Accuracy of core needle biopsy in diagnostics of soft tissue sarcomas: Diagnostic errors and their effect on patient treatment

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Tiivistelmä - Referat – Abstract

Accurate pre-operative identification and grading of soft tissue sarcomas is required for their correct treatment. While core needle biopsy has been recognized accurate for identifying and grading soft tissue sarcomas, data is still lacking on diagnostic errors, their underlying reasons and the effects any errors may have on patient treatment.

We retrospectively analysed data on all 313 patients treated for soft tissue sarcomas of the trunk and extremities whose core needle biopsies were analysed between 2000 and 2012 at Helsinki University Central Hospital. The final analysis included 297 patients with a primary soft tissue sarcoma who had their surgical specimen evaluated at Helsinki University Central Hospital.

We found 48 diagnostic errors with the ability to affect subsequent treatment: 19 non-sarcomatous, 25 incorrect low-grade and five pre-operative diagnoses with errors in subtype. Core needle biopsies of myxoid soft tissue sarcomas appeared challenging to interpret. Twenty-five treatment inaccuracies were found in 18 patients, twelve of these were related to inadequate surgery and one had not received chemotherapy. On re-examination of the core needle biopsy, we reached the correct diagnosis in 20 patients. In addition six patients got a more correct diagnosis.

Core needle biopsy is reliable for identifying mesenchymal malignancy and guiding treatment planning at our institution. We recommend it for diagnosis of all soft tissue sarcoma suspicious tumours with interpretation done by an experienced soft tissue sarcoma pathologist. Special caution must be taken when evaluating myxoid tumours.

Avainsanat – Nyckelord – Keywords

Soft tissue sarcoma; STS; core needle biopsy; CNB; diagnosis; grading

Säilytyspaikka – Förvaringställe – Where deposited

Muita tietoja – Övriga uppgifter – Additional information

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1 Introduction

Soft tissue sarcomas (STSs) are a heterogeneous group of malignant tumours with mesenchymal differentiation. They usually present as a painless enlarging mass without systemic symptoms.

STSs are primarily treated with a wide-margin surgery trying to preserve limb function. Surgery can be combined with both chemotherapy and radiotherapy. However, surgery remains the only curative treatment. Inadequately resected STSs tend to reoccur locally while high-grade STSs are prone to develop pulmonary metastasis and have worse outcome than low-grade tumours.

To initiate correct treatment, a biopsy, most often a core needle biopsy (CNB) should be performed on all STS suspect masses before any treatment. The biopsy method of choice should be able to differentiate STSs from both non-mesenchymal tumours and benign soft tissue tumours (STTs) to avoid surgery with inadequate margins. In addition, the biopsy should be able to separate STSs into low- and high-grade STSs to enable identification of patients who might benefit from neoadjuvant treatment. Identification of certain STS subtypes is also beneficial for treatment planning. The final histologic diagnosis and grading are based on microscopic evaluation of the resected surgical specimen.

In this study we aim (i) to evaluate the accuracy of CNB in diagnosing and grading primary STSs located in the trunk and extremities treated by the soft tissue sarcoma group at Helsinki University Central Hospital (HUCH) during 2000-2012 using a modified 4-grade Broders grading system (1), (ii) to recognize any major grading or diagnostic errors and their underlying reason and (iii) to evaluate the possible effects of the errors on the treatment according to current treatment guidelines at HUCH.

2 Literature review

2.1 Overview

Most STSs occur in adults and they account for approximately 1 % of all malignant tumours diagnosed in adulthood (2), whereas STSs represent 7 % of all malignant

tumours in patients younger than 20 years (3). Rhabdomyosarcoma (40 %) and fibrosarcoma (29 %) are the two most common STSs in children younger than 20 years (3), whereas liposarcoma (29 %) and malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma (25 %) are the most common STSs in the extremities of adults (4).

STSs are most often located in the extremities (59.5 %) followed by the trunk (17.9 %) (5). However, they can occur virtually anywhere in the body outside bone. Seventy-six percent of STSs of the extremity are situated beneath the deep fascia (4).

2.2 Aetiology

The aetiology of STSs is largely unknown and in most cases an underlying cause cannot be identified. Neurofibromatosis type I, Li-Fraumeni syndrome, hereditary retinoblastoma, chronic lymphedema, Epstein-Barr virus and exposure to ionizing radiation are best known predisposing factors for STSs (6). In addition, certain chemicals have been indicated to increase the risk for STSs (7).

Radiotherapy, in a cohort study, increased the risk for STSs, with a peak incidence of STSs at 10-14 years after radiotherapy (8). About three times more sarcoma-cases (including both bone and soft tissue sarcomas) than expected were reported starting ten years after exposure to radiotherapy. Patients treated with radiotherapy when younger than 55 years were in particular at an increased risk of developing a STS later in life (8). About four times more cases of sarcomas than expected were reported for this group compared with only approximately two times more cases reported for patients older than 55 years starting ten years after treatment with radiotherapy.

The most common subtypes of post-irradiation sarcomas, as reported in a study of a nationwide registry of Finland from 1953 to 1988 (9), are osteosarcoma, malignant fibrous histiocytoma and fibrosarcoma. Most tumours (31/33) were high-grade sarcomas. Only 29 % of patients with post-irradiation sarcoma in the same study were alive after five years. In another study, of patients from 1973 to 1997 with post-irradiation sarcomas of the breast, angiosarcoma was the most common subtype (56.8 %) (10).

2.3 Classification

Histologically STSs are mainly classified according to their resemblance to differentiated mesenchymal tissue with further subgroups (11). In certain cases however, the tumour tissue is not related to the differentiated tissue as is the case with synovial sarcoma (12). Also STSs do not arise from fully differentiated tissue, but from mesenchymal stem cells (13).

More than 50 STS subtypes are described in the current WHO classification of bone and soft tissue tumours from 2013 (14). To aid classification, a number of tissue-specific immunohistochemical markers are in clinical use (11). They are particularly useful for typing differentiated sarcomas but do not always provide definite evidence (11).

Genetically STSs can be divided into two groups. Certain STSs have an abnormal karyotype where no specific changes can be identified (group I), whereas for quite a few STSs specific translocations and gene mutations (group II) have been identified that can be used for classification (15). An example is synovial sarcoma in which a specific translocation t(X;18)(p11.2;q11.2) can be found in more than 90 % of patients (11).

2.3.1 Grading

For grading of STSs, the most common system used, is the French grading system (FNCLCC) (16). It is a three-grade system taking into account tumour differentiation, amount of mitoses and necrosis. However, a modified 4-grade Broders system, where grade one and two are low-grade tumours and grade three and four are high-grade tumours (1), is used at HUCH. It takes into account tumour cellularity, pleomorphism, nuclear atypia, necrosis, mitotic activity and in certain cases the histologic subtype (17). Compared with a 3-grade system, a 4-grade system is able to predict outcome more accurately in patients with high-grade tumours (18). STSs can also be grouped namely into low- and high-grade tumours.

Grading is very useful for predicting overall survival and the risk for metastatic disease (4, 16) and thus find patients eligible for (neo)adjuvant treatment. However, not all STS

subtypes are gradable. These include clear cell sarcoma and soft-part alveolar sarcoma that are by definition high-grade tumours and angiosarcoma where grade does not correlate with the normal parameters used for grading (11).

