Computers in Biology and Medicine 39 (2009) 1 – 7

Contents lists available at ScienceDirect

Computers in Biology and Medicine

journal homepage: www.elsevier.com/locate/cbm

Staging of upper limb lymphedema from routine lymphoscintigraphic examinations

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ARTICLE INFO

Article history:
Received 26 March 2007
Accepted 15 October 2008

Keywords:
Quantitative lymphoscintigraphy
Secondary lymphedema of upper limbs
Staging
Bayesian evaluation
Probabilistic mixtures

ABSTRACT

Secondary lymphedema of upper limbs, a frequent complication after a breast cancer therapy, can be successfully treated only when diagnosed at an early, ideally latent, stage. Lymphoscintigraphy is a promising candidate to this purpose. A slow lymphatic dynamics of upper limbs allows, however, a routine collection at most three images reflecting it. This makes an exploitation of lymphoscintigraphy to early-stage diagnosis a complex task. Recently, a Bayesian methodology extracting diagnostic information from the available sparse data has been developed. It properly detects lymphedema occurrence but not a desirable disease staging.

The present paper proposes Bayesian diagnostic processing of lymphoscintigraphic *and* routine clinical data. Its staging ability was tested on diagnostic data of 88 women at the age of 39–84 years (60.2 ± 10.4) with a suspicion of unilateral secondary lymphedema of upper limbs caused by a breast cancer treatment. Less than 20 of them had simply detectable disease stages. Information about accumulation dynamics of the lymphatic system contained in lymphoscintigraphic images was quantified via estimation of a simplified accumulation model [P. Gebouský, M. Kárný, A. Quinn, Lymphoscintigraphy of upper limbs: a Bayesian framework, in: J.M. Bernardo, M.J. Bayarri, J.O. Berger (Eds.), Bayesian Statistics, vol. 7, University Press, Oxford, 2003, pp. 543–552]. The sole use of this approach, referred as "Bayesian quantitative lymphoscintigraphy", was found insufficient for a finer staging of the disease to typical categories (healthy, latent, reversible, spontaneously irreversible, elephantiasis). For this reason, the results of Bayesian quantitative lymphoscintigraphy were attached to routinely available qualitative lymphoscintigraphic inspection and clinical data. These combined data were modelled by normal probabilistic mixtures. Their Bayesian estimates were used for a computerized disease staging.

The resulting model predicts expert's conclusions on the presence of a lymphedema in 95% cases. A finer staging is successful in 85% cases of suspicious limbs. Model cross-validation and a closer look on patients' data indicate that the combined data are still insufficiently informative. It calls for the further improvements of the inspection methods. Even under the current inspection conditions, the proposed processing provides clinicians a reliable quantitative "second" opinion on the disease staging.

1. Introduction

A lymphedema, an edema caused by a lymphatic system insufficiency, is a chronic disease that is frequently misdiagnosed, treated too late, or not treated at all. At the same time, the success and efficacy of its therapy strongly depend on a disease stage [1,2].

The secondary upper limb lymphedema can have many causes. Often, it arises as a consequence of a breast-cancer radiation therapy and (or) an axillary lymph node dissection. This cause concerns a significant group of patients, for example, about 4000 women in the Czech Republic yearly. The frequency of the lymphedema incidence is relatively high, about 5–30% [3]. The prospective study [4] even found that the lymphedema affected 42% women after the axillary lymph node surgery. This state calls for an efficient and reliable method allowing a safe diagnostic of the early lymphedema stages. Besides the basic clinical assessment, lymphoscintigraphy used for judging the state of lymphatic system seems to be an adequate and sensitive method at disposal.

Available publications provide limited information concerning quantitative lymphoscintigraphy and lymphedema staging. Existing evaluation studies are hardly comparable due to the lack of the standard imaging protocol. The clinical and experimental studies differ in used radiopharmaceuticals, imaging time moments,

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doi:10.1016/j.compbiomed.2008.10.003

administered radiopharmaceutical activities, etc. [3]. The common conclusions are: (i) the qualitative evaluation of lymphoscintigraphic images sufficiently characterizes lymphatic morphology; (ii) the treatment-critical recognition of the latent disease stages is poorly supported [5].

