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Clinical advances in musculoskeletal imaging: spondylodiscitis and pediatric oncology

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Chapter 9

General discussion

General discussion

PART I. Spondylodiscitis

Early and accurate diagnosis is considered crucial to improve the outcome of patients with spondylodiscitis. CT-guided biopsy is currently a cornerstone in the diagnostic work-up of spondylodiscitis. It is performed in patients with MRI findings suggestive of spondylodiscitis and whose blood cultures remain negative. However, the diagnostic yield of this invasive procedure should be known and weighed against its clinical impact in terms of treatment changes and patient outcome.

Multiple previous studies on percutaneous CT-guided biopsy in patients with suspected spondylodiscitis have been performed. Previously reported culture yields vary widely, ranging between 19% to 91% [1-4]. However, these previous studies suffered from several methodological shortcomings, such as possible data contamination with spondylodiscitis mimickers (such as Modic type I degeneration, acute Schmorl node, and (osteoporotic) fracture), the inclusion of patients with a previous history of spondylodiscitis, unclear patient referral criteria for CT-guided biopsy, and erroneous exclusion of patients with negative blood and biopsy cultures when calculating the culture yield of CT-guided biopsy [1-4]. We investigated the cultural yield of CT-guided biopsy in patients suspected of spondylodiscitis in **Chapter 2**. The biopsy yield percentage from our study may be more realistic than previously reported numbers that suffered from the above-mentioned methodological flaws. In our study, one-third of patients suspected with spondylodiscitis yielded a positive culture. Of note, laboratory, clinical, and MRI findings did not have a significant association with a positive culture in our study, which indicates that an a priori prediction of the culture yield of the biopsy may be impossible. This contradicts some previous studies that reported that several parameters, such as CRP levels and leukocyte counts [5, 6] were associated with positive biopsy cultures. Nevertheless, these previous results may be unreliable due to the previously mentioned methodological flaws of these studies. In our study, a positive cultural yield provided additional information to clinicians for guiding antimicrobial treatment in approximately 75% of patients. This result seems to support the routine use of CT-guided biopsy in patients with suspected spondylodiscitis and negative blood cultures, and is in line with general consensus as described in the Infectious Diseases Society of America (IDSA) guidelines [7]. On the other hand, CT-guided biopsy was useful to tailor antibiotic treatment in

only 25% of patients among the entire population. Another interesting result is that we did not find a significant difference in outcome between culture-positive patients treated with tailored antibiotics and culture-negative patients treated with empirical antibiotics. Outcome for both groups was almost the same in terms of survival and absence of signs of infection at the end of the therapy. A previous study by Kim et al. [8] reported similar results. In addition, in our study, more than 95% of patients without clinical findings suspicious for “atypical” pathogens would have been adequately covered with empiric antibiotic therapy. Furthermore, it should be noted that CT-guided biopsy has several disadvantages, being costly, invasive with possible associated complications, and uses potentially harmful ionization radiation. Given these findings and considerations, the routine use of CT-guided biopsy in spondylodiscitis patients may be reconsidered. On the other hand, an important disadvantage of an empirical antibiotics approach is the risk of resistance development, and its effect in regions that actually suffer from antimicrobial resistance is doubtful. It is more likely that in these regions patients would be referred to a CT-guided biopsy. A future randomized prospective study, in which an algorithm of [clinical symptom criteria → blood culture and imaging criteria → biopsy → treatment] will be compared to an alternative algorithm of [clinical symptom criteria → blood culture and imaging → treatment], would be of value to gain more insight into the utility of CT-guided biopsies in spondylodiscitis. Importantly, immunocompromised patients should be excluded from such a study, because these patients may present with (opportunistic) micro-organisms that are not covered by empirical antibiotics. Nevertheless, until the results of such a future study become available, an empiric treatment strategy could be offered/reserved to patients with contra-indication for CT-guided biopsy, for example patients requiring general anaesthesia or haemorrhagic diatheses.

