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Cancer associated macrophage-like (CAMLs) cells in blood predict progression and survival for all stages of solid tumors

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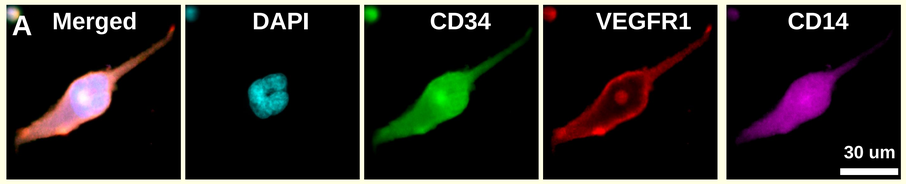
ABSTRACT

We previously demonstrated that cancer associated macrophage-like cells (CAMLs) are cancer specific giant polyploid cells circulating in the blood of patients with solid tumors. Building on our initial discovery, others have shown that these hyperploidy cells are an innate immune response associated with decreased survival. However to date, no studies have been done to elucidate their clinical significance in relation to the various stages of cancer. We established a 4 year prospective study of 315 patients from a variety of solid tumors (breast, prostate, lung, renal cell, pancreas, and esophageal) in both early and late stage disease as they relate to progression free and overall survival (PFS/OS). These data suggest that CAML size has a strong negative correlation with PFS and OS in cancer, irregardless of stage, indicating their possible use as a non-invasive blood based biomarker in solid tumors.



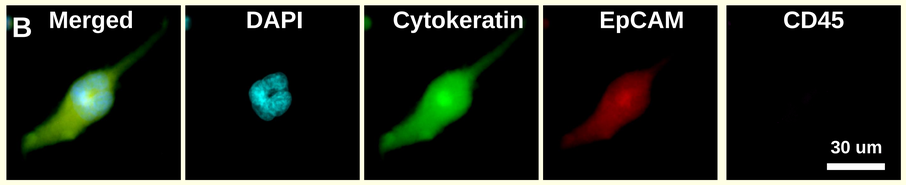


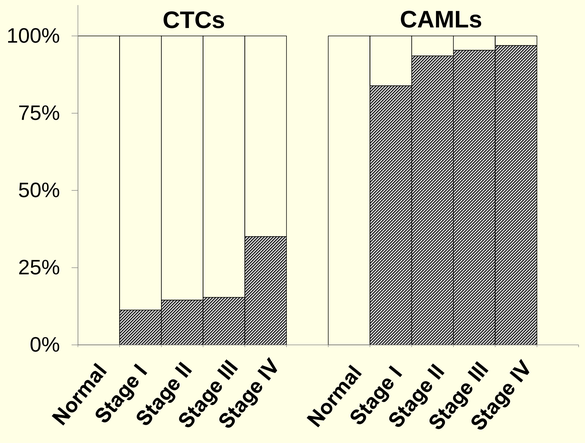
Figure 1. Example of subtyping markers on CAMLs, including myeloid (CD14), epithelial (Cytokeratin/EpCAM), white blood cell (CD45), & stem (CD34), and angiogenic (VEGFR1).

INTRODUCTION

CAMLs are specialized myeloid polyploid cells transiting the circulation of patients in various types of solid malignancies and appearing in all stages of cancer[1-4]. While CAMLs are easy to identify by their large size and polyploid nucleus, they appear to present as stem cell like phenotype with multiple heterogeneous epithelial, myeloid, and endothelial markers.

Size exclusion is the only known technique for isolating large cells from peripheral patient blood irrespective of their surface markers. CellSieve™ microfilters are size exclusion membranes which efficiently isolate CAMLs and circulating tumor cells (CTCs) from whole blood, making it possible to study both cell types in relation to malignant disease[1-4].

