





**Fig. 1 Semantic map showing the best linking among selected variables in the study population.** The numbers on connecting lines indicate normalized correlations (between 0 and 1). The line thickness corresponds to the strength of association (thin line <0.6; medium line 0.6–0.79; thick line  $\geq 0.8$ ). DFS: disease-free survival; hi: high; lo: low; LMM: lentigo malignant melanoma; MM: malignant melanoma; OS: overall survival; SLN: sentinel lymph node; SSM: superficial spreading melanoma; thick: thickness; VEGF: vascular endothelial growth factor.

shown that VEGF-C could be involved in lymphatic hyperplasia and metastatic lymph nodes spread by activating VEGFR-2 and VEGFR-3 (1, 8–10). Increasing evidence shows a specific role of VEGF-C and VEGF-R3 in tumour lymphangiogenesis and lymphatic metastasis in multiple malignancies (1, 8–10). Recent studies have revealed a positive association between VEGF-C expression and both progression stage and lymph node metastasis (1, 8, 11). In our study high values of VEGF-C were directly associated with thick MM, which was connected to many other prognostic factors. In fact, the VEGF-C/VEGFR-3 axis plays an important role in inducing enlargement of peritumoural lymphatic vessels and increasing lymph flow, which promotes lymphatic invasion and lymph node metastasis (1, 8, 11). Furthermore, VEGF-C participates in tumour cell chemotaxis, which is an independent, yet interlinked and important step in the process of cancer metastasis (1, 8, 9, 11). In similar studies VEGF-C expression was found significantly increased in metastatic MM compared to non-metastatic MM (1, 12–14).

One possible limitation of this study was a technical limit during the preparation of TMAs as described elsewhere (1). Furthermore, the analysis was mainly exploratory and specific hypotheses emerging from the map should be better tested in further *ad hoc* studies. Another limitation was the relatively low number of patients included in the analysis, which does not allow generalization of results.

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