At present, the regional lymph-node accumulation and the clearance rate from the radiopharmaceutical injection site are taken as quantitative expressions of the lymphatic system's state [6–8]. Some studies question usefulness of these characteristics. For instance, the accumulation in axillas' region was found non-informative whenever axillas are dissected [7]. Scoring systems were also suggested to enhance diagnostic differentiation [9–12]. They are time-consuming and susceptible to subjective errors of the evaluator.

Slow dynamics of the upper-limb lymphatic system makes its diagnostics specific. Slowness critically reduces the number of measurements routinely available. The limitation stems from the constrained time-capacity of the gamma camera and from a limited ability of patients to endure a desirable number of examinations within the time interval covering dynamics of the upper-limb lymphatic system. The realistic, routinely accessible, number of images on each limb is two or three. The small amount of available data makes a diagnostic inference hard as the formally evaluated traditional physiological indicators are unreliable. In summary, a few published quantitative evaluation techniques lack sufficient reliability, sensitivity and accuracy and *no reliable, clinically accepted, quantitative evaluation of the upper-limb lymphoscintigraphy is at disposal.*

A promising quantification method was proposed in [1]. It was inspired by the depot-clearance-rate technique [13,14], which models the dynamics of the colloid accumulation at the injection site. The accumulation and clearance near the injection site predominantly depend on the flow rate and local diffusion. Thus, they provide a little information about the limb state. The proposed quantification, which models the colloid accumulation within the remaining part of the limb, reflects more characteristics of the inspected lymphatic system, including a lymph formation. Moreover, the adopted regional modelling of limb parts respects that a lymphedema may appear locally within the limb.

The discussed method uses simplified modelling of the lymphatic flow within the limb. This facilitates estimation of its patient-specific parameters from a small amount of uncertain data. The Bayesian estimation framework was chosen [15], as it (partially) compensates the lack of data by prior information. This processing, recalled briefly in Section 2.4, resulted in the routinely applicable Bayesian quantitative lymphoscintigraphy of the upper limb lymphedema [1]. The processing also resolved various decision subtasks, for instance, the choice of suitable time moments for imaging [16].

The inspection of the Bayesian quantitative lymphoscintigraphy, summarized in [1], indicates that the method is efficient and increases the diagnosis accuracy. At the same time, experiments shown that a reliable lymphedema staging is impossible without a full exploitation of all routinely available information sources. Data offered by them differ in a form, reliability and precision, so that their combination is non-trivial.

The present paper proposes an algorithm mapping the routinely available diagnostic information on an estimate of the lymphedema stage and tests the algorithm's reliability. The paper inspects importance of items within the record with explanatory data created from the clinical, qualitative and quantitative scintigraphy examinations. The importance of items arising from the Bayesian quantitative lymphoscintigraphy is of a special interest.

The combination of the disparate explanatory data is based on an exploitation of well-established probabilistic mixtures, for a good classical exposition see [17]. For the purpose of this paper, it suffices to take the mixtures as multi-modal distributions describing probability of occurrence of data records, consisting of the predicted disease stage and of the corresponding explanatory diagnostic data, in multivariate data space. Uni-modal components of the mixture characterize (possibly overlapping) clusters of similar records. The complete estimation of the mixture includes also structure estimation, which decides on the number of components and importance of respective items incorporated into the processed data records, see [18]. After such estimation, the unknown stage is predicted using the patient-specific explanatory data record.

2. Materials and methods

Eighty-eight women at the age 39–84 years (60.2 ± 10.4, mean $\pm$ standard deviation), with a suspicion on unilateral secondary lymphedema of upper limbs due to the breast cancer treatment, participated in the study. The patients predominantly with latent and early disease stages were chosen as their diagnostics is difficult and can be critical. Each patient underwent both lymphoscintigraphic and clinical examinations. All patients gave written consent to additional processing of their diagnostic data.

The subsequent sections describe the respective data sources and their evaluation in detail.