2.4 Growth pattern

Enneking and colleagues summarized the growth pattern of STSs in an article from 1981 (19). STSs expand spherically, pushing surrounding tissue out of the way. This is called pushing border growth. A zone of reactive tissue, a so called pseudocapsule, develops around the tumour and the compressed tissue. High-grade STSs often infiltrate into surrounding tissue, though some low-grade STSs also have this growth pattern (20). This infiltrative growth pattern has been recognised as a risk factor for metastatic spread (RR 4.6, $p = 0.001$) and local reoccurrence (RR ∞, $p = 0.001$; no STS with a pushing border reoccurred locally). Centrally a necrotic core often develops due to the tumour outgrowing the blood supply (21).

Tumour tissue from low-grade STSs is seldom found in surrounding normal tissue but high-grade tumour tissue is frequently found there (19). Rather than being direct extensions of the tumour, they may be short distance metastases, so called skip metastases. They are often situated close to blood vessels.

STSs seldom perforate fascia and thus they do not normally spread from one anatomic compartment to another (19). When this happens, it happens mainly around blood vessels or because of improper surgery. Likewise tumour spread to bone is very uncommon.

Lungs are the most frequent location of STS metastases. Nineteen percent of patients with extremity STSs develop pulmonary metastases at some point (22). Lymph node metastases are uncommon. Only 3.7 % of patients with extremity STSs develop metastatic disease to lymph nodes (23). However, angiosarcoma, clear cell sarcoma, embryonal rhabdomyosarcoma and epithelioid sarcoma are more likely to spread to lymph nodes (23). In addition, myxoid liposarcoma is known to send metastases to extra-pulmonary soft tissue sites (24). Thirteen months was reported as the latent time from diagnosis to development of metastatic disease in the largest study of extremity STSs (4).

2.5 Prognostic factors

STSs have had low survival rates but prognosis has improved. Patients treated at HUCH for extremity and trunk STSs between 1987 and 2002 had 5-year survival rates of 75 % (95 % CI 0.70–0.80) and 10-year survival rates of 71 % (95 % CI 0.64–0.76) (25). In another study of 1 041 patients with extremity STSs, 5-year disease-specific survival was 76 % (4). However, a significant difference in 5-year disease-specific survival rates was reported between low-grade (94.7 %) and high-grade tumours (65.7 %; p = 0.0001).

Grade is the most important prognostic factor for 5-year overall survival with a relative risk of 4.0 (95 % CI 2.5–6.6) (4). Other factors, recognized in the same study, with negative impact on 5-year disease-specific survival were deep location (RR 2.8), diameter greater than 5 cm (RR 2.1), proximal location in lower extremities (RR 1.6), microscopically positive surgical margins (RR 1.7) and local recurrence (RR 1.5). Leiomyosarcoma (RR 1.9) and malignant peripheral nerve sheath tumour (MPNST) (RR 1.9) were associated with worse 5-year disease-specific survival (4). Another study of 997 patients with extremity STSs identified high grade, deep tumour location, large size, positive surgical margins and both MPNST and synovial sarcoma as adverse prognostic factors for disease-specific survival (26). Grade was also reported in this study as the most important adverse factor for disease-specific survival: grade two and three tumours had relative risks of 5.37 and 8.80 respectively compared with grade one tumours.

Metastatic disease is associated with low survival rates. Pisters and colleagues reported that only 28 % of patients who developed metastatic disease were alive at the last follow-up (4). The median follow-up period was 3.95 years among survivors in the above mentioned study. The median lifetime was 14.5 months from discovery of metastatic disease. Patients with a primary tumour greater than 10 cm in diameter were identified as having worse post-metastatic survival (RR 1.5).

The most important prognostic factor associated with an increase in the risk for metastatic disease is high grade, with a risk ratio of 4.3 (95 % CI 2.6–6.9) compared to low grade tumours (4). Other adverse factors for metastatic disease, were presence of

locally recurrent disease (RR 1.5), deep location (RR 2.5), large tumour size (RR 1.9 for 5-10 cm tumours and RR 1.5 for >10 cm tumours) and leiomyosarcoma (1.7). Patients with liposarcomas were less likely to develop metastatic disease (RR 0.64). Size, grade and histologic subtype were also reported as significant prognostic factors for metastatic disease in another study (26). It also identified grade as the most important risk factor for metastatic disease, with risk ratios of 4.49 for grade two and 6.98 for grade three STSs (compared to grade one STSs).

Local recurrence is a common trait of STSs. Five-year local control of STSs of the trunk and extremities was 76.4 % among patients treated at HUCH between 1987 and 1997 (27). When local treatment was adequate, 84.2 % of patients with STSs did not develop a local relapse. A study reported a median time of 17 months for development of local recurrence (4). A positive surgical margin was identified as an important adverse factor, with a risk ratio of 1.8 (95 % CI 1.3−2.5) (4). The study also reported that patients older than 50 years (RR 1.6), with previous locally recurrent STS (RR 2) or with fibrosarcoma (RR 2.5) or MPNST (RR 1.8) were more likely to develop a local recurrence. Positive surgical margins, histologic subtype and lack of radiotherapy were also reported as adverse prognostic factors for local recurrence in another study (26).

2.6 Diagnosis

At diagnosis most STSs appear as painless enlarging masses without systemic symptoms. Symptoms mainly develop late due to compression of adjacent tissue. Nineteen percent of STS patients experience pain (4) due to compression of nerves. STS may also disturb joint function and vein and lymphatic vessel compression may cause swollenness. At initial diagnosis 53 % of STSs are already greater than 5cm in diameter (4).

To initiate correct treatment of STSs, a preoperative biopsy should be done. At HUCH it is most often a CNB. The biopsy should be able to differentiate benign STTs from STSs, low-grade from high-grade STSs and non-mesenchymal from mesenchymal tumours. Identifying certain STS subtypes is beneficial for treatment planning. These include synovial sarcoma and myxoid liposarcoma. Imaging is used to evaluate the extent and

spread of the tumour, its location to neighbouring neurovascular structures and for staging as well as to evaluate malignancy.

At HUCH the CNB is obtained under ultrasound-guidance. However, in patients where the tumour is difficult to access, CT- or MRI-guidance may be used. A fine-needle aspiration (FNA) specimen is obtained simultaneously but it is of limited value in diagnostics of STSs at HUCH. The CNB and FNA specimen are then evaluated by an experienced musculoskeletal pathologist to determine diagnosis and grade. Patients with myxoid liposarcoma at HUCH undergo a full-body CT-scan, while all patients with a high-grade STS undergo a CT of the thorax before surgery. A plain radiograph of the thorax is obtained preoperatively of patients with a low-grade STS.

2.6.1 Biopsy

Open biopsy has been regarded as the golden standard for diagnosis of STS (21). It was reasoned that core needle biopsy did not provide adequate tissue for diagnosis and grading (28). In particular evaluating mitotic activity and necrosis accurately from CNB specimens can be difficult (6). Thus grade is often underrepresented in CNBs.