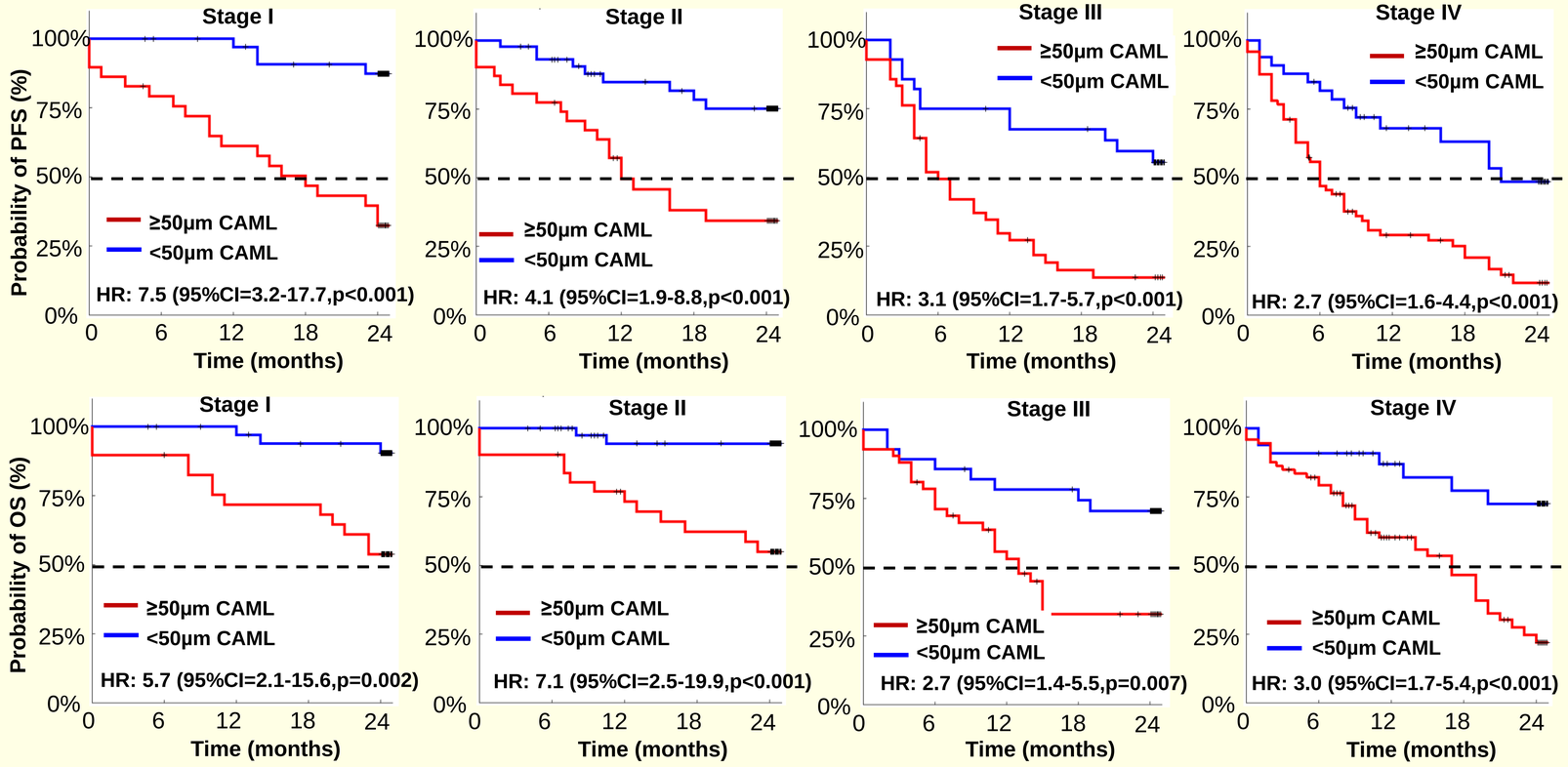
Figure 2. Patients positive for CTCs and CAMLs



MATERIALS & METHODS

A prospective multi-institutional study used anonymized peripheral blood (7.5 mL) from 315 cancer patients [stage I (n=62), stage II (n=73), stage III (n=67) & stage IV (n=103), unknown stage (n=10)] from subjects with breast (n=59), esophageal (n=27), lung (n=59), renal cell carcinoma (n=37), prostate (n=74), pancreas cancers (n=59). CAMLs were isolated by the CellSieve™ microfiltration technique at 5 institutions and stained for cytokeratin 8, 18, & 19, CD14 and CD45. After imaging, a size based threshold ≥50µm was used to separate the patient cohorts, based on previously published assessments.

Figure 3. Analysis of OS and PFS based on size of CAMLs.



RESULTS

- CAMLs were found in 92% (n=289/315) of all cancer patients (n=266/293), but in none of the healthy control samples (Fig. 2)
- CAML sensitivity: Stage I (86%), Stage II (90%), Stage III (97%) & Stage IV (95%), Figure 2.
- Overall, CAMLs of <50µm in size had superior PFS (HR: 3.8; 95% CI 2.8-5.3; (p<0.001) and OS (HR=3.8; 95% CI 2.6-5.7;p<0.001)
- Using a <50µm cut off was prognostic for PFS and OS in each stage.

CONCLUSIONS

- In a large scale prospective study on the clinical utility of CAMLs, CAMLs were common in all stages of invasive solid cancers.
- Smaller CAML size appeared associated with improved survival outcome and longer PFS.
- In a multivariate analysis, CAML size was the most predictive variable for PFS & OS and independent of other clinical variables.
- CAMLs assessment may constitute a new real time predictor of progression. and survival in both early and late stage disease.

References

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