overall, 855 (76%) of the 1,126 patients in the 4-year study period had only had an MRI before referral. 60 (5%) had only had a CT scan before referral, and 109 (10%) had had both an MRI and a CT scan before referral. The remaining 102 patients (9%) had neither had an MRI nor a CT scan before referral. The reasons for not performing a scan before referral were as follows: (1) Confirmed histological diagnosis (24 patients). These patients had an MRI scan performed in the center as part of the surgical preparations. (2) Scanning not needed for the final diagnosis or operability (59 patients). (3) MRI scan performed at the center as part of the diagnostic program (19 patients).

The proportions of patients with an MRI scan, a CT scan, both an MRI scan and a CT scan, or no scans before referral remained fairly constant when calculated for each year of the study period, and there were no apparent changes before and after the implementation of CPPs.

Symptoms

The alarm symptom/clinical finding with the highest sensitivity (45%) and PPV (25%) was "tumor > 5 cm in diameter" for soft-tissue tumors. For bone tumors, the alarm symptom "deep persisting bone pain" yielded the highest sensitivity (82%) and PPV (23%). Values for all of the 5 alarm symptoms defined in the CPP are shown in Table 2. The combination of symptoms with the highest sensitivity for detecting sarcoma (21%) was a soft-tissue tumor > 5 cm that was deep-seated (Table 3). These analyses were performed on the entire study population. We also performed the analyses with patients separated into 3 age groups (< 49, 40–59, > 60 years). There were no differences in sensitivity and specificity between the groups; it was mainly the specificity and the NPV that varied between the age groups, with the highest values in younger patients. The patients were also divided according to sex, and the analyses repeated. This showed similar predictive values between the sexes.

Sarcoma patients referred for reasons other than alarm symptoms

Of the 258 patients who were diagnosed with a sarcoma, 79 (31%) were not referred due to any of the 5 alarm symptoms/clinical findings defined in the CPP for sarcomas. 7 were referred after an accidental finding during imaging of the area for other purposes. 6 of these patients had a bone sarcoma and 1 had a soft-tissue sarcoma. After removal, the soft-tissue sarcoma was found to be a deep-seated tumor > 5 cm in diameter. 64 patients were referred with a confirmed histological diagnosis of sarcoma. 3 of these were bone sarcomas and 61 were soft-tissue sarcomas. At surgical removal of the 61 soft-tissue sarcomas, 42 were found to be located subcutaneously and 19 were found to be deep-seated. Of these, 8 of the subcutaneous tumors and 9 of the deep tumors were found to be > 5 cm in diameter. 5 were referred with a suspicion of recurrence of known sarcoma. They were all soft-tissue sarcomas, and after removal of the tumor 2 were found to be subcutaneous and 3 were deep-seated. Of these, none of the subcutaneous tumors and 2 of the deep tumors were found to be > 5 cm in diameter. 3 patients did not have any of the alarm symptoms, nor any of the referral modes described above. Patient 1 presented with hemoptysis, and the tumor was later found to be situated below the fascia, but no record of the tumor size was found in the medical files. Patient 2 had a bone sarcoma and presented with weight loss and fatigue. Patient 3 had a soft-tissue sar-

Table 2. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for sarcomas with single symptoms and combinations of symptoms and signs that have been defined as inclusion criteria for soft-tissue tumors in the Cancer Patient Pathway, in suspected sarcoma patients

	Soft-tissue tumors (n = 706)							
	Sarcoma		Non-sarcoma		Sensitivity	Specificity	PPV	NPV
Symptom [a]	(n = 174)		(n = 532)		% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Present	+	–	+	–				
1	78	96	233	299	45 (37–53)	56 (52–61)	25 (20–30)	76 (71–80)
2	76	98	293	239	44 (36–51)	45 (41–49)	21 (17–25)	71 (66–76)
3	50	124	164	368	29 (22–36)	69 (65–73)	23 (18–30)	75 (71–79)
1 + 2	36	138	91	441	21 (15–28)	83 (79–86)	28 (21–37)	76 (73–80)
2 + 3	5	169	34	498	3 (1–7)	94 (91–96)	13 (4–27)	75 (71–78)
1 + 3	6	168	31	501	3 (1–7)	94 (92–96)	16 (6–32)	75 (71–78)
1 + 2 + 3	26	148	37	495	15 (10–21)	93 (91–95)	41 (29–54)	77 (74–80)

[a] Symptom 1: soft-tissue tumor > 5 cm; symptom 2: soft-tissue tumor on or under the fascia; symptom 3: fast-growing soft-tissue tumor.

Table 3. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for sarcomas with single symptoms and combinations of symptoms and signs that have been defined as inclusion criteria for bone tumors in the Cancer Patient Pathway, in suspected sarcoma patients

	Bone tumors (n = 420)							
	Sarcoma		Non-sarcoma		Sensitivity	Specificity	PPV	NPV
Symptom [a]	(n = 84)		(n = 336)		% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Present	+	–	+	–				
4	12	72	44	292	14 (8–24)	87 (83–90)	21 (12–34)	80 (76–84)
5	69	15	237	99	82 (72–90)	30 (25–35)	23 (18–28)	87 (79–92)
4 + 5	8	76	14	322	9 (4–18)	96 (93–98)	36 (17–59)	81 (77–85)

[a] Symptom 4: palpable bone tumor; symptom 5: deep persisting bone pains.

coma and presented with a subcutaneous soft-tissue tumor < 5 cm in diameter.

Patients who presented with solitary symptoms

We calculated the number of patients who would be excluded from the CPP for sarcomas if any of the 5 defined alarm symptoms were to be removed from the inclusion criteria. If "soft-tissue tumor > 5 cm" were to be excluded, 10 sarcoma patients would be lost. If "deep-seated soft-tissue tumor" were to be excluded, 9 sarcoma patients would be lost. If "fast-growing soft-tissue tumor" were to be excluded, 14 sarcoma patients would be lost. If "palpable bone tumor" were to be excluded, 4 bone sarcoma patients would be lost. If "deep persisting bone pain" were to be excluded, 61 bone sarcoma patients would be lost.

Discussion

We found that only about two-thirds of our 258 sarcoma patients had been referred with 1 or more of the defined alarm symptoms, and the remaining had been found accidentally. The symptoms with the highest sensitivity and positive predictive value were "size > 5 cm" for soft-tissue tumors and "deep persisting bone pain" for bone tumors. "Soft-tissue tumor > 5 cm that was deep-seated" was the symptom combination with the highest sensitivity. It was mainly the specificity and the negative predictive values that were affected when we divided patients into different age groups, and there were no significant differences when they were divided by sex. Furthermore, we found that approximately 90% of the sarcoma patients had had an MRI or CT scan performed before referral.

The strengths of the present study lay in the large number of patients. Collection and registration of data from medical files was performed by the same person (HBD), and variables were supplemented with data from 2 existing Danish sarcoma databases, thus reducing information bias. Furthermore, information concerning symptoms was based on data from medical files documented at the time of tumor presentation, and it was therefore not affected by recall bias in the form of patients' long-term recollection of symptoms several years after tumor presentation.

Our results may have been subject to selection bias, as the study population included only patients who had been referred from hospitals other than Aarhus University Hospital, and not patients who had been referred directly by their GP. This may

have caused a falsely high prevalence of alarm symptoms among our suspected sarcoma patients, as ideally, patients without these symptoms in 2009 and 2010 would not have been referred to the Sarcoma Center, after the implementation of the CPP in 2009. However, this was not the case for patients referred in the period 2007–2008, and considering the large proportion of patients referred without alarm symptoms (one-third), this bias would appear to be of less importance for the purposes of our study. Another limitation of the study was the possibility of information bias, as it was designed as a retrospective study of medical files. It is possible that the registration methods used in the medical files had changed during the 4-year study period, and there is also the fact that notes in the medical files had been made by more than one surgeon. During the 4-year study period, the number of surgeons involved was limited to 4; these people worked in close cooperation, thus reducing the degree of interpersonal differences in medical file notations. Finally, there is the question of whether the medical files and referrals could be relied upon to contain information on all symptoms—or just the ones that were most apparent.

Our results showed that soft-tissue tumor size over 5 cm in diameter gave the highest sensitivity and PPV. Deep location gave approximately the same high sensitivity, which correlates well with other studies showing a high frequency of these symptoms in sarcoma patients (Johnson et al. 2001, Hussein and Smith 2005). For bone sarcomas, deep persisting bone pain gave the highest sensitivity, and many patients presented with this as the only symptom. George and Grimer (2012) also found that this symptom was present in 88% of their bone sarcoma patients. However, pain is the symptom that is less consistently included in clinical guidelines for referral of sarcoma, and it has been suggested that using "pain" as an indicator of malignancy in soft-tissue tumors may mislead general practitioners (Styring et al. 2012b). The Danish CPP for sarcomas includes pain only as a criterion for bone tumors, and our results show that this is a clear indicator of malignancy. Finally, the sensitivity and specificity that we calculated for the various symptoms were lower than results from other studies (Johnson et al. 2001, George and Grimer 2012), but the proportion of sarcomas in these study populations was far greater than in our study population, and this makes it difficult to compare them. The finding of higher specificity and NPV in younger patients and no differences in predictive values between the sexes was not unexpected, as younger patients are less likely to have cancer and sarcoma is not a sex-specific cancer form.

We found that approximately one-third of our sarcoma patients were not referred due to one or more of the alarm symptoms, and a large proportion of these patients were biopsied or operated on before referral. This result has also been found in other studies, but with a much lower frequency (Styring et al. 2012a, George and Grimer 2012). To improve the future referral of sarcomas in the CPP, it would be interesting to know why these patients were not included from any of the defined alarm symptoms. Some of them had symptoms qualifying them for CPPs for other cancer forms, such as breast cancer and testicular cancer. Many skin tumors are handled by dermatologists, and many soft-tissue sarcomas are incorrectly diagnosed as benign lipomas. It is a problem that tumors without any of the alarm symptoms fall outside of the CPP and are operated upon elsewhere. The 5 defined alarm symptoms are the hallmark of a tumor that has been present for some time, and the patients might have developed alarm symptoms if given more time. Thus, the way forward should be to identify earlier symptoms of a sarcoma, through research on presenting symptoms in primary care. Education of both patients and primary physicians is also important, as the alarm symptoms develop slowly and may be clinically difficult to discover for a long period of time.

There is a lack of reports on the frequency of alarm symptoms of sarcoma and their predictive values in primary care. Studies on sarcoma patients referred to specialist sarcoma centers in the UK have found that there is a large discrepancy between the symptoms described in the referral from general practice and the symptoms found in the patient at the specialist center (Malik et al. 2007, Pencavel et al. 2010). A possible reason for this is that doctors in primary and secondary care define symptoms differently, and this becomes a problem as most referral guidelines are created based on research derived from specialist care (Hamilton 2009). This is also the case for the Danish CPP for sarcomas. Our results—with PPVs for each single symptom in the range of 20–25%—appear to leave no doubt that these symptoms are highly indicative of malignancy. However, the situation in primary care is quite different, as one must consider the prevalence of the disease in the population, and the prevalence of sarcoma in the general population is low. In a systematic review of studies on alarm symptoms of cancer performed in primary care, Shapley et al. (2010) found that a PPV of 5% or more for a cancer symptom may be regarded as highly predictive. This seems to be a surmountable number, but studies on alarm symptoms performed in primary care show that many well-known alarm symptoms of highly prevalent cancer forms fall below this limit when investigated in a primary-care setting (Jones et al. 2007, Ingebrigtsen et al. 2013). In their studies on alarm symptoms in primary care, Ingebrigtsen et al. found that the symptom "lump" as a predictor of malignancy had a PPV in the range of 1%, and a sensitivity of 5%, but this was for all cancer forms, not for sarcoma exclusively. One can therefore expect that predictive values for sarcomas in primary care would be even lower than this, and probably fall beneath the 5%. This indicates that the generalization of our results to primary care is difficult, if not impossible. However, when used in secondary care in specialist centers, our results can be a valuable tool in the evaluation of a referred tumor.

Finally, the present study is a reminder that a diagnostic program like the Danish CPP for sarcomas does not accommo-

date all sarcoma patients, and the selection of alarm symptoms as inclusion criteria may exclude patients with the disease.

Conclusion

The 5 alarm symptoms of sarcoma defined in the CPP are prevalent among sarcoma patients. However, the CPP for sarcomas should not be considered as a guarantee for identification of all sarcoma patients, as our results demonstrate that a rather large proportion of the patients do not conform to the defined inclusion criteria. None of the symptoms were present in all sarcomas, and this makes the development of clear-cut guidelines challenging. Further studies on the presenting symptoms of sarcomas in primary care are needed to evaluate the predictive values of alarm symptoms in an unselected population, and thereby improve early diagnosis of sarcomas.