Non-diagnostic CNB rates between 6 and 22.5 % are reported in literature (21, 29, 30, 31, 32, 33). The CNB can easily be repeated if the original CNB is non-diagnostic. A number of factors have been identified affecting the rates of non-diagnostic CNBs. Image-guided CNBs more often obtained adequate tissue compared to free-hand CNBs with adequate tissue obtained in 100 % and 86 % of CNBs respectively ($p < 0.01$) (34). The image-guidance method, however, does not affect diagnostic yield ($p = 0.07867$) (33). A study recommended obtaining four CNB specimens from STTs to optimize diagnostic yield, obtaining more than four CNB specimens did not improve diagnostic yield (35). The same study found that specimen length correlated with diagnostic yield: < 5mm, 5−10mm and > 10mm had diagnostic yields of 42 %, 61 % and 82 % respectively ($p < 0.001$). The study also reported that larger musculoskeletal tumours had better diagnostic yields: tumours < 2 cm, tumours 2−5 cm and tumours > 5 cm had diagnostic yields of 54 %, 75 % and 86 % respectively ($p < 0.001$). Diagnostic yield in heterogeneous STTs is lower compared to homogenous STTs (81.4 vs 97.5 %, $p = 0.0036$) (33).

CNB has acceptable accuracy rates (78−99 %) and low complication rates (0−2.6 %) in diagnosis of soft tissue and musculoskeletal tumours (Table I). While open biopsy in comparison, is more accurate with accuracy rates from 95 to 100 % (21, 40, 43, 49, 50), a high complication rate (15.9 %) was described in a study of 597 patients (51).The complications consisted of skin, bone and soft tissue problems. In 16.6 % of all STT biopsies in the same study, treatment was altered due to issues with the biopsy ($p < 0.001$). It is also noteworthy that CNB costs a fraction of the price of open biopsy (39).

Studies have further evaluated CNB as a diagnostic tool for diagnosis of STTs and musculoskeletal tumours and demonstrated that very few false-positive results occur with specificity rates of 82 to 100 % reported (Table I). Meanwhile false-negatives do happen more often with sensitivity rates of 79 to 100 %. Likewise studies that have reported on the accuracy of grading STSs, have generally noted satisfactory accuracy rates from 83 to 100 % (Table I), with no STSs being falsely designated as high-grade (48). Tumours falsely designated as low-grade do occur more often with sensitivity rates of 81 and 89 % reported (40, 48). The low sensitivity rates have been explained by the small amount of tissue CNB provides, thus underrepresenting mitoses and necrosis. On the other hand, CNB enables collection of tissue from multiple locations whereas open biopsy only enables sampling from a superficial area that may not be representative of the core tumour (36, 43). STS subtype is accurately specified from 56 to 100 % (Table I) of CNB specimens. However, subtyping has limited value in initial clinical decision making with the exception of myxoid and synovial sarcomas.

Most importantly CNB has been shown to initiate definitive treatment and enable one-stage surgery for STSs. Of patients undergoing CNB, 95 % were treated with a one-stage surgery (28). A study reported on biopsy errors in bone and soft tissue tumours and identified seven patients of 223 in whom a benign tumour turned out malignant after surgery (29). Nevertheless, they were all correctly treated. In addition 24 errors in grade or subtype were found in the same study but neither did they affect treatment. Another study found only minor histopathological errors in 1.1 % of patients with no impact on treatment (31).

Table I Summary of studies of CNB accuracy in diagnostics of soft tissue and musculoskeletal tumours

Study	Grading	Values based on comparison between	Number of tumours with CNB (STSs)	Accuracy %	Sensitivity %	Specificity %	Grading accuracy %	STS Subtype %	CNB Complications %
Ball et al 1990 (36)	NS	STSs – Other	52 (45)	94	93	-	88	85	1.9†‡
Barth et al 1992 (37)	NS	Sarcomas – Benign	38 (16)	96	100	91	100	-	2.6†§
Fraser-Hill et al 1992 (38)	-	Primary tumours	92	83	-	-	-	-	-
Skrzynski et al 1996 (39)	-	STTs	62	78	-	-	-	-	1.6†
Heslin et al 1997 (40)*	LG-HG	Malignant – Benign STTs	56	95	93	100	93	-	-
Serpell et al 1998 (41)	-	Malignant – Benign STTs	31 (14)	84	94	100	-	100	-
Yao et al 1999 (42)	-	STTs	141	82	-	-	-	-	-
Welker et al 2000 (43)	NS	Malignant – Benign STTs	161 (83)	92.4	81.8	100	88.6	-	1.1
Hoeber et al 2001 (44)*	NS	STSs – STTs	259 (180)	99.2†	99.4	98.7	84.9	79.9	-
Torriani et al 2001 (45)	-	Musculoskeletal tumours	48	97	96	100	-	-	0
Ray-Coquard et al 2003 (46)*	-	Sarcomas – Other	103 (65)	95	92	100	-	-	1
Yang et al 2004 (47)	NS	Primary musculoskeletal tumours	42	93	-	-	83	-	-
Altuntas et al 2005 (48)	-	STTs	50	80	-	-			
Mitsuyoshi et al 2006 (32)*	-	Malignant – Benign STTs	163	94	-	-	-	-	0.61†
Ogilvie et al 2006 (30)	-	Primary musculoskeletal tumours	58	-	72	98	-	-	-
Woon et al 2008 (28)	-	STSs – STTs	68 (23)	83.6	91.3	100	-	70	-
Narvani et al 2009 (34)	-	STTs	111	88.29	-	-	-	-	-
Sung et al 2009 (33)	-	STTs	122	79,1	-	-	-	-	0
Kasraeian et al 2010 (21)	AJCC	STTs	57	81	79	82	-	-	-
Strauss et al 2010 (48)	FNCLCC	STSs – STTs	376 (225)	97.6	96.3	99.4	86.3	88.6	0.40‡
Verheijen et al 2010 (49)	-	STSs – STTs	116 (90)	78	-	-	-	56	-
Pohlig et al 2012 (50)	-	STSs	46 (13)	84.6	81.8	100	-	-	-

*Excluded non-diagnostic CNBs from study ; †Calculated afterwards using data provided in study; ‡Intra- or retroperitoneal tumours; §Fine-needle aspiration specimen obtained simultaneously

AJCC = American Joint Committee on Cancer; CNB = Core-needle biopsy; FNCLCC = French Federation of Cancer Centres Sarcoma Group; HG = High-grade; LG = Low-grade NS = Not specified STS = Soft tissue sarcoma; STT = Soft tissue tumour

There are, however, a few studies that indicate that CNB would not provide adequate information for correct treatment. One recent prospective study reported that CNB would only provide enough information in 49.1 % of patients to initiate correct treatment (21). Open biopsy proved clinically useful in all patients. Another study found only 63 % of STS CNBs clinically useful (30). These articles however, do not state why clinical usefulness was so low.

Studies have identified a number of factors affecting the accuracy of CNBs in diagnostics of STSs. Image-guided CNBs had a higher diagnostic accuracy (95 %) compared to free-hand CNBs (78 %) in a non-randomized study ($p \leq 0.025$) (34). Another study reported that the number of CNB specimens did not influence grading accuracy (29).

Histological factors affecting CNB accuracy include myxoid tumour nature. In a study only 11 % of the CNBs of myxoid tumours were clinically useful, compared with 80 % of CNBs of non-myxoid tumours being useful ($p = 0.001$) (30). Higher rates of diagnostic errors were also found in another study in CNBs of myxoid tumours ($p = 0.021$) (29). This is a result of the small amount of cells in the rich connective tissue. Papers have also identified well-differentiated liposarcomas as often being misdiagnosed (28, 32, 48). It is noteworthy that these tumours can be challenging to differentiate from benign lipomas even in the surgical specimen (36). More importantly, well-differentiated liposarcomas are treated with enucleation; a faulty diagnosis does not affect treatment.

