



The necessity of bilateral staging bone marrow examinations for paediatric solid tumours



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Background: Bone marrow aspirates and trephine biopsies (BMATs) form an important part of staging to detect bone marrow metastases of both haematological and nonhaematological neoplasms.

Aim: The study's primary aim was to determine whether it is necessary to perform bilateral BMATs on paediatric cancer patients as opposed to unilateral BMATs for the staging of solid tumours.

Setting: The Paediatric Oncology Unit at Universitas Academic Hospital (UAH) in Bloemfontein, Free State, South Africa.

Methods: A retrospective descriptive study was performed using laboratory reports from 01 January 2015 to 31 December 2019. Data were collected and reported on regarding the total number of staging BMATs performed, the average length of the trephine biopsies, the number of BMATs used for primary diagnosis, the number of bone marrow specimens where metastases were detected (left, right or both), the type of primary cancer and demographic information.

Results: One hundred and eighteen patients were included for interpretation. Bone marrow metastases were detected in 28 patients, of which five patients had discrepant left and right results. These five cases included nephroblastoma ($n = 2$), Hodgkin lymphoma ($n = 2$) and a germ cell tumour ($n = 1$).

Conclusion: Discrepant results were found in five cases ($n = 28$; 17.8%). Ultimately, the clinical implication of incorrectly staging solid tumours outweighs the small risks and discomfort of a bilateral bone marrow biopsy.

Keywords: bone marrow aspirate and trephine biopsy; solid tumour; staging; metastases; childhood cancer.

Introduction

Childhood cancers, which make up only about 1% of all cancers, are considered relatively uncommon.^{1,2} In addition, the low cumulative risk of development (estimated at 1.0–2.5 per 1000 in children under 15 years), with the general potential for cure, may negate the perceived seriousness.^{1,3} Yet with a recorded global increase in incidence, cancer forms a significant cause of childhood mortality.⁴

As reviewed by Otoo et al., approximately 300 000 new childhood cancer cases are diagnosed every year, with over 36 000 cases in Africa alone.^{2,5} Between 1987 and 2012, the South African Childhood Tumour Registry has reported 600–700 new childhood cancer cases annually. More recent epidemiological studies are lacking.⁴

Internationally, haematological malignancies, particularly acute lymphoblastic leukaemia, are the most commonly occurring childhood malignancy. This is also reflected in South African statistics, where leukaemia accounts for 25.4% of all paediatric cancers.¹ Using medicine claims data, Otoo et al., also identified leukaemias as the most prevalent malignancy in the private health sector of South Africa (39.9% of cancer cases), followed by lymphomas (13.9%) and central nervous system malignancies (11.0%).²

The reported incidence rates, however, remain lower in African populations, partly explained by underdiagnosis, misdiagnosis and underreporting.⁵ Population-based cancer registries cover only an estimated 2% of the total African population.⁶ Limited access to health care facilities and the

necessary technology to confirm diagnoses not only skews epidemiological data but ultimately affects survival.⁵ The 5-year survival rate of approximately 80% in the United States (US) and Europe contrast the near 60% mortality rate of children diagnosed with cancer in Africa.⁵

Another factor impacting survival is the adequate staging of cancers. Cancer staging refers to the tumour size and extent of spread in the body. The cancer stage affects patient prognosis and guides treatment.⁷ As previously reviewed, in addition to the staging of known cancers, detection of bone marrow involvement may be the first evidence of an underlying malignancy.^{8,9} Bone marrow metastasis is associated with advanced-stage disease and negatively impacts overall survival.¹⁰

The bone marrow forms the primary source of haematological malignancies and is an important site for metastases of solid tumours. Bone marrow aspirate and trephine biopsies (BMATs) are therefore vital tools in the staging of cancers.⁹ Bone marrow aspirate and trephine biopsies are generally regarded as safe, reliable and cost-effective.^{9,11} Bone marrow aspirates are a cytological smear preparation of bone marrow ideal for morphological evaluation of cells.¹² Trephine biopsies provide a more holistic assessment of bone marrow architecture and haematopoiesis.¹¹ Normally trephine biopsies are considered the best method for detecting bone marrow metastases, with aspirates detecting only 1 in 20 cases of Hodgkin lymphomas in one study and missing up to a third of non-Hodgkin lymphomas.¹¹ Occasionally, however, metastasis may be present on aspirates only, supporting the notion that these two procedures should be performed simultaneously and regarded as complementary techniques.^{11,12,13}

