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

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Submitted 2014-03-20. Accepted 2014-06-12

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.

DOI 10.3109/17453674.2014.957086

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] Present	(n = 174) +	–	(n = 532) +	–	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
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] Present	(n = 84) +	–	(n = 336) +	–	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
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.

The project was funded by Professor Cody Bünger from project 8427 CE-spine: "Cost effectiveness of new treatment strategies in spine surgery: Evaluation of patient-based and social economic consequences in Denmark". Case number 09-065229 at "Strategisk Forskningsråd ved Forsknings- og Innovationsstyrelsen".

No competing interests declared.

Design of the study: HBD, AS, KMN, and JK. Data collection: HBD, AS, KMN, BHH, PHJ, TBH, and JK. Manuscript preparation and statistics: HBD. Revision of manuscript: all authors.

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