Developing Diagnostic Guidelines for the Acute Radiation Syndrome

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Abstract. Diagnostic guidelines seem to be promising for improving medical care. One aspect of a diagnostic guideline for the acute radiation syndrome has been tested against an extensive case history database. Subsequently, the guideline has been optimised for a small set of case histories. The improved performance has then been proven by a test against the rest of the case history database.

1. Introduction

Clinical guidelines created by medical bodies are systematically developed statements to render decision support to physicians for specific clinical circumstances. Generally, guidelines aim at enhancing the quality of care by reduction of commonplace errors, by diffusion of optimal care delivery, through increased efficiency of diagnosis, and by allowing for scientific evaluation through means of feedback and statistical tests. Even though, the above advantages seem very much obvious, clinical guidelines have but scarcely been tested. In this presentation one guideline will be tested against reality, i. e., case histories in a database.

2. Research objectives

Nowadays, clinical guidelines are developed on the basis of experts' knowledge. The necessary formalisation process may corrupt the expert's knowledge, leading to a lack of generality and sub-optimal performance. Clinical guidelines, however, should perform well for the majority of possible case types in an application domain. A means to improve clinical guidelines could be the case-oriented refinement based on tests against real cases ascertaining the correctness of the guideline. This would add more objectivity to the experts' opinion.

A diagnostic guideline for the acute radiation syndrome (ARS) has been tested against case histories to get an impression of its correctness. As a first step, the test was limited to the granulocyte concentration changes which serve as the most decisive indicator for the grading of the ARS. Since the results have shown a mediocre performance of the guideline, it has been carefully considered how the performance could be improved. The guideline has been optimised for a small set of test cases and evaluated against a large number of real cases.

3. Methods

In the last years a Clinical Pre Computer Proforma (Baranov 1994) has been developed for the standardised structured documentation of ARS case histories. This questionnaire has been accepted by the 8 WHO Collaborating Centres on Radiation Emergency Medical Preparedness and Assistance (WHO 1993). Hundreds of case histories have since been collected world-wide and inserted into the International Computer Database for Radiation Exposure Case Histories. These case histories served as test set.

In 1979 the International Commission on Radiological Protection (ICRP) devised a guideline for the medical management of persons accidentally exposed to ionising radiation (ICRP 1980). Concerning the haematological disorders only qualitative descriptions were

included. In 1985 the German Commission on Radiological Protection (BMI 1986) decided to create more precise recommendations by defining leukocyte concentration intervals between day 4 and 7 to predict the clinical outcome of the disorders related to the haemopoietic system (see figure 1).

	degree	BMI-ICRP-classification
transient mild granulocytopenia	1	I, II
mild depression of haemopoiesis	2	III
spontaneous recovery of haemopoiesis	3	IV
no spontaneous recovery due to lack of stem cells	4	V
no spontaneous recovery due to insufficient stroma	5	VI

Figure 1. Degrees of the clinical outcome of the haemopoietic disorders of the ARS.

The leukocyte concentration intervals between day 4 and day 7 are given in figure 2 as time-concentration-rectangles. The degrees of the clinical outcome are marked in or immediately below the rectangles. The leukocyte concentrations of one real case are depicted as circles. In the guideline no information has been given how to interpret the measurements, provided more than one degree can be taken into account. The best estimates for real cases are obtained deciding for the highest degree. Thus, the clinical outcome of the case in figure 2 is classified as of degree 2.

In order to evaluate the ICRP based guideline it was tested against 159 real case histories of the International Computer Database for Radiation Exposure Case Histories.

The correct estimates for each degree of clinical outcome are indicated by the red characters. The guideline underestimates the degree of severity of the haemopoietic syndrome systematically as can be seen by the high percentages on the left hand side of the highlighted numbers.

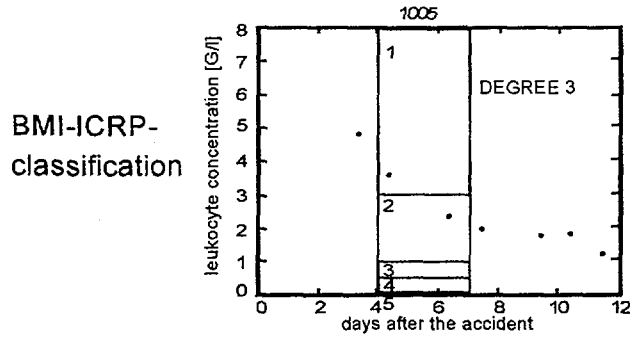

Figure 2. Classification schema based on the ICRP recommendations applied on one case history.

Less measurement noise can be obtained by taking into account the granulocytes as the main fraction of leukocytes only. Their correlation to the clinical outcome is even better.

After radiation leukocytes and granulocytes do not decrease on straight-lines, but, on curves. Therefore, curves yield better classification. Instead of polynomials exponential functions as output functions of a bi-compartmental models have been used as discriminating curves.

The bi-compartmental model is shown in figure 4. The model is a simplification of the well-known structure of granulocytopoiesis (Fliedner 1988).