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Paper III

Characteristics of 64 sarcoma patients referred to a sarcoma center after unplanned excision

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Characteristics of 64 Sarcoma Patients Referred to a Sarcoma Center After Unplanned Excision

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Background and Methods: Unplanned excision of sarcoma before referral to specialist centers can affect prognosis and surgical outcome. The diagnostic pathway of these patients is uncertain and needs to be reviewed. We aimed to describe patient and tumor characteristics, initial symptoms, initial and final diagnosis, and explore reasons for unplanned excision in this patient group. From a previous study on 258 sarcoma patients, we identified 64 patients referred after surgery. Medical records were reviewed.

Results: The majority were soft tissue sarcomas, most often with thoracic location. Leiomyosarcoma was the most frequent final diagnosis, lipoma, and fibroma/dermatofibroma the most frequent initial diagnoses. Fifty percent were superficial small tumors, and 60.9% had not received diagnostic imaging before surgery. Fifty percent were referred from public surgical departments, and 1/3 from private specialists. Twenty-three patients had initial presence of alarm symptoms registered before surgery, the remaining 2/3 fell outside referral criteria or alarm symptoms were not discovered.

Conclusions: Patients referred after unplanned excision often have small superficial tumors and the majority fall outside of defined referral criteria. Referral criteria are not a guarantee for detection of all sarcomas and surgeons should always be aware of the possibility of malignancy when removing a tumor.

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KEY WORDS: **sarcoma; unplanned excision; cancer patient pathways; alarm symptoms; referral criteria**

INTRODUCTION

Sarcomas are rare with only 300 new cases seen annually in Denmark [1]. They present with few symptoms, often merely the presence of a painless lump [2]. Furthermore, benign tumors present with similar symptoms, thus challenging the diagnosis. It is widely agreed that biopsy and surgical treatment of sarcomas should be centralized to tumor centers with specialist expertise, and several countries, including Denmark, have implemented referral guidelines to ensure this [3–6].

However, a number of sarcomas are often (accidentally) treated surgically before referral to specialist centers, an unplanned excision [7,8]. This problem has been widely described in the literature [8–23]. Biopsy of a tumor is a hazardous procedure, and if performed by inexperienced surgeons, it may result in a higher complication rate, more errors in diagnosis and changes in course or outcome compared to biopsies performed in specialist centers [19,24]. An unplanned excision entails a risk of inadequate excision leaving positive surgical margins. In studies on patients referred after unplanned excisions, over 50% had residual disease at re-excision [7,9,15,16,23]. Patients with a positive surgical margin after resection have poorer outcomes regarding local recurrence and mortality than patients with wide margins [7–10,25–27]. Local recurrence is not necessarily synonymous with distant metastases [28,29], but local recurrence in itself may affect the survival and should thus be avoided [27].

Even though survival after re-excision is comparable to that of patients with planned surgeries [10,14,30], inadequate primary excision can result in more mutilating re-excision surgery [7–9,12,16,22,31], for example, due to lack of adherence to surgical oncological rules regarding incision, placement of drains, and contamination of uninvolved joints [16,17,31]. For some patients, an amputation might be the only option to achieve local control [22]. The patient is left with poorer cosmetic results, loss of function, and the psychological distress of repeated surgery.

Few studies report on events prior to the unplanned excision. The implementation of referral guidelines has been done in an attempt to detect all cancer patients at an earlier stage. However, as some patients do experience unplanned excisions, we need knowledge of why they did not follow the specific sarcoma pathway. Analyzing sarcoma patients referred to our center after unplanned excision, the purpose of this study was to describe patient and tumor characteristics, initial symptoms, initial and final diagnosis, and explore reasons for the unplanned excision.

MATERIALS AND METHODS

Setting

Aarhus Sarcoma Center (ASC) is one of two centralized sarcoma centers in Denmark and handles most referrals from the Jutland region (approx. 2.5 million inhabitants). The national cancer patient pathway

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(CPP) for sarcoma (implemented January 1, 2009) recommends that all patients presenting with one or more of the defined alarm symptoms/signs (Table I) should be referred to a local orthopedic department for clinical examination and magnetic resonance imaging (MRI) or other suitable imaging modalities. If the MRI and clinical examination confirms the suspicion, the patient should immediately be referred to a sarcoma center for biopsy and treatment, ideally leaving the tumor untouched before referral [32].

Patient Population

We previously examined time intervals and presenting symptoms among 1,126 patients referred to ASC with a suspicion of sarcoma from hospitals in the Jutland region (Aarhus region omitted as patients living in this area are referred directly to ASC as their local orthopedic department and thus do not follow the CPP). The patients were referred in the period between January 1, 2007 and December 31, 2010. Further details of this population have been described elsewhere [6,33]. Of the 1,126 referred patients, 258 patients had a sarcoma, of which 64 were referred with a histologically confirmed sarcoma, after either a biopsy or a surgery. The latter patient population forms the study population in this study.

Variables

Patient and tumor characteristics were collected from medical files and variables included sex, age, symptom duration, tumor tissue type (soft tissue or bone), malignancy grade, tumor size and site, treatment at ASC, and final histological diagnosis. Symptom duration was registered as the interval between the first noticed symptoms as stated by the patient and the first appointment at ASC, thus a combination of the patient interval and the diagnostic interval according to the Aarhus Statement [34]. The histological type was determined by the histological revision of the resection specimen performed by a pathologist associated with ASC. For malignancy grade, the Trojani classification was used [35]. Grade 1 tumors were classified as low grade tumors, grade 2 or 3 as high grade tumors. Tumor size was defined as the largest diameter of the tumor found in the pathology report. Tumor depth was found in the pathology report and classified as either subcutaneous or subfascial. Referrals were reviewed for information on treatment and imaging procedures performed before referral, referring instance, initial diagnosis, and initial symptoms. For most patients, the patient record annotations from the referring hospital were included in the referral papers, making collection of this information possible. Presenting symptoms as described by the patient and presenting symptoms/signs annotated in the referral papers by the physician were both registered. When evaluating whether the patient fell outside of referral guidelines or not, one of the five alarm symptoms were only considered to be present if there was a mentioning of the symptom/sign annotated in medical files before surgery/biopsy at the local hospitals. For example, if a tumor was described as subcutaneous and smaller than 5 cm at the clinical evaluation, but after surgery were revealed to be over 5 cm, the patient was considered to have presented with a tumor under 5 cm.

TABLE I. The Five Defined Alarm Symptoms/Signs in the Cancer Patient Pathway for Sarcomas That Should Cause a Referral to the Local Orthopedic Department for Further Investigations

Alarm symptoms/signs
Soft tissue tumor over 5 cm
Soft tissue tumor situated on or below the deep muscle fascia
Fast growing soft tissue tumor
Palpable bone tumor
Deep persisting bone pains

Statistical Analyses

Descriptive statistics was used to describe the patient population. Continuous variables such as age, symptom duration, and tumor size were found to be non-normally distributed and were presented as medians and interquartile intervals (IQI). Differences between groups were tested with the Mann–Whitney *U*-test. All *P*-values are two sided.

RESULTS

Patient Characteristics

Of the 64 patients, 26 (40.6%) were females. Median age was 58.2 years (IQI = 42.5–70.7) (females 51.7 years [IQI = 40.1–64.17] and males 62.2 years [IQI = 46.7–71.0]). Median symptom duration (patient interval + diagnostic interval) was 87 days (IQI = 27.5–120) for the entire group (females 180 days [IQI = 60–731], males 46.5 days [IQI = 27.5–120]). The difference in symptom duration between males and females was statistically significant ($P = 0.0457$).

Tumor Characteristics and Diagnoses

There were 61 (95.3%) soft tissue sarcomas and three (4.7%) bone sarcomas. For five patients, the tumor size could not be found. For the remaining 59 patients, the median tumor size was 35 mm (IQI = 20–50) (females 30 mm [IQI = 20–50], males 40 mm [IQI = 23–55]). Eighteen (30.5%) tumors were over 5 cm. Of the 61 soft tissue sarcomas, 19 (31.1%) were located beneath the deep fascia, and nine (47.4%) of the 19 subfascial sarcomas were over 5 cm. For one soft tissue sarcoma, the depth was not noted in medical records. In the total study population of 64 patients, 32 (50%) sarcomas were superficial tumors under 5 cm. Twenty-seven (42.2%) of sixty-four tumors were low grade and thirty-seven (57.8%) were high grade sarcomas. Tumor location and final histological diagnosis are presented in Table II. The most frequent initial diagnoses were lipoma in 10 (15.6%) of the 64 patients and fibroma/dermatofibroma in eight patients (12.5%). Eight (12.5%) of the sixty-four patients were initially diagnosed with other malignancies (see all initial and corresponding final diagnoses in Supplementary Appendix 1).

Referring Instance, Pre-Surgery Investigations, and Subsequent Treatment

Thirty-six (56.3%) of the sixty-four patients were referred from surgical public hospital departments, the rest from various other hospital departments and private specialists (Table III). Thirty-nine (60.9%) of the sixty-four patients received no imaging investigations before surgery/biopsy, fourteen (21.9%) patients received an ultrasound, three (4.7%) an MRI, one (1.6%) had plain radiographs, and seven (10.9%) had various combinations of ultrasound, CT-scan, and radiographs.

The performed surgical procedure before referral to ASC was a biopsy for seven (10.9%) of the 64 patients and surgical removal of the tumor for the remaining 57 (89.1%) patients. At ASC, 55 (85.9%) patients received a surgical re-excision, 1 (1.6%) patient received re-excision elsewhere, 1 (1.6%) patient was treated with chemotherapy, and 1 (1.6%) patient with radiation. Six (9.4%) patients were not re-excised, just allocated to continuing follow-up appointments to detect possible recurrences of the disease.

Presenting Symptoms

The most frequently stated symptom by the patients was a lump (58 of 64 patients [90.6%]), and pain (18 of 64 patients [28.1%]). Twelve (18.8%) of the sixty-four patients reported that it was the second removal of a tumor in the same area. Five (7.8%) patients reported recent changes in a dormant tumor that had been present for years. Among our 64 patients, the presence of one or more of the five CPP

TABLE II. Final Diagnosis and Tumor Location for 64 Sarcoma Patients Referred After Unplanned Excision

Final diagnosis	n	%
Leiomyosarcoma	13	20.3
Dermatofibrosarcoma protuberans	11	17.2
MFH	9	14.1
Liposarcoma	8	12.5
Angiosarcoma	6	9.4
Other malignant	3	4.7
Unclassified	3	4.7
Chondrosarcoma	2	3.1
Extraosteal chondrosarcoma	2	3.1
Malignant schwannoma	1	1.6
Extraosteal osteosarcoma	1	1.6
Rhabdomyosarcoma	1	1.6
Synovial sarcoma	1	1.6
Fibrosarcoma	1	1.6
Solitary fibrous tumor	1	1.6
Osteosarcoma	1	1.6
Location	**n**	**%**
Thorax	10	15.6
Thigh	7	10.9
Lower arm	7	10.9
External genitalia	6	9.4
Lower leg	5	7.8
Abdomen/low back	5	7.8
Shoulder	4	6.3
Head/neck	4	6.3
Gluteal	3	4.7
Knee	3	4.7
Mamma	3	4.7
Hand/wrist	2	3.1
Ribs (bone tumor)	1	1.6
Foot/ankle	1	1.6
Lung	1	1.6
Tibia (bone tumor)	1	1.6
Vertebra (bone tumor)	1	1.6
Total	64	100

criteria had been detected and annotated in the medical records before surgery in 25 (39.1%) patients. The remaining 39 (60.9%) patients fell outside of defined inclusion criteria or the presence of alarm symptoms were not detected by the referring instance (Fig. 1).

DISCUSSION

We found that the majority of sarcomas referred after surgery were soft tissue sarcomas, most often located in the thoracic region, lower arm, or thigh. Leiomyosarcoma, dermatofibrosarcoma protuberans, and MFH were the most frequent final diagnoses, whereas lipoma and fibroma/dermatofibroma were the most frequent initial diagnoses. Half of the sarcomas were superficial tumors under 5 cm, and six out of 10 had not received any diagnostic imaging before surgery. Half of the patients were referred from surgical departments at public hospitals, one-third from private specialists. For 6 out of 10, alarm symptoms/signs were not registered before surgery.

