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PREDICTION OF METASTATIC DISEASE BY COMPUTER AIDED INTERPRETATION OF TUMOUR MARKERS IN PATIENTS WITH MALIGNANT MELANOMA: A FEASIBILITY STUDY

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Abstract

Malignant melanoma of the skin potentially leads to widespread metastasis. Prediction of metastasis could be improved by using tumour markers. A reduction of additional diagnostic workup potentially increases well-being of the patients and may reduce costs. The challenge is to design a knowledge based system for the prediction of metastasis, by combining prognostic values and the results of the tumour markers, using artificial neural network (ANN) and logistic regression. The areas under the curve of the ROC plots for detecting metastasis range from 0.676 to 0.769.

Keywords – melanoma, logistic regression, neural network, prediction, tumour marker

1. Background, Motivation

A variety of papers report a worldwide increasing occurrence of malignant melanoma (MM) [8, 10]. Early diagnosed melanomas have a substantially better prognosis than metastasizing MM. Additionally, Bosserhoff et al [2] suggest that MM have a tendency to metastasize in early stages.

1. 1. Malignant melanoma

Currently, clinical and radiological investigations are common to establish gold standards to diagnose metastasis of MM. Early detection of the disease's progression is of utmost importance. Therefore, a clinical test detecting metastasis at a preclinical stage would be of great value [6]. Hein et al [3] assume that early diagnosis of the involvement of lymph nodes or organs is exceedingly important. But early detection of metastases in blood samples was not successful until today. One must consider that the mean appearance of metastases at the sentinel lymph nodes and their echelon is 24 months and 33 months for distant metastases.

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1. 2. Follow-up examinations

Patients suffering from MM require a number of follow-up examinations. The indication and lag of follow-up examinations depend on the tumour thickness according to Breslow and the time-interval to the date of diagnosis. As suggested by Hengge et al [6], follow-up contains of clinical examinations of the skin, including dermoscopy of conspicuous nevus cell nevi (NZN) and the palpation of three regions (at the primary tumour, the echelon of lymph nodes and the abdomen). Follow-up examinations should also imply clinical imaging procedures and serologic blood testing. Chest X-ray, sonography of the echelon of lymph nodes, sonography of the abdomen and positron emission tomography (PET) once a year, are the common imaging procedures for patients with MM. Furthermore, a serological blood test is performed, interpretating soluble S100 molecules and/or MIA (facultative). Depending upon the stage of MM, a single examination or a combination of examinations is applied.

1. 3. Prognostic parameters

There are prognostic parameters for the identification of patients at high risk for metastatic disease. Also, statements about disease progression can be made. The most important prognostic factors at melanoma stage I and II are, in order of importance, tumour thickness, ulceration, age, localization, stage of invasion and gender [11]. Hengge et al [6] and Jäckel et al [7] obtained the same results in their research concerning prognostic parameters.

Balch et al [1] recently published the revised American Joint Committee on Cancer (AJCC) Melanoma Staging and Classification. It derives from TNM (an abbreviation of “Tumour thickness”, “No. of metastatic nodes” and “No. of distant metastasis”) and structures the clinical and pathological staging for MM, which is divided into tumour stage I – IV, incl. subgroups.

1. 4. Tumour markers

Ugurel [12] describes tumour markers as molecules, which are associated with the quality and quantity of expression of a malignant disease. Normally, tumour cells are responsible for the expression of tumour markers. In some cases, other cell types may also be responsible. Ideally, tumour cells only secrete tumour markers after the malignant transformation.

Furthermore, it is important to know that a single value is not expressive for interpretation. Only the time progression of the tumour markers is interpretable [5]. S100β, MIA and LDH are the most important tumour markers for the wide clinical usage [12].

2. Material & Methods

Our primary goal is to design a knowledge based system for the prediction of metastatic events in patients with MM. The knowledge based system permits a combination of prognostic evidence, given by historical data (Breslow level, Ulceration and Sentinel node status) and tumour markers. Therefore it provides a quantitative analysis of certainty for the final decision. The data set for quantitative analysis includes three tumour markers (S100β, MIA, LDH) as well as the presence or absence of metastasis. The final system aims to produce results that are compatible with gold-standard diagnosis.

To obtain reliable results for the final decision, the knowledge based system is split up in two parts:

- The interpretation of the *pre-test probability,* according to TNM using Arden Syntax [4] and
- The quantitative analysis of the *tumour markers,* realized by logistic regression and artificial neural networks (ANN).

A further goal is the project implementation as a clinical decision support system in a hospital information system (HIS).

2. 1. Technical methods

Matlab R2009b and SPSS Statistics 17 were used for various calculations, particularly for ANNs, logistic regression and receiver operating characteristic curves (ROC-curves). In Matlab it was possible to construct an individual ANN by using scaled conjugate gradient optimization. Standard settings for all ANN calculations were 70% training, 15% validation and 15% testing, with 20 hidden neurons in each case.