Focal bone marrow involvement of some haematological and nonhaematological neoplasms have traditionally favoured the practice of routine bilateral BMATs.¹⁰ Bilateral BMATs ensure the acquisition of a greater quantity of histological tissue that is more representative, and the physician is therefore less likely to miss a diagnosis in case of discrepancy between sites.¹⁴

Wang et al. reported several studies emphasising the usefulness of bilateral BMATs for improved cancer staging, increasing detection rates by up to 22%.¹⁰

However, it should be noted that BMATs are not risk-free. Bleeding, infection and needle-related incidents (e.g. needles breaking off in biopsy sites) are commonly reported complications.¹⁵ Bilateral BMATs also increase the time (for the procedure and laboratory assessment) and cost. All these factors need to be weighed against the benefit of bilateral sampling.¹⁶

The Paediatric Oncology Unit at Universitas Academic Hospital (UAH) routinely performs bilateral staging BMATs

on all patients newly diagnosed with solid tumours. In addition to a staging tool, bone marrow investigations are often performed for primary diagnosis in cases where the primary tumour cannot be biopsied because of difficult access, tumour size or potential complications associated with the procedure.

This study aimed to determine whether bilateral BMATs, as opposed to unilateral BMATs, are necessary for staging solid tumours in children at the Paediatric Oncology Unit at UAH.

Methods

This retrospective descriptive study included all reported cases of solid tumours in children aged 0–13 years who underwent BMAT at UAH, Bloemfontein, South Africa, from 1 January 2015 to 31 December 2019.

The Paediatric Oncology Unit of UAH provided a list with hospital numbers of all the notified paediatric cancer cases (excluding acute leukaemia) within the study period. The hospital numbers were used to obtain the corresponding laboratory reports from the National Health Laboratory Service (NHLS). Study numbers were assigned in ascending order of collection, thereby pseudo-anonymising the study participants, and these study numbers were used to record and analyse data. Additional data regarding the total number of staging BMATs performed, the average length of the trephine biopsies, the number of BMATs used for primary diagnosis, the number of bone marrow specimens where metastases were detected (left, right or both), the type of primary cancer and demographic information were also collected. All acute leukaemias, restaging or end-of-treatment BMATs and cases with missing data sets were excluded.

Data analysis

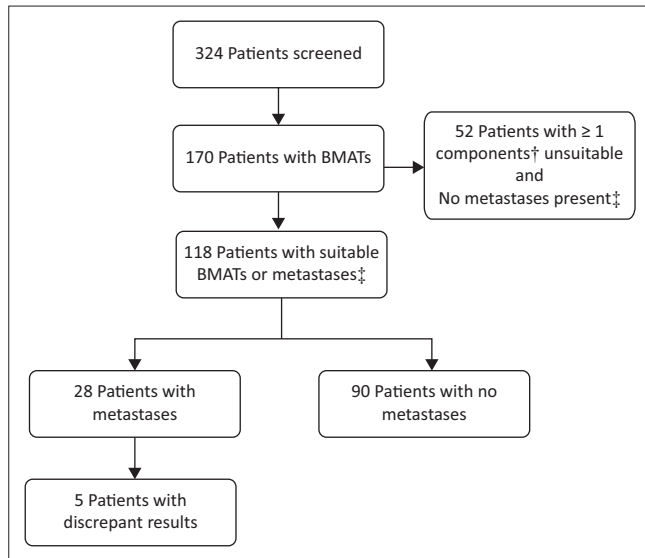
Descriptive statistical analysis using means and medians was performed by the Department of Biostatistics, the University of the Free State.

Ethical considerations

Approval to conduct the research was obtained from the Health Sciences Research Ethics Committee (HSREC) of the University of the Free State (ref. no. UFSHSD2020/0332) as well as from the Free State Department of Health.

Results

During the study period, 170 of the initial 324 patients screened met the inclusion criteria. Fifty-two of the 170 patients were excluded because, although no metastases were present, one of the four components (left aspirate, left trephine, right aspirate and right trephine) was considered unsuitable for interpretation. A total of 118 patients had either suitable bilateral bone marrow aspirates and trephine biopsies or an unsuitable component but with metastases present on any other suitable parts (Figure 1).



