Karolinska Institutet

Institutionen för Onkologi och Patologi

Karolinska Universitetssjukhuset Solna

Clinical and epidemiological studies on prognostic and predictive factors in cutaneous melanoma

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Welandersalen B2:00, Karolinska Universitetssjukhuset Solna

Fredagen den 18 oktober, 2013, kl 09:00

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Stockholm, 2013

ABSTRACT

Background Cutaneous malignant melanoma (CMM) is one of the most rapidly increasing cancers in Sweden, as in many other western countries. In clinical practice, the histopathological evaluation has remained the basis for staging the CMMs and, thus, providing important information on prognosis and on therapeutic recommendations. Interobserver variation regarding the histopathological evaluation is known to exist. However, few studies have investigated how clinical, biological and social mechanisms interact and influence the prognosis in CMM. For patients with advanced disease progress of the treatment options has been achieved for tumours carrying $BRAF^{V600}$ mutations by the development of specific small-molecule BRAF inhibitors. The development of these targeted therapies thus mandates determination of *BRAF* mutation status. This thesis aims to describe the interobserver variability in evaluating histopathological prognostic factors, to assess the association between education as well as cohabitation status and prognosis in patients with a primary CMM, and also to analyze the patterns of $BRAF^{V600E}$ protein expression in primary and metastatic CMMs.

Methods In Paper I, a total of 234 cases of invasive CMMs from the Stockholm–Gotland Healthcare Region in Sweden were included in the study**.** In Papers II and III, 27,235 patients diagnosed with a primary invasive CMM between 1990 and 2007 were identified from the Swedish Melanoma Register. Data were linked to nationwide, population based, health and census registers with a follow-up through 2010. In Paper IV, a total of 200 CMMs were stained by immunohistochemistry (IHC) using a $BRAF^{V600E}$ specific monoclonal antibody (VE1).

Results Overall, interobserver variability between a general pathologist and an expert review was 79% in Paper I. The best agreement was found for tumour thickness, but 15.5% of the tumours were re-classified after review in a sub-set of thin (≤ 1 mm) CMMs 15.5% were re-classified.
In Paper II, we found significantly elevated odds ratios (OR) of higher disease stage at diagnosis among lower education groups after adjustments for other prognostic factors (OR stage II vs. I = 1.6; 95% confidence interval (CI) = 1.5-1.7. OR stage III–IV vs. I = 2.3; 95% CI = 1.8-2.9). The risk of dying of CMM, was significantly increased in patients with low education after the final adjustments for all clinical and histopathological prognostic factors (hazard ratio (HR) low vs. high = 1.13; 95% CI=1.01-1.27; p = 0.04).
In Paper III, after adjustments for established prognosticators and education, the ORs of higher clinical stage at diagnosis were significantly increased among men living alone vs. men living with a partner (OR stage II vs. stage I = 1.42; 95% CI = 1.29-1.57. OR stage III-IV vs. stage I = 1.43; 95% CI = 1.14-1.79). The ORs for higher stage among women living alone were also increased (OR stage II vs. stage I = 1.15; 95% CI = 1.04-1.28. OR stage III-IV vs. stage I = 1.04; 95% CI = 0.79-1.37). After adjustments for all potential and established prognostic factors, HR for CMM death for men living alone vs. living with a partner was 1.33 (95% CI = 1.19-1.49; p<0.0001), indicating a residual adverse effect on survival not accounted for by these parameters.
In Paper IV, the VE1 IHC staining intensity varied between primary CMMs and matched metastases in 47% of the cases, as well as between separate metastases. We found a sensitivity of the VE1 antibody of 97% and a specificity of 80% for detection of $BRAF^{V600E}$ mutations. A comparable sensitivity was obtained for primary CMMs and metastases when analyzed separately. However, the specificity was lower among primary CMMs (71%) compared to metastases (93%).

Conclusions Our results imply that the recommendation of surgical excision margins and/or sentinel node biopsy changed in subgroups of thin CMMs after a CMM-expert pathology review. Moreover, the results emphasize the need for improved early detection strategies directed towards specific patient groups to improve the CMM-specific survival. IHC using the VE1 antibody should be used in combination with genomic testing in primary CMMs specifically in cases with weak/moderate staining to accurately predict $BRAF^{V600E}$ status, whereas in metastases with strong VE1 staining no further mutation testing seems to be required.

ISBN 978-91-7549-252-0