Prediction of Metastatic Events in Patients With Cutaneous Melanoma

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***Abstract*— Cutaneous melanoma, one of the most aggressive malignant tumors, potentially leads to widespread metastasis. The prediction of early metastatic events by using clinical information and data from specific tumor markers could substantially augment the quality of diagnostic and treatment decisions. To predict potential metastatic events during follow-up in patients with cutaneous melanoma, a knowledge-based system will be used during clinical routine by interpreting data from clinical history of the patient in combination with data from tumor markers. Specifically, data will be sent to an expert system including a rule engine which offers the physician a risk assessment and decision support. The interpretation of the tumor markers (n=493) resulted in a prediction sensitivity and specificity of 77.80% and 69.55% while using the multivariate combination of MIA, S100β and LDH. Additionally, the risk of metastasis was calculated based on fitted survival functions and was integrated into our system. Currently this knowledge-based system will calculate the individual likelihood for metastatic events based on the risk of the primary tumor, the duration of observation since the primary event and the recent values of tumor markers. The system aims to produce results that are compatible with medical expert's opinion.**

Keywords- cutaneous melanoma; TNM classification; artificial intelligence; decision support; knowledge-based system

I. BACKGROUND & MOTIVATION

There is substantial evidence that cases of cutaneous melanoma (CM) are still increasing worldwide. The increase of the incidence amounts to about 4-8% [1, 2]. According to Meves, a duplication of the incidence until 2020 is conceivable [3]. Today's incidence in Germany and Austria ranges between 12-15 / 100,000 inhabitants [2].

Clinically, primary CM is usually diagnosed by the naked eye and is supported by the use of diagnostic algorithms (ABCD algorithm) [4-7]. Usually, CM is initially treated by surgical excision. After excision, tumors are classified according to the American Joint Committee on Cancer (AJCC) published TNM classification for CM, based on studies from Balch et al. [8, 9]. The AJCC classification [10] allows to stratify CM into different categories, predicting the risk for widespread metastatic disease. Numerous studies showed that metastasizing CM have a distinctly poorer prognosis than non-metastasizing CM [9, 11]. Consequently, the diagnosis of CM at an early stage and additionally the prediction of metastasis as early as possible stage of development are essential.

Patients suffering from CM require a number of follow-up examinations over a long period of time. These examinations include several imaging modalities like X-Ray, computed tomography (CT), magnetic resonance tomography (MRT) or positron emission tomography (PET) [12]. Additionally, blood tests are commonly used during follow-up, examining the serum concentration of the tumor markers such as S100β protein, melanoma inhibitory activity (MIA) and lactatdehydrogenase (LDH) [13, 14].

A. Relevance of tumor markers

Generally, tumor markers are circulating molecules, which will be obtained from blood or other body fluids. According to Bosserhoff et al. [1], the presence of metastatic disease correlates with the concentration of tumor markers. Hence, it should be probably possible to predict the metastasis and the progression of the disease in CM patients [15-17].

The already routinely established tumor markers for CM are S100β, MIA and LDH. These parameters were chosen

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for our predictive model [13, 15, 18-21]. In a retrospective study, performed by Schlager et al [15], tumor markers of patients with CM were already collected. The data included 176 patients with 493 single examinations. Every patient received state of the art imaging modalities like CT, MRT or PET. In 85 cases metastases were found. Univariate examinations clearly demonstrated the predictive power of these tumor markers clearly. The area under the curve (AUC) calculated by receiver-operator-characteristic-analysis (ROC) was 0.676 for S100β, 0.721 for MIA and 0.725 for LDH, respectively.

B. *Pretest probability for a metastatic event*

In this context, the term *pretest probability* describes the statistical probability of developing metastases before tumor marker levels are taken into account. According to Bayes' rule [22, 23], the posterior (posttest) probability is the arithmetic product of the pretest probability and the likelihood ratio. Assigning a numerical value to the pretest probability amounts to quantifying the clinical expertise of a physician who is able to build an internal, "holistic" impression of a patient that forms the baseline of his or her assessment of that patient. Results of medical tests are then interpreted against this baseline, in the sense that the same test result will be interpreted differently, depending on this baseline. Bayesian statistics offers a means to formalize and numerically represent this procedure.

II. MATERIALS & METHODS

The assessment of the patient's pretest probability is based on predictive characteristics from the literature. These include the tumor thickness according to Breslow [24], mitotic rate and ulceration which can be used to make conclusions about the behavior of the tumor.