BMATs, bone marrow aspirate and trephine biopsies.

†, Components: left and right bone marrow aspirates and left and right trephine biopsies; ‡, Patients with metastases were included in the analysis despite having one or more of the four components unsuitable.

FIGURE 1: Outline of selection of final study population.

TABLE 1: Demographics of study participants.

| Demographic categories | Percentage of patients |
|------------------------|------------------------|
| Gender | |
| Male | 54.2 |
| Female | 45.8 |
| Race | |
| Black participant | 87.0 |
| Mixed race participant | 8.5 |
| White participant | 3.4 |
| Asian participant | 0.8 |

The average age of the 118 patients was 5.81 years, with a male to female ratio of 1.19.

Table 1 summarises the racial distribution of the study population.

Bone marrow aspirate and trephine biopsies were predominantly performed for staging purposes ($n = 81$; 68.6%); however, in 31.4% of cases ($n = 37$), the primary diagnosis was sought.

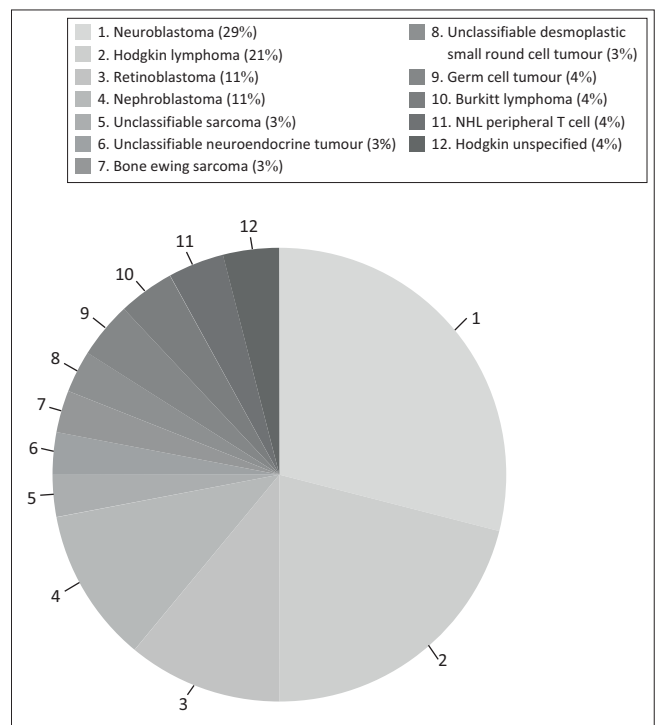
The cancers for which BMATs were most frequently performed are summarised in Table 2, and the cancers for which bone marrow metastases were detected are depicted in Figure 2.

Bone marrow metastases were detected in 28 of the 118 patients, of which five patients ($n = 28$; 17.85%) had discrepant results on their bilateral BMATs. Malignancies with discrepancies were neuroblastoma ($n = 2$), Hodgkin lymphoma ($n = 2$) and a germ cell tumour ($n = 1$).

Discrepancy in the detection of bone marrow metastases between the aspirate and the trephine biopsy occurred in 11 cases (39.29%, $n = 28$). In three cases (27.27%, $n = 11$), metastases were detected on the bone marrow aspirate only, whilst in eight cases (72.73%, $n = 11$) metastases were detected

TABLE 2: Summary of the tumours for which staging bone marrow aspirate and trephine biopsies were performed.

| Tumour | Frequency | Percentage |
|---|-----------|------------|
| Nephroblastoma | 27 | 22.9 |
| Hodgkin lymphoma | 18 | 15.3 |
| Retinoblastoma | 17 | 14.4 |
| Sarcomas, carcinomas and unclassified tumours | 17 | 14.4 |
| Non-Hodgkin lymphoma | 13 | 11.0 |
| Neuroblastoma | 11 | 9.3 |
| Rhabdomyosarcoma | 8 | 6.8 |
| Germ cell tumours | 4 | 3.4 |
| Ewing sarcoma | 2 | 1.7 |
| Mesothelial mesonephric blastoma | 1 | 0.8 |



NHL, non-Hodgkin lymphoma.