TABLE III. Distribution of the Referring Instance for 64 Sarcoma Patients Referred After Unplanned Excision

Operating physician/department	n	%
Surgical department, public hospital	17	26.6
Orthopaedic department, public hospital	13	20.3
Private surgeon	7	10.9
Private orthopaedic surgeon	6	9.4
Private dermatologist	5	7.8
General practitioner	4	6.3
Urology department, public hospital	4	6.3
Private hospital	2	3.1
Medical department, public hospital	2	3.1
Department of plastic surgery, public hospital	1	1.6
Private ear/nose/throat specialist	1	1.6
Private plastic surgeon	1	1.6
Department of thoracic surgery, public hospital	1	1.6
Total	64	100

Strengths and Weaknesses

The small patient number and the selected patient group limit our study. This affects the statistical possibilities and the generalizability of our results, but our study offers a good description of patients referred after unplanned sarcoma excision in Denmark. Furthermore, the design is retrospective, making the presence or absence of initial symptoms difficult to evaluate. Especially tumor growth is difficult to assess precisely as most patients report this symptom to the inquiring physician. This may be due to increased awareness of the tumor, not necessarily a genuine tumor growth. The retrospective nature of the study is a weakness in itself, but for natural reasons, an unplanned excision cannot be studied prospectively. Strengths include the fairly large study population from which these 64 patients originate (in the original population over 1,700 medical records were reviewed) and the completeness of the registered data. Nearly, all referring hospitals had forwarded their medical records and there were few missing data. However, we did not have full access to data from the referral hospital, and it is possible that alarm symptoms were present, but not noted in the medical files. Information on performed imaging might also be excluded from the referral material.

Comparison With Other Studies

The proportion of small superficial sarcomas in our patient population was high, which is consistent with findings in other studies on unplanned excision [15,16], and this serves as a reminder that sarcomas start out as small tumors and many sarcomas are superficial. Rydholm et al. report that 1/3 of all soft tissue sarcomas are located in the subcutaneous region [36], Salas et al. report a proportion of 11.8 % [37]. At ASC, around 28% of soft tissue sarcomas are superficial [38]. Subcutaneous sarcomas are often smaller and of a lower malignancy grade than deep-seated sarcomas and have a better prognosis both regarding local recurrence and survival [36,37,39]. However, close to 60% of the patients in our population had a high malignancy grade.

Proper imaging before surgical removal of a sarcoma is paramount, with MRI being the preferred modality. A larger proportion of patients in our study had not had imaging before initial surgery, which has also been reported in similar studies on unplanned excisions. Siebenrock et al. found that 69% of their patients had not had any imaging before surgery [31]. In the study by Manoso et al., only eight of 38 patients had undergone an MRI, and in six of these the MRI could not rule out malignancy [13]. Hoshi et al. reported that eight out of 38 patients had received MRI or CT before surgery [16], and in the study by Wong et al., 16 out of 18 patients had received no investigations before surgery [12]. On the other hand, one-third of our patients had received preoperative imaging and their tumors were still resected as presumed benign tumors. One can thus only speculate as to whether preoperative imaging would have resulted in a reconsideration of the diagnosis.

A large proportion of our patients were referred from surgical departments at public hospitals, fairly evenly distributed between general surgery and orthopedic surgery. Rougraff et al. reported that general surgeons were more likely to refer after surgery compared to orthopedic surgeons [14], whereas Hoshi et al. found an even distribution between general and orthopedic surgeons [16], similar to our study. The distribution of referring specialties show that sarcomas

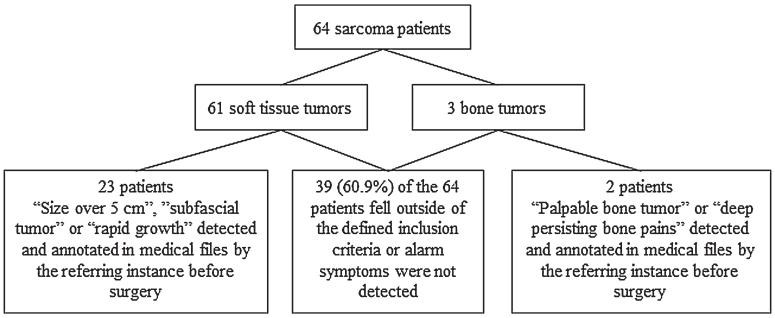

Fig. 1. Presence or absence of inclusion criteria defined in the cancer patient pathway for sarcomas before surgery among 64 sarcoma patients referred after unplanned excision.

are handled by a wide variety of physicians, both in public hospitals and in the private health care sector. Educational initiatives and referral guidelines should thus be mediated to all parts of the health care sector, not just to the orthopedic specialists.

Nearly all our patients received a re-excision and this is in concordance with the practice elsewhere [7,9,10,13]. It has been shown that patients referred after surgery or not referred to a sarcoma center at all undergo more operations than patients referred before surgery [30]. A second removal of a tumor is distressing for the patient as they did not expect the diagnosis, and patients are often concerned by the prognosis [17,22]. Their trust in the health care system might also be affected owing to the initial reassurance that the tumor was benign. Unplanned excisions most often result in repeated surgery for the patient, and this should be avoided.

Few studies have investigated presence of initial alarm symptoms before unplanned excision in sarcoma patients. Wong et al. found that 12 out of 18 patients had presented with alarm symptoms before unplanned excision [12], and Kang et al. reported initial alarm symptoms in approximately 50% of their patients referred after unplanned excision [21]. Chandrasekar et al. found that 96% of their unplanned excision patients had presented with alarm symptoms defined in the British NICE guidelines for referral of sarcomas [15]. These results could indicate that the cause of unplanned excision is ignorance of referral criteria at local hospitals. However, the large proportion of patients falling outside of defined referral criteria in our population suggests that unplanned excision of sarcoma in Denmark may largely be due to the fact that patients simply do not fit into the CPP for sarcomas. Standardized diagnostic pathways can only accelerate the diagnostic process and treatment if the patients are included. It has been shown for several cancer types that a larger proportion of patients are diagnosed outside of the standardized pathways [40,41]. This might also be the case for sarcomas.

CONCLUSIONS

Referral after unplanned excision is still an issue among sarcoma patients. We have shown that a larger part of patients referred after unplanned excision have small superficial tumors and fall outside of the CPP referral criteria.

Clinical Implications

The CPP for sarcomas is not a guarantee for detection of all sarcomas and surgeons should always be aware of the possibility of malignancy when removing a tumor. Apart from the inclusion criteria, changes in previously dormant tumors and regrowth of previously excised tumors should cause suspicion and referral to a specialized sarcoma center. Tumors should be screened with ultrasound or MRI before surgical removal and continuous education of medical students and surgeons in training is vital to ensure awareness and correct referral of these tumors.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

Appendix 1: Initial and final diagnosis of 64 sarcoma patients referred after unplanned excisions

Initial diagnosis	Final diagnosis
Recurrence of previous neurilemmoma	Malignant schwannoma
Testicular malignancy	Liposarcoma
Lipoma	PEComa
Ganglion cyst	Extraosteal chondrosarcoma
Hematoma/pseudoaneurism	Leiomyosarcoma
Papillary hemangioma	Angiosarcoma
Kidney malignancy	Classic chondrosarcoma
Recurrence of previous ateroma	MFH
Sequelae from previous vasectomy	Liposarcoma
Bursitis	Synovial sarcoma
Osteochondroma/fibrous dysplasia	Classic chondrosarcoma
No presumed diagnosis mentioned	Leiomyosarcoma
Infected ateroma	Dermatofibrosarcoma protuberans
Dermatofibroma	Dermatofibrosarcoma protuberans
Keratoacanthoma	MFH
Dermatofibroma	Leiomyosarcoma
Benign skin condition	Dermatofibrosarcoma protuberans
Lipoma at the GP/ cancer occulta at hospital	Angiosarcoma
Benign skin tumor	Angiosarcoma
Leiomyoma	Leiomyosarcoma
Lymph node metastasis	Undifferentiated spindle cell sarcoma
Psoriasis	Rhabdomyosarcoma
Benign tumor	Unclassified sarcoma
Lipoma	MFH
Lipoma	Liposarcoma
Lipoma	Solitary fibrous tumor
Fibroma	MFH
Lipoma at GP/dermatofibrosarcoma protuberans at plastic surgeon	Dermatofibrosarcoma protuberans
Lipoma	Liposarcoma
Fibroma	Hyperplastisk sarkom
Hernia	Liposarcoma
Abscess	Dermatofibrosarcoma protuberans
Ganglion cyst	Leiomyosarcoma
Fibroma	Leiomyosarcoma
Trauma sequelae	Leiomyosarcoma
Spermatocele	Liposarcoma
Benign tumor	Dermatofibrosarcoma protuberans
Dermatofibroma	Dermatofibrosarcoma protuberans
Lymph node conglomerate	Liposarcoma
Benign tumor	MFH
Benign skin tumor	Leiomyosarcoma
Recurrence of previous breast cancer	Angiosarcoma
Lipoma	Dermatofibrosarcoma protuberans
Pyogenic granuloma	Myxoid sarkom
Granuloma	Leiomyosarcoma
Dermatofibroma	Dermatofibrosarcoma protuberans
Benign giant cell tumor	Classic osteosarcoma
Lymph node	Fibrosarcoma
Hypertrophic scar tissue	Dermatofibrosarcoma protuberans
Lung cancer	Extraosteal chondrosarcoma

Benign tumor	Leiomyosarcoma
Benign tumor	MFH
Ateroma	Leiomyosarcoma
Granuloma/scar tissue	Dermatofibrosarcoma protuberans
Benign tumor	Extraosteal osteosarcoma
Lipoma/vascular malformation	Unclassified sarcoma
Malignant tumor	MFH
Hematoma	MFH
Breast cancer	MFH
Hernia+hematoma	Leiomyosarcoma
Malignant melanoma	Angiosarcoma
Benign hemangioendothelioma	Angiosarcoma
Fibroma	Leiomyosarcoma
Lipoma/ateroma	Liposarcoma

Paper IV

Routes to diagnosis for suspected sarcoma – the impact of symptoms and clinical findings on the diagnostic process

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Submitted

Abstract

Background and objectives

Sarcoma patients often experience delay before diagnosis. We examined the association between presenting symptoms/signs and time intervals for suspected sarcoma patients.

Methods

545 consecutive patients suspected for sarcoma referred over a one-year period were included. Data on routes to diagnosis were collected from medical records and questionnaires.

Results

102 patients (18.7%) had a sarcoma, 68 (12.5%) had other malignancies. The median patient, primary care, local hospital, sarcoma center, diagnostic and total interval for sarcoma patients were 77, 17, 29, 17, 65 and 176 days, respectively. Sarcoma patients visited more hospital departments and had longer median primary care (+10 days) and diagnostic intervals (+19 days) than patients with benign conditions. Median primary care (-19 days) and sarcoma center (-4 days) intervals were shorter for patients with a lump vs no lump. Median patient (+40 days), primary care (+12 days), diagnostic (+17 days) and total intervals (+78 days) were longer for patients presenting with pain vs no pain. GP suspicion of malignancy shortened local hospital (-20 days) and total intervals (-104 days).

Conclusions

The main part of delay could be attributed to the patient and local hospitals. Length of time intervals was associated with presenting symptoms/signs and GP suspicion.

Introduction

Sarcoma is one of the rarer cancer types and patients are often prone to delay before diagnosis [1,2]. Whether this affects the prognosis is debated. Some studies show that long symptom duration improves survival [3,4], others show a poorer survival with increasing symptom duration [5,6], and some show no difference [7-11]. A review concluded that an expedited diagnosis improved cancer outcomes overall, but that this varied with cancer type [12]. Further, lower use of the English 2-Week Wait pathway by GPs has been associated with an increased mortality among cancer patients [13]. Apart from affecting prognosis, delays affect patients' evaluations and give rise to psychological distress and patient complaints [14,15].

Fast track referral pathways have been implemented in some countries to reduce delays [16-18], and the Danish Cancer Patient Pathways (CPPs) have reduced time between referral to a specialized sarcoma center and initiation of treatment in sarcoma patients [19]. However, this is only a small part of the pathway as the main part of the diagnostic route lies with the patient, the general practitioner (GP) and local hospitals. Approximately 85% of all cancer patients in Denmark initiate their diagnostic route in general practice [20], and GPs are important in sarcoma diagnosis. This task is not easy as only one in 100 soft tissue lumps are malignant [21], and a GP may see only one sarcoma in their entire career. Furthermore, the CPPs are based on alarm symptoms qualifying the patient for referral to the fast track-pathway, and patients without alarm symptoms may thus experience delays.

Studies have investigated presenting symptoms among confirmed sarcoma patients at time of diagnosis in highly specialized sarcoma centers, and the symptom duration is usually reported as a total sum from first symptom to diagnosis. However, this approach sheds no light on the initial symptoms and does not include the population of benign tumors from which sarcomas have to be separated. Thus, we need detailed information on the milestones and how the presenting symptoms affect the length of time intervals to be able to optimize the diagnostic pathway for sarcoma patients.

We aimed to examine time intervals, symptom presentation and routes to diagnosis from first perceived symptom to diagnosis at a specialist center among patients referred to the CPP for sarcomas. We hypothesized that the time to diagnosis for suspected sarcoma patients differ depending on the presenting signs and symptoms.