The final version of the seventh edition of the AJCC melanoma staging and classification [9] includes the revised TNM classification for CM. This classification is particularly well suited for rule-based programming languages because it consists of IF-THEN rules. Consequently, to a certain extent, it is possible to parameterize the pretest probability and therefore it can be used for the generation of automated decisions. The tumor classification of CMs using the categories of the TNM classification allows prognostic statements of the disease and often determines further therapies.

A. *A knowledge-based system*

The knowledge base developed in this project calculates the present risk for metastasis in CM patients. Calculations are based on the pretest probability for metastasis in combination with the recent results from the tumor markers stated above. Artificial intelligence and rule based systems provide decision support. More precisely, the knowledge base will be a combination of multiple risk assessments:

- Rule-based interpretation of the TNM classification according AJCC
- Interpretation of the tumor markers S100β, melanoma inhibitory activity (MIA) and lactatdehydrogenase (LDH) by a multivariate artificial neural network analysis
- Risk assessment of survival function (present statistical mortality risk) based on the recent published results of the AJCC

The knowledge-based system (KBS) is able to support the physician by calculating the tumor stage. Furthermore, the KBS offers an interpretation whether a given pattern of tumor markers is suspicious for an underlying metastatic event.

Matlab R2009b and SPSS Statistics 17 were used for various calculations, particularly for ANNs, logistic regression [25-27] and ROC-curves [28]. Matlab was used to construct an individual ANN by using scaled conjugate gradient optimization. Standard settings for all ANNs were 70% training, 15% validation and 15% testing, with 20 hidden neurons in each case.

The study included calculations in variant types, whereby every calculation involved the computation of ROC-curves (Fig. 1).

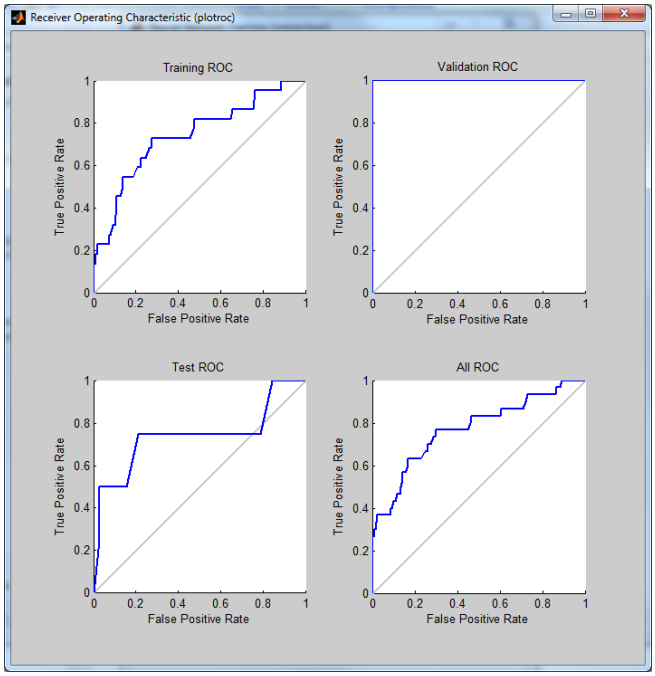

Figure 1. ROC curves for S100β/MIA/LDH.

Pretest probability according to TNM was implemented in Arden Syntax [29, 30]. The rules are grouped in modules, called Medical Logic Module (MLM). An example of an implemented rule is showed in Fig. 2.