FIGURE 2: The proportion of cases with bone marrow metastases, according to the primary tumour.

by the trephine biopsy only. Of note, seven of these eight were Hodgkin lymphoma cases. The detection rate of bone marrow aspirates versus trephine biopsies in the study's cohort was thus 71.43% and 89.29%, respectively.

The average length of trephine biopsies considered suitable for interpretation was 13.00 mm for the left side and 11.75 mm for the right side.

Discussion

Bone marrow examination is an indispensable investigation in the diagnosis of bone marrow disorders, including assessment of suspected bone marrow metastases.¹⁷ In addition to tumour staging, the metastatic lesions in the bone marrow may aid in the diagnosis of the primary tumour.⁸ Bone marrow aspirate and trephine biopsies were predominately performed for the purpose of staging of the study cohort ($n = 81$; 68.6%). However, in 31.4% of cases ($n = 37$), the procedure was performed in an effort to diagnose

the primary lesion. The presence of bone marrow metastases impacts the type of treatment the patient will receive, the clinical course, the prognosis and the overall survival.¹⁰

Bone marrow aspirate and trephine biopsies is an easy, sensitive and cost-effective method for assessing bone marrow metastases.¹⁸ Specialised imaging techniques such as magnetic resonance imaging (MRI) and F-2-fluoro-2-deoxy-D-glucose positron emission tomography-computerised tomography (FDG PET-CT) have shown sensitivity equal to and even superior to BMAT.^{19,20} However, the affordability and accessibility of these modalities is very limited in the South African context.²¹ Advanced radiological techniques may, at times, miss bone marrow metastases, which is why BMAT is still considered the gold standard for this purpose.⁸

Barbara Bain conducted a survey on adverse events related to BMATs reported by the British Society of Haematology members. Of the 58 596 procedures performed over seven years, only 26 adverse events were reported (0.12%).¹⁵ Bleeding was the most common and most severe complication, reported on 14 occasions. Notably, most of the patients who experienced this complication had identifiable risk factors for bleeding, including antiplatelet and anticoagulant drug use. Despite three documented deaths, at least one of which can be directly attributed to the bone marrow procedure, Bain concluded that serious adverse events rarely occurred.¹⁵

Riley et al. reviewed the complications related to BMAT and also identified bleeding as a rare complication, which can usually be easily controlled with local pressure.²² Patients with the highest risk of developing severe bleeding complications are those patients who have underlying bone and bone marrow diseases, for example, osteoporosis, Paget's disease and myeloproliferative neoplasms. Another very uncommon complication of the procedure is that the bone marrow needle may break or the handle may become separated upon insertion of the needle into the bone. In sporadic cases, patients were reported to have experienced unilateral numbness and weakness of the lower extremities after the procedure. These symptoms were, however, not permanent.²² Children can also be fearful or anxious about this invasive procedure. It is therefore important to compare the risks to the benefits of doing bilateral biopsies in every patient and only proceed when the benefits outweigh the risks.¹⁶

In the paediatric age group, neuroblastoma, rhabdomyosarcoma, Ewing sarcoma and retinoblastoma are often cited as the most common solid tumours to metastasise to the marrow.^{10,18} Similarly, the most frequently detected bone marrow involvement was neuroblastoma, followed by Hodgkin lymphoma. Nephroblastoma was the tumour for which staging bone marrows was most commonly performed ($n = 27$). Bone marrow metastases in nephroblastoma are rare and typically diagnosed at disease progression or relapse.²³ Interestingly, bone marrow involvement by nephroblastoma

was the fourth most common metastases in the study cohort (11%, $n = 28$), with all three patients diagnosed with bone marrow metastases at first presentation. Our patient cohort's mean age was 5.81 years, which falls within the age range of 1–12 years internationally reported for paediatric cancers with bone marrow involvement.^{16,18} A slight male predominance was also noticed. A recent South African study analysed epidemiological trends of childhood cancer in the private health sector. The mean age of their study population was 10 years, with the majority of children falling in the age group of 5–9 years, and they also found an increased male to female ratio of 2.2.² Both national and international studies have corroborated the higher incidence of childhood cancer in male patients, whilst previous South African studies have reported the highest age-specific incidence rate in the under 5-year age group.²

