Metastatic melanomas of unknown primary show better prognosis than those of known primary: A systematic review and meta-analysis of observational studies

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Background: Melanoma of unknown primary (MUP) is a condition of metastatic melanoma without a primary lesion.

Objective: We sought to identify the prognosis of MUP compared with melanoma of known primary (MKP).

Methods: We searched for observational studies containing at least 10 patients with MUP from MEDLINE and EMBASE from inception to December 22, 2012. The outcomes of interest were overall and disease-free survival; meta-analyses of hazard ratio stratified by stage using a random effects model were performed. In addition, second systematic review identified risk factors influencing the survival of patients with MUP.

Results: Eighteen studies including 2084 patients with MUP and 5894 with MKP were included. MUP had a better overall survival compared with MKP in stage III (15 studies; hazard ratio 0.83, 95% confidence interval 0.73-0.96, P = .010) and stage IV (6 studies; hazard ratio 0.85, 95% confidence interval 0.75-0.96, P = .008). Secondly, 22 studies including 3312 patients with MUP were reviewed, and increased stage and old age were the risk factors in patients with MUP.

Limitations: Diverse observational studies were reviewed, and selection and reporting biases are possible.

Conclusions: The current meta-analyses suggest better survival outcomes in patients with MUP than those in patients with MKP with the same corresponding tumor stage. (J Am Acad Dermatol 2015;72:59-70.)

Key words: malignant melanoma; melanoma; melanoma, unknown primary; meta-analysis; prognosis; systematic review.

Melanoma of unknown primary (MUP) is defined as the presence of histologically confirmed melanoma in a lymph node, visceral organ, or distant skin/subcutaneous tissues without a history or evidence of a cutaneous, mucosal, or ocular primary lesion.[1] After this entity of MUP was proposed by Das Gupta et al[2] in 1963, there have been a number of reports concerning the phenomenon.

Recently, the comprehensive review performed by Kamposioras et al[3] delineated the clinical features

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of MUP. MUP accounts for 3.2% of all melanoma cases, and consistent male predominance was observed. Approximately 60% of MUP cases involve lymph nodes, and the remaining cases involve the distant skins/subcutaneous tissue, lung, brain, and gastrointestinal tract.

The prognostic significance of MUP was not specified in the American Joint Committee on Cancer 2009 melanoma staging system, and it was stated to be classified as stage III or IV instead.[4] When patients with MUP have an initial presentation of metastases in the lymph nodes or the skin/subcutaneous tissues, stage III disease should be presumed, whereas all other presentations of MUP should be categorized as stage IV.

CAPSULE SUMMARY

- Melanoma of unknown primary accounts for 3.2% of all melanoma cases.
- Melanoma of unknown primary could represent a specific subgroup with prognostic considerations distinct from melanoma of known primary.

There are conflicting results concerning the survival consequence of MUP. In 1952, Pack et al[5] originally described 29 patients with MUP with a poor 5-year cure rate of 5.9% in a series of 1190 cases of melanoma. In 1963, Das Gupta et al[2] revealed that 10 (41.7%) of the 24 patients with nodal MUP lived 5 years or more, and 13 with distant MUP had an average survival of 3 months. While Milton et al[6] demonstrated that the prognosis for patients with MUP was slightly worse than that in patients with cutaneous melanoma with lymphatic involvement, Balch et al[7] reported that MUP was associated with slightly better survival. Many studies have been reported in succession; nevertheless, no obvious conclusion has been achieved.

The knowledge of prognosis for patients with MUP could be helpful to understand this peculiar condition, so the prognostic significance needs to be clarified. We herein have reviewed the literature thoroughly and performed meta-analyses of all relevant reports to evaluate the prognosis of MUP compared with melanoma of known primary (MKP). In addition, we sought to review all available evidence of risk factors associated with survival of patients with MUP.

METHODS

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[8] Firstly, a quantitative synthesis of all relevant studies that compared the prognosis of MUP with that of MKP was planned. The primary outcome of interest was overall survival (OS), which was defined as time from melanoma diagnosis to death or last follow-up. Secondary outcome was disease-free survival (DFS), defined as time from melanoma diagnosis to local or systemic relapse or last follow-up after appropriate curative surgery, especially in stage III disease. In the second review, risk factors influencing the survival of patients with MUP were examined.

The first systematic review and meta-analysis for the prognosis of MUP compared with that of MKP

Search strategy. A comprehensive database search was performed independently by 3 reviewers (J. M. B., Y. Y. C., and D. S. K.). Computerized database searches of MEDLINE (accessed by PubMed) and EMBASE were supplemented by hand searches of references from relevant articles. We also manually scanned abstracts of the last 5 years from major cancer meetings, including the Annual Meeting of the American Society of Clinical Oncology, Joint Congress of European Cancer Organization—European Society for Medical Oncology Congress, Annual Cancer Symposium of the Society of Surgical Oncology, and International Melanoma Congress of the Society for Melanoma Research.

All studies containing at least 10 patients with MUP from inception to December 22, 2012, were selected. The following search terms were used for MUP: "melanoma," "unknown primary," "occult," and "indolent." All hospital-based and population-based studies were included, and there were no restrictions on language, publication date, or publication status.

Selection of the articles. We set minimum criteria on the basis of which studies were deemed eligible for this meta-analysis. The criteria were as follows: (1) presence of a case group of patients with MUP and a comparator group of patients with MKP of the same stage, (2) independence from other published studies to prevent giving double weight, (3) comparing outcomes in terms of OS and/or DFS, and (4) presence of sufficient information to estimate the hazard ratio (HR) and 95% confidence interval (CI). The eligible studies had to provide either HR or crude data, and corresponding standard errors (SE), variance, CIs, or *P* value of the significance of the estimates. Otherwise, the studies should have included the survival curves with the number in each group to estimate the HR.[9] To avoid a possible double counting of patients included in more than 1 report by the same authors or working groups, study periods were evaluated.