Materials and methods

Setting

The study was performed at Aarhus Sarcoma Center, which is one of the two centralized sarcoma centers in Denmark, with a catchment area of approximately 2.5 million inhabitants from the Jutland area. In the CPP for sarcomas Aarhus Sarcoma Center functions mainly as the highly specialized sarcoma department, to which all patients found to have a suspicion of sarcoma after initial investigations at local hospitals in the catchment area are referred. Further, Aarhus Sarcoma Center also serves as the local orthopedic hospital department for suspected sarcoma patients living in Aarhus Municipality (approx. 330.000 inhabitants), and GPs in this area may refer directly to Aarhus Sarcoma Center for initial investigations.

Study population and data collection

The study entailed a population based retrospective collection of data on the diagnostic route before referral to Aarhus Sarcoma Center and a prospective recording of the pathway from first visit at Aarhus Sarcoma Center until diagnosis and treatment. All consecutive patients referred to the CPP for sarcoma at Aarhus Sarcoma Center in the period from 1st of September 2014 to 31st of August 2015 were invited to participate in the study. Data collection was performed by a combination of questionnaires and medical record review. We developed two questionnaires, one for patients and one for GPs. They included items from similar questionnaires for other cancer forms [22], and were adapted for sarcoma patients. The patient questionnaire was pilot tested on a group of 15

consecutive patients, and the GP questionnaire was pilot tested firstly by questionnaire experts, and later by five practicing GPs to ensure understanding. Small adjustments were made before start-up of data collection.

The patients received their questionnaire by mail before the first appointment at the sarcoma center, and were encouraged to answer the questions beforehand. Patients were interviewed after the appointment, thus ensuring correct completion of questions. An informed consent was provided at this time. The GP questionnaire was sent to the patients' GP if either the medical record showed, or the patient stated that they had visited their GP in relation to the present pathway. GPs received no remuneration for answering the questionnaire. GPs were reminded with a new questionnaire after 4-5 weeks, followed by a telephone reminder after a further three weeks. The patient's route to diagnosis was tracked backwards and data from local hospitals involved in the diagnostic route was collected from medical records. Final diagnosis and treatment was collected from medical records containing pathology reports at Aarhus Sarcoma Center.

Variables

Tumor grade for sarcoma patients was classified by the Trojani classification system [23]. For analyses, grade 2 and 3 were defined as high grade, and grade 1 and borderline malignancies as low grade tumors.

Tumor size was measured as the largest diameter on MRI or CT. If none of these scans were performed, size was taken from the pathology and, if not removed, from ultrasound, x-ray or clinical measurement. Tumor depth was classified as subcutaneous or subfascial relative to the deep muscle fascia.

Questions about primary symptoms and development in symptoms were answered by the patients in free text, and each reported symptom was coded with an individual number. No grouping of symptoms into categories was done during the recording. The recorded codes could then later be divided into groups suitable for analyses. We could not use validated coding systems such as the

International Classification of Primary Care (ICPC) as these systems are too organ specific and would not give us the necessary detail for the purposes of our study. Sarcomas can arise in any anatomical location and the symptoms do not fit into regular coding systems for presenting symptoms based on organ of origin.

The GPs were asked to report their tentative/suspected diagnosis in free text. Each diagnosis was coded with a unique number using the same approach as for presenting symptoms, and all codes corresponding to a suspicion of any malignancy were classified as GP suspicion being present.

Information on time points was collected from several sources. Patients reported date of symptom debut and date of first doctor visit. GPs reported date of first visit and date of referral for further investigation at hospitals. Date of first appointment and date of referral for each local hospital department was collected from medical records. From the sarcoma center, the date of received referral and date of decision of diagnosis and/or initial treatment was collected. If the patient or the GP had stated only a month and year in their reported dates, the 15th of that month was chosen as the specific date. If only a year was stated, the 1st of July that year was chosen as the specific date. For patients with missing GP data, the patient reported date for first doctor visit was used to calculate patient interval and diagnostic interval. Time intervals are measured in calendar days and defined in accordance with the Aarhus Statement [24]. We defined six time intervals; patient, primary care, local hospital, sarcoma center, diagnostic and total interval (Figure 1). Patient interval was defined as time from first symptom to first doctor visit. Primary care interval was defined as time from the first visit at the GPs office to referral to hospital. The local hospital interval was defined as time from referral to first local hospital to final referral to the sarcoma center and the sarcoma center interval as time from received referral at the sarcoma center to the date where a decision on the final course of treatment was made (decision of a final treatment modality or decision of no treatment). This decision date was also the end point of the diagnostic and total interval, and this date was chosen to ensure comparativeness of time intervals between

patients regardless of final diagnosis. The treatment interval is thus not included. The starting points of the diagnostic interval and the total interval were the first doctor visit and the date of first symptom, respectively.

Ethical approval

The study was approved by the Danish Data Protection Agency (journal number 2007-58-0010), and all patients provided their written consent to participation. Approval from the Committee on Health Research Ethics of the Central Denmark Region was not needed according to Danish law.

Statistical analysis

Descriptive statistics were used to test differences between participants and non-participants (chi-squared test (gender) and Wilcoxon Rank sum test (age)). Number of local hospital departments visited and number of GP consultations were compared with the Wilcoxon Rank Sum test. Time intervals were highly right-skewed, and are reported as medians with interquartile intervals (IQI). Comparisons of time intervals at the 50^{th} and 75^{th} percentile between different groups were performed with quantile regression analyses, using the procedure written by Miranda [25]. The 75^{th} percentile showing differences in waiting times for the 25% of patients waiting the longest was included to portray any differences in the size of the right-skewed tail inherit to waiting time data. Gender distribution was found to be equal in all groups, and was thus not adjusted for. Age differed between groups and was adjusted for as a categorical variable (<20, 20-39, 40-59 and ≥60 years). Quantile regression analyses were repeated with adjustments for both age and gender to assess the effect of gender on estimates. This resulted in no or very small changes in the estimated differences, thus supporting our decision to exclude the gender variable in our reported analyses. P-values of 5% or less were considered significant in all analyses, and all p-values are two-sided. Statistical calculations were performed using Stata® statistical software, version 13.

Results

Patient and GP participation

During the inclusion period a total of 607 patients entered the sarcoma CPP at Aarhus Sarcoma Center. Of these, 545 (89.8%) patients were included as 56 patients did not want to participate in the study, five were not mentally able to answer questionnaires, and one did not speak Danish or English. Non-participants did not differ significantly from participants with regards to age or gender. 466 GP questionnaires were sent out, of which 400 (85.5%) were completed. For 42 (9.0%) patients with a non-responding GP, information on dates and performed imaging investigations at the GPs office could be collected from the GP referral or the medical records.

Patient and tumor characteristics

Of 545 included patients, 102 (18.7%) were diagnosed with a sarcoma and 68 (12.5%) with other malignancies, giving a total proportion of malignancies of 31.2%. There were no significant differences in gender or age distribution between sarcoma patients, patients with other malignancies and patients with benign conditions (Table 1). There were 56 patients below the age of 18, of which eight (14.3%) were diagnosed with a sarcoma and eight (14.3%) with other malignancies. The most frequent sarcomas were liposarcoma (n=20, 19.6%), malignant fibrous histiocytoma/undifferentiated pleomorfic sarcoma (n=12, 11.8%) and leiomyosarcoma (n=9, 8.8%). The most frequent other malignant diagnoses were metastasis (n=30, 44.1%), lymphoma (n=23, 33.8%) and myelomatosis (n=6, 8.8%). Most frequent benign diagnoses were lipoma (n=60, 16.0%), reactive tissue changes (n=46, 12.3%) and schwannoma/neurofibroma (n=23, 6.1%). Forty-five (44.1%) sarcomas were grade 3 tumors, 24 (23.5%) grade 2, 25 (24.5%) grade 1 and eight (7.8%) borderline malignancies. Seven (6.9%) had metastases at time of diagnosis. Further patient and tumor characteristics are summarized in Table 1.

Routes to diagnosis

Most frequent reasons for seeking medical care for the total patient population were pain, wanting to know what it was, consulting for something else, being urged by others and incidental findings on imaging (Appendix 1). Characteristics of the patients' routes to diagnosis are presented in Table 2. The majority had first presented to their GP (83.7 %). The number of local hospital departments visited between the GP and Aarhus Sarcoma Center was statistically significantly higher both for sarcoma patients compared to patients with benign conditions (p=0.001), and for patients with other malignancies compared to patients with benign conditions (p<0.001). There was a trend towards a higher number of GP consultations for sarcoma patients compared to patients with benign conditions (p=0.051).

Time intervals

Median days with interquartile intervals (IQI) for all time intervals are presented in Table 3. Overall, the longest intervals were seen for the patient interval and the local hospital interval contributing to a median total interval of 155 days and where the 25% that waited longest had a time interval of 423 days from first symptom to decision. In general, differences in symptoms and signs modified some of the intervals. Note especially, that presence of pain prolonged the intervals and GP suspicion shortened the intervals.

Table 4 presents the estimated differences in time intervals at the 50^{th} and 75^{th} percentile level adjusted for age. Patients with sarcoma tended to have longer time intervals compared to patients with benign conditions. For patients with other malignancies the reverse relationship was found, as these patients had shorter time intervals than patients with benign conditions. The median sarcoma center interval was approximately one week statistically significantly longer for patients with other malignancies compared to patients with benign conditions. Sarcoma patients with high grade tumors had a significantly shorter median total interval compared to sarcoma patients with low

grade tumors due to a shorter patient interval, whereas the diagnostic interval was longer for high grade tumors.

It is worth noticing that patients presenting with a lump tended to have a longer patient interval compared to patients without a lump, whereas the primary care interval and sarcoma center intervals were statistically significantly shortened (-19 days and -4 days, respectively). For patients presenting at the sarcoma center with a tumor over 5 cm, the patient interval and thus the total interval was statistically significantly longer compared to patients with smaller tumors (+26 days and + 51 days, respectively). Patients with subfascial soft tissue tumors had a statistically significantly shorter patient interval (-31 days) compared with patients with subcutaneous tumors.

Focusing on the 25% of patients waiting longest (the 75th percentile) accentuated the described differences.

Discussion

Summary of main results

The GP was involved in the diagnostic route for the majority of patients. The reasons for help seeking was mainly pain, wanting to know what it was, consulting for something else and being urged by others. One third of the patients referred to the CPP had a cancer. Patient interval and local hospital interval constituted the main parts of the total time from first symptom to diagnosis. Sarcoma patients had longer time intervals and patients with other malignancies had shorter time intervals compared to patients with benign conditions. Patients with malignancies visited more local hospital departments than patients with benign conditions. Presence of a lump, large tumor size and presence of pain increased patient intervals, whereas patients with subfascial tumor location and high malignancy grade had shorter patient interval. High tumor grade and presence of pain increased health system intervals, whereas large tumor size, presence of a lump and initial GP suspicion shortened health system intervals. Differences were more pronounced at the 75th percentile level.

Strengths and limitations

The strengths of our study lie in a high participation rate and high completeness of data. Non-participants were similar in age and gender distribution to participating patients. We have no information on the number of malignancies or the length of time intervals among non-participants and no specific indication of whether there could be a special selection as we included all consecutive patients referred to the CPP. However, the small number of non-participants limits the effect of this possible selection bias. Regarding non-participating GPs, it could be that GPs of patients with delays would decline to answer, which would cause an underestimation of time intervals. To minimize this, we used the patient reported dates to calculate the patient interval and diagnostic interval for patients with missing GP response. Nonetheless, the calculation of primary care interval may be underestimated. Data collected from patients were validated with interviews, improving the completeness and quality of patient reported data. GPs were encouraged to consult medical records when filling out the questionnaire to reduce recall bias. Studies on sarcomas inherit a low statistical precision due to the low incidence. However, compared to other sarcoma studies we were able to include a reasonably large number of malignancies to estimate differences with good statistical precision.

Comparison with literature

We found that reasons for health care seeking mainly were pain, unspecific worry or being there for something else. Sarcoma symptoms are unspecific and probably frequent in a general population. In a large randomly selected Danish population, 811 participants (1.6%) reported experiencing a lump within the last four weeks, and 41.5% of these had consulted a GP for that problem [26]. In our study, it seems that pain was the main reason for sarcoma patients to access medical help, and the presence of pain in sarcomas has also been reported by others [27]. Pain is very often encountered among patients in general practice and therefore is a symptom with low positive predictive value,

but still with a relatively high sensitivity. The use of pain as an alarm symptom in sarcomas is debated, and it has been suggested that this feature should be removed from referral guidelines for sarcomas [28,29]. In the Danish CPP for sarcomas, pain is defined as an alarm symptom for bone sarcoma, and 12 out of 14 bone sarcomas in our study had pain. However, 50% of the soft tissue sarcomas also presented with pain, contradicting the perception that soft tissue sarcomas are not painful. Further investigation of how pain can be used as an alarm symptom is needed.