A recent study suggested that the grade assigned by CNBs is not ideal for evaluating patient prognosis (52). The grade established (FNCLCC) for extremity spindle-cell STSs by CNB, did neither correlate with metastasis free survival ($p = 0.59$) nor disease free survival ($p = 0.50$). Meanwhile open biopsy was able to predict both disease free survival ($p = 0.001$) and metastasis free survival ($p < 0.001$).

Fine needle aspiration cytology (FNAC) is an even less-traumatic and cheaper biopsy method than CNB. It is generally considered insufficient for diagnosis of STTs, with accuracy rates from 38 to 88 % reported for malignancy (21, 37, 46, 49). In all of the above mentioned studies, evaluation of CNBs provided better accuracy rates.

Evaluating tumour architecture from FNA specimens is not possible and may not provide enough material for further study (53). For diagnosis of recurrent high-grade STSs FNAC may be able to provide enough material (37). It can also be useful in cases where the tumour is situated close to neurovascular structures.

Certain STS treatment centres however, use FNAC routinely in diagnostics of sarcomas. Studies from these treatment centres have reported sensitivity rates from 86 to 92 % for mesenchymal malignancy (when excluding inadequate specimens) (54, 55, 56). Ninety percent of STSs were correctly graded as high- or low grade STSs (55). STS subtyping based on FNA specimens is generally not possible (54). In the same study, 83 % of the FNA specimens were able to guide definite treatment of STSs. In one study, 11 of 271 patients had an incorrect malignant diagnosis set by the FNA specimen when the tumour was benign (56). Consequently seven of these eleven patients had inappropriate surgery with wide or radical margins.

Kilpatrick and colleagues recognized on site-evaluation as the main strength of FNAC and recommended FNAC mainly for diagnosis of STTs when the specimen can be evaluated on-site (54). Otherwise they thought CNB is preferable, to guarantee enough material for further studies.

2.7 Treatment

2.7.1 Surgical treatment

According to current knowledge the best choice of initial treatment for STSs is surgery with a wide margin that preferably preserves limb function. This is because a positive surgical margin is the most important adverse factor for local recurrence (57) and the wider the margin the better local control (27). In addition, any biopsy tracts have to be removed, because of contamination when obtaining the CNB specimen (58). Thus correct classification of STSs based on the preoperative biopsy is important to enable adequate surgery with a wide margin. At the time of writing, surgery is the only curative treatment for STSs.

A study from 1981 by Enneking and colleagues examined the impact of STS grade on the margins required to obtain local control (19). They concluded that high-grade STSs

require more radical surgery than low-grade tumours to obtain similar local control rates (19). In addition they concluded that while limb-sparing surgery with wide margins is usually possible for intracompartmental STSs, amputation is required for extracompartmental STSs to obtain adequate margins.

In a more recent study an adequate margin was defined as 2–3 cm as measured from the reactive zone because it provided reasonable local control regardless of grade (27). With a smallest margin of 2.5 cm, 89.2 % achieved local control. However, a smaller margin is adequate if it contains an intact fascia. Surgery with negative margins alone in small (≤ 5 cm), superficial STSs was reported to result in good local control and overall survival in a non-randomized prospective study (59).

2.7.2 (Neo)adjuvant therapy

Radiotherapy and chemotherapy can be administered both as adjuvant and neoadjuvant treatment. Neoadjuvant therapy is indicated in patients in whom imaging shows surgery would result in intralesional removal of the tumour or amputation. Neoadjuvant treatment may shrink the tumour and thus improve the chances for marginal or limb sparing-surgery (60). Correct identification of malignant mesenchymal neoplasms and grade is thus imperative to find patients eligible for neoadjuvant therapy.

External-beam radiotherapy administered post-operatively improved local control in both high- and low-grade STSs ($p = 0.0028$) in a randomized study (61). However, the study found no statistically significant improvement in overall survival. Another randomized study, where radiotherapy was administered as brachytherapy for fully resected STSs, found statistically significant improvements in local control limited to high-grade STSs ($p = 0.0025$), in the group receiving radiotherapy (62). No statistically significant improvements in overall survival or decrease in metastatic disease were observed. A similar randomized study analysing the impact of brachytherapy on low-grade STSs reached similar results, failing to demonstrate an improvement in local control (63). As a result, Yang and colleagues hypothesized that external-beam radiotherapy could be clinically superior to brachytherapy in local control of STSs (61).

Neoadjuvant radiotherapy, administered as external-beam radiotherapy, was reported in a randomized study to be a marginally more effective than adjuvant radiotherapy with regards to survival: 78 % of patients who received neoadjuvant and 68 % who received adjuvant radiotherapy being alive at the last follow-up ($p = 0.0481$) (64). The median follow-up was 3.3 years. The same study, however, found neoadjuvant radiotherapy associated with more frequent wound complications (64). The difference in wound complications was 18 % ($p = 0.01$) in favour of post-operative radiotherapy, though the target area for radiotherapy was smaller when it was administered pre-operatively.

According to current recommendations at HUCH adjuvant radiotherapy is administered to improve local control when the tumour is removed marginally or intralesionally and a re-resection with a wide margin is not feasible.

The role of chemotherapy in treatment of STSs is still disputed. A meta-analysis of 18 randomized studies associated combination chemotherapy of doxorubicin and ifosfamide with an absolute risk reduction of 11 % and relative risk of 0.56 for overall survival ($p = 0.01$) in patients with a STS (65). For metastatic recurrence, an absolute risk reduction of 10 % and a risk ratio of 0.61 were reported ($p = 0.02$). A statistical improvement in local control was not found. However, when including studies using single-agent doxorubicin, a risk ratio of 0.73 ($p = 0.02$) for local control was found. The authors pointed out that due to the toxicity of the chemotherapy, patient selection is vital. Synovial sarcoma is particularly responsive to chemotherapy compared to other STSs (66).

Doxorubicin alone was associated with an improvement in overall survival and decrease in distant recurrences but not as much as when it was combined with ifosfamide (65). Another randomized meta-analysis however, indicated that adding ifosfamide would not improve 1-year survival rate, only tumour response rate ($p = 0.009$) (67). They thus recommended adding ifosfamide only in cases where the tumour is inoperable to try to make it resectable.

Combination chemotherapy of doxorubicin and ifosfamide is reserved at HUCH for patients younger than 70 years who are in good health and have a high-grade tumour.

In addition two of the following criteria must be fulfilled: presence of vascular invasion, diameter greater than 8 cm or presence of necrosis. However, for synovial sarcoma the diameter criterion is 5 cm.

2.8 Treatment errors

On clinical inspection, a STS often appear as a growing painless mass that seldom functionally disturb the surrounding tissue. Neither are systemic symptoms normally present. As a result, the correct diagnosis is often delayed or the tumour is removed inadequately based on clinical findings without adequate preoperative diagnostics. In a series of 100 patients viewed retrospectively, the median time from the onset of symptoms to histologic diagnosis was six months (68). A delay longer than six months was associated with an increased risk for metastatic disease at diagnosis ($p = 0.048$). Fifty-one percent had metastatic disease compared with 31 % in those who received their diagnosis within six months. The same study also reported that in those who did not have metastatic disease at diagnosis (n=82), a delay longer than six months between initial symptoms and starting of treatment was associated with worse five-year survival (59.7 % vs 77.0 %, $p = 0.04$) and greater chance of metastatic spread during the follow-up (38.8 % vs 76.5 %, $p = 0.04$).