While the diagnostic strategy after an initial negative CT-guided biopsy remains unclear based on available evidence, IDSA guidelines recommend repeating image-guided biopsy or proceeding to open surgical biopsy because it is considered important to identify the target microorganism before accurate therapy can be administered [7]. The advantage of a second image-guided biopsy is that it is less invasive than a percutaneous endoscopic approach (PEDD) or open excisional biopsy. However, the cultural yield of a second image-guided biopsy after an initial negative image-guided biopsy is still unclear. There are limited numbers of studies on this topic with relatively small sample sizes and heterogeneous methodology. In **Chapter 3**, we performed a systematic review of published data on this topic. This investigation showed that the positive cultural yield percentages of a second

CT-guided biopsy range between around 10% and 50%. Notably, the 33% (5/15) positive culture yield of repeated biopsies in our own study as described in **Chapter 2** falls within these ranges. However, these results should be interpreted cautiously because methodological quality assessment in our systematic review shows that all studies were at risk of bias and all studies had concerns regarding applicability. For example, the reason why only a minority of patients underwent a second biopsy, was not clearly described. In the majority of included studies, the reason to rebiopsy was most likely based on clinical and radiological grounds. There was also poor reporting on the use of MRI prior to biopsy. MRI criteria for spondylodiscitis, in- or exclusion of patients with a previous history of spondylodiscitis, and time between MRI and biopsy were not reported either. Despite the variations in patient populations and methodology, proportions of positive cultural rebiopsy yields were statistically homogeneous among included studies and may be considered to reflect actual clinical practise. Although our systematic review provides some insight into the culture yield of a second image-guided biopsy in spondylodiscitis, the exact role of this procedure and which strategy (second biopsy, PEDD, open biopsy, empiric antibiotic treatment) is most effective after negative initial biopsy (both in terms of culture yield and patient outcome), remain unclear. Future studies are necessary to define the best (diagnostic) strategy after an initial negative biopsy in suspected spondylodiscitis.

PART II. Pediatric oncology

Bone sarcomas are rare entities and often are associated with delayed diagnosis. It is essential to establish the correct diagnosis as soon as possible so accurate and prompt treatment can be initiated since these are associated with better outcome. Ewing sarcoma is a primary malignant bone tumor, second in incidence to osteosarcoma.

The differential diagnosis of Ewing sarcoma includes both benign and malignant conditions. The most common benign condition is subacute osteomyelitis. Differentiation of these two entities is very important since treatment and outcome are completely different.

In **Chapter 4** we investigated the value of several potentially useful MRI signs in differentiating Ewing sarcoma from osteomyelitis. Two radiologists reviewed a dataset in a random order while being blinded to each other's assessment. MRI scans were evaluated with regard to several MRI signs including transition zone of the bone lesion (sharp or unsharp), presence of an associated soft-tissue mass,

the presence of intra- or extramedullary fat globules, and the penumbra sign (i.e., a T1 hyperintense and contrast-enhancing peripheral layer surrounding a cavity in either the bone marrow or adjacent soft tissues. Inter-observer agreement of these signs was also assessed. The most valuable MRI sign for discriminating Ewing sarcoma from osteomyelitis was the presence of a soft-tissue mass with an accuracy of around 80%. This finding was also applicable to the discrimination of Ewing sarcoma or other malignancy from osteomyelitis or other benign lesions. Transition zone of the bone lesion was only of moderate value with an accuracy of around 60%. Diagnostic accuracies of the presence of fat globules and the penumbra sign were <50%. Another relevant finding was that the size of the accompanying soft-tissue mass (if present) was found to be useful in differentiating Ewing sarcoma from osteomyelitis. Larger soft-tissue mass diameters favour Ewing sarcoma over osteomyelitis. However, inter-observer agreements with regard to the assessment of the presence of a soft-tissue and transition zone of the bone lesion were relatively low with moderate k values. Inter-observer agreement of soft-tissue mass diameter measurements was also low. The latter may be due to the fact that accompanying soft-tissue masses frequently have a complex three-dimensional configuration, which causes variability in location and orientation of caliper measurements that are done by the radiologist. Future studies should assess if (semi-)automated volume measurements with dedicated software provide more reproducible results.