2.1. Scintigraphic data and a clinical assessment

A qualitative inspection of scintigraphic images, see Section 2.3, is a decisive part of the routine diagnostics nowadays. The Bayesian quantitative lymphoscintigraphy [1] extends its outcomes. The data reflecting clinical examination include a categorized therapy history, patients' subjective feelings of edema and pain as well as clinical findings. The therapy history contains a treatment type (mastectomy, chemotherapy, radiotherapy, etc.), the number of removed nodules and the number of the malignant ones. The part of the limb where the clinician found the edema is recorded. The clinician provides a subjective assessment of the disease stage on the ordinal scale $(0, 1, 2, 3, 4)$= (healthy, latent, reversible, spontaneously irreversible, elephantiasis). This choice is close to the recommendation in [19] but other, even substantially finer, staging scales exist.

2.2. Lymphoscintigraphy

The following routine procedure was applied in acquiring lymphoscintigraphic data.

Lymphoscintigraphic inspections were performed on both upper limbs. The healthy limb served as the patient-specific standard. A radiopharmaceutical of the volume 0.1–0.2 ml were injected subcutaneously into the first and the fourth inter-digital web space of each hand.

In our study, 20 MBq of the 99 mTc-labelled sulfur colloid was administered to 32 patients. For the rest of the patients, the sulfur colloid was replaced by the 99 mTc-serum albumin colloid. The replacement was enforced by the terminated production of the former radiopharmaceutical. The enforced change of radiopharmaceutical had no observable consequences on the results.

The initial calibrating image of the injection site was stored into (128×128) image matrix. This 60 s image was collected immediately after the injection. Then, the patients performed flexions and extensions for 30 min to stimulate the lymphatic flow. Then, three images reflecting morphology and dynamics of the lymphatic system were collected within the time span 30–180 min after the radiopharmaceutical administration. The whole arm was imaged in a supine position with the lead shielding the hand and the wrist. The gamma camera Sopha DXT with a LEHR collimator having the peak 140 keV summed the recorded scintillation impulses into the (64×64) image matrix for 60 s. The markers on all images indicated elbows, wrists and shoulders.

For the quantitative evaluation, the regions of interest (ROI) were drawn around the axillary and the supraclavicular region, the forearm and the upper arm. The overall number of impulses recorded over the ROI within the 60 s acquisition time, so called an integral count, characterized the activity accumulated within each ROI. The integral counts were corrected to the physical decay of the tracer over the examination period.

2.3. Qualitative evaluation of lymphoscintigraphic images

The trained nuclear-medicine expert inspected the lymphoscintigraphic images and evaluated them qualitatively according to the number of visible arm and cubit nodules, the lack of a transit in the application site, the visibility of the extended lymphatic vena and the existence of the dermal back-flow. A level of the dermal back-flow and its local position were differentiated. The findings on the affected limb were compared with the image of the contra-lateral limb. Primarily, the late images served to the qualitative evaluation. Other images served to a finer differentiation. The outlined qualitative evaluation of the scintigraphic images led to the expert's assessment of the lymphedema stage on the same ordinal scale as the clinician's.

2.4. Quantitative evaluation of lymphoscintigraphic data

The routine acquisition way of scintigraphic data, described Section in 2.2, implies that a small amount of data is available. Consequently, any quantification technique has to rely on a simplified modelling and an exploitation of the available prior information. The technique proposed in [1] is outlined here as its outcomes are used in the discussed staging.

2.4.1. Radio-tracer accumulation model

The accumulation dynamic is modelled by a linear discrete-time (t in minutes) dynamic model. A specific model is built for each individual ROI. It relates the administered activity (model's input) to the integral counts (the model's outputs).

The relative scintigraphic response is modelled, i.e., the time–activity curve (TAC, its values are denoted x) of the accumulated colloid normalized by the administered activity. A cascade of the first-order linear models (compartments) with a common gain parameter b is used. The cascade has d compartments with a common dynamical parameter a. This model structure is a flexible compromise between the need to characterize the complex distributed nature of the lymphatic system and the need to get a model with a few unknown parameters. TAC is modelled at time moments $t = 0, 1, 2, \ldots$ counting minutes from the administration time. At time t, the TAC value x_t is related to the model parameters b, d, a by the formula

$$x_t = b \times \frac{d \times (d+1) \times \cdots \times (t+d-1)}{t!} \times a^t. \tag{1}$$