STSs are often resected inappropriately without a proper preoperative diagnosis based on clinical findings. The pseudocapsule-structure of STSs represents a particularly tempting way of excising the tumour. However, because tumour tissue is frequently found outside this capsule, high rates of local recurrence are noted when the STS is resected inappropriately without neoadjuvant radiotherapy (19). Only 46.2 % of patients with inadequate local treatment did not have a local relapse in five years (27). Thus enucleation that is suitable for treatment of benign soft tissue tumours (STT) is an unacceptable treatment method for STS.

A retrospective study of the South-East Thames region found that 40.1 % of STS were resected without a pre-operative biopsy while as many as 63.3 % were resected without any imaging of the primary tumour (69).

Residual STS tissue was found in 59 % of re-resection specimens after an unplanned resection of a STS (70). Research indicates that re-resection of the tumour bed with a

wide margin provides similar local control as initial surgery with wide margins (71). Thus re-resection should be performed whenever possible after inadequate primary surgery. However, a second surgery with wide margins might not always be possible and nonetheless increases costs, prolongs treatment and can result in unnecessary complications.

Additionally, postoperative hematoma after initial surgery may allow the tumour to spread widely and thus contaminate a large area and subsequently force an amputation (72). In addition a skin incision placed transversely may lead to a wider resection of muscles, result in poorer functional outcome and enlarge the PTV (72).

While a biopsy should be performed before any treatment, it should not be done outside the final treatment centre. This is because diagnostic errors are done on 27.4 % on biopsies in referring centres compared with 12.3 % at specialized treatment centres (51). In addition a bigger percentage of biopsies done at referring centres were not properly performed or were found inadequate. Most importantly in 36.3% of biopsies done at referring centres, patients required alterations in the treatment plan, compared with only 4.1 % at treating centres. An inappropriately placed CNB tract may also jeopardize limb-sparing surgery (58).

Thus, to obtain optimal treatment results, all STS suspect masses should be referred untouched to a treatment centre with a specialized STS team. Following the foundation of a STS group at HUCH, both overall survival and local control has improved (73). Superficially located tumours greater than 5 cm in diameter as well as any tumour located deep should be considered as STS suspect and should be referred to a specialized treatment centre (74).

2.9 Aims

In this study we aim (i) to evaluate the accuracy of core needle biopsy in diagnostics of soft-tissue sarcomas, (ii) to identify any diagnostic errors and their underlying reasons and (iii) to identify any treatment inaccuracies resulting from an incorrect pre-operative diagnosis.

3 Methods

We retrieved information on all patients older than 17 years who underwent CNB for a STS of the extremities or trunk that was analysed at HUCH between January 1, 2000 and December 31, 2012 from the database at the Department of Pathology. We identified 313 patients and searched through the pathology records on pre-operative biopsies and surgical specimens. We took note of (i) the pre- and postoperative histologic diagnosis and (ii) grade (as set by the modified Broders grading system). Patients were excluded from further analysis based on the following criteria: (i) primary lesion of STS diagnosed prior to 2000 (n=7) and (ii) lack of surgical specimen to confirm diagnosis (n=9). These criteria yielded a remaining total of 297 patients.

In the remaining patients we identified all inaccuracies between the CNB and surgical specimen that had the potential of influencing treatment. Such inaccuracies were pre-operative diagnoses of (i) benign or non-sarcomatous tumours that on examination of the surgical specimen were STSs, (ii) low-grade STSs that were high-grade STSs, (iii) well-differentiated liposarcomas that were any another STS subtype and (iv) any STSs not identified correctly as synovial sarcoma. We also obtained from the pathology records: the site, depth and size (as defined by the pathologist on macroscopic examination of the surgical specimen) of the tumours as well as any explanations of why the pre-operative diagnosis might have differed from the final one.

We retrieved all histologic slides that had provided an incorrect diagnosis and had an experienced musculoskeletal pathologist re-evaluate them to establish whether a correct diagnosis could have been reached on the basis of the CNB. We were unable to retrieve the histologic slides of three patients due to them being stored outside HUCH and thus we did not evaluate the treatment they received. In addition we failed to retrieve the slides of two patients despite them being stored at HUCH, though these two patients treatment was evaluated. To try to eliminate possible bias on re-evaluation, the pathologist was blinded.

To determine whether the incorrect pre-operative histologic diagnosis or grade had had an impact on pre-operative staging and treatment we examined the patient files and compared the treatment they had received with present treatment guidelines. If

surgery with a wide margin would not have been possible even with correct diagnosis, the surgery was deemed correct and instead we examined whether the patients could have been eligible for neoadjuvant therapy.

4 Results

We found errors in the CNB diagnosis with potential of influencing treatment in 48 (16.2 %) of 297 patients. Thus, in 249 (83.8 %) of 297 patients, CNB provided all information required for planning of definitive treatment and pre-operative staging according to current treatment guidelines at HUCH. The characteristics of the tumours with an incorrect diagnosis set by CNB are summarized in Table II. The incorrect pre-operative diagnoses were evenly distributed between 2000−2012.

The sensitivity for mesenchymal malignancy in this study was 93.6 %. A pre-operative sarcoma-suspicion was not considered diagnostic for mesenchymal malignancy. No low-grade STSs were falsely designated as high-grade STSs by the CNB. Though, 24 high-grade STSs were designated as low-grade STSs by the CNB. Thus the overall accuracy of grading STSs (low-grade – high-grade) was 91.4 % when excluding CNB diagnoses of benign, sarcoma-suspect and non-mesenchymal tumours.

In the 48 patients with diagnostic errors: 19 patients had a non-sarcomatous diagnosis (Table III), 24 had the grade wrongly assigned as low grade (Table IV) and five patients had errors in the subtype with the potential of affecting treatment (Table V). Two patients had errors in both subtype and grade that had the possibility of influencing treatment. They are listed in Table IV.

A total of 25 treatment and staging inaccuracies were found in 18 patients in this study (Table II). Twelve patients had surgery with an inadequate margin while one patient could have been eligible for neoadjuvant chemotherapy. The remaining twelve errors were limited to inadequate pre-operative staging as a result of inaccuracies in the diagnosis set by CNB.

