Clinical Application of Circulating Tumor Cells in Melanoma Patients – Overview of Current Available Data

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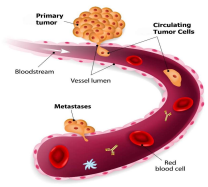
ISPOR Improving healthcare decisions

MT21

INTRODUCTION

Background CTCs

Circulating Tumor Cell (CTC) enumeration is a liquid biopsy testing approach for which the peer-reviewed evidence base has grown rapidly in recent years. The CellSearch® (CS) CTC assay was cleared by the US FDA for breast, colorectal and prostate cancers, and a melanoma specific lab-developed CTC test has been available since 2011. In this research, we aimed to assess the published peer-reviewed evidence of clinical utility for the CellSearch® CTC Test in melanoma.



Background cutaneous melanoma

Cutaneous melanoma incidence is increasing worldwide. The prognosis is variable for patients with stage III melanoma, with 5-year survival rates ranging from 93% to 32% for patients with stage IIIA–IIID, respectively, according to the American Joint Commission on Cancer (AJCC) 8th edition. Identifying patients who are at higher risk of relapse is important since immunotherapies have been shown to decrease the risk of relapse. However, these treatments can have significant side effects, so are therefore used selectively in patients with stage III disease. Consequently, it would be optimal to use such treatments in the higher-risk groups who stand to benefit most, while potentially avoiding their use in lower-risk populations where the possible benefit is smaller. A blood-based biomarker for identification of higher-risk stage III melanoma is a great unmet need in patient treatment.

CTCs in cutaneous melanoma

A large meta-analysis (*n*>5,000) published in 2006 paved the way for Circulating Tumor Cell (CTC) assessment as a biomarker in cutaneous melanoma.[1] The analysis included 53 studies with ~80% of patients having stage III-IV cutaneous melanoma. A statistically significant correlation was found for CTC counts, disease stage and survival. However, standardization in more homogeneous patient populations for CTC assessment is warranted to better determine the utility in melanoma.

CellSearch CTC collection and reporting process

RESULTS

Methods

A comprehensive PubMed literature search and review was conducted investigating the clinical utility of the melanoma-specific CellSearch® CTC assay in cutaneous melanoma. Clinical utility was defined as clinical usefulness in: Cancer staging/ stratifying tumor aggressiveness, and prognosis; treatment selection; and monitoring cancer progression/ treatment response. More than 150 relevant peer-reviewed publications from 2004–2023, including meta-analyses that included CellSearch® CTC, were identified and reviewed. When the search identified preliminary study results in peer-reviewed publications, we also included any follow-on study results published in conference proceedings.

Studies with CS CTCs in melanoma

Eleven prospective studies were identified that provided data on clinical utility of CS CTC. All 11 studies (*n* ranging from 9–243, total *n*=1,000) confirmed the correlation of CTC counts with stage and/or prognosis. The majority of patients in these studies were stage III-IV (91%).

Ref	Stage (*n*)	FU	CTCs	Findings
Steen 2008[2]	Stage II (1) Stage III-IV (8)	2-18 mos	≥1 in 4 (44%)	CTCs were more likely to be found with an increasing stage of disease. Survival correlated with the extent of CTC positivity.
Rao 2011[3]	Stage III (5) Stage IV (39)	10 mos	≥2 in 12 (27%)	CTCs significantly associated with outcome.
Khoja 2013[4]	Stage IV (101)	6 mos	≥1 in 40 (40%)	CTCs significant independent prognostic marker for median OS. CTC changes during treatment provide additional prognostic information.
Roland 2015[5]	Stage IB/II (39) Stage III-IV (46)	not provided	≥1 in 37 (43%)	CTCs associated with histologic subtype, especially in stage I/II disease (superficial spreading 18% vs. acral lentiginous 75%).
Hida 2016[6]	Stage II (3) Stage III-IV (12)	30 mos	≥1 in 3 (20%)	CTCs segregate patients with poorer prognosis.
Hall 2018[7]	Stage IV (93)	17 mos	≥1 in 39 (42%)	CTCs significantly associated (p=0.005) with PFS.
Li 2018[8]	Stage I-II (51) Stage III-IV (49)	26 mos	≥6 in 43 (43%)	CTCs correlated with short OS and considered an independent prognostic factor. CTC alteration before and after treatment associated with PFS and DSS.
Cayrefourcq 2019[9]	Stage IV (44)	7 mos	≥2 in 10 (23%)	CTCs showed a significant association with OS (p=0.006). No other clinical features provided prognostic information.
Lucci 2020[10]	Stage III (243)	17 mos	≥1 in 90 (37%)	Baseline CTCs significantly associated with decreased 6-month RFS and 54-month RFS.
Kaminska 2023[11]	Stage IV (35)	not provided	≥1 in 19 (54%)	CTCs correlated with progression. No other clinical features provided prognostic information.
Lucci 2023[12]	Stage III (325)	48 mos	≥1 in 217 (67%)	CTCs significantly correlated with relapse (p< 0.001). Patients with positive imaging and CTC results revealed 76% (108/143) were CTC+ 9 mos before radiological identification of relapse.