We found that the main part of the total interval was caused by the patient, followed by the local hospital interval. Other studies have attributed delay in sarcoma patients to GPs in primary care [1,2], but in our material this was not the case as median primary care interval constituted eight days. Still, a tail of 25% waited more than a month in primary care to be referred. Our findings are similar to the primary care interval reported for Danish lung cancer patients of seven days, and for English sarcoma patients of seven days [30,31]. The patient interval has been reported by others to be the main part of delay for other cancer forms [32,33], and the local hospital is also reported as a major contributor to delay [34]. There seems to be a possibility to reduce the waiting time for investigations at local hospitals, for example by providing yes/no investigations (e.g. ultrasound) to GPs for faster work-up of the patients [35]. Overall, the median total interval from first symptom to diagnosis is long for the patients in our population compared to that of other cancer forms [30,31], and as the time intervals are highly right skewed many patients experience considerably longer intervals.

Sarcoma patients tended to have longer waiting time in all time intervals and a higher number of hospital departments seen before referral to a specialist sarcoma center compared to patients with benign conditions, suggesting that sarcoma patients were a complicated patient group to diagnose. This is consistent with findings in an English study showing that the route to diagnosis for sarcoma patients differed from the routes for other cancer forms, as only 12.1% were referred via the Two Week Wait compared to 25% for all other malignancies [36]. We also found that sarcoma patients with a higher malignancy grade had shorter time intervals. This difference was mainly driven by a

shorter patient interval, indicating that aggressive tumors could have more pronounced symptoms that make the patient seek help faster. It may also be a result of recall bias as patients with clearer symptoms may remember the symptom onset more precisely. More surprisingly, the diagnostic interval was longer for patients with high grade tumors. This is opposite of findings for other cancer forms where the patients referred under urgent referral guidelines and thus having the shortest diagnostic intervals have a higher malignancy grade than patients with longer diagnostic intervals [37]. Whether a longer diagnostic interval leads to higher grade is not known, but should definitely be considered.

A relatively large proportion of the patients referred to the CPP had cancer. This can be explained by the selection process, where most patients had been investigated at local hospitals before referral to the sarcoma center. This highlights the importance of easy and direct access to investigations from general practice. However, the selection we see in this study may also be due to a wait-and-see strategy which could lead to later stage at treatment.

The proportion of patients with an initial GP suspicion of malignancy was about one third for sarcomas, suggesting that two thirds of all sarcomas are found on vague, common or non-specific symptoms. This is consistent with English findings showing that sarcomas are more likely to go unnoticed in primary care and be referred outside of the Two Week Wait referral pathway, often by an “elective inpatient” route, suggesting that the patients were admitted for another tentative diagnosis than sarcoma [36]. Symptoms from the musculoskeletal system have been showed to generate low suspicion of cancer among Danish GPs [38]. Initial GP suspicion significantly reduced the time intervals in our cohort, and this importance of GP suspicion in Denmark has been showed for other cancer forms [30,39,40], with a positive predictive value of a GP suspicion of 16.4% [38]. The correct identification and selection of patients for inclusion in fast track referral programs is important as waiting times outside the fast track program may be longer to accommodate for the fast track referrals [41]. Our findings indicate that awareness of sarcoma symptoms among GPs is

of high importance in earlier diagnosis of sarcoma but also that such a strategy must be followed by other ways of investigating patients with non-alarm symptoms.

We confirmed that time intervals differ depending on presenting symptoms. Deeply situated tumors had shorter time intervals in our study, which has also been previously reported [42]. Our data showed increased time intervals with presence of pain. This can be due to the fact that in general practice pain is a common symptom and has a low positive predictive value for serious disease as described earlier – in particular a seldom sarcoma. Musculoskeletal pain is more often attributed to benign conditions. Regarding tumor size, it has been reported that tumors larger than 5 cm have shorter time intervals [42]. This was also the case in our study when it comes to the local hospital delay, and this in combination with our finding that patients presenting with a lump had a significantly shorter primary care interval supports conclusions from other studies reporting shorter time intervals if alarm symptoms are present [43-45]. On the other hand, the patient interval was longer for patients with a lump and patients with tumors over 5 cm. This association may be explained by larger tumor size due to prolonged patient interval, but the observational design of our study prohibits any conclusion of causality. It may also be that patients with a visible tumor can better recall the start of their symptoms, compared to patients with vague symptoms.

Conclusions

We found that the time to diagnosis was associated with the presenting signs and symptoms and presence of GP suspicion. Sarcoma patients were a difficult patient group to diagnose and had longer waiting times than patients with benign conditions. Patients presenting atypically seem to experience longer waiting times before diagnosis, which may be a possible side effect of having alarm symptom based fast-track referral programs such as the CPPs. The main part of the total time was spent in the beginning of the diagnostic pathway and it would be relevant to look further into reducing the patient interval to support earlier diagnosis. The local hospital delay should also be addressed for example by providing easy and quick access to diagnostic investigations locally.

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Figure 1: Overview of time points and calculated time intervals [24].

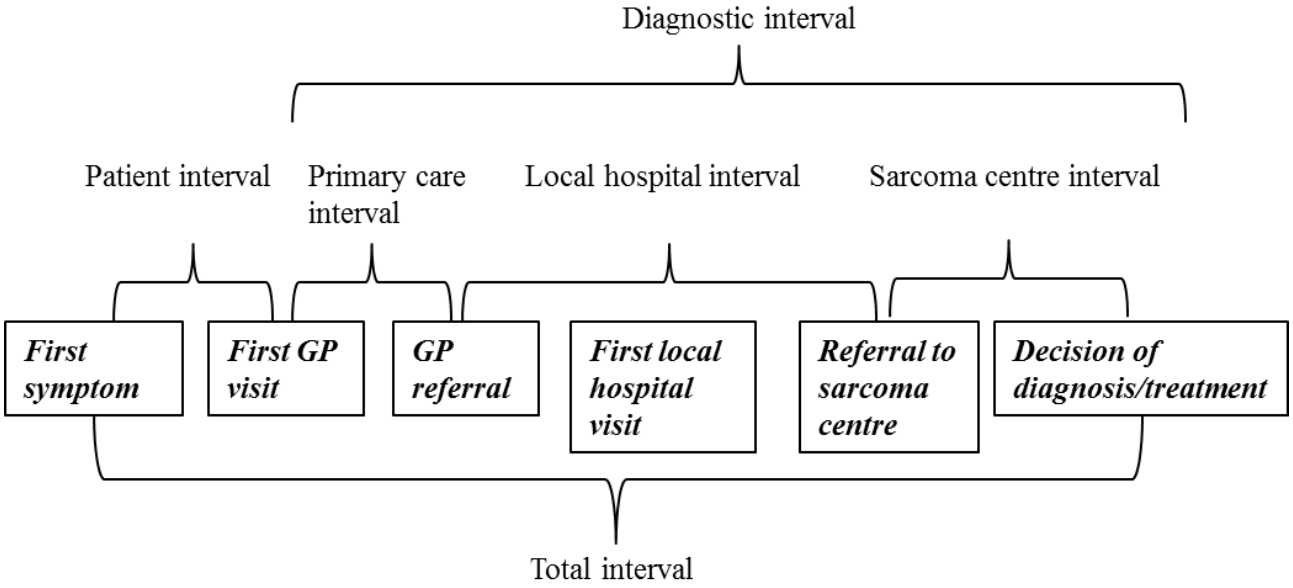

Table 1: Patient and tumor characteristics of 545 patients referred to the Cancer Patient Pathway for sarcomas

	Benign tumors (n=375)	**Other malignancies (n=68)**	**Sarcomas (n=102)**
Age			
Median (IQI)	52.0 (36.0-64.0)	68.5 (55.5-75.0)	55.0 (44.0-70.0)
Gender distribution			
Female (n (%))	181 (48.3)	31 (45.6)	48 (47.1)
Male (n (%))	194 (51.7)	37 (54.4)	54 (52.9)
Tissue type			
Soft tissue (n (%))	255 (68.0)	40 (58.8)	88 (86.3)
Bone (n (%))	120 (32.0)	28 (41.2)	14 (13.7)
Tumor size[1]			
Median (IQI)	3.2 (2.0-5.5)	3.8 (2.6-6.5)	5.75 (4.0-9.0)
Mean (SD)	4.4 (4.0)	5.4 (4.1)	7.2 (5.8)
Size over 5 cm (n (%))	123 (32.8)	26 (38.2)	63 (61.8)
Size under 5 cm (n (%))	232 (61.9)	35 (51.5)	33 (32.4)
Missing	20 (5.3)	7 (10.3)	6 (5.9)
Tumor depth for soft tissue tumors	**(n=255)**	**(n=40)**	**(n=88)**
Subcutaneous (n (%))	108 (42.4)	25 (62.5)	34 (38.6)
Subfascial (n (%))	147 (57.6)	15 (37.5)	54 (61.4)
Geographic area			
Aarhus Municipality (n (%))	117 (31.2)	11 (16.2)	15 (14.7)
Rest of Jutland area (n (%))	258 (68.8)	57 (83.8)	87 (85.3)

[1]Measured on diagnostic MRI or CT for most patients. If this procedure was not performed, size was measured by pathology report if the tumour was removed. If tumor was not removed, size was measured by ultrasound if this was performed or by clinical measurement.

Table 2: Routes to diagnosis for 545 patients referred to the Cancer Patient Pathway for sarcomas

	Benign (n=375)	Other malignancies (n=68)	Sarcomas (n=102)	Total population (n=545)
First physician patient presented to (n (%))				
GP	320 (85.3)	47 (69.1)	89 (87.3)	456 (83.7)
Private specialist	3 (0.8)	1 (1.5)	2 (2.0)	6 (1.1)
Hospital doctor	44 (11.7)	18 (26.5)	9 (8.8)	71 (13.0)
Out of hours GP	2 (2.9)	2 (2.9)	2 (2.0)	9 (1.7)
Other[1]	3 (0.8)	0 (0.0)	0 (0.0)	3 (0.6)
GP initially suspected malignancy[2]				
Yes	94 (30.6)	25(46.8)	27 (32.9)	146 (33.5)
No	213 (69.4)	22 (53.2)	55 (67.1)	290 (66.5)
Number of GP visits				
Mean (SD)	1.4 (0.9)	1.5 (1.0)	1.6 (1.1)	1.4 (0.9)
Median (IQI)	1 (1-1)	1 (1-2)	1 (1-2)	1 (1-2)
Number of hospital departments visited				
Mean (SD)	0.8 (0.7)	1.1 (0.6)	1.1 (0.7)	0.9 (0.7)
Median (IQI)	1 (0-1)	1 (1-1)	1 (1-1)	1 (0-1)
Referral with histological diagnosis of sarcoma (n (%))				
Yes	4 (1.1)	5 (7.4)	31 (30.4)	40 (7.3)
No	371 (98.9)	63 (92.7)	71 (69.6)	505 (92.7)
Referred with regrowth of previously removed tumor (n (%))				
Yes	4 (1.1)	1 (1.5)	11 (10.8)	16 (2.9)
No	371 (98.9)	67 (98.5)	91 (89.2)	529 (97.1)
Referred after incidental findings on imaging (n (%))				
Yes	33 (8.8)	9 (13.2)	5 (4.9)	47 (8.6)
No	342 (91.2)	59 (86.8)	97 (95.1)	498 (91.4)
Referred with suspected recurrence of previous sarcoma (n (%))				
Yes	6 (1.6)	0 (0.0)	7 (6.9)	13 (2.4)
No	369 (98.4)	68 (100.0)	95 (93.1)	532 (97.6)

[1]One patient presented to her father who was a doctor, one patient was a doctor and referred himself and one patient presented to a friend who was a doctor.

[2]Percentages calculated from the total of patients who had data available for this variable, meaning that the patient had been seen by their GP and the GP had provided an answer for this question (n=307 for benign conditions, n=47 for other malignancies, n=82 for sarcomas, n=436 for the total population).