Table II Characteristics of faulty (N=48) CNB diagnoses

Characteristics (N=48)		Number (%)
Location		
	Proximal upper extremity	6 (12.5)
	Distal upper extremity	3 (6.3)
	Proximal lower extremity	25 (52.1)
	Distal lower extremity	8 (16.7)
	Trunk	6 (12.5)
Depth		
	Deep	41 (85.4)
	Superficial	7 (14.6)
Size (cm)*		
	<5	12 (25.0)
	5−10	19 (39.6)
	>10	10 (20.8)
	Unknown	7 (14.6)
Final diagnosis		
	Angiosarcoma	2 (4.2)
	Clear-cell sarcoma	2 (4.2)
	Epithelioid sarcoma	1 (2.1)
	Fibrosarcoma	1 (2.1)
	Leiomyosarcoma	1 (2.1)
	Liposarcoma	17 (35.4)
	MFH	12 (25.0)
	MPNST	2 (4.2)
	Sarcoma NS	6 (12.5)
	Synovial sarcoma	4 (8.3)
Final grade		
	LG	8 (16.7)
	HG	40 (83.3)
Treatment errors (n=25)		
	Inadequate surgical margins	12 (26.7)
	No preoperative chemotherapy	1 (2.2)
	No pre-operative CT of thorax	10 (22.2)
	No pre-operative CT of whole body	2 (4.4)

*As defined by macroscopic examination of the surgical specimen by the pathologist

MFH = Malignant fibrous histiocytoma; MPNST = Malignant peripheral nerve sheath tumour; NS= Not specified; LG = Low-grade; HG = High-grade

Table III List of patients with a benign (n=11), sarcoma-suspect (n=5) or malignant non-mesenchymal (n=3) diagnosis set by CNB

	Year	Location	Depth	Size‡‡ (cm)	CNB diagnosis	Grade	CNB re-evaluation	Grade	Final diagnosis	Grade	Treatment error(s)
*	2001	Shoulder	Deep	6	Neurofibroma	-	Neurofibroma	-	MPNST	4	Surgery, pre-op CT of thorax
†	2001	Thigh	Deep	3.5	Reactive process	-	Inflammatory MFH	LG	Inflammatory myxoid MFH	2	Surgery, pre-op CT of thorax
†‡	2001	Thigh	Deep	8§§	Reactive process	-	Inflammatory MFH	LG	Inflammatory MFH	3	-
	2001	Foot	Deep	3	Benign mesenchymal tumour	-	Clear-cell sarcoma	NS	Clear-cell sarcoma	NS	-
§	2002	Thigh	Deep	10	Reactive process	-	Myxoid liposarcoma	2	Myxoid liposarcoma	2	Pre-op CT of body
‖	2002	Shoulder	Deep	5	Sarcoma suspicion	-	Synovial sarcoma	NS	Spindle-cell sarcoma	4	Surgery, pre-op CT of thorax
¶	2004	Thigh	Deep	4	Reactive process	-	Tumour of unknown malignancy	-	MFH	4	Surgery, pre-op CT of thorax
**	2005	Groin	Deep	6	Carcinoma metastasis	-	NE	-	Epithelioid sarcoma	NS	NE
	2006	Groin	Superficial	11.5	Benign mesenchymal tumour	-	Benign neurogen tumour	-	Spindle-cell sarcoma NOS	2	Pre-op CT of thorax
	2006	Groin	Deep	5.5	Mesenchymal tumour of unknown malignancy	-	Condroid lipoma	-	Sarcoma NOS	LG	-
	2007	Elbow	Deep	4.5	Melanoma, clear-cell sarcoma possible	-	Melanoma	-	Clear-cell sarcoma	HG	-
	2008	Back	Deep	10	Benign mesenchymal tumour	-	Mesenchymal tumour of unknown malignancy	-	Myxoid MFH	2	Surgery
*	2008	Trunk	Deep	5	Neuroendocrine tumour	-	Carcinoma metastasis	-	Glandular MPNST	HG	Surgery
†††	2008	Breast	Superficial	5§§	Malignant phyllodes tumour	-	Angiosarcoma	NS	Angiosarcoma	NS	Pre-op CT of thorax
*	2009	Thigh	Deep	5	Benign mesenchymal tumour	-	Spindle-cell sarcoma of unknown malignancy	-	Undifferentiated liposarcoma	3	Surgery, pre-op CT of body
¶††	2009	Upper arm	Deep	1.8	Mesenchymal tumour of unknown malignancy	-	NE	-	Myxoid MFH	2	NE
‖	2011	Knee	Deep	4	Myxoma	-	Myxoid liposarcoma	2	Myxoid MFH	3	Surgery, no pre-op CT of thorax
††	2012	Breast	Superficial	4.5	Fibrosis	-	Reactive process	-	Angiosarcoma	NS	-
	2012	Armpit	Deep	3	Malignancy suspicion	-	NE		Sarcoma NOS	HG	Surgery

* Heterogen tumour with more than one component; † Difficult to classify even from surgical specimen; ‡ Open biopsy before surgery also indicated a reactive process; § Small abnormal tissue spot on CNB noted on initial examination; ‖ Small CNB specimen; ¶ Evaluation of CNB difficult; ** CNB immunohistochemistry not suiting final diagnosis; †† CNB done elsewhere; ‡‡ As reported by macroscopic evaluation of the surgical specimen by pathologist; §§ As reported by radiologist

CNB = Core-needle biopsy; HG = High-grade; LG = Low-grade MFH = Malignant fibrous histiocytoma; MPNST = Malignant peripheral nerve sheath tumour; NE = Not evaluated; NOS = Not otherwise specified; NS = Not specified; Pre-op = Pre-operative

Table IV List of patients with an incorrect low-grade soft tissue sarcoma diagnosis (n=24) set by CNB

	Year	Location	Depth	Size** (cm)	CNB diagnosis	Grade	CNB re-evaluation	Grade	Final diagnosis	Grade	Treatment error(s)
*	2000	Armpit	Superficial	7	Sarcoma NOS	LG	Myxoid MFH	LG	Round-cell liposarcoma	3	Surgery, pre-op CT of thorax
	2000	Groin	Superficial	-	Myxoid mesenchymal tumour	2	Myxoid liposarcoma	2	Round-cell liposarcoma	3	Pre-op CT of thorax
*	2000	Thigh	Deep	17	Myxoid liposarcoma	2	Round-cell liposarcoma	3	Round-cell liposarcoma	3	-
	2000	Thigh	Deep	4	Sarcoma NOS	LG	Mesenchymal tumour of unknown malignancy	-	MFH	3	-
*†	2001	Knee	Deep	7††	Myxoid liposarcoma	2	Mesenchymal tumour of unknown malignancy	-	Round-cell liposarcoma	3	-
‡	2002	Leg	Deep	18	Myxoid liposarcoma	2	Myxoid liposarcoma	2	Round-cell liposarcoma	3	-
*	2002	Thigh	Deep	8	Spindle-cell sarcoma NOS	2	Spindle-cell sarcoma NOS	3	Undifferentiated liposarcoma	4	-
§	2004	Thigh	Deep	10	Sarcoma NOS	LG	Synovial sarcoma	NS	Synovial sarcoma	NS	-
*‡	2004	Thigh	Deep	9.5	Well-differentiated liposarcoma	1	Myxoid liposarcoma	2	Round- cell liposarcoma	3	Surgery
†	2004	Thigh	Deep	13	Myxoid liposarcoma	2	Round-cell liposarcoma	3	Round-cell liposarcoma	3	-
	2005	Thigh	Deep	10††	Sarcoma NOS	2	Spindle-cell sarcoma NOS	3	MFH	4	-
	2005	Wrist	Deep	9.5	Sarcoma NOS	LG	Spindle-cell sarcoma NOS	3	Sarcoma NOS	3	-
‖	2007	Thigh	Deep	7.3	Leiomyosarcoma	LG	NE	-	Leiomyosarcoma	4	NE
*	2008	Thigh	Superficial	5.5††	Myxoid liposarcoma	2	Round-cell liposarcoma	3	Round-cell liposarcoma	3	-
*	2009	Leg	Deep	6	Myxoid liposarcoma	2	Myxoid liposarcoma	2	Round-cell liposarcoma	3	-
	2009	Foot	Deep	5.5	Sarcoma NOS	LG	Spindle-cell sarcoma NOS	LG	Fibrosarcoma	3	-

