**Software tools for the evaluation of clinical signs and symptoms in the medical management of acute radiation syndrome – a 5 year experience**

Matthias Port1, Patrick Ostheim1, Julian Haupt1, Matthäus Majewski1,2, Stephanie E. Combs3,4,5, Klaus-Rüdiger Trott3, Mike Atkinson6, Michael Abend1

1 Bundeswehr Institute of Radiobiology affiliated to the University Ulm, Neuherbergstrasse 11, 80804, Munich, Germany

2 Department of Urology, Bundeswehrkrankenhaus Ulm, 89081 Ulm, Germany

3 Department of Radiation Oncology, Technical University of Munich (TUM), Ismaninger Straße 22, 81675 Munich, Germany

4 Institute of Innovative Radiotherapy (iRT), Department of Radiation Sciences (DRS), Helmholtz Zentrum München (HMGU), Oberschleißheim, Germany

5 Deutsches Konsortium für Translationale Krebsforschung (DKTK), Partner Site Munich, Germany

6 Department of Radiation Sciences (DRS), Institute of Radiation Biology, Helmholtz Zentrum München, Oberschleißheim, Germany

**Keywords**

Radiobiology; Health Effects; Education; vomiting; diarrhea; erythema

version

Sent for

publication

to

Health Physics

on

Jan 2020

# Figures 2

# Tables 3

Corresponding Author: Michael Abend, M.D.; Bundeswehr Institute of Radiobiology affiliated to the University Ulm, Neuherbergstrasse 11, 80804, Munich, Germany Tel.: +89-992 692 2280; FAX: +89-992 692 2255; e-mail: michaelabend@bundeswehr.org

**Abstract**

A suite of software tools have been developed under the auspices of NATO for dose estimation (BAT, WinFRAT) and prediction of acute health effects (WinFRAT, H-Module). These use input from clinical signs and symptoms, such as vomiting, diarrhea, erythema or changes in blood cell counts. We have systematically examined the contribution of each parameter, based upon their predictive limitation (specificity) and strength (early occurrence, ease of ascertaining), for the correct prediction of clinical outcomes such as the severity of the acute radiation syndrome (ARS) and their utility in recommending early hospitalization and treatments. For educational and training purposes we have constructed a database of 191 cases that were generated using input from eitehr **Me**dical **Tre**atment **P**rotoc**ol**s for Radiation Accident Victims (METREPOL, n=167) or real-case descriptions (n=24) from an exisiting database or **e**valuation and **a**rchiving of **r**adiation accidents based on **c**ase **h**istories (SEARCH). The cases ranged from unexposed (response category 0, RC0, n=89)) to mild (RC1, n=45), moderate (RC2, n=19), severe (RC3, n=20) and lethal ARS (RC4, n=18).This database was used in 2015 for the first time for a NATO exercise involving eight clinical expert teams. From 2015 we have used the software in teaching MSc level radiobiology students in the context of a 15 h annual class. In 2019 we organized the first NATO workshop, introduced the participants to the use of the software tools for the medical management of ARS.. Over this 5-year period we have evaluated the outcomes using the same input datasets with a total of 32 teams and 93 participants. We have established that: (1) Unexposed (RC0) and mildly exposed individuals (RC1) could not be discriminated; (2) The severity of RC2 and RC3 were systematically overestimated by most teams, but almost all lethal cases of ARS (RC4) were correctly predicted by all teams; (3) Introducing a educational phase for non-physicians significantly increased the correct predictions of RC, ARS and hospitalization by around 10% (p<0.005) from an already high 86.8% without training to 96.2% with a three-fold reduction in variance and a halving of the time per case; (4) Training outcome was not dependent on the software tools used but was significantly associated with the educational phase. (5) The preferred combination of software tools were WinFRAT for dose estimation and H-Module for outcome prediction). (6) Comparing the dose estimates generated by the teams with the HARS severity reflected known limitations of dose alone as a surrogate for HARS severity at doses below 1.5 Gy, but identification of HARS 2-4 and support of clinical decision making at dose estimates > 1.5 Gy.

Our experience shows that even inexperienced users can use the software to apply somewhat unspecific early pre-clinical parameters to successfully make accurate treatment recommendations with a 98% accuracy. Training significantly improved the quality of decision making and enabled participants lacking a medical background to perform to a level comparable to that of the best clinical teams.

**Introduction**

In radiological exposure scenarios (e.g. the Goiânia accident, malevolent radiological dispersion devices (RDD or “dirty bomb”), nuclear detonation scenarios (e.g. improvised nuclear devices) or nuclear power plant accidents (e.g. Chernobyl and Fukushima) the number of affected individuals may range from a few to several tens of thousand (International Atomic Energy Agency., 1988; International Atomic Energy Agency. and World Health Organization., 2000; Laiakis et al., 2017). To husband the limited clinical resources in such a situation it is important to be able to rapidly discriminate unexposed and low level exposed persons not requiring immediate care from those highly exposed individuals likely to suffer the life threatening acute health effects of the acute radiation syndrome/sickness (ARS). At the same time the earliest possible hospitalization and treatment (e.g. administration of cytokine countermeasures (Farese et al., 2014) of highly exposed individuals will have a positive impact on the outcome of ARS.