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logic:
//Thickness classification
if thickness =0 AND not ulceration then T :=
"Tis";
elseif thickness <1.01 AND (ulceration OR
mitosis >=1) then T := "T1b";
elseif thickness <1.01 AND not ulceration AND
(mitosis <1 OR mitosis = null) then T := "T1a";
//mitosis not available
elseif thickness <2.01 AND not ulceration then T
:= "T2a";
elseif thickness <2.01 AND ulceration then T :=
"T2b";
elseif thickness <4.01 AND not ulceration then T
:= "T3a";
elseif thickness <4.01 AND ulceration then T :=
"T3b";
elseif thickness >4 AND not ulceration then T :=
"T4a";
elseif thickness >4 AND ulceration then T :=
"T4b";
else T := "errT";
endif;
```

Figure 2. Example rule for the classification of tumor thickness

B. Work in progress

As an element of work in progress we recently implemented our knowledge base as clinical decision support system (CDSS) in a huge hospital information system (HIS). A screenshot of the implemented form in the HIS is showed in Fig. 3. We aim to validate the system now during clinical routine. This approach has been acknowledged by the local ethical board (EK Nr. 1110/2010).

C. Workflow of the clinical study

The CDSS integrates completely into the workflow of the HIS. A feature of the system is the implementation of parameterized documents (PMD) for retrieval of relevant data. Specifically, results from tumor markers are automatically fed into decision support system via the laboratory information system. Additionally, clinical data are extracted from patient's history and from the histopathological report. As a result these steps of data extraction feed the CDSS with all relevant data.

III. RESULTS

Currently, the CDSS calculates the probability whether not a given pattern of tumor markers is suggested for metastatic disease, but will not display this result to the user. The response system is received just in the background and not shown to the physician. Instead, the user is prompted to give his or her expert opinion whether or not the given pattern is suggestive for metastatic disease. Up to now (October 2012) we gathered n=214 clinical cases.

At the end of the clinical study phase, the agreement between the clinical expert decisions versus the CDSS will be analyzed. Technically, we do not experience any problems during the clinical study phase. The system appears to be well accepted by the clinical experts. The median additional overhead of time caused by using the CDSS was 62 seconds.

Initial data show that the comparison of the physicians' decisions with the CDSS resulted in 106 (49.53%) complete matches, which implies that the CDSS and the physician completely agreed. In 48 (22.43%) cases, the system calculated a lower risk for the patient, whereby in 10 (4.67%) cases the calculations resulted in a higher risk, respectively. In 50 (23.36%) cases, no decision was neither possible for the CDSS nor for the physician, due to the lack of parameters. A comparison of the results is shown in Table I.

A. Problem analysis

During the routine workflow, it was not always possible to respond to all parameters required for the CDSS, leading to missing data. Additionally, distinct subtypes of CM were not clearly defined by the TNM/AJCC classification system. For example, tumor thickness of uveal melanoma cannot be exactly identified. Yet, the tumor thickness is a mandatory field and a mandatory parameter to classify the tumor according to AJCC.

TABLE I. THE AGREEMENT BETWEEN THE CDSS RATING AND THE EXPERT PHYSICIANS

Comparison of the results	Sum	Frequency
Complete match	106	49.53%
Risk assessment by CDSS is lower	48	22.43%
Risk assessment by CDSS is higher	10	4.67%
No decision possible	50	23.36%
Total	214	100%

IV. CONCLUSION AND FUTURE WORK

The CDSS, developed in the context of this clinical study, facilitates the calculation of the tumor stage for patients with CM and additionally provides a meaningful risk assessment of possible metastatic events. Our preliminary data show, that our system is well accepted by physicians. We think, this is mainly due to the fact that the CDSS is almost seamlessly integrated into the routine HIS. Parameters are automatically extracted from its data sources without any hassle for the physicians in charge. The performance of the system is still under investigation.

Early data indicate a promising agreement between the CDSS and expert physician's judgment. However, the risk analysis has not been finalized yet and a clear decision on benefit and hazard cannot be given at the moment.

Based on the experience made during this project, we are convinced that the integration of CDSS are in different fields of medicine might be useful. The appreciation and compliance with physicians is astonishingly high. Future prospective and controlled studies are mandatory for balancing benefit and risk of CDSS in the clinical domain.

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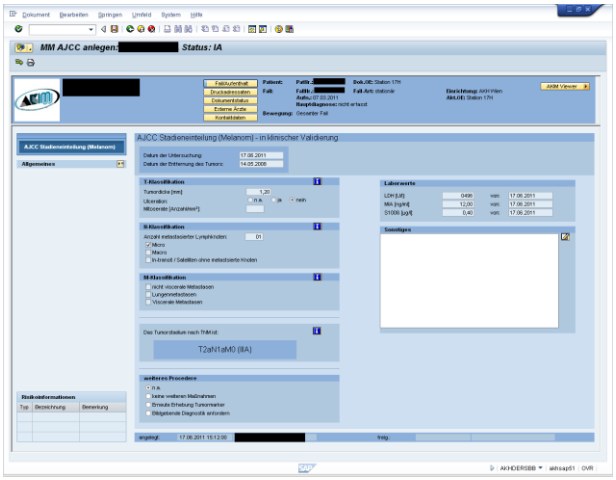

Figure 3. Integration of the clinical decision support system in a hospital information system.