* Heterogen tumour with more than one component; † Even small spot with grade three sarcoma found on initial inspection of CNB; ‡ First CNB non-diagnostic; § CNB immunohistochemistry not suiting final diagnosis; ‖ CNB done elsewhere; ¶ Difficult to classify even from surgical specimen; ** As reported by macroscopic evaluation of the surgical specimen by pathologist; †† As reported by radiologist

CNB = Core-needle biopsy; HG = High-grade; LG = Low-grade MFH = Malignant fibrous histiocytoma; MPNST = Malignant peripheral nerve sheath tumour; NE = Not evaluated; NOS = Not otherwise specified; Pre-op = Pre-operative

Table IV List of patients with an incorrect low-grade soft tissue sarcoma diagnosis (n=24) set by CNB (cont.)

	Year	Location	Depth	Size** (cm)	CNB diagnosis	Grade	CNB re-evaluation	Grade	Final diagnosis	Grade	Treatment error(s)
*	2009	Thigh	Deep	14	Pleomorphic liposarcoma	2	Pleomorphic liposarcoma	HG	Pleomorphic liposarcoma	4	-
	2010	Shoulder	Deep	6	MFH	LG	Myxoid liposarcoma	2	Myxoid MFH	3	Chemotherapy
*	2010	Thigh	Deep	30	Myxoid liposarcoma	2	Round-cell liposarcoma	3	Round-cell liposarcoma	3	-
	2011	Thigh	Deep	17.5	Sarcoma NOS	LG	MFH	LG	Myxoid MFH	3	-
*	2011	Leg	Deep	4.3	Myxoid liposarcoma	2	Round-cell liposarcoma	3	Round-cell liposarcoma	3	-
	2011	Forearm	Superficial	4.2	MFH	LG	Myxoid MFH	3	MFH	3	-
	2012	Shoulder	Deep	2	MFH	LG	Myxoid MFH	2	Myxoid MFH	3	-
¶	2012	Thigh	Deep	15	Sarcoma NOS	LG	Sarcoma NOS	3	Sarcoma NOS	3	-

* Heterogen tumour with more than one component; † Even small spot with grade three sarcoma found on initial inspection of CNB; ‡ First CNB non-diagnostic; § CNB immunohistochemistry not suiting final diagnosis; ‖ CNB done elsewhere; ¶ Difficult to classify even from surgical specimen; ** As reported by macroscopic evaluation of the surgical specimen by pathologist; †† As reported by radiologist

CNB = Core-needle biopsy; HG = High-grade; LG = Low-grade MFH = Malignant fibrous histiocytoma; MPNST = Malignant peripheral nerve sheath tumour; NE = Not evaluated; NOS = Not otherwise specified; Pre-op = Pre-operative

Table V List of patients with incorrect diagnosis of well-differentiated liposarcoma (n=2) or sarcoma other than synovial sarcoma (n=3) by CNB

	Year	Location	Depth	Size‡ (cm)	CNB diagnosis	Grade	CNB re-evaluation	Grade	Final diagnosis	Grade	Treatment error(s)
	2000	Thigh	Deep	7	Malignant hemangioperiocytoma	-	Synovial sarcoma	NS	Synovial sarcoma	NS	-
	2003	Leg	Deep	6§	Sarcoma NOS	3	Synovial sarcoma	NS	Synovial sarcoma	NS	-
*	2003	Thigh	Deep	20	Well-differentiated liposarcoma	1	Well-differentiated liposarcoma	1	Liposarcoma	2	Surgery
	2004	Back	Deep	7.5	Sarcoma NOS	LG	Synovial sarcoma	NS	Synovial sarcoma	NS	Pre-op CT of thorax
†	2004	Thigh	Deep	13	Well-differentiated liposarcoma	1	NE		Myxoid liposarcoma	2	-

* First CNB non-diagnostic; † Heterogen tumour with more than one component; ‡ As reported by macroscopic evaluation of the surgical specimen by pathologist; § As reported by radiologist

CNB = Core-needle biopsy; LG = Low-grade; NOS = Not otherwise specified; NS = Not specified; Pre-op = Pre-operative

On re-examination of the CNBs, the diagnosis was changed for a more correct one in 26 (54.2 %) of 48 patients. Five patients with a pre-operative diagnosis of a benign or non-mesenchymal tumour, twelve patients with a pre-operative diagnosis of a low-grade STS and three patients whose synovial sarcoma was not recognized correctly pre-operatively had their pre-operative diagnosis changed to the correct diagnosis. In addition, two patients with a benign diagnosis and one with a well-differentiated liposarcoma had their pre-operative diagnosis changed to a low-grade tumour though their final diagnosis was a high-grade STS. Three tumours were considered suspicious for malignancy with the original pre-operative diagnosis of a benign tumour. In addition two patients had their pre-operative diagnosis changed from a STS to a possibly malignant tumour.

STSs with a myxoid nature constituted 20 (41.7 %) of 48 of the erroneous CNB diagnoses: 13 of these were liposarcomas and seven were MFHs. In eleven myxoid liposarcomas, the errors were limited to not recognizing the presence of round-cell liposarcoma pre-operatively. In three CNBs of myxoid liposarcoma, the pathologist originally identified a small area that he pointed out could represent an area of higher malignancy. Tumour heterogeneity was additionally noted in the pathology reports of two MPNSTs, one MFH, one pleomorphic and two undifferentiated liposarcomas.

In four patients, the pathologist noted that the CNB was not optimal for diagnosis. Another four patients had tumours that were challenging to accurately specify even from the surgical specimen. Two of these were inflammatory MFHs, one was an angiosarcoma and one was an unspecified high-grade sarcoma. Though, on re-evaluation the pathologist was able to make the correct diagnosis in all but one of the patients with an inflammatory MFH where the grade was incorrectly assigned. In three other patients the pathologist had originally suggested the correct diagnosis (epithelioid sarcoma, clear-cell sarcoma and synovial sarcoma) as plausible but that the profile was more suited for another diagnosis.

5 Discussion

The findings in our study support the belief that CNB is very accurate for identifying mesenchymal malignancy (93.6 %) and differentiating low-grade STSs from high-grade STSs (91.4 %) using a modified Broders-grading system (1). Most importantly we found that CNB provides correct information for planning of definitive treatment in 83.3 % of patients when evaluated by an experienced STS pathologist. Interpreting CNBs of myxoid STSs was associated with a significant challenge: 20 (41.7 %) of the 48 erroneous diagnoses had a myxoid stroma.

While this is one of the largest studies on the accuracy of CNB in diagnostics of STSs, the lack of benign STTs is problematic. Firstly, we are unable to confirm that we do not "over-diagnose" our patients, thus obtaining higher rates for mesenchymal malignancy but simultaneously "over-treating" benign STT. However, no low-grade STSs were diagnosed as high-grade STSs by CNB. Secondly, because we only re-evaluated CNBs that had provided an incorrect diagnosis, it is possible that the pathologist may have been more eager to interpret the slides as more malignant than he normally would. Thus, the 26 diagnoses we obtained on re-evaluation may not be obtainable in clinical practice. The lack of any background information on the patients and their STSs may have also influenced the diagnosis we obtained on re-evaluation. In certain patients this could have provided information that could have altered the final CNB diagnosis.