Abbreviations used in table: DSS = disease-specific survival, FU = follow-up, OS = overall survival, PFS = progression-free survival, RFS = relapse-free survival.

Percentage of patients with CTCs

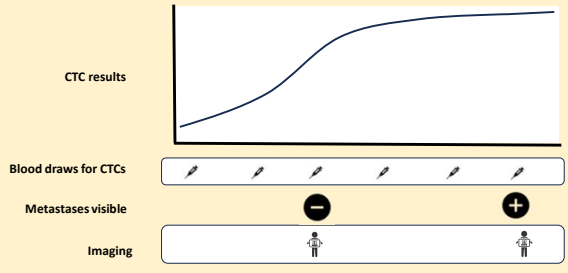
When focusing on the 7 studies that used ≥1 CTC cut-off as CTC-positive: 324 patients were stage III, with 53% having ≥1 CTCs detected; 249 patients were stage IV, with 44% having ≥1 CTCs.

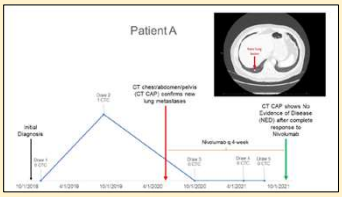
CTCs significantly associated with outcome

In all studies for which survival data was available, CTCs were significantly associated with outcome (decreased recurrence-free, and/or, disease-free and/or overall survival).

CTC detection precedes radiological relapse

In the study by Lucci et al,[12] CTCs were found 9 months prior to radiological identification of the disease: Within a 325-patient cohort, 143 patients (44%) had recurrence, with a median follow-up of 52 months from diagnosis. The cohort (*n*=143) with positive imaging and CTC results revealed 76% of patients (108/143) had CTC+ results before the radiological identification of relapse. The median time between detection of positive CTC and positive imaging was 9 months.





Patient A

Patient with positive CTC prior to positive imaging who achieved CTC clearance

Findings, conclusions and future recommendations

- Current prognostic tools for cutaneous melanoma are insufficient for optimal therapeutic management.
- CTCs are found in over 50% of stage III/IV melanoma patients.
- CTCs are significantly correlated with patient long term outcomes (PFS/DFS and OS).
- CTCs are independent biomarkers of prognosis in multivariate analysis.
- CTCs often (76%) precede radiological relapse.
- CTCs could identify higher-risk patients who may benefit from early intervention (i.e., prior to radiological relapse).
- Serial sampling provides a real-time dynamic picture of disease trajectory (response/progression).
- Neoadjuvant immunotherapy (which has been shown to lead to improved event-free survival over adjuvant[13]) should be conducted to determine if immunotherapy can eradicate CTCs.

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CONCLUSIONS

Peer-reviewed literature confirms the clinical utility of CTC enumeration in cutaneous melanoma patients for prognosis and risk stratification. Because there are few prognostic blood-based biomarkers for melanoma, this pooled data highlights the need for consideration of implementing CTC evaluation into clinical practice as a tool for risk stratification that could help guide treatment decisions. Risk profiling afforded by CTC data could also result in more efficient allocation of healthcare resources and potential cost reduction overall.

ISPOR Europe 2023, 12-15 November
Copenhagen, Denmark
Session Date: November 13, 2023; 15:30 – 18:30
Poster Session 2, Medical Technologies, MT21

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