Table 3: Median number of days (interquartile intervals) spent in each interval of the diagnostic process from first symptom to decision of diagnosis/treatment

	Patient Interval Median (IQI) *n* = 545	Primary Care Interval Median (IQI) *n* = 416	Local Hospital Interval Median (IQI) *n* = 386	Sarcoma Centre Interval Median (IQI) *n* = 545	Diagnostic Interval Median (IQI) *n* = 545	Total Interval Median (IQI) *n* = 545
All patients	54 (12:241)	8 (1:36.5)	26.5 (13:58)	15 (9:22)	50 (30:98)	155 (61:423)
Gender						
Female	48.5 (9:182)	11 (1:39.5)	23 (13:60)	16 (11:23)	52 (31:98)	144.5 (60:341)
Male	59 (13:319)	4 (1:35)	28 (13:54)	15 (8:22)	50 (29:99)	158 (62:507)
Age						
< 20	31 (15:84)	22 (2:73)	21 (11:58)	15 (8:20)	55 (30:139)	118 (47:259)
20–39	76 (21:539)	12 (1:49)	36.5 (18.5:102)	17 (11:25)	57 (33:148)	184 (77:924)
40–59	110 (17:349)	7.5 (1:36)	32.5 (16:72)	15 (8:22)	62 (31:106)	225 (78:591)
≥ 60	36.5 (4:134)	3.5 (1:33)	21 (11:43)	15 (9:23)	42.5 (27:78)	99 (46:240)
Pt had or developed lump						
No	38.5 (1:215)	22 (4:58)	24 (9:67)	19 (11:28)	57.5 (35:116.5)	147 (49.5:342.5)
Yes	59 (17:251)	3 (1:31)	28 (15:54)	15 (9:21)	49 (28:98)	156 (63:507)
Patient had or developed pain						
No	33.5 (3:236.5)	1 (1:31)	23.5 (12:47)	15 (9:21.5)	41 (26:84)	95 (43.5:389.5)
Yes	76 (20:241)	13 (1:44)	29 (14:65.5)	16 (9:22)	58 (34:134)	182 (77:465)
Tumour size[1]						
Under 5 cm	46 (11:194)	8 (1:35)	29 (14:59)	15 (8:21.5)	50.5 (29.5:92)	140.5 (54:374.5)
Over 5 cm	65 (15:353.5)	8 (1:37)	23 (12:52)	16 (10:23)	52 (31:104)	180 (70.5:605.5)
Tumour depth[2]						
Subcutaneous	86 (15:528)	1 (1:36)	28 (15:54)	13 (8:20)	42 (28:91)	181 (60:734)
Subfascial	58.5 (14:234)	7 (1:29)	29 (15:56)	15 (9:21)	55 (31.5:100.5)	147 (65:416)
GP suspected malignancy at initial referral[3]						
No	81 (22:319)	9 (1:45)	38 (20:78)	15 (9:22)	63 (38:139)	197 (90:690)
Yes	45 (11:141)	4 (1:25)	18 (9.5:28)	15 (8:21)	34 (21:58)	94 (45:215)
Referred from Aarhus local uptake area						
No	55 (11:227)	8 (1:40)	28 (15:58)	15 (9:22)	35 (21:88)	158 (63:401)
Yes	43 (13:323)	3 (1:28)	18 (6:47)	16 (9:25)	56 (33:106)	135 (51:469)
Diagnosis						
Sarcomas	77 (11:261)	17 (1:56)	29 (15:56)	17 (10:24)	65 (42:133)	176 (83:673)
Other malignancies	38 (6:97)	12.5 (1:25)	15 (7:32)	20 (14:26)	44 (27.5:68)	103 (49.5:202.5)
Benign	54 (13:296)	4 (1:35)	28 (16:62)	15 (8:21)	48 (29:91)	158 (59:507)
Malignancy grade[4]						
Low-grade	213 (26:963)	21.5 (1:50)	29 (19:47)	17 (8:23)	60 (43:103)	250 (108:1665)
High-grade	41 (8:154)	17 (1:57)	29 (13:58)	17 (13:25)	71 (42:140)	164 (69:376)

n = total number of patients with available dates for calculation of this interval.
[1]Anaysis included only patients with data, 33 patients with missing data on tumour size excluded.
[2]Analysis included only patients with soft tissue tumours.
[3]Analysis included only patients with data available for this variable. Patients who were not seen by the GP and patients where the GP had not answered the question were excluded from the analysis.
[4]Analysis included only sarcoma patients.

Table 4: Estimated differences in time intervals at the 50th and 75th percentiles, Measured as difference in calendar days with 95% confidence intervals (CI), calculated by quantile regression.

	Patient Interval	Primary Care Interval	Local Hospital Interval	Sarcoma Centre Interval	Diagnostic Interval	Total Interval
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
Sarcoma patients vs patients with benign conditions						
50th percentile	16 (-37:69)	**10 (4:15)**	0 (-9:10)	0 (-9:10)	**19 (10:28)**	26 (-34:86)
75th percentile	-7 (-18:5)	**24 (9:39)**	-2 (-12:9)	-2 (-12:9)	**30 (14:45)**	**206 (145:267)**
Patients with other malignancies vs patients with benign conditions						
50th percentile	**-21 (-30:-12)**	9 (-3:22)	**-13 (-18:-8)**	**5 (3:8)**	-2 (-9:6)	**-47 (-60:-34)**
75th percentile	**-211 (-226:-196)**	**-6 (-11:-2)**	**-27 (-36:-17)**	**4 (0:7)**	-15 (-43:13)	**-285 (-296:-274)**
Patients presenting with a lump vs patients presenting without a lump						
50th percentile	26 (-3:56)	**-19 (-26:-12)**	4 (-2:10)	**-4 (-7:-1)**	-9 (-22:3)	-4 (-40:31)
75th percentile	**39 (11:67)**	**-30 (-42:-17)**	**-21 (-28:-14)**	**-7 (-10:-3)**	-11 (-52:29)	**121 (75:167)**
Patients presenting with pain vs patients presenting without pain						
50th percentile	**40 (18:61)**	**12 (1:23)**	5 (-3:13)	1 (0:3)	**17 (12:21)**	**78 (60:96)**
75th percentile	19 (-10:47)	**14 (5:23)**	**16 (7:26)**	1 (-2:4)	**37 (23:51)**	**82 (58:105)**
Patients where GP initially suspected malignancy vs patients where GP did not suspect malignancy[1]						
50th percentile	**-41 (-54:-28)**	-1(-12:10)	**-20 (-29:-11)**	-1 (-2:1)	-31 (-68:7)	**-104 (-117:-91)**
75th percentile	**-187 (-202:-171)**	**-21 (-28:-15)**	**-50 (-62:-38)**	-2 (-5:2)	**-74 (-112:-35)**	**-480 (-516:-445)**
Tumour size over 5 cm vs tumour size under 5 cm[2]						
50th percentile	**26 (7:45)**	0 (-4:4)	**-5 (-9:-2)**	1 (0:3)	2 (-12:15)	**51 (34:69)**
75th percentile	**117 (86:147)**	6 (-7:19)	-6 (-20:8)	2 (-1:4)	15 (-9:39)	**232 (216:249)**
Subfascial depth vs subcutaneous depth[3]						
50th percentile	**-31 (-49:-12)**	2 (-2:5)	3 (-8:14)	1 (-1:3)	**9 (2:16)**	-34 (-81:13)
75th percentile	**-306 (-319:-293)**	-2 (-17:13)	-4 (-16:7)	2 (0:4)	5 (-9:19)	**-296 (-309:-283)**
High-grade tumours vs low-grade tumours[4]						
50th percentile	**-160 (-191:-129)**	-1 (-11:8)	0 (-5:5)	0 (-4:4)	**21 (11:31)**	**-104 (-110:-98)**
75th percentile	**-1195 (-1281:-1110)**	7 (-2:16)	**20 (11:28)**	**4 (1:7)**	**38 (29:46)**	**-1270 (-1288:-1253)**

All estimates are adjusted for age. Bold numbers indicate statistical significance at the 5% level.

[1]Analysis included only patients with soft tissue tumours.

[2]Anaysis included only patients with data, 33 patients with missing data on tumour size excluded.

[3]Analysis included only patients with data available for this variable. Patients who were not seen by the GP and patients where the GP had not answered the question were excluded from the analysis.

[4]Analysis included only sarcoma patients.

Appendix 1: Main reason for seeking medical care as stated by the patient.

	Benign (n=375)	Other malignancies (n=68)	Sarcomas (n=102)	Total population (n=545)
	n (%)	n (%)	n (%)	n (%)
Increasing size of the tumor/swelling	20 (5.3)	3 (4.4)	7 (6.9)	30 (5.5)
Promptly reacted to the presence of swelling/lump	25 (6.7)	7 (10.3)	9 (8.8)	41 (7.5)
Tumor/swelling/pain did not disappear	24 (6.4)	3 (4.4)	6 (5.9)	33 (6.1)
Pain	77 (20.5)	17 (25.0)	15 (14.7)	109 (20.0)
Bothered to much	6 (1.6)	1 (1.5)	6 (5.9)	13 (2.4)
Afraid that it was cancer	22 (5.9)	3 (4.4)	5 (4.9)	30 (5.5)
Was worried/unsecure about the symptoms	18 (4.8)	2 (2.9)	6 (5.9)	26 (4.8)
Wanted to know what it was	34 (9.1)	1 (1.5)	12 (11.8)	47 (8.6)
Could not work/hindered at work	5 (1.3)	0 (0.0)	1 (1.0)	6 (1.1)
Restriction of movement	4 (1.1)	0 (0.0)	0 (0.0)	4 (0.7)
Hindered in daily activity	13 (3.5)	0 (0.0)	4 (3.9)	17 (3.1)
Affected night sleep	1 (0.3)	0 (0.0)	1 (1.0)	2 (0.4)
Were at the doctor's office for something else	45 (12.0)	11 (16.2)	9 (8.8)	65 (11.9)
Wanted it removed	2 (0.5)	0 (0.0)	3 (2.9)	5 (0.9)
Concerned for the cosmetical appearance	1 (0.3)	0 (0.0)	1 (1.0)	2 (0.4)
Weight loss	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)
Thought it was side effects to medicine	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)
Thought it was an insect bite	2 (0.5)	0 (0.0)	0 (0.0)	2 (0.4)
Urged to seek doctor by others	35 (9.3)	6 (8.8)	10 (9.8)	51 (9.4)
Wanted a referral to scanning	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)
Had many moles and are aware of skin changes	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.2)
Read cancer awareness brochure	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)
Thought it was a hernia	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.2)
Thought it was a fractured bone	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.2)
Fatigue	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)
Wanted antibiotics	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)
Previously had cancer, and are aware of any lumps	1 (0.3)	2 (2.9)	2 (2.0)	5 (0.9)
Wanted referral to physical therapy	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)
Incidental finding on imaging	33 (8.8)	9 (13.2)	5 (4.9)	47 (8.6)

Paper V

Imaging investigations before referral to a sarcoma center delays the final diagnosis

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Abstract

Background and purpose

The use of point-of-care or local investigations before referral to specialist sarcoma centers as part of a fast-track diagnostic pathway differs and may affect the diagnostic interval. We aimed to describe differences in time intervals and malignancy proportion between patients referred after initial diagnostic investigations performed locally and patients referred without these investigations.

Methods

We included 545 consecutive patients referred to Aarhus Sarcoma Center for suspected sarcoma. Data on time intervals and performed investigations was collected from questionnaires and patient records. Patients referred from outside Aarhus uptake area after initial MRI/CT or histology performed locally were compared with patients referred from Aarhus uptake area without these investigations.

Results

The median total interval from first symptom to diagnosis was 188 days for outside patients referred with MRI/CT or histology, which was 91 (95%CI:76-106) days longer compared to local patients referred without MRI/CT or histology. The median diagnostic interval was 41 (95%CI:30-51) days longer affecting both primary care and hospital intervals. Both the proportion of malignancies (37.5% vs 14.3%) and the proportion of sarcomas (23.5% vs 6.7%) was higher in the group referred with MRI/CT/histology compared to the group without MRI/CT/histology ($p<0.001$).

Interpretation

Pre-referral investigations at a local hospital increased the diagnostic interval with at least one month for 50% of the patients, and the malignancy proportion was more than doubled to nearly 40%. If investigations are to be performed before referral to a sarcoma center the investigations should be part of the fast-track to ensure timely diagnosis.

Introduction

Sarcoma is a rare cancer originating in connective tissue, and treatment should be centralized to highly specialized sarcoma centers (Clasby et al. 1997, Rydholm. 1998, Bhangu et al. 2004). Magnetic Resonance Imaging (MRI) is the preferred diagnostic imaging modality for patients with suspected sarcoma (Bloem et al. 1997, Gielen et al. 2004). Further, Computed Tomography (CT) has a place in the diagnostic work up of bone tumors and tumors of the pelvis and abdomen, and is also used for staging (Grimer et al. 2010, Ilaslan et al. 2010).