Diagnostic approaches such as dose estimation, using either individual physical dose reconstruction or biological dosimetry, will be not available immediately, and when available are limited in their use for the prediction of severity of ARS (Port et al., 2019). Physiological changes that occur within hours and days of high dose irradiation include recognisable symptoms such as vomiting, diarrhea, erythema, a rise of body temperature and changes in blood cell counts and constitute the pre-ARS stages (prodromes). Prodromes present the earliest, albeit unspecific, indications of both the absorbed dose and potential outcome, and are easy to examine in an emergency situation (Anno et al 1989). Software tools designed to assess the prodome have been developed under the umbrella of the NATO Human Factor Medicine 222 “Research Task Group on Ionizing Radiation Bioeffects and Countermeasures”. These tools provide a dose estimation (Biodosimetry Assessment Tool (BAT) (Sine et al., 2001), First-responders Radiological Assessment Triage FRAT (“Biodosimetry Tools | Uniformed Services University,” n.d.)) or predict the severity of haematological ARS based on early changes of the blood cell count (H-Module (Port et al., 2017)). They are designed to be accessible to non-medical experts but the influence of training on their use and effectiveness has not yet been systematically tested.

We now report a 5-year evaluation of the use of these tools by individuals without specific experience in the medical management of ARS cases following a standardized short introductory training. For this we developed a 15 hour medical management module including classes on theoretical knowledge about radio-nuclear scenario-effects, the diagnosis and treatment of radiological injuries and in the practical use of the software tools. From 2015-2019 the class was given to groups of graduate students attending a masters degree program in radiation biology at the Technical University of Munich. In 2019 we organized a second trial as part of an international NATO workshop for individuals involved in the medical management decision making process for ARS patients.

**Material and Methods**

*Scenario, exercise and task*

The scenario was based on a Radiological Exposure Device (“RED”) that had been hidden in a long-distance train. This resulted in a potential radiation exposure of 191 people (Dörr et al., 2017). Depending on distance and shielding from the source and the individual radio sensitivity, different clinical signs and symptoms were assumed. The duration of exposure was equal to the travel time of one hour. ARS cases were generated by extracting suitable cases from either **the** METREPOL or SEARCH database (Friesecke et al., 2000) . An organ specific grading of radiation effects was generated HOW DID THIS HAPPEN Referernces??? for the neurovascular (N), hematopoietic (H), cutaneous (C) and gastrointestinal system (G). This organ specific grading is translated into a grading code (1-4) that generates general response categories (RC) ranging from RC 1 (autologous recovery certain) to RC 4 (autologous recovery most unlikely) for each individual patient. The complete data set of 191 indivdiuals including 24 real cases from SEARCH (RC2, n=2; RC3, n=10; RC4, n=12), 78 cases from METREPOL (RC1, n=45; RC2, n=17; RC3, n=10; RC4, n=6) and 89 unexposed cases based on normal values (RC0). The data available for use was restricted to clinical data that included for the first three days after radiation exposure. Gaps in the data obtained for the real case histories were retained to realistically reflect a real scenario. Each evaluation team consisted of two to three participants to reflect the required degree of teamwork needed to manage the workload and to discuss the possible clinical outcome predictions. The teams were asked to classify cases in the response categories RC0-4; to identify cases with clinically relevant ARS (RC 2-4l, to make decisions on hospitalization and to provide an estimate of absorbed dose (Gy).

*Software Tools and Prodrome List*

The Biodosimetry Assessment Tool (BAT) (Sine et al., 2001) and First-responders Radiological Assessment Triage FRAT (WinFRAT) (“Biodosimetry Tools | Uniformed Services University,” n.d.)) were developed by the Armed Forces Radiobiology Research Institute (AFRRI) to identify radiation exposed individuals, support diagnostic and dose assessment. Gastrointestinal, neurovascular and cutaneous clinical signs and symptoms, as well as haematopoetic changes are taken into account (Blakely et al., 2010).

The H-Module uses real case histories to predict late occurring haematological acute radiation syndrome (HARS) using measurements of radiation-induced changes of the blood cell counts (Lymphocytes, Neutrophils and Platelets) obtained during the first three days after exposure. The tool was developed by the Bundeswehr Institute of Radiobiology as a Microsoft Excel macro (Port et al., 2017) and has been converted into a PC App (online available probably in 2020) that was used in this study (Majewski et al.2018).

*Participants and backgrounds*

 THIS COHORT DOD NOT RECEIVE PRIOR TRAINING !!!!!!!!!!!!