There are two previous studies on the discrimination between Ewing sarcoma and osteomyelitis [1, 2]. Both previous studies and our own study included patients with bone lesions of unknown nature with a differential diagnosis of Ewing sarcoma. However, the previous two studies excluded patients who were eventually diagnosed with another entity. Therefore, the present results may demonstrate more clinical applicability. Nevertheless, both previous studies also reported relative high diagnostic accuracies (79% in the Henniger et al. study [1] and 76% in the McCarville et al. study [2]) for the presence of a soft-tissue mass in diagnosing Ewing sarcoma. A noticeable difference is that Henniger et al. [1] reported a diagnostic accuracy of 100% for the transition zone of the bone lesion while McCarville et al [2] reported an accuracy rate of only 45%. The result of the present study for the transition zone agree with the latter study. Several other studies which included only osteomyelitis patients have proposed that the penumbra sign and the presence of intra- or extramedullary fat globules might be specific for osteomyelitis and maybe useful for differentiating osteomyelitis from malignancy [3, 4]. However, none of these signs were found to be of diagnostic value in the present study.

Overall, two MRI signs appear to be useful in the differentiation of Ewing sarcoma from its well-known mimicker osteomyelitis, i.e. the presence and size of a soft-tissue mass and the sharpness of the transition zone of the bone lesions. Unfortunately, none of these MRI assessments reached a sufficiently high positive predictive value or negative predictive value to reliably rule in or rule out Ewing sarcoma. Therefore, there is a need for more accurate non-invasive diagnostic tools. Future studies may investigate if functional MRI sequences such as diffusion-weighted, and perhaps MRI spectroscopy, may improve the differentiation between Ewing sarcoma and osteomyelitis. There may also be a role for ^{18}F -fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) or FDG-PET/MRI, but these are more expensive examinations that are currently not performed upfront for the evaluation of a bone tumor of unknown nature.

Biopsy of musculoskeletal lesions is essential in the diagnostic work-up and management of bone tumors. Biopsy of the tumor can be performed by a percutaneous CT-guided core needle biopsy or open surgical biopsy. Although open surgical biopsy provides higher diagnostic yields, CT-guided biopsy is the preferred method for initial tissue sampling because it is less invasive and associated with fewer complications [5]. A few studies reported that CT-guided biopsy in pediatric patients is a safe procedure with a diagnostic yield comparable to that in adults and is a valid alternative to direct open biopsy [6-8].

In **Chapter 5**, we assessed the frequency of indeterminate percutaneous CT-guided bone biopsy results in a pediatric population, the subsequent management of these indeterminate biopsy results, and the factors associated with an indeterminate biopsy result. Our results show that one-third of CT-guided biopsies of unclear bone lesions in pediatric patients yields material that is judged by the pathologist to be inadequate or inconclusive. None of the 29 bone lesions with indeterminate results on initial CT-guided biopsy in our study proved to be malignant after subsequent tissue samplings and follow-up. Lack of symptoms related to the bone lesion, lack of visibility of the bone lesion at CT, the presence of a sclerotic rim, absence of cortical destruction, absence of an associated soft-tissue mass, smaller tumor diameter, and a smaller biopsy sample length were univariately significantly associated with an indeterminate biopsy result. This can be explained by the fact that these features have already been described to be more frequently exhibited by benign than malignant bone tumors. We also found positive relationships between lower age and female sex with indeterminate CT-guided biopsy results, but this reasons for these findings remain unclear.

A previous study by Hryhorczuk et al. [7] also evaluated indeterminate CT-guided biopsies in pediatric patients and assessed a percentage of 23%. Their percentage of indeterminate CT-guided biopsy results (23%) is lower than in the present study, but Hryhorczuk et al. [7] reported that CT-guided biopsy is frequently performed to confirm the benign origin of a lesion in their institution. This may explain their lower indeterminate biopsy yield percentage. Importantly, all bone lesions with indeterminate initial CT-guided biopsies as reported by Hryhorczuk [7], proved to be benign on subsequent tissue samplings or follow-up.

Overall, indeterminate CT-guided bone biopsy results in children appear to be relatively common and it is unlikely that these bone lesions have a malignant nature. However, this is based on our own retrospective study in 89 patients and the retrospective study by Hryhorczuk et al. [7] in 61 patients. Furthermore, both studies were performed in tertiary academic medical centres. Therefore, future (prospective) studies in different settings (both academic and non-academic) are necessary to confirm these results. It should be kept in mind that a confident exclusion of malignancy is crucial, since failure to timely diagnose a primary bone malignancy may have severe consequences due to disease progression. Multidisciplinary meetings remain essential to discuss imaging and pathology results, and the need to take further diagnostic steps, including repeat biopsy.