While the expression (1) models the whole scintigraphic response on a fine time grid, its noisy measurements y_t are made for a small subset t^* of discrete time moments $t = 0, 1, 2, \ldots$. Recall that measurements are normalized integral counts over the modelled ROI at time t. Thus, the processed measurements are sums of raw counts over pixels forming the ROI. Consequently, the overall noise effect can be modelled by a zero-mean normal noise e_t, i.e.,

$$y_t = x_t + e_t, \quad e_t \text{ is normal zero-mean normal noise with variance } r, t \in t^*. \tag{2}$$

The significant difference of measurement times justifies the assumption that the noise samples e_t and e_τ, $t \neq \tau$, $t, \tau \in t^*$, are mutually independent. The normalization implies that the noise variance r can be assumed approximately constant. These assumptions complete probabilistic modelling relating the model parameters to measurements.

2.4.2. Use of prior information for the estimation of model parameters

The parametric model (1), (2) is completely characterized by the quartet $\Theta = (r, b, d, a)$ to be estimated.

The noise variance r reflects measurement process independent of the inspected patient, limb and ROI. Thus, data from various ROIs and patients can be used for its estimation. The sufficient amount of these data, corrupted by the noise with the same variance r, implies that the prior distribution of r has a limited influence on the posterior distribution. Therefore, computationally advantageous conjugate prior distribution [15] can be used. The conjugate prior distribution leads to the posterior distribution of the same functional form. Consequently, a low-dimensional statistic has to be numerically handled only.

The remaining three parameters (b, d, a) are strictly patient-specific. They depend on the modelled limb as well as on the ROI and have to be estimated using three available total counts. This is impossible without a prior information. Its systematic use is the key advantage of the Bayesian paradigm adopted for the inference from these sparse data. The prior information is expressed through intervals of a priori expected values of (b, d, a). Let us list and briefly comment the used prior information on these patient-specific parameters.

- b $(0 < b < 1)$—the parameter describes the gain of the model (1). The restriction respects that the lymphoscintigraphic response is non-negative and that it cannot exceed the applied input. Taking into account that no activity is created within the limb, a tighter upper bound $b_{max} < 1$ was derived and used. It is a function of the inspected a, d, [16].
- d $(1 < d \leqslant 6)$—the parameter describes the penetration rate through the limb and modifies the shape of the TAC. For $d = 1$, the model (1) would coincide with the exponential model used for depot-clearance-rate technique. The chosen upper bound is a very conservative guess.
- a $(0 < a < 1)$—the parameter determines the dynamics of the model (1). The specified interval reflects the fact that the inspected responses are stable and non-oscillatory. During implementation, this interval was shrunk to reflect the slow accumulation dynamics. Typically $0.9 < a < 0.999$. The specific choice respected the inspected number of compartments d.

The above information items were converted into a complete prior distribution on the patient-specific unknown parameters (b, d, a). Since no further detailed information is available for them, uniform distribution on the above ranges were chosen. This choice can be justified via the insufficient-reasons' principle [20].

2.4.3. Processing of information sources

With the measured data, the chosen model and the specified prior distribution, a relatively straightforward Bayesian evaluation of the posterior distribution [15]provides point estimates of parameters as well as their precisions. The patient-specific parameters and the noise-free TAC x_t, at any discrete time moment $t = 1, 2, 3, \ldots$, are estimated on each ROI.

The disease staging addressed in this paper is a classical but difficult pattern-recognition problem [21]. Primarily, it requires selection of features that allow reliable differentiation of the lymphedema stages. The estimates of the triples of the patient-specific parameters (for each ROI) are obvious candidates to this purpose. Besides these estimates, the value and position of the TAC maximum were

considered as promising features. They represent the counterpart of the late uptake and appearance time used in [5,7]. The residence time, widely accepted in nuclear medicine as a quantitative characteristic of accumulation dynamics [22]was considered, too. With the adopted scaling and sampling, the residence time in minutes coincides with the area under the TAC estimate.

Note that just point estimates were passed to the further processing described below. Attempts to exploit their uncertainties increased computational demands without an observable improvement of the evaluation outcomes.