In later years, much attention has been given to fast-track diagnostic pathways to ensure timely diagnosis, and such pathways have been implemented in some countries, including Denmark (Prades et al. 2011, Styring et al. 2012, Probst et al. 2012, National Institute for Health and Excellence (NICE). 2015). The conversion rate (number of fast-track referrals resulting in a cancer diagnosis) is important for a fast-track referral program. It should be high enough to prevent overburdening of specialist centers, and low enough to ensure that general practitioners (GPs) can refer patients without barriers and delays. All diagnostic programs for suspected sarcoma patients include imaging investigations with MRI/CT; however, the timing of these investigations differs. In Denmark, the patient must be seen at a local hospital and investigated with imaging before referral to a sarcoma center but these investigations are not part of the urgent referral pathway (Sundhedsstyrelsen. 2012). Contrary, in Sweden, direct referral based on clinical suspicion alone is advocated (Styring et al. 2012). Until 2015, English NICE guidelines stated that a patient with sarcoma symptoms should be seen by a specialist within two weeks without pre-referral imaging, but recently a pre-referral ultrasound has been included in guidelines. Imaging at local hospitals prior to referral has been shown to reduce the number of referrals (Rowbotham et al. 2012), but may also delay the diagnosis if scans are not part of the urgent referral pathway or are of poor quality and have to be repeated (Ashwood et al. 2003).

The effects of pre-referral investigations on time intervals and conversion rate for suspected sarcoma have not been investigated in a Danish setting. We aimed to describe differences in time intervals and proportion of malignancies (conversion rate) between patients referred from outside the Aarhus uptake area after initial MRI and/or CT and/or histology performed locally and patients referred from Aarhus uptake area without any of these investigations. Furthermore, we assessed the extent of repeated scans. We hypothesized that pre-referral investigation at local hospitals lengthens the diagnostic process and increases the proportion of malignant diagnoses.

Materials and methods

Setting

Sarcoma diagnostics and treatment is centralized to two centers in Denmark. Aarhus Sarcoma Center handles all referrals from the Jutland region (approx. 2.5 million inhabitants). On the 1st of January 2009, the Cancer Patient Pathway (CPP) for sarcomas was officially implemented in Denmark (Probst et al. 2012). The CPP is a fast-track referral system that describes the ideal way through the health care system for a standard patient suspected of having a sarcoma. The CPP defines a set of alarm symptoms/criteria that should give a suspicion of sarcoma and result in a prompt referral to further diagnostics. Upon discovery of symptoms, the GP should refer to the local orthopedic department for clinical evaluation and imaging, preferably an MRI-scan. Only when the suspicion is justified by imaging and clinical evaluation at a local hospital should the patient be referred to Aarhus Sarcoma Center for biopsy, final diagnosis and treatment. The fast-track pathway only starts when the referral is received at the sarcoma center.

However, for the patients residing in the local catchment area of Aarhus University hospital, the orthopedic department containing Aarhus Sarcoma Center is the local orthopedic department. The GPs in this area may thus refer directly to the sarcoma center without pre-referral scans. This

enables us to compare the two referral pathways for sarcomas (Figure 1). Still, some patients do not follow these exact pathways which we were able to take into consideration as well.

Study population and data collection

The study was part of a larger data collection, where all consecutive patients referred to the CPP for sarcomas during a 1-year period from 1st of September 2014 to 31st of August 2015 were invited to participate. Data was collected from patient and GP questionnaires and patient records. Questionnaires were developed specifically for the study based on similar questionnaires for other cancer forms (Jensen et al. 2014a), and pilot tested to ensure understanding. Patients received their questionnaire by mail before first sarcoma center appointment. After giving informed consent, the patient underwent a short interview based on the questionnaire to ensure completeness of data. The GP questionnaire was sent out after the interview if the patient or the patient record indicated that the GP had been involved. No remuneration was given to GPs. A reminder with a new questionnaire was sent after 4-5 weeks, with a telephone reminder after a further 3 weeks. Data from local hospitals were collected by tracing the diagnostic route backwards through patient records. Data on final diagnosis was collected from patient records at Aarhus Sarcoma Center which also included pathology reports.

Variables

Final diagnosis was collected from the pathology report if the tumor was biopsied or removed, and from the consensus decision based on imaging, clinical evaluation and follow up if the tumor was not removed.

Information on GP investigations was collected from the GP questionnaires were the GP was asked to specify which diagnostic investigations they had requested. Diagnostic investigations at local hospitals and the sarcoma center were collected from patient records.

Dates of the diagnostic process were given by the patient, the GP, the local hospital and the sarcoma center. We defined six time intervals; patient, primary care, local hospital, sarcoma center, diagnostic and total interval (Figure 2). Specifically, the local hospital interval was defined as time from referral to first local hospital to final referral to the sarcoma center. The sarcoma center interval was calculated as time from received referral at the sarcoma center to the date where a decision on the final course of treatment was made (decision of a final treatment modality or decision of no treatment). This decision date was also the end point of the diagnostic and total interval, and was chosen to ensure comparativeness regardless of final diagnosis. The treatment interval is thus not included. Definition of time intervals was based on guidance from the Aarhus Statement (Weller et al. 2012). If a date was only reported as a month and year, the 15th of that month was chosen as the specific date. If only a year was stated, the 1st of July was chosen as the specific date. For patients with missing GP data, the patient reported date for first doctor visit was used to calculate patient interval and diagnostic interval. Intervals are measured in calendar days.

Ethics

The study was approved by the Danish Data Protection Agency (journal number 2007-58-0010), and all patients provided a written consent. Approval from the Committee on Health Research Ethics of the Central Denmark Region was not necessary as no biomedical intervention was performed, according to Danish Law.

Statistical analyses

Descriptive statistics were used to calculate participation rates. Differences between groups were tested with chi-squared test for categorical variables and Wilcoxon Rank Sum test for continuous variables. For comparison of time intervals the population was divided into groups depending on whether they were referred from the Aarhus area or not and whether they had been investigated with an MRI and/or CT and/or histology or not. Time intervals were non-normally distributed, and are reported as medians with interquartile intervals (IQI). Comparisons of time intervals between groups were done at the 50^{th} and 75^{th} percentile with quantile regression analyses, using the procedure written by Miranda (2006). Gender distribution was equal in all groups, and was not adjusted for in the final model. Age differed between groups and was adjusted for as a categorical variable (<20, 20-39, 40-59 and =>60 years). Only the two groups following the referral pathways described in the CPP were compared. The remaining two groups were left out in the statistical tests comparing time intervals and malignancy proportions. For the analysis on proportion of repeated scans, the entire patient population of 545 patients was included in analyses. We also repeated the quantile regression with adjustment for both age and gender and this had no or little effect on our estimates, thus assuring us in the exclusion of this variable. P-values of 5% or less were considered statistically significant. Analyses were performed using Stata® statistical software, version 13.

Results

Patient and GP participation

A total of 607 patients entered the sarcoma CPP during the study period. Of these, 545 (89.8%) patients accepted participation. Of 62 non-participants, 56 did not wish to participate, 5 were not mentally able to answer questionnaires, and 1 did not speak Danish or English. The non-participating patients did not differ statistically significantly from participants with regards to age or

gender distribution. Of the 466 distributed GP questionnaires, 400 (85.5%) were returned with answers. For a further 42 patients (9.0%) with a non-responding GP, information on dates and performed imaging investigations at the GPs office could be retrieved from the referral or the patient records.

Patient characteristics

Of the 545 patients, 143 (26.2%) were referred from the local uptake area of Aarhus University Hospital. Ninety-one (16.7%) were referred from the local area without pre-referral MRI and/or CT and/or histology and 357 (65.5%) were referred from outside the local uptake area after investigation with MRI and/or CT and/or histology (Table 1). The percentage of women was 47.7%, with no significant difference in gender distribution between referral groups (p=0.883). Median age was 55 (range 0-93) years. 56 patients were under 18 years, of which eight (14.3%) had a sarcoma and eight (14.3%) had other malignancies.

Time intervals

Table 1 describes median and interquartile intervals for the time intervals for the four different referral groups. The two groups that followed the official referral pathway outlined in the CPP for sarcomas are compared in Table 2. The median patient interval did not differ statistically significantly between the groups. The primary care, local hospital, diagnostic and total interval were all statistically significantly longer in the outside group with MRI/CT/histology compared to local patients without MRI/CT/histology. The difference in the diagnostic interval is illustrated by a cumulative frequencies diagram in Figure 3.

Conversion rates

Overall, 102 (18.7%) patients had a sarcoma, and 68 (12.5%) were diagnosed with other malignancies giving a total number of malignancies of 170 (31.2%). The proportions of malignancies in the different referral pathway groups are presented in Table 3. There was a statistically significantly higher proportion of malignancies and sarcomas in the outside group referred after MRI/CT/histology compared to the group referred from the local area without pre-referral MRI or CT or histological diagnosis ($p<0.001$).

Proportion of repeated scans

345 (63.3%) patients were referred with an MRI-scan, and 78 (14.3%) were referred with a CT-scan. 38 (7.0%) patients had both scans performed before referral. 19 (5.5%) of the 345 MRI-scans had been repeated locally before referral because the initial scan had been performed without contrast. Twelve (3.5%) of the 345 MRI-scans had to be repeated at the sarcoma center before decision of diagnosis/treatment, and none of the CT scans were repeated**.**

Discussion

Main results

The median time from first symptom to decision of diagnosis/treatment was 91 days longer for patients referred after MRI/CT/histology at local hospitals outside Aarhus uptake area compared to patients referred without these investigations from the local Aarhus uptake area. The median diagnostic interval was 41days longer in the outside group, produced both by longer primary care and local hospital intervals. This indicates that when pre-referral imaging is not part of the urgent referral pathway both access to and speed of investigations are disadvantaged. The conversion rate was significantly higher in the patient group investigated with MRI/CT/histology (37.5% vs

14.3%). Only 3.5% of MRI scans performed locally before referral had to be repeated at the sarcoma center.

Comparison with literature

Conversion rates in fast-track pathways differ between countries. A London-based study reported that 2% of patients referred on clinical features alone had a sarcoma, compared to 17% of patients referred after local investigations (Pencavel et al. 2010). In Birmingham, 13% of patients referred on clinical sarcoma suspicion alone had a malignancy, versus 49% among patients referred after imaging (Taylor et al. 2010). Smolle et al. (2015) surprisingly found a higher malignancy proportion among patients referred without imaging, and attributed this to more obvious symptoms (confounding by severity).This may also be the reason for the fairly high proportion of malignancies in our groups referred without imaging. In Sweden, no pre-referral imaging is required and a malignancy proportion of 24% (16% sarcomas) is reported (Styring et al. 2012), which is higher compared to our findings (13% and 6%). However, several patients in the Swedish study had undergone pre-referral imaging. In accordance with other studies, our results show that pre-referral investigations can reduce the number of referrals (Pencavel et al. 2010, Rowbotham et al. 2012, Shah et al. 2015). We did not find a high proportion of repeated scans, as reported from other countries (Ashwood et al. 2003, Styring et al. 2012).

Contrasting the benefit of increased conversion rate is the lengthening of time intervals for patients referred after local imaging investigations. The difference in diagnostic interval was 41 days at the median and 91 days at the 75th percentile, indicating that the difference in waiting times is more pronounced among the 25% of patients waiting the longest. Other studies have shown that local investigations before referral produce delay for cancer patients (Ashwood et al. 2003, Styring et al. 2012, van der Geest et al. 2014, Rubin et al. 2015), and direct referral of suspected sarcoma

patients have been suggested by other authors (Ashwood et al. 2003, Seinen et al. 2010, Styring et al. 2012). Although the CPP for sarcomas reduced the waiting times at Aarhus Sarcoma Center (Dyrop et al. 2013), the waiting times occurring locally outside Aarhus Sarcoma Center are still very long. The Danish CPP contains no time limits for the diagnostic process at local hospitals, and our results show that when the CPP for sarcoma does not include pre-referral imaging as a part of the fast-track program a large group of patients have a delayed diagnosis. The main change following CPP implementation in Denmark was a shift from serial investigations to parallel investigations, but starting only when the patient is seen at the sarcoma center and thus not at local hospitals. Investigations in primary care and at local hospitals are still done in a serial manner, according to the same waiting time regulations and limited access to imaging as before the CPP implementation.

A possibility to reduce the waiting time before diagnosis for patients residing outside Aarhus uptake area could be to remove the demand for local MRI/CT-investigations before referral to the CPP, and perform all MRIs at the sarcoma center. However, this can overburden the sarcoma center capacity. Other possibilities would be to extend the CPP time limits to include the local hospital work-up, or improve GPs' access to diagnostics at local hospitals. In Denmark, only hospital physicians can order an MRI or CT of musculoskeletal tumors and GPs have to refer to a local hospital instead of referring directly to imaging. Better access to imaging for GPs has been indicated as the way forward in Danish cancer diagnostics (Guldbrandt et al. 2013, Hjertholm et al. 2014, Jensen et al. 2014b), but reports on such initiatives differ. In the UK primary care investigations significantly lengthened the primary care interval for cancer patients without reducing referral delay (Rubin et al. 2015). A Danish trial on direct GP access to chest CTs for patients suspected of lung cancer showed unchanged CT usage and a decrease in specialist time

spent per patient (Guldbrandt et al. 2013). This solution may be worth exploring for suspected sarcoma patients in Denmark.