Metastatic status at diagnosis is the strongest prognostic factor across different treatment strategies in Ewing sarcoma. However, prognosis is also influenced by primary tumor volume [9, 10]. Larger tumors have a worse prognosis. In Europe, primary tumor volume is also used to tailor chemotherapy in newly diagnosed Ewing sarcoma. The optimal cut-off value for prognostic stratification is still underinvestigated, although patients with a primary tumor volume of more than 200 mL have been reported to have worse survival rates [11].

In **Chapter 6** we investigated the inter- and intra-observer agreement of MRI-based simplified primary tumor volume measurements in newly diagnosed Ewing sarcoma patients. We also compared these measurements with actual primary tumor volume on MRI and with metabolically active tumor volume (MATV) as measured on FDG-PET/CT. The results of our study show that observer variability of MRI-based simplified tumor volume measurements was high, especially for larger tumors. In contrast, both inter- and intra-observer agreement of dichotomized measurements (<200 vs. >200 mL) were good to very good. The same results apply to the agreement between MRI-based simplified tumor volume and MRI-based actual tumor volume measurements. These results indicate that MRI-based

simplified primary tumor volume measurements can be regarded as quite robust to stratify patients into good and poor prognostic groups according to the 200 mL threshold. Previous studies dating back to the 1980s and 1990s validated the prognostic value of primary tumor volume in newly diagnosed Ewing sarcoma based on measurements on plain radiography[9,10]. However, MRI is now the method of choice for local tumor evaluation. Remarkably, there have not been any studies that assessed the prognostic value of tumor volume measurements on MRI. Such studies are warranted to support the routine use of primary tumor volume measurements on MRI in newly diagnosed Ewing sarcoma.

In our study, we also found that both simplified and actual primary tumor volume measurements poorly to moderately agree with FDG-PET-based MATV. Tumor volumes were (nearly) significantly lower for FDG-PET-based MATV. A possible explanation for this finding is that gadolinium-enhancement does not only occur in tumor-invaded tissue but also in unaffected surrounding tissue, which can result in an overestimated measurement of the tumor volume. On the other hand, it has not been proven that FDG-PET-based MATV reflects the true primary tumor volume due to a lack of histopathological correlation. FDG is not tumor-specific and uptake in surrounding inflammatory tissue may cause overestimated tumor volumes. In the last decades, advanced MRI sequences such as diffusion-weighted imaging [12] have emerged and the latter may potentially be more accurate to discriminate viable tumor from surrounding (inflammatory) tissue. However, since Ewing sarcoma is generally treated with neoadjuvant chemotherapy before surgery, it would be meaningless to validate volume measurements on imaging with volume measurements on the resected specimen. Instead, future studies should compare MRI-based volume measurements (without and with diffusion-weighted imaging) to FDG-PET-based MATV with regard to the prediction of patient outcome (in terms of progression-free or overall survival). Such studies will demonstrate which imaging modality is most suited for primary tumor volume measurements in newly diagnosed Ewing sarcoma.

There is no universally accepted staging work-up scheme for newly diagnosed Ewing sarcoma patients, but the staging examinations that are used in most centres are conventional radiographic and MRI examinations of the primary tumor site, chest CT to detect lung metastases, whole-body bone scintigraphy for the detection of osseous metastases, and blind bone marrow biopsy of the posterior iliac crest (usually bilateral) for bone marrow assessment. Bone marrow biopsy, however, is an invasive procedure that carries a small but non-negligible risk of (haemorrhagic) complications [13], and is often performed under general anaesthesia in this mainly

pediatric population. Meanwhile, FDG-PET/CT is increasingly used as a new staging method in Ewing sarcoma [14]. One of the advantages of FDG-PET/CT is that it can visualize the entire body, including the bone marrow. It can be hypothesized that FDG-PET/CT may replace blind BMB of the posterior iliac crest if sufficiently accurate to detect bone marrow involvement.