2.5. Disease staging

As stated in Introduction, a computerized support of the staging assessment is the ultimate aim of the data processing discussed here. Thus, an algorithmically feasible mapping

$$\text{explanatory data } D \rightarrow \text{estimate } \hat{S} \text{ of the disease stage } S \qquad (3)$$

is constructed.

Data sparsity is the decisive feature of the addressed pattern-recognition problem. Indeed, the diagnostic data related to each limb provided data records D with 41 items of meaningful explanatory variables. The subjective staging made by the clinician and the scintigraphic expert, labelled S_C and S_S, respectively, was attached to the records D. The available diagnostic data concerned 88 patients. Thus, we got 176 learning data (D, S_S, S_C) for relating 41 explanatory variables to the unknown scalar stage S.

With a few data available, the Bayesian framework was again adopted as it combines consistently the available learning data, model of the inspected relations and prior information. Normal probabilistic mixture [17]was selected as the probabilistic model relating the explanatory data D to the stage S. The available learning data were used for estimation of its structure and parameters. Numerical processing was performed by Jobcontrol system [26]that covers all major tasks related to the mixture estimation. The corresponding theory is in [18].

The maximizer $\hat{S}$ of the learnt probabilistic mixture, evaluated for the patient-specific explanatory data D, is taken the stage estimate: the learning and maximization define the constructed staging algorithm (3), referred as the *computerized staging* in the rest of the paper.

Note that during the learning, the scintigraphic staging S_S was taken as a better measurement of the stage S. The clinical staging S_C was used for a comparison only. This choice was motivated by the fact that the clinicians ask for the scintigraphy whenever they are uncertain about own staging of the lymphedema.

The choice of the mixture model was the key step in constructing the staging algorithm. The following reasons singled out this model class:

- Probabilistic models "naturally" respect discrepancies of experts' opinions. Both scintigraphic and clinical staging are just subjectively influenced reflections of the real disease stage. Moreover, the boundaries between the respective disease stages are not sharp and the modelled relationship is stochastic by its nature.
- The expert's staging S_S has the discrete values $\{0, 1, 2, 3, 4\}$ and the explanatory data D contain continuous-valued entries. Thus, categorical regression is to be learnt, which is known to be hard computational problem [23]. This regression can be, however, approximated by a normal mixture if variances of the individual mixture components are kept small enough.
- Normal mixtures formally coincide with an artificial neural network made of Gaussian radial basis functions. This network is known to approximate (almost) any multivariate mapping [24]. Therefore, it suits for the considered exploratory data analysis in which the relation D to S is poorly known.
- Efficient algorithms exist for an approximate Bayesian estimation of normal mixtures. They include the needed structure estimation and a model validation [18,25].

3. Results

The examination and evaluation results concerned 88 patients, i.e., 176 limbs. The clinician's and scintigraphic-expert's staging differed in 37 cases. It means that the scintigraphic S_S and the clinical S_C staging coincided in 78.9% cases. A finer distribution of these opinions is reflected in Table 1.

The figures present the portion of the computerized staging, see Section 2.5, which coincided with the scintigraphic expert's staging.

The extent of the exploitation of the available explanatory data distinguishes the columns in the respective figures. "All" means that no available explanatory data were omitted. "Sci" used union of the data provided by the scintigraphic expert (except his/her staging) and the data gained from the quantitative scintigraphy, i.e., with the features derived from the estimated model (1), (2). "SciKv" refers to the sole use of the features gained from the quantitative scintigraphy. "Cli" relied on the diagnostic data provided by the clinician (except of his/her staging). "Rest" predicted the stage using the combination of the data provided by the scintigraphic expert and the diagnostic data provided by the clinician (again except of their staging).

The *left dark columns* in Figs. 1–4 correspond with the results obtained when *all considered data were used for learning*, i.e. for mixture estimation, cf. Section 2.5. The *right light columns* in Figs. 1–4 reflect the *cross-validation results*: the mixture was learnt on all considered data records except one on which the stage was estimated. All considered data records gradually played the role of the exceptional one. This technique is known as the leave-one-out cross validation [21].