Considering that nonhaematological malignancies often display focal bone marrow involvement supports the rationale for bilateral sampling. Small foci of metastases can easily be missed, resulting in false-negative cases with inappropriate staging and subsequent management.¹⁸ A study by Menon et al. to assess the benefit of bilateral BMATs to detect lymphomatous bone marrow involvement found a 26% increased yield in positive marrows when bilateral sampling was done.^{24,25,26} Likewise, Brunning et al. reported an increased detection of 11.00% – 22.00% when a second biopsy was examined.²⁶ However, whether two BMATs from two different sites on the same side may yield similar results as bilateral BMATs remains uncertain.²⁵ Haddy et al. assessed the importance of multiple bone marrow samples for accurate staging of non-Hodgkin lymphomas. They concluded that bilateral samples still had a greater yield for detection compared with ipsilateral samples.²⁷ The present study's finding of a 17.85% discrepancy mirrors the aforementioned international findings. The consensus on universal bilateral BMAT is not shared by all authors. With a discrepancy rate of only 2.50% in patients with intermediate and high grade lymphomas, Ebie and colleagues proposed that bilateral bone marrow biopsy be advised only in certain patients.²⁸ Grimm et al. considered their discrepancy rate of 1.20% low enough to omit bilateral sampling when fluorescence *in situ* hybridisation (FISH), fluorescent-labeled probes targeting specific deoxyribonucleic acid (DNA) sequences, and other cytogenetic studies for staging can be performed.¹⁶ Furthermore, an argument can also be made to only consider bilateral BMAT for malignancies with a high rate of discrepancy such as Hodgkin lymphoma, sarcoma and carcinoma.¹⁰

Compared with the aspirate, the trephine biopsy gives more extensive information about the cellularity and haematopoiesis of the bone marrow.¹¹ The combination of a bone marrow aspirate and trephine biopsy is the most sensitive modality to safely exclude bone marrow metastases.¹⁸ When seen as two separate investigations, they do not enjoy similar sensitivities of detection, also mirrored by the present study's findings. A recent publication from an Indian centre found bone marrow

trephine biopsies to be the most sensitive modality to diagnose bone marrow metastases.²⁹ This superior sensitivity of the trephine biopsy is indeed reported almost unanimously.^{11,30,31} Rani et al. also found trephine imprint cytology superior to bone marrow aspirates.²⁹ Trephine imprint biopsies are not routinely performed at the researchers' centre and are reserved as a second line modality when the bone marrow aspiration is dry or aparticulate. The addition of a touch or imprint biopsy for staging BMATs at the centre might lead to faster diagnosis of metastases, as decalcification and trephine processing takes 24 h – 48 h. The faster turnaround time of the bone marrow aspirate still reserves its role in the assessment of bone marrow disease, including metastases. The two procedures serve to complement one another and should be performed together for the most sensitive and time-efficient results.

A large proportion of the initial study population could not be included in the final data set as a result of suboptimal bone marrow sampling. The interpretable trephine biopsies had an average length of 13.00 mm left and 11.75 mm for right-sided biopsies. This average is markedly smaller than what is advised in the literature. Goyal et al. advised that best results are found between 17.00 mm and 20.00 mm core length, with no added benefit when biopsies were longer than 20.00 mm.¹¹ This is mirrored by Lee et al., who advise a minimum length of 20.00 mm to increase the likelihood that focal disease is included and to allow for expected processing shrinkage.¹⁷ This guidance is for adult biopsies and is probably not translatable to the paediatric patient. As there is no clear and recent recommendation for trephine length in paediatric patients, the researchers' centre follows the suggestion by Bain which states that at least five intertrabecular spaces should be present.³²

Conclusion

Ultimately, the clinical implication of down-staging solid tumours outweighs the small risks and discomfort of a bilateral bone marrow biopsy. As a discrepancy of 17.8% was found in the study population, the current local practice of bilateral bone marrow sampling is supported by the findings.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

All authors contributed to concept and design of the study. A.-C.V.M., L.H., I.C., W.B., J.E., M.S., H.v.d.W., M.v.G. and R.V. collected the data. A.-C.V.M. wrote the first draft of the article and approved its final version. L.H. edited the first draft of the article and approved its final version. All the authors interpreted the results and approved the final version of the manuscript.

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Data availability

Data will be available from the corresponding author, A.-C.v.M., upon reasonable request and subject to ethical clearance if indicated.

Disclaimer

The views expressed in the submitted article are the authors' own and not an official position of the institution.

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