In **Chapter 7** we investigated the feasibility of FDG-PET/CT as a potential alternative to blind bone marrow in newly diagnosed Ewing sarcoma. The results of our study showed that FDG-PET/CT and blind bone marrow biopsy of the posterior iliac crest were in agreement in almost all cases (total of 20 patients who underwent 38 blind bone marrow biopsies). Only one patient had a disagreement between the two procedures. Bilateral bone marrow biopsies were negative while FDG-PET/CT showed pathologic uptake at both posterior iliac crests in this patient. FDG-PET/CT also indicated extensive bone marrow involvement outside the iliac crests in this case, which suggested that the two blind bone marrow biopsies in this patient were false negative. Note that the detection of additional bone marrow metastases is valuable information because the number of bone lesions has been shown to correlate with a worse prognosis [11, 15]. The findings of our study indicate that the routine use of blind bone marrow biopsy should be reconsidered when FDG-PET/CT is available. Rather than completely abandoning the bone marrow biopsy, FDG-PET/CT may be used to screen for bone marrow metastases, and, if positive, subsequent CT-guided bone biopsy may be performed for histological confirmation. This biopsy can then be targeted at the lesion that is most FDG-avid. Previous studies reported that approximately 10% of patients have bone marrow metastasis [16]. Given these facts, it can be hypothesized that approximately 90% of the patients can be spared invasive bone biopsy with such a diagnostic algorithm.

Despite the value of imaging in this setting and the drawbacks of blind bone marrow biopsy, several guidelines such as the National Comprehensive Cancer Network (NCCN) and

European Society for Medical Oncology (ESMO) guidelines [16, 17] still recommend blind bone marrow biopsy. However, these recommendations are mostly based on expert opinions. A previous study on this topic by Newman et al. [18] reported that all patients with positive blind bone marrow biopsies were also positive for bone marrow metastatic disease on FDG-PET/CT in their study. Additionally, FDG-PET/CT suggested bone marrow biopsy in three patients who had negative blind bone marrow biopsy results [18]. These findings are completely in line with our study. To the best of our knowledge, there are no other studies that explicitly compared FDG-

PET/CT and bone marrow biopsy in Ewing sarcoma. Further research is needed to definitely establish FDG-PET/CT as a (partial) alternative to (blind) bone marrow biopsy in Ewing sarcoma.

After completion of therapy with curative intent, it is common practice to perform routine surveillance MRI of the location of the primary tumor site in Ewing sarcoma. MRI (with intravenously administered contrast agents) has reported high accuracy rates in detecting local recurrent disease [19]. However, despite second-line therapy the general prognosis of recurrent Ewing sarcoma is very poor.

In **Chapter 8** we assessed the frequency of locally recurrent Ewing sarcoma on surveillance MRI and the outcome of these patients. In our study, 32 patients underwent a total of 176 surveillance MRI scans. Surveillance MRI detected five (16%) locally recurrent Ewing sarcomas. One of the most important findings of our study was that patients with locally recurrent Ewing sarcoma had a poor outcome with all patients succumbing to their disease within 1 year, despite second-line therapy. This means that early detection of local recurrence did not improve outcome with currently available treatment regimens. An additional finding was that simultaneous recurrent metastatic disease can also occur, both without and in combination with a local recurrence. This finding is in line with a previous study by Bacci et al. [20]. Besides the poor outcome of these patients, MRI costs and potential side effects should also be taken account when considering the utility of surveillance MRI. In our study, an average of 35.4 scans was performed to detect one local recurrence, which corresponds to a total amount of approximately \$10,000. Another point of concern is that all patients received repeated doses of gadolinium-based contrast agents for surveillance MRI. Several studies have reported that gadolinium-based contrast agents accumulate in the deep nuclei of the brain and the question arises whether this deposition might cause any harm [21]. Although adverse clinical effects related to gadolinium deposition in the brain have not been reported yet, the use of these contrast agents should be restricted as much as possible. An alternative approach may be to perform surveillance MRI with unenhanced sequences only. However, this may go at the expense of a decrease in diagnostic precision.

Overall, a limited number of patients has locally recurrent Ewing sarcoma on surveillance MRI. These patients often have simultaneous recurrent (metastatic) disease elsewhere, and their outcome is poor. Moreover, some patients present without locally recurrent disease on MRI but disease recurrence elsewhere.

Therefore, surveillance MRI currently seems to have little value and should be reconsidered, also given the costs and the repeated exposure of surviving patients to gadolinium-based contrast agents.

In conclusion, this thesis investigated several standard musculoskeletal imaging procedures for spondylodiscitis and pediatric patients with primary (malignant) bone tumors. The results of this thesis underline the value of imaging and image-guided biopsy in these settings, but also indicate that certain aspects need revision or further evaluation to improve diagnostic yield, decrease patient burden, and reduce costs.

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