The figures differ in an exploitation degree of the learning data and also present the reduced dichotomous staging (healthy/unhealthy). Let us describe them individually.

The left column graph in Fig. 1 displays the correspondence of the computerized staging with that provided by a scintigraphic expert. The right column graph in Fig. 1 shows the same dependence evaluated for records related to limbs that are suspicious of lymphedema, i.e., one half of the data records (88) was used. This reduction suppressed the influence of the results from the limbs that were a priori taken as healthy.

The left column graph in Fig. 2 deals only with the data of those patients for which the scintigraphic and the clinical staging coincided (139 cases). This reduction suppressed the influence of experts' subjectivity. The right column graph in Fig. 2 reflects the results obtained when the limbs suspicious of lymphedema and with the stage identically classified by experts were inspected.

The left column graph in Fig. 3 gives up distinctions between the sparsely populated higher stages of lymphedema providing just the dichotomic statements: the limb does not have or does have

Table 1
The experts' staging of the lymphedema

Scintigraphic staging, S_s	Clinical staging, S_c				
	0	1	2	3	4
0	*98*	*10*	*1*	*0*	*0*
1	*1*	*19*	*4*	*2*	*0*
2	*3*	*5*	*11*	*5*	*0*
3	*0*	*0*	*2*	*10*	*3*
4	*0*	*0*	*0*	*1*	*1*

Italics entries mean the numbers of limbs with the staging pair(S_s, S_c).

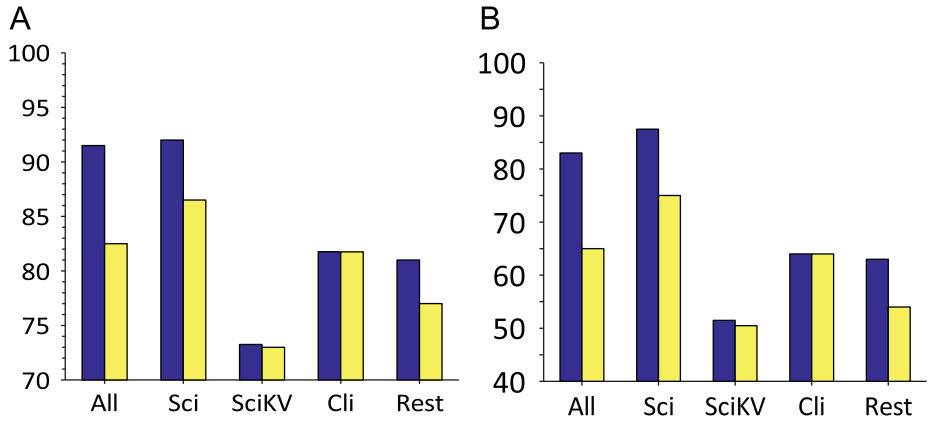

Fig. 1. The accuracy of the *lymphedema-stage classifier*: the correspondence of the classified stage for all (the left column graph) and suspicious (the right column graph) limbs.

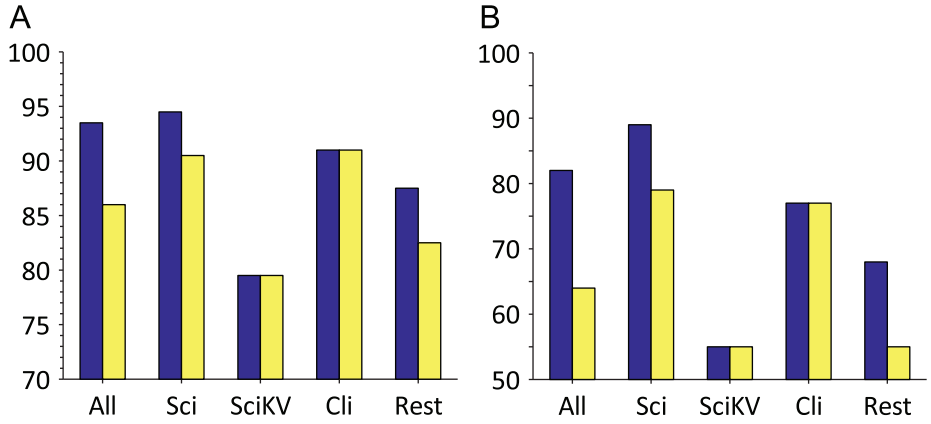

Fig. 2. The accuracy of the *lymphedema-stage classifier*: the correspondence of the classified stage for all (the left column graph) and suspicious (the right column graph) limbs *identically classified* by the clinician and the scintigraphic expert.

