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Research Paper

Pre-treatment serum lactate dehydrogenase and alkaline phosphatase as predictors of metastases in extremity osteosarcoma

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ABSTRACT

Background: The prognosis of patients with metastatic osteosarcoma remains poor. However, the chance of survival can be improved by surgical resection of all metastases. In this study we investigate the value of serum alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) in predicting the presence of metastatic disease at time of diagnosis.
Methods: Sixty-one patients with histologically confirmed conventional osteosarcoma of the extremity were included in the study. Only 19.7% of cases presented without evidence of systemic spread of the disease. Pre-treatment serum ALP and LDH were analysed in patients with and without skeletal or pulmonary metastases.
Results: Serum LDH and ALP levels were not significantly different in patients with or without pulmonary metastases ($p=0.88$ and $p=0.47$, respectively). The serum LDH and ALP levels did however differ significantly in patients with or without skeletal metastases ($p<0.001$ and $p=0.02$, respectively). The optimal breakpoint for serum LDH as a marker of skeletal metastases was 849 IU/L (AUC 0.839; Sensitivity=0.88; Specificity=0.73). LDH >454 IU/L equated to 100% sensitivity for detected bone metastases (positive diagnostic likelihood ratio (DLR)=1.32). With a cut-off of 76 IU/L a sensitivity of 100% was reached for serum ALP predicting the presence of skeletal metastases (positive DLR=1.1). In a multivariate analysis both LDH ≥ 850 IU/L (odds ratio [OR]=9; 95% confidence interval (CI) 1.8–44.3) and ALP ≥ 280 IU/L (OR=10.3; 95% CI 2.1–50.5) were predictive of skeletal metastases. LDH however lost its significance in a multivariate model which included pre-treatment tumour volume.
Conclusion: In cases of osteosarcoma with LDH >850 IU/L and/or ALP >280 IU/L it may be prudent to consider more sensitive staging investigations for detection of skeletal metastases. Further research is required to determine the value and the most sensitive cut-off points of serum ALP and LDH in the prediction of skeletal metastases.

1. Introduction

Osteosarcoma is the most common primary bone cancer in children and adolescents [1]. Surveillance, Epidemiology and End Results (SEER) programme data indicates an annual incidence of 4.4 per million population in patients younger than 25 years of age [2]. The presence of metastases, at time of presentation, has been shown to be an independently significant risk factor in the prognosis of a patient with osteosarcoma [3]. Pakos et al. analysed the prognostic factors in 2 680 osteosarcoma cases in an international multicentre study and found that metastases at diagnosis increased the risk of mortality by a factor of 2.89 [4]. In developed regions approximately 15% of patients with osteosarcoma present with metastatic disease [5]. In under-developed regions higher rates of metastases have been found at time of diagnosis. This is illustrated in previous studies from South Africa, where evidence of systemic spread was found in 47–66% of patients at time of presentation [6,7].

Implementation of contemporary treatment protocols, incorporating adjuvant chemotherapy, have resulted in an improvement in the prognosis of patients diagnosed with osteosarcoma over the past

Abbreviations: ALP, alkaline phosphatase; AUC, area under curve; CI, confidence interval; CT, computed tomography; DLR, diagnostic likelihood ratio; ESMO, European Society of Medical Oncology; FDG-PET, 18F-fluorodeoxy-D-glucose positron emission tomography; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; OR, odds ratio; ROC, Receiver operating characteristic; SD, standard deviation; SEER, Surveilance, Epidemiology and End Results

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decades. The overall 5-year survival rate has improved from less than 20% in the 1960s to approximately 60% [8]. The prognosis, however, remains unsatisfactory in cases with metastases, with an overall 5-year survival rate of less than 30% [8]. Owing to the fact that long-term survival can be improved to over 40%, the European Society of Medical Oncology (ESMO) recommends mandatory excision of all metastatic lesions in patient diagnosed with osteosarcoma [8,9]. It is therefore essential that all patients with metastatic disease are identified timeously. In addition, there is a need for markers which identify patients with a poor prognosis so that more aggresive treatment options can be implemented in an effort to improve their prognosis [9].

In this retrospective review of a cohort of patients with high-grade conventional osteosarcoma of the extremity, we investigate the value of serum alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) in predicting the presence of pulmonary and skeletal metastates at time of diagnosis.

2. Methods

A retrospective review was performed of the records of all patients with osteosarcoma who were referred to our tertiary level orthopaedic oncology unit, over the 5 year period from 2010 to 2014. Ethical approval was obtained from the relevant ethics review board prior commencement of the study (UHERB Ref No. 02–012013). All patients with histologically confirmed high-grade conventional osteosarcoma of an extremity were included in the study. Exclusion criteria included involvement of the axial skeleton, soft tissue osteosarcoma, surface lesions and other osteosarcoma subtypes.