The study includes calculations in variant types, whereby every calculation involves the computation of a ROC-curve. Initially, logistic regression was applied in each case to every single tumour marker (S100β, MIA, LDH). Furthermore, the same raw data was applied to an ANN in different combinations (all tumour markers incl. missing values, all tumour markers excl. missing values, every tumour marker by itself).

Pre-test probability according to TNM was implemented in Arden Syntax. The data sample for the testing of the pre-test probability was artificially generated.

3. Results

Within the scope of a retrospective study tumour markers of 176 patients with overall 493 single visit records were collected at our Department. The timeframe of the data collection involved patients from January 2001 to June 2008 and contained a collective of patients with MM stage I to IV. 85 of these 493 single visit records showed a presence of metastatic events, in contrast to 408 without metastatic events. In some cases it was not possible to acquire all serological parameters. Hence, there are some visit records with missing values.

The raw data used for all calculations contains S100β, with a median of 0.06 µg/l (mean value of 0.15 µg/l, range of 0.002 µg/l - 7.81 µg/l). In contrast, MIA has a median about 7.175 ng/ml (mean value of 14.96 ng/ml, range of 90 ng/ml – 1023 ng/ml). The third tumour marker, LDH, has a median of 175 U/l (mean value of 204.56 U/l, range of 90 U/l – 2842 U/l).

After normalization of the raw data, a 3D plot was generated to identify the positions of the combined tumour markers separated in two groups. Group 1 contains patients without metastatic events (X) and group 2 includes patients with metastatic events (circles). One can observe that the data sets with the absence of metastasis are near zero and the data sets with presence of metastasis are mostly spread around widely.

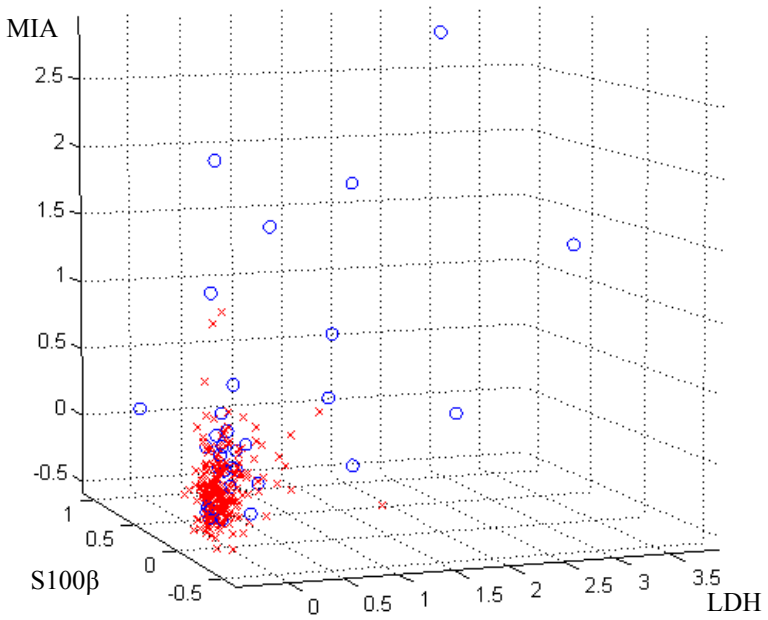

Figure 1: 3D Plot of the tumour markers (S100β, MIA, LDH)

3. 1. Logistic regression

Table 1: Results from ROC analysis (Logistic regression)

	Data sets	Metastasis pos./neg.	AUC	95% CI	max. sensitivity / specificity
3.1. 1. S100β	469	70 / 399	0.676	0.601 – 0.750	61.40% / 58.40%
3.1. 2. MIA	489	83 / 406	0.720	0.651 – 0.789	63.90% / 66.01%
3.1. 3. LDH	280	42 / 238	0.724	0.630 – 0.818	69.00% / 71.00%

3. 2. Artificial neural network

Table 2: Results from ROC analysis (ANN)

	Data sets	Metastasis pos./neg.	AUC	95% CI	max. sensitivity / specificity
S100β, MIA & LDH incl. missing values	493	85 / 408	0.769	0.709 - 0.830	68.20% / 68.60%
S100β, MIA & LDH excl. missing values	270	37 / 233	0.765	0.671 – 0.858	73.00% / 68.20%
3.2. 1. S100β	469	70 / 399	0.676	0.601 – 0.750	54.30% / 66.90%
3.2. 2. MIA	489	83 / 406	0.720	0.651 – 0.790	63.90% / 66.01%
3.2. 3. LDH	280	42 / 238	0.724	0.630 – 0.818	69.00% / 71.01%