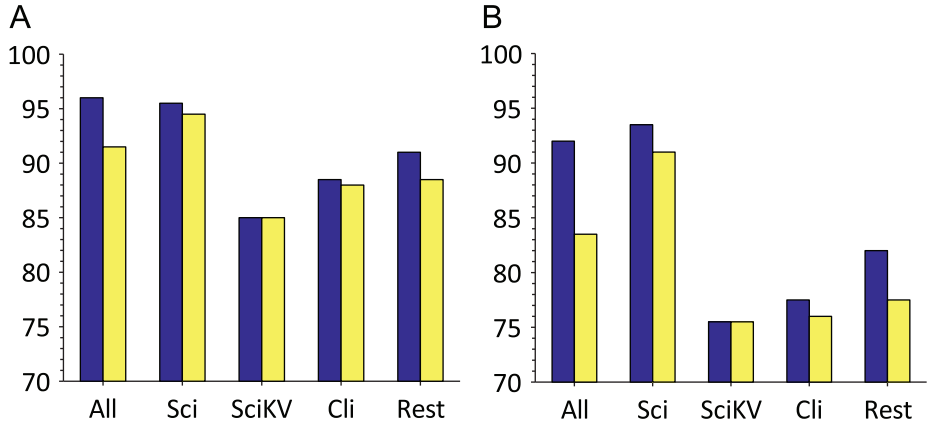

Fig. 3. The accuracy of the *dichotomous classifier*: the correspondence of the classified lymphedema for all (the left column graph) and suspicious (the right column graph) limbs.

lymphedema. The same evaluation reflected in the right column graph of Fig. 3 concerned the suspicious limbs only.

The left column graph in Fig. 4 gives up distinctions between the sparsely populated higher stages of lymphedema providing just the dichotomic statements and deals only with the data of those patients for which scintigraphic and clinical evaluations coincide (139 cases). The right column graph in Fig. 4 shows dichotomous results for identical staging and suspicious limbs only.

4. Discussion and conclusions

The results imply the following conclusions:

- *The use of all scintigraphic data, including features from the Bayesian quantitative lymphoscintigraphy, is obligatory* (see Figs. 1–4).
- The sole evaluation of either clinical data (see the left column graphs in Figs. 2 and 3 and the right column graph in Fig. 3) or the

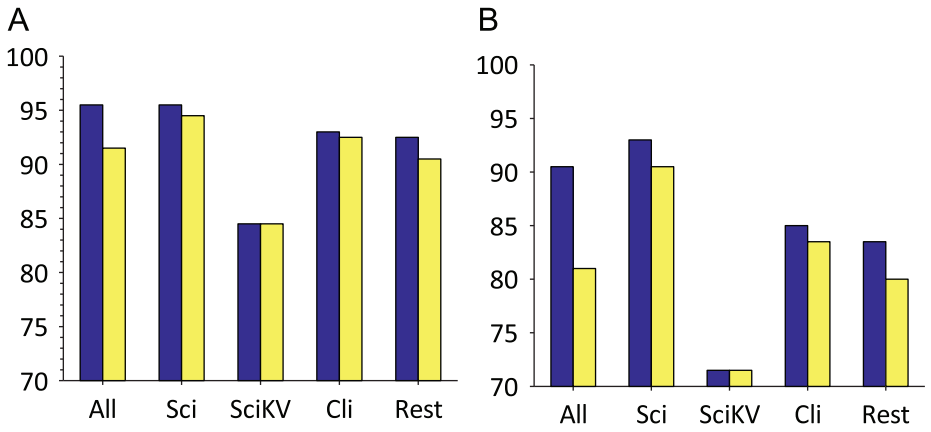

Fig. 4. The accuracy of the *dichotomous classifier*: the correspondence of the classified lymphedema for all (the left column graph) and suspicious (the right column graph) limbs *identically classified* by the clinician and the scintigraphic expert.