2.1. Pre-treatment evaluation

Systemic staging involved standard laboratory investigations (including serum ALP and LDH), CT-scan of the patient's chest and abdomen, as well as a Technesium bonescan. The patient's charts were subsequently reviewed and data extracted in order to describe the patient demographics, ALP and LDH levels, tumour volume, as well as the presence of pulmonary or skeletal metastases. Pulmonary metastases was defined as both parenchymal and pleural metastatic lesions, while skeletal metastases included both skip lesions and peripheral bony metastases. A bonescan was not performed on four patients due the fact that their general condition did not permit transport to the centre where this was performed. Serum LDH, reported in International Units per Liter (IU/L) was determined using the Dimension® LDI method (Siemens, Munich, Germany). Serum ALP (IU/L) was determined using Dimension® ALPI method (Siemens, Munich, Germany). Tumour volume was calculated based on MRI (magnetic resonance imaging) images using the formula for an ellipsoidal tumour mass, where volume $=(\pi/6) \times$ length $\times$ width $\times$ height, as previously described [10,11]. Histology was obtained by formal incisional biopsy in all cases and the diagnosis was subsequently confirmed at a combined radiology-histology meeting.

2.2. Statistical analysis

Data were processed and analysed using Stata 13.0 SE (StataCorp, 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP) and R statistical package 3.0.3 (R Core Team, 2015. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). Differences in mean age, LDH and ALP by metastases were tested using the standard two-sample t-test. Receiver operating characteristic (ROC) curves were used to determine the optimal breakpoint for the classification of metastatic cancer based on LDH and/or ALP levels. The criterion of the point on the ROC curve closest to the point (0,1), i.e, upper left corner of the unit square, was used to identify the optimal breakpoints [12,13]. The discriminatory power was evaluated by the area under the ROC curve (AUC). An AUC value of 0.5 indicates no discriminative ability while an AUC exceeding 0.8 suggest good to excellent predictive capability. Sensitivity and specificity based on the optimal identified cut-points were also calculated, along with 95% confidence intervals. Logistic regression analysis was then employed to estimate the strength of association between categorical ALP and LDH versus metastases. A p-value of <0.05 was considered statistically significant for all tests.

3. Results

Sixty-seven patients were identified with histologically confirmed osteosarcoma involving an extremity. Six patients were excluded from study. One patient passed away prior to completion of systemic staging investigations and five patients were diagnosed with osteosarcoma variants. Sixty-one patients met the inclusion criteria and their clinical characteristics are listed in table 1. The mean patient age was 21 years (standard deviation [SD] 11.9 years) and there was an equal distribution between male and female patients (50.8 vs 49.2%). The incidence of pulmonary and skeletal metastases did not vary significantly according to the age ($p=0.16$ and $p=0.27$, respectively). The majority of patients (98%) where of African descent. The femur (57%) and tibia (31%) were involved in the majority of cases.

Only 19.7% ($n=12$) of patients had no evidence of metastatic disease at time of presentation. Seventy-two percent ($n=44$) had pulmonary metastases. No other visceral metastases, including liver metastases, were detected on the chest and abdominal CT-scans. Twenty eight percent ($n=16$) of patients who had a bone-scan had evidence of skeletal metastases at the time of presentation. The incidence of pulmonary and skeletal metastases did not vary significantly according to patient age ($p=0.10$ and $p=0.14$, respectively). The serum levels of LDH were not significantly different in patients with or without pulmonary metastases ($p=0.88$ and $p=0.47$, respectively) (Table 2). The serum LDH and ALP levels did however differ significantly in patients with or without skeletal metastases ($p<0.001$ and $p=0.02$, for LDH and ALP, respectively).

Optimal breakpoint analysis of serum LDH as a predictor of pulmonary metastases revealed an area under the receiver operator curve (AUC) of 0.569 (Fig. 1). The optimal breakpoint for serum LDH as a marker of skeletal metastases was 849 IU/L (AUC 0.839; sensitivity=0.88; specificity=0.73) (Fig. 1). Serum LDH of 454 IU/L equated to 100% sensitivity for detected bone metastases with a positive diagnostic likelihood ratio (DLR) of 1.32 (95% CI 1.1–1.6). The optimal breakpoint analysis of ALP and pulmonary metastases revealed poor correlation (AUC 0.516). The optimal breakpoint for serum ALP as a marker of skeletal metastases was 283 IU/L (AUC 0.771; sensitivity=0.81; specificity=0.76) (Fig. 2). A serum ALP level of 76 IU/l was 100% sensitive in predicting the presence of skeletal metastases (positive DLR 1.1; 95% CI 1.0–1.2).

Logistic regression analysis confirmed that serum LDH and ALP were significant prognostic factors for skeletal metastases at time of presentation. Univariate analysis of serum LDH >850 IU/L revealed an odds ratio (OR) of 10.9 (95% CI 2.6–46.1) for the presence of skeletal metastases ($p<0.01$) and for serum ALP >280 IU/L the OR was 12.4 (95% CI 2.9–53.0). In a multivariate analysis of serum ALP and LDH both factors remained predictive of skeletal metastases. However, with the addition of pre-treatment tumour volume LDH lost its significance (Table 3).