3. 3. Pre-test probability

The TNM classification, written in Arden Syntax, will be presented by this short code snippet, which classifies the tumour thickness in combination with ulceration and is representative for the further source code. This part should illustrate the usage of Arden Syntax.

```
[...]
if     thickness is in (null,0)  AND ulceration is in (null,false)  then let T be "Tis";
elseif thickness <=1             AND ulceration is in (null,false)  then T := "T1a";
elseif thickness <=1             AND ulceration = true              then T := "T1b";
elseif thickness <=2             AND ulceration is in (null,false)  then T := "T2a";
elseif thickness <=2             AND ulceration = true              then T := "T2b";
elseif thickness <=4             AND ulceration is in (null,false)  then T := "T3a";
elseif thickness <=4             AND ulceration = true              then T := "T3b";
elseif thickness >4              AND ulceration is in (null,false)  then T := "T4a";
elseif thickness >4              AND ulceration = true              then T := "T4b";
endif;
[...]
```

3. 4. Technical system integration

As the knowledge based system described in this paper depends on reliable input data for evaluating prognostic evidence, integration with a clinical host system seemed promising. For the pilot project, the HIS currently being set up at Vienna General Hospital has been chosen as host system because it can deliver the necessary input data (laboratory data received from a dedicated laboratory information system, clinical data stored in native documents on the HIS).

Furthermore, to achieve good workflow integration for the clinical physician, it was decided also to use the HIS as user interface for the expert system. This means that its results are displayed in documents, views and work lists of the HIS [9].

Compared with a standalone knowledge based system, the chosen integrated solution shows benefits regarding data quality and might also lead to better user acceptance – this needs to be verified in further research.

4. Discussion

The univariate analysis using logistic regression and ANN resulted in an area under the curve (AUC) ranging between 0.676 and 0.724. However, at multivariate analysis applying an ANN showed slightly better results ranging between 0.765 and 0.769. Generally, ANNs achieve results comparable to logistic regression. In univariate analysis, LDH showed a slightly better performance than MIA and a recognizable better performance than S100β. Especially, the combination of the tumour markers improved the results as contrasted with the univariate analysis. Additionally, it has to be noted that the multivariate analysis resulted a slightly larger AUC if missing values were included as compared with multivariate analysis without missing values.

The AUC's are good but not impressive; consequently, there is room for improving the efficacy of the data modelling tools. The machine learning system is not intended for a standalone system but rather in the next step the results will be joined with the pre-test probability of metastatic events.

Referring to the current results, it is possible to apply ANNs or logistic regression for the prediction of metastases in patients with MM. In addition, prognostic values are used to reduce false positives and false negatives by joining the results of the tumour markers and the results of the prognostic values.

The main benefit of this project could be an increased wellbeing of the patients, due to a reduction of stress caused by additional examinations, such as chest X-ray, PET and other clinical imaging tools, when the knowledge based system computes a low risk for metastatic events.

To confirm our hypothesis, there is need of further prospective, controlled studies. A first pilot study is scheduled for midyear 2010. The current status concerning Medical Devices Act and the legal aspects is currently not applicable within this approach. However, before deploying the system into real life these questions need to be answered appropriately.

5. References

[1] BALCH et al. Final Version of 2009 AJCC Melanoma Staging and Classification. Journal of Clinical Oncology 2009

[2] BALCH et al. Prognostic Factors Analysis of 17,600 Melanoma Patients: Validation of the American Joint Committee on Cancer Melanoma Staging System. Journal of Clinical Oncology, 2001

[3] BOSSERHOFF, A.-K. et al. MIA ("melanoma inhibitory activity"). Hautarzt (49), 1998

[4] HEALTH LEVEL 7. The Arden Syntax for Medical Logic Systems, Version 2.7. Ann Arbor, MI: Health Level Seven, Inc., 2008

[5] HEIN, R. et al. Tumormarker beim malignen Melanom. Deutsches Ärzteblatt (14), 2006

[6] HENGGE, U. R., & DUMMER, R., Malignes Melanom. Köln: Deutscher Ärzte-Verlag, 2006

[7] JÄCKEL, A. et al. S100Beta-Protein im Serum als Tumormarker beim malignen Melanom. Hautarzt (50), 1999

[8] LEISCHNER, H. Basics Onkologie. Elsevier: Urban&FischerVerlag, 2007

[9] MEHL, T. et al. Integration of clinical decision support into a hospital information systems to predict metastatic events in patients with melanoma. Vienna, submitted to eHealth 2010

[10] MEVES, A. Intensivkurs Dermatologie. Urban&FischerVerlag, 2006

[11] REINIGER, I. “Melanoma inhibitory activity” (MIA): a promising serological tumour marker in metastatic uveal melanoma. Graefe's Archive for Clinical and Experimental Ophthalmology (243), 2005

[12] UGUREL S. Serummarker des malignen Melanoms. Der Hautarzt., 2005

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