Strengths and limitations

Our results are strengthened by the high participation rate and completeness of data. Age and gender did not differ between participants and non-participants; however we could not obtain information on the proportion of malignancies or time intervals among non-participants. The direction of any selection bias cannot be evaluated, but the small number of non-participants limits the effect. The primary care interval could be underestimated if non-responding GPs were reluctant to answer due to long delays. For calculation of patient interval and diagnostic interval the patient's date for first doctor's visit was used for patients with non-responding GPs, thus abating the problem of missing dates for these intervals. Patient reported data were validated with interviews to improve completeness and quality of data. GPs were asked to consult patient records when answering the questionnaire to reduce recall bias. Sarcoma studies often have a low statistical precision due to low incidence, but we were able to include a large sample of malignancies to estimate differences with good statistical precision. Our results should be interpreted with referral bias in mind, as we only have data on patients who were referred to the fast-track. It is fairly certain that all sarcoma patients were referred as sarcoma treatment is centralized, but there is a large population of patients with benign conditions and other malignancies which were not referred.

Conclusions

Pre-referral investigations at a local hospital increased the diagnostic interval with at least one month for 50% the patients. The conversion rate was more than doubled to nearly 40%. If investigations are to be performed before referral to a sarcoma center the investigations should be

part of the fast-track to ensure timely diagnosis. Future efforts should be put into providing easier access to imaging and reducing time spent at local hospitals before referral.

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Contributions of authors

Design of the study: HBD, PV, AS and JK

Data collection: HBD and MR

Statistical analyses and first draft: HBD.

All authors participated in interpretation of results and manuscript revision.

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Figure 1: The two official referral pathways in the Danish Cancer Patient Pathway for sarcoma

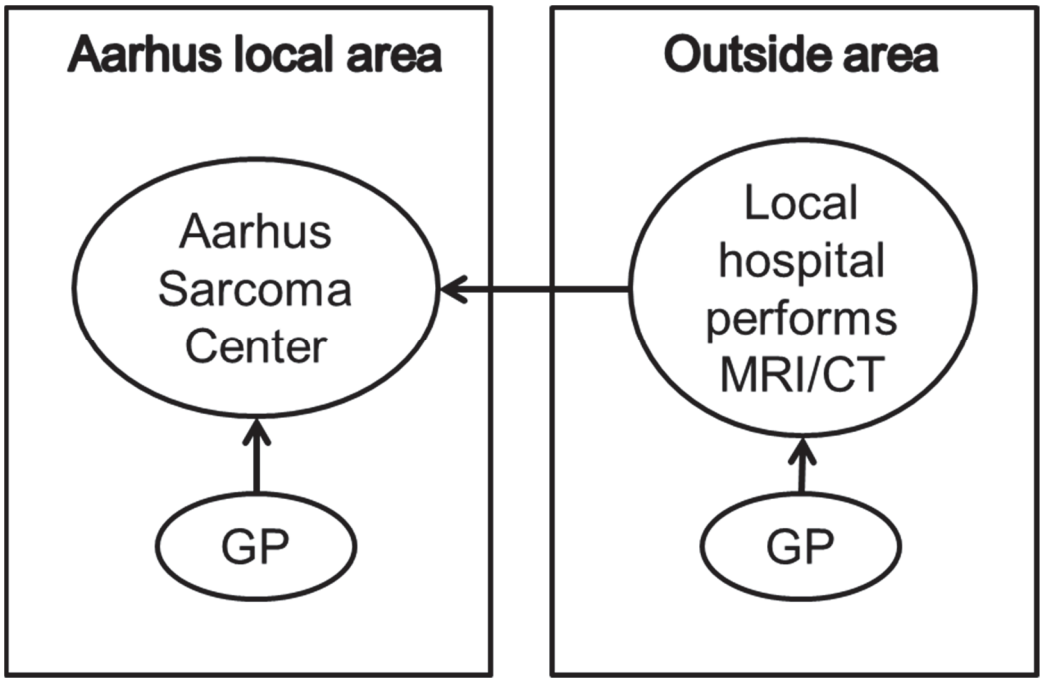

Figure 2: Overview of time intervals in the diagnostic process of patients suspected of sarcoma (Weller et al. 2012)

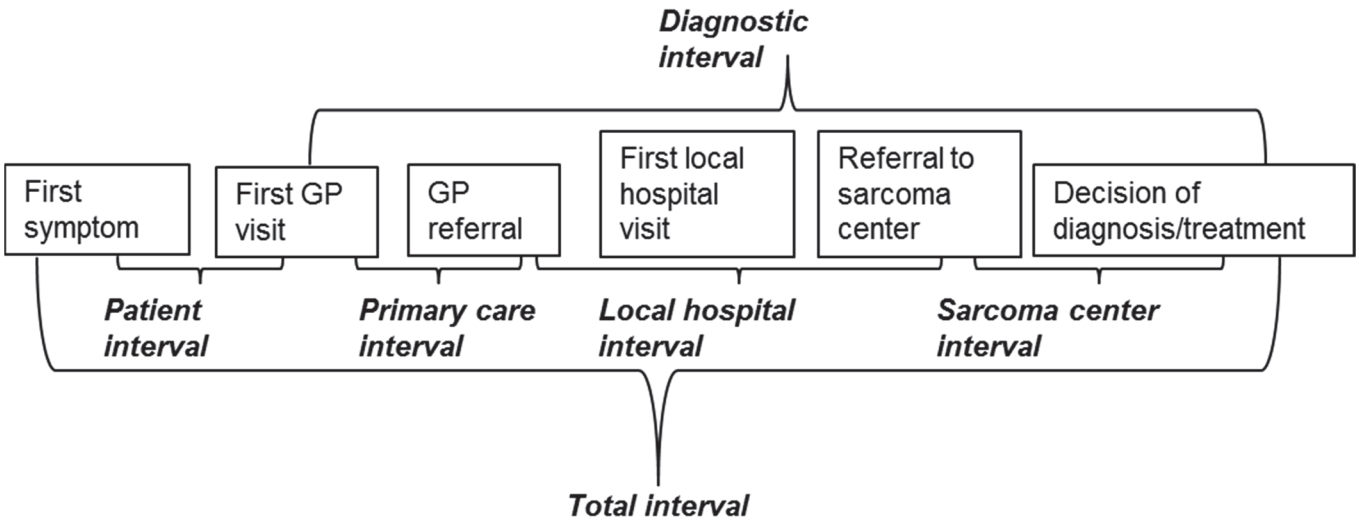

Figure 3: Cumulative frequencies of diagnostic interval in the local Aarhus area group referred without pre-referral MRI/CT/histology and the outside group referred after pre-referral MRI/CT/histology. Diagnostic intervals exceeding 365 days plotted as 365 days for illustration purposes.

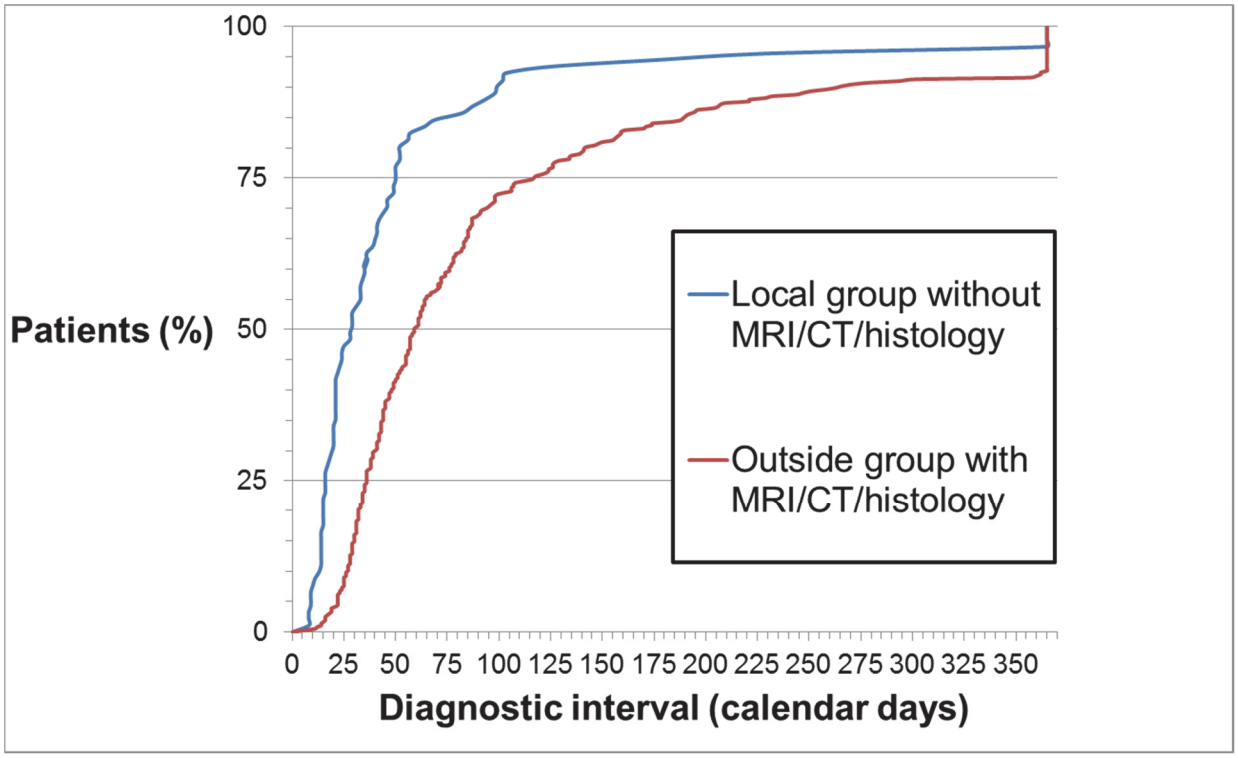

Table 1: Number of days presented as median and interquartile interval (IQI) spent in each phase of the diagnostic process from first symptom to decision of diagnosis/treatment, by referral pathway

Referral pathway	Patient Interval	Primary care Interval	Local Hospital Interval	Sarcoma Center Interval	Diagnostic Interval	Total Interval
	Median (IQI)	Median (IQI)	Median (IQI)	Median (IQI)	Median (IQI)	Median (IQI)
Referred from Aarhus local uptake area						
With MRI/CT/histology (n=52)	40.5 (9.5:368)	32 (13:80)	28 (14:105)	13.5 (8:20.5)	71.5 (32:179)	188.5 (64.5:837)
Without MRI/CT/histology (n=91)	45 (18:247)	1 (1:13)	8 (1:19)	18 (13:29)	29 (16:50)	93 (49:356)
Referred from outside Aarhus uptake area						
With MRI/CT/histology (n=357)	59 (12:241)	11 (1:45)	29 (15:59.5)	15 (9:22)	59 (36:117)	166 (73:465)
Without MRI/CT/histology (n=45)	36 (8:135)	2 (1:16)	15 (12:30)	15 (9:23)	28 (17:50)	64 (35:210)

Table 2: Estimated difference in time intervals between patients referred from outside the Aarhus Local uptake area after MRI and/or CT and/or histology performed locally vs patients referred from Aarhus local uptake area without MRI and/or CT and/or histology performed locally. Measured as difference in calendar days at the 50th percentile and 75th percentile with 95 % confidence intervals (CI), calculated by quantile regression.

Percentile	Patient Interval	Primary care Interval	Local Hospital Interval	Sarcoma Center Interval	Diagnostic Interval	Total Interval
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
50th percentile*	13 (0:27)	**14 (9:19)**	**27 (16:38)**	-3 (-7:1)	**41 (30:51)**	**91 (76:106)**
75th percentile*	**-47 (-61:-32)**	**37 (27:48)**	**51 (36:65)**	**-6 (-8:-4)**	**61 (29:94)**	**110 (95:124)**

*All analyses adjusted for age.

Bold numbers indicate statistical significance at the 5 % level.

Table 3: Proportion of malignancies and sarcomas, by referral pathway

Referral pathway	Proportion of malignancies (n (%))*	Proportion of sarcomas (n (%))
Referred from Aarhus local uptake area		
With MRI or CT or histology (n=52)	13 (25.0)	9 (17.3)
Without MRI or CT or histology (n=91)	13 (14.3)	6 (6.6)
Referred from outside Aarhus uptake area		
With MRI or CT or histology (n=357)	134 (37.5)	84 (23.5)
Without MRI or CT or histology (n=45)	10 (22.2)	3 (6.7)

*Includes all sarcomas and other malignancies