Because we are unable to calculate the statistical significance of our findings from the material we collected, we cannot confirm whether myxoid STSs were truly more often misdiagnosed. Neither can we evaluate whether other factors were risk factors for misdiagnosing STSs. Also, our study does not answer whether complications occur in CNB of STSs and if these affect subsequent treatment.

Our results compare favourably to other studies. In the two largest studies on the accuracy of CNB in diagnosis of STSs with 180 and 225 STS patients, sensitivity rates for mesenchymal malignancy of 99.4 % and 96.3 % were reported (43, 48), while grading accuracies of 84.9 % and 86.3 % were reported respectively. The fact that our study had a lower sensitivity for mesenchymal malignancy but a higher grading accuracy is somewhat surprising. However, Hoeber and colleagues excluded non-diagnostic CNB

specimens and had more false-positive diagnoses for mesenchymal malignancy than false-negatives (43). Different grading systems used may have also explained the differences. Strauss and colleagues used the FNCLCC system (48) while Hoeber and colleagues did not specify the grading system used. Image-guided CNB specimens were excluded by Strauss and colleagues and they included all palpable STSs regardless of location. It is possible that smaller tumours, from which obtaining adequate material is challenging (35), were excluded, thus affecting accuracy rates.

It is probable that open biopsy would have provided better sensitivity for mesenchymal malignancy and better grading accuracy than CNB in our patients, because accuracy rates from 95 to 100 % are reported in literature for diagnosis of STTs by open biopsy (21, 40, 43, 49, 50). However, open biopsy is associated with a high complication rate (15.9 %) and open biopsy affected subsequent treatment negatively in 16.6 % of patients (51). Additionally, open biopsy is time-consuming and expensive. Thus we consider that open biopsy should never be the primary method of choice for diagnosis of STS suspect tumours.

Studies evaluating FNAC have reached similar sensitivity rates for mesenchymal malignancy (54, 55, 56) and grading (55) as we did for CNB in our study. However, these studies excluded inadequate specimens and included local and metastatic recurrences. Thus the accuracy rates obtained in these studies are not directly comparable to our results.

Kilpatrick and colleagues recommended FNAC for diagnosis of STSs when on-site evaluation of the specimen is available (54). Otherwise they thought CNB would be superior to ensure adequate tissue for further study. We believe CNB may be slightly more sensitive in recognizing STSs than FNAC and more accurate at grading STSs.

Domanski and colleagues reported how FNAC and CNB supplemented each other in the diagnostics of STSs (53). In seven patients CNB was inconclusive while FNAC enabled diagnosis and in three patients the diagnosis was set on the basis of the CNB because FNAC was inconclusive. Thus obtaining both a CNB and FNAC specimen from STS suspect tumours is recommended, though FNAC results are of limited value at HUCH.

Heterogeneous and myxoid STSs, which were often misdiagnosed or graded in our study, are recognized as adverse factors for correct diagnosis in literature. A study reported that adequate tissue is only obtained from 81.4 % of heterogeneous tumours, compared to 97.5 % of homogeneous tumours (p = 0.0036) (33). CNBs of non-myxoid tumours were more often useful for diagnosis (80 %) than CNBs of myxoid tumours (11 %, p = 0.001) (30). Higher rates of diagnostic errors were also found in another study in CNBs of myxoid tumours compared to non-myxoid tumours (p = 0.021) (29).

Treatment inaccuracies were sparse and occurred in only 18 patients. In five patients errors were confined to pre-operative imaging and staging. While single-stage surgery is preferable to maximise patient comfort and to minimize the risk for complications, re-resection of the tumour after initial inadequate surgery results in comparable rates of local recurrence and overall survival (71). However, the possibility for neoadjuvant chemotherapy was lost in a patient, thus possibly affecting outcome negatively.

Most diagnostic errors were related to rare tumour subtypes and inadequate sampling of tumour tissue from heterogeneous and myxoid tumours. CNBs of myxoid STSs were challenging to interpret correctly with 20 (41.7 %) of the 48 of the erroneous diagnoses being myxoid. Thirteen were myxoid liposarcomas, though eleven of these were correctly recognized, but the presence of round-cell liposarcoma was not noted. Thus they were graded incorrectly. The presence of merely 5 % of the round-cell component in a myxoid liposarcoma is associated with worse outcome and these tumours should be treated as high-grade STSs (75). Tumour heterogeneity was additionally noted in six sarcomas. Thus sampling tumour tissue from multiple locations is required for the correct diagnosis and grading of myxoid and heterogeneous STSs.

CNB specimens of certain uncommon STS subtypes appeared as challenging to interpret, thus emphasising the requirement for an experienced STS pathologist. The fact that certain surgical specimens were hard to evaluate emphasizes this point.

Immunohistochemistry and genetic analysis are important ancillary techniques in diagnostics of STSs (6). It is very possible that some STSs in our study could have been correctly diagnosed with CNB if the pathologist had asked for correct ancillary studies. In our study, four synovial sarcomas had an incorrect pre-operative diagnosis. For

synovial sarcoma epithelial markers are often positive and a chromosome translocation t(X;18)(p11.2;q11.2) is present in most synovial sarcomas (6). All four CNBs were on re-evaluation suspicious for synovial sarcoma. Thus it is very possible that the correct diagnosis could have been reached in all four patients. In one patient, however, the immunohistochemical profile was not suited for synovial sarcoma. No synovial sarcomas have been incorrectly diagnosed since 2004, thus raising the possibility that these STSs are nowadays correctly identified from CNBs.

Two angiosarcomas, clear-cell sarcomas and one epithelioid sarcoma were incorrectly diagnosed as benign or non-mesenchymal tumours from the CNB in our study. For these sarcomas there are known immunohistochemical markers and a chromosome translocation t(12;22)(q13;q12) that can be used to identify clear-cell sarcoma (6). While both angiosarcomas and one clear-cell sarcoma were recognized on re-evaluation of the CNBs, the pathologist was unable to recognize one of the clear-cell sarcomas and we did not obtain the CNB of the epithelioid sarcoma.

Our study suggests that even higher accuracy rates for mesenchymal malignancy and grade can be achieved than the original ones we observed. Twenty-six patients got a more correct diagnosis on re-evaluation and in 20 patients the new diagnosis was able to provide all information for planning of definitive treatment. Most importantly seven STSs, not recognized as such by the CNB, were identified as mesenchymal malignancies and five of these were graded correctly on re-evaluation of the CNB. In addition three CNBs of benign tumours were considered STS suspect. Consequently, an additional four patients would have probably undergone single-stage surgery with a wide margin.

Image-guided CNB is highly sensitive for identifying mesenchymal malignancy and grade when performed at our institution, with few patients with STSs treated inadequately. We recommend image-guided CNB as the primary method for diagnosis of STSs but advise caution in evaluating CNB specimens of tumours with a myxoid nature. Due to the challenge of interpreting CNBs of STSs, we suggest concentrating STS suspicious CNB specimens to experienced STS pathologists to maximise diagnostic accuracy and avoid subsequent incorrect treatment.

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