data from the Bayesian quantitative lymphoscintigraphy (visible in all figures) was found insufficient for a reliable staging.
- The extension of the scintigraphic data by the clinical ones may be advantageous (see the left column graphs in Figs. 3 and 4).
- The overall number of the available learning data was still too small. The visibly poorer cross-validation results than those obtained from all data confirmed it (all figures).
- The cross-validation results indicate that the explanatory data are still insufficiently informative. This is the probable cause of a higher robustness of the simpler models (see the columns "All" vs. "Sci" in the left column graphs of Figs. 1, 2, 4 as well as of the models dealing with the discrete-valued data only (see the column "Cli" in all figures).
- The quality of the dichotomic staging is very high (see the left column graph in Fig. 3 and both graphs in Fig. 4).

The derived methodology of computerized staging confirmed that:

- Complete scintigraphic evaluation is necessary for recognition of the early (latent) stages of the disease (all figures).
- The quantitative characteristics of the model (1), (2) are insufficient for the staging (see the columns "SciKv" in all figures) but contribute significantly to the qualitative scintigraphy in the way, which cannot be substituted by the clinical evaluations only (see the columns "Sci" and "Rest" in all figures).
- Combined data from the qualitative and the quantitative scintigraphy can be used for a very reliable indication of lymphedema presence even at the early stage (see Fig. 4 and take into account discrepancies in staging provided by the experts involved).

At the methodological level, the following main conclusions can be made:

- The presented results indicate that the proposed processing provide a reliable "second" opinion on the lymphedema staging based on both lymphoscintigraphic and clinical data.
  The term "indicate" stresses the fact that the processed data set was not rich enough to make conclusions sufficiently reliable and statistically sufficiently supported.
- The formerly proposed "Bayesian quantitative lymphoscintigraphy" [1], which still has no real competitor, helps significantly even in lymphedema staging.
- Bayesian estimation of probabilistic mixtures that estimates also their structure [18] suits for clustering and diagnostically oriented pattern recognition even with data of a mixed (categorical and numerical) nature.
- Bayesian processing is the first-option method when dealing with sparse data as it properly exploits the available prior information complementing data-based information.

Future research has essentially two directions:

- The above-described studies should be performed on a substantially wider set of patients' data. Statistical significance of the results and sensitivity to various optional parameters of the staging algorithm are worth of study when such a set of data will be available.
- The dependence of categorical variables on the numerical ones should be modelled in a better way. It is a well-known hard problem solved at small scales by logistic-type regression or inspected asymptotically. The considered intermediate-scaled problem is poorly supported by the available statistical tools.

5. Summary

The paper presents an application of advanced modelling and estimation methods to an important and difficult problem of staging of secondary lymphedema. The secondary lymphedema of upper limbs, a frequent complication after a breast cancer therapy, can be successfully treated only when it is diagnosed in an early stage. Use of, otherwise well-established, lymphoscintigraphically supported staging is inhibited by a slow lymphatic dynamics of upper limbs, which allows a routine collection at most three images reflecting it. A Bayesian methodology coping with this problem is described in the paper.

The properties of the proposed method are demonstrated on the study of 88 women at the age 39–84 years (60.2 ± 10) with a suspicion on a unilateral secondary lymphedema of upper limbs due to a breast cancer treatment. Less than 20 of them had simply detectable disease stages.

The proposed Bayesian staging methodology relies on a simplified accumulation model to get quantitative lymphoscintigraphy. It uses normal probabilistic mixtures for a computerized disease staging that exploits fully the routinely available information. The overall procedure predicts expert's conclusion on the presence of a lymphedema in 95% cases. A finer staging is successful in 85% cases of suspicious limbs. A model cross-validation and a closer look on patients' data attribute this difference to insufficiently informative data. The success rate is, however, high enough to justify further inspection of the proposed methodology and its use as a "second" opinion on the disease stage offered to the clinicians.

Conflict of interest statement

None of the authors faces any conflict of interests in connection with this paper.

Acknowledgments

This research was supported by MŠMT ČR by Grants 2C06001 and 1M0572.

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