- clinical course vs. ICRP-BMI-guideline
- κ-coefficient (Cohen 1968) = - 0.02
- correspondance is inadequate

	0	1	2	3	4	5
0	0	0	0	0	0	0
1	6	21	0	0	0	0
2	2	67	8	0	0	0
3	0	75	34	0	0	0
4	0	3	24	9	7	0
5	0	0	0	0	0	0

Figure 3. Results of the ICRP based classification schema tested against 159 case histories.

It is composed solely of a maturing and a blood granulocyte (functional) pool. The predecessors of the maturing cells were neglected, due to the radio sensitivity of dividing cells.

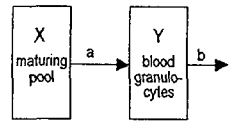

Figure 4. Simplified physiological bi-compartmental model of granulocytopoiesis.

They will only if at all come into play after a longer period of time. A full maturing and functional pool were assumed as initial conditions. Assuming the maturing and functional pool to be completely filled is justified since their cellular content is not very sensitive to ionising radiation. These initial conditions and the loss of granulocytes *b*, which is not significantly changed by radiation, have already been measured in reality.

classification based on the bi-compartmental model

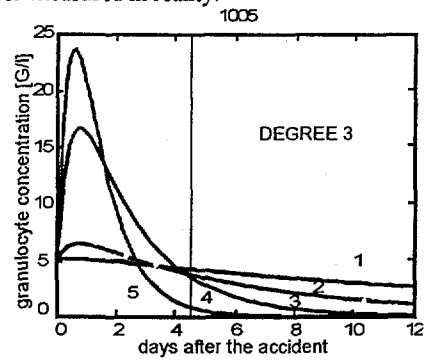

Figure 5. Classification schema based on the physiological model applied on a real case history.

Ionising radiation changes the transit time *a*, because substances (cytokines) will be liberated according to the intensity of the radiation to mobilise the cells of the maturing pool. The stress causing the change of transit time *a* is strongly correlated to the prognosis of the future granulocyte level over time.

Taking the parameters *X(0)*, *Y(0)*, and *b* from experimental results four output functions optimally differentiating between the 5 degrees of clinical outcome for 39 cases have been estimated by adapting the parameter *a*. (see figure 5). The discrimination curves correctly partition off the different degrees from day 4.5 onward due to the overlap during the first days. If a granulocyte measurement lies in one of the spaces then its degree indicated by the numbers

1 to 5 is assumed. E. g., all the granulocyte measurements (circles) of a real case with a clinical outcome of degree 3 lie between two discrimination functions in the space marked with (degree) 3.

Even after optimisation of the parameter a for the four discrimination functions the partitioning between the degrees was not a hundred percent successful.

4. Results

The above presented diagnostic guideline to predict the severity of the haemopoietic lesions after total body irradiation has been tested against 120 real cases. The classification results are shown in figure 6.

Nevertheless, classification errors have occurred. The confusion of degree 3 with degree 4 during the diagnostic process will be hazardous for the patient. The guideline is quite good in differentiating between degree 3 and degree 4. Only 2% of degree 3 were misclassified as degree 4 and only 6% vice versa.

- clinical course vs. exponential classifier
- only cases
- κ-coefficient = 0.74
- correspondance is good

	1	2	3	4	5
1	21	0	1	0	0
2	5	26	6	0	0
3	0	7	35	2	0
4	0	0	1	15	0
5	0	0	0	0	1

Figure 6. Results of the exponential classificator tested against 120 case histories.

Already existing guidelines and the experts' formalised knowledge were too weak to achieve a proper problem-solving behaviour as has been shown in figure 3. The partitioning curves can be applied as a relatively simple grading scheme, working like a nomogramm, on paper. The guideline cannot only be justified by the authority of experts, but, by physiology and statistics.

5. Conclusion

Only one aspect of the ARS could be discussed in this short paper. Even for the haematopoietic syndrome other parameters like lymphocytes, reticulocytes have to be taken into account. The same should be performed for other affected organs systems to create a general guideline for the ARS. The results must and will be revised by an expert panel later-on.

One necessary prerequisite for this approach is a standardised collection of a large number of comprehensive case histories. Nowadays only few international standardised case history databases exist. Introducing the electronic medical record may facilitate the collection of large numbers of case histories.

6. References

[1] Baranov A. E., Densow D., Fliedner T. M., Kindler H.: "Clinical Pre Computer Proforma for the International Computer Database for Radiation Exposure Case Histories", Springer, Heidelberg, 1994

[2] BMI (ed.): "Medizinische Maßnahmen bei Kraftwerksunfällen", Veröffentlichungen der Strahlenschutzkommission 4, Gustav Fischer, Stuttgart, 1986

[3] Fliedner T. M., Steinbach K. H.: "Repopulating Potential of Hemopoietic Precursor Cells", Springer Verlag, New York, Blood Cells 14, 1988, 393-410

[4] ICRP (ed.): "Annals of the ICRP - The Principles and General Procedures for Handling Emergency and Accidental Exposures of Workers", ICRP Publication 28, Pergamon Press, Oxford, 1980

[5] World Health Organisation (ed.): "Fourth Co-ordination Meeting of WHO Collaborating Centres in Radiation Emergency Medical Preparedness and Assistance", report PEP/93.2, confidential, 1993