International study designed to identify melanoma patients with high-risk disease

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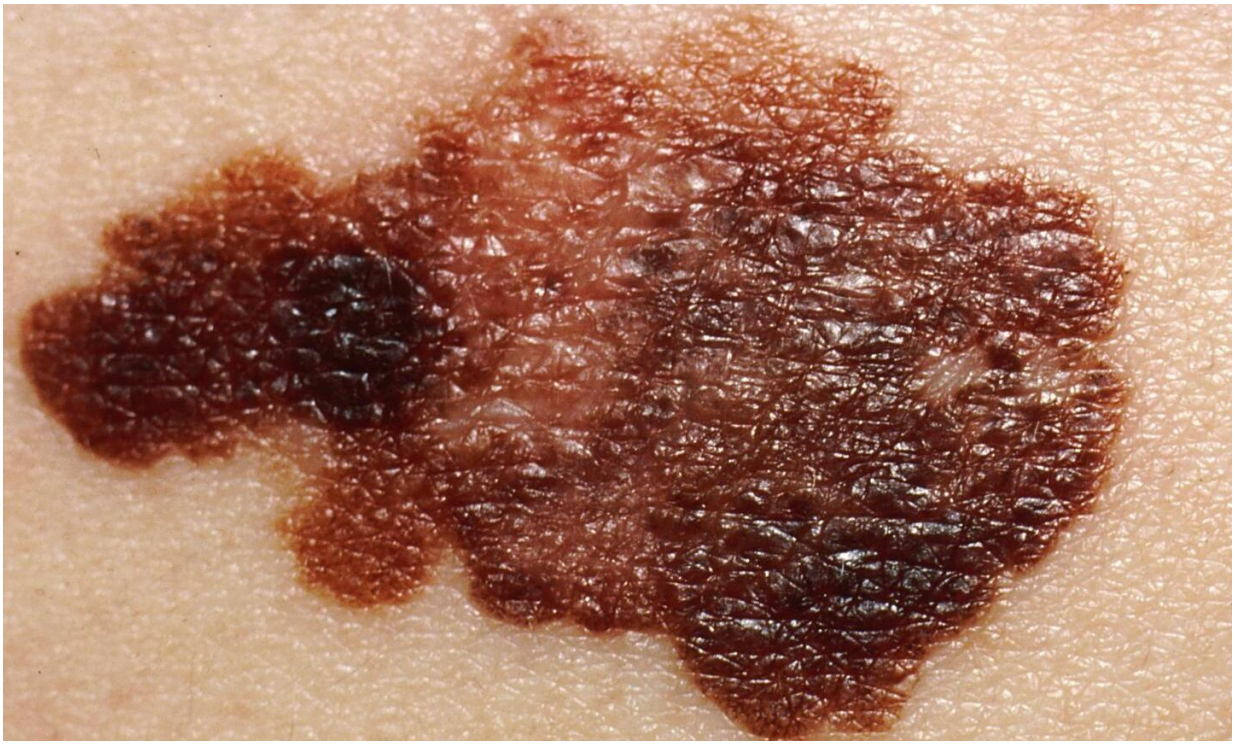

Melanoma. Credit: Wikimedia Commons/National Cancer Institute

The use of additional adjuvant therapy beyond initial treatment has greatly improved outcomes and reduced the risk of disease recurrence for high-risk patients with melanoma. While there is a consensus regarding the use of adjuvant therapy in many high-risk patients, the use of adjuvant therapy in patients with early stage 3A disease is unclear. In

a new study published in the *Journal of Clinical Oncology*, Moffitt Cancer Center physicians, along with a team of international researchers from eight other cancer centers, report on their identification of high-risk patients with stage 3A disease and microscopic lymph node metastases who would benefit from adjuvant therapy.

Physicians choose therapies for patients with melanoma according to the stage and characteristics of the primary tumor, the presence or absence of metastatic disease that has spread to other sites and other patient characteristics. Stage 3 disease represents patients who have metastatic spread to the local/regional lymph nodes and is commonly treated with either neoadjuvant therapy or upfront surgery followed by adjuvant therapy plus or minus further surgery for high-risk patients or the patients who had neoadjuvant therapy.

This stage is heterogeneous and includes stage 3A that has metastases that can be seen only with a microscope, up to stage 3D that involves bulky regional lymph node metastases. Currently, the indications for when to use adjuvant therapy in patients with stage 3 melanoma are more routinely used with higher risk, stage 3B to 3D tumors; however, it is unclear when to recommend adjuvant therapy for patients with stage 3A disease.

A team of researchers from North America, Australia and Europe conducted a study to determine which patients with stage 3A disease were at high risk for poor outcomes and could benefit from adjuvant therapy. They included 3,607 patients in their study who had early-stage primary melanoma and underwent a biopsy of their lymph node closest to their primary tumor, known as the sentinel lymph node. Of these patients, 3,199 were determined to have thinner and earlier stage primary melanoma (stage 1B) tumors that did not have microscopic metastases detected in their sentinel lymph node, while the remaining 408 patients were classified as stage 3A due to the presence of sentinel

lymph node microscopic metastases.

The researchers analyzed the survival patterns of the patients with stage 3A disease. They determined that the number of lymph nodes affected with metastases did not have an impact on survival outcomes, but the size of the microscopic metastases did. Patients who had metastases less than 0.3 millimeters had a significantly better survival than patients who had metastases greater than or equal to 0.3 millimeters.

The five-year disease-specific survival rate was 94.1% for patients who had metastases less than 0.3 millimeters and 80.3% for patients with metastases greater than or equal to 0.3 millimeters. Similar differences in survival were observed between the groups for overall disease-free survival and distant metastasis-free survival. Furthermore, the researchers determined that the low-risk stage 3A group of patients had similar survival outcomes to patients with stage 1A disease.

These combined observations demonstrate that patients who have stage 3A disease with metastases of greater than or equal to 0.3 millimeters are at a higher risk of disease progression and worse outcomes, while patients with stage 3A disease and metastases of less than 0.3 millimeters have better outcomes similar to those seen in patients with stage 1A disease. As a result, these patient subgroups may benefit from different treatment strategies.

"The data suggest that early stage 3A patients with micrometastases of maximum tumor dimension less than 0.3 millimeters could be considered for observation and might not benefit from adjuvant therapy, whereas patients with micrometastases of greater than or equal to a 0.3 millimeter maximum tumor dimension might derive the most benefit from adjuvant therapy when looking at subgroups of stage 3A patients," said Jonathan Zager, M.D., principal investigator of this study and senior member of Moffitt's Department of Cutaneous Oncology.

Zager added these recommendations differ somewhat from current treatment guidelines and could change patient management guidelines in the future with more data from larger retrospective reviews with more centers or from clinical trials investigating this observation. The researchers hope their observations will lead to better clarity regarding the need for adjuvant therapy in populations of stage 3A patients, improve patient outcomes among high-risk patients and reduce the need for unnecessary treatments among low-risk patients.

More information: Marc D. Moncrieff et al, Clinical Outcomes and Risk Stratification of Early-Stage Melanoma Micrometastases From an International Multicenter Study: Implications for the Management of American Joint Committee on Cancer IIIA Disease, *Journal of Clinical Oncology* (2022). DOI: 10.1200/JCO.21.02488

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