 From 2015-2019 the training course was given to groups of graduate students attending a masters degree program elective in radiation protection. The students were international and most had no medical background. Students received lessons about the medical management of ARS and the diagnostic tools in a three day (3 x 5h) class. At the end of the class the students were asked to perform the NATO table-top exercise Altogether 15 teams consisting of 2-3 students participated. . Other than the NATO exercise 2015 students were asked to use certain tools in combination covering diagnosis based on dose estimation and effect prediction. Only in 2019 it was the student’s choice to use the tools they felt comfortable with. The restriction to certain tools per team was previously introduced, because of the NATO 2015 exercise results indicating that certain diagnostic tools might provide advantages in ARS diagnosis over others.

In 2019 we organized a second trial as part of an international NATO workshop for individuals involved in the medical management decision making process for ARS patients (*“****S****oftware* ***t****ools for* ***T****riage of the* ***A****cute* ***R****adiation* ***S****yndrome,* a practical workshop” (StTARS). This group included clinicians (e.g. nuclear medicine experts), teacher(?????), radiation protection experts and participants from government agencies. Comparable to the students program we introduced participants into medical management of ARS, the diagnostic tools and provided insights into current and future developments regarding diagnosis and therapy of ARS. Participants decided about the use of tools themselves and were divided into teams of 2-3 for the exercise.

YOU NEED A SECTION ON PARAMETERS MEASURED

The category “missing” was introduced for missing entries in addition to the original categories “yes”, “no”, “uncertain” for the variable ARS. Reported RC0 and RC1 were merged into RC0-1, reported RC2 and RC3 into RC2-3 and reported RC3 and RC4 into RC3-4 for a later comparison of true RC-categories with reported RCs.

When comparing participants predictions on RCs, ARS and their recommendations for hospitalization to the documented outcomes

*Statistics*

SAS (SAS 9.2, 2010, Cary, NC: SAS Institute, USA) was used for descriptive statistics, frequency distributions and associated statistical tests. Tests for examining significant differences among groups were performed using either the t-test or a nonparametric test, where applicable. or frequency distributions (building groups with >/< 55 % correct predictions, chisquare-p= 0,67

All graphs were created using Sigma Plot (Version 14.0, Jandel, Scientific).

**Results**

*Team Characteristics, Apportionment of Work*

Altogether 93 individuals in 32 teams participated in the Medical Management exercise/course during the last 5 years (table 1). Physicians were in the majority in the 2015 and 2019 NATO exercises (table 1). The MSc students were primarily biologists, physicists or biotechnologists, except in 2018 where physicians from NATO countries were included in the course. The ability of teams to make correct predictions (performance) was not influenced by the presence or absence of a physician (t-test, p=0.81, Chisquare-p= 0,67). NO DATA ON APPORTIONING OF WORK WAS SUBJECTED TO TESTING. leave out!!!!

*Comparing True RCs with Reports on RCs, ARS and hospitalization*

YOU NEED TO CONDUCT SENSITIVITY AND SPECIIFICITY CALCULATIONS ON THIS DATA SET

Comparison on team´s performances over time

The percentage of correct predictions of e.g. ARS among teams of the NATO 2015 exercise showed differences ranging between 76.4% (team 1) and 95.8% (team 3) and a variance of 6.3 % (standard deviation, table 3). With the MSc Radiobiology teaching classes from 2016-2019 and the NATO StTARS workshop mean correct ARS predictions in the range of 93.3-97.8% per year were comparable to the best performing NATO 2015 team (table 3, figure 1). Also, the variance decreased about two to six-fold (from 6.3% in 2015 to 2.6%, 0.1%, 1.9% and 0.8% in 2016-2018, respectively, table 3, figure 1). Based on the absence (2015 NATO expert teams) or presence of an educational phase ahead of the exercise (2016-2019 non-expert teams), a significant (p=0.005) about 10% increased ARS prediction from 86.8% (stdev 6.3) to 96.2% (stdev 2.1) could be observed (insert figure 1), respectively. At the same time, the variance decreased 3-fold. A similar pattern was found over the years for correct RC prediction and correct hospitalization decisions (table 3, figure 1). Comparison on both groups based on the presence/absence of an educational phase on average resulted in correct predictions of RC and hospitalization with significant increases from 89.6% (stdev 3.3) to 96.7 (stdev 1.8, p=0.0008) and 88.8% (stdev 4.6) to 96.6 (stdev 1.9, p=0.002), respectively while the variance decreased about two-fold (figure 3, insert).

The number of classified cases per hour showed a high variance (standard deviation) over classes (e.g. 10.7% in 2015 or 24.9% in 2019) and almost all years (table 3, second column, figure 1). A maximum of up to 118 cases could be classified within an hour (team 2 in 2018, table 3), so that the clinical data of 2 cases were analysed within about 1 min. Merging teams into two groups regarding the absence/presence of an educational phase revealed that the number of cases examined per hour increased about two-fold with an educational phase, from 19.6 cases/h (stdev 10.7) to 54.7 (stdev 26.1, p=0.1, figure 1, insert), respectively. In summary, non-clinicians after joining a teaching class showed a 10% increased performance along with an up to 3-times lower variance and on average processed about two-times more cases per hour with high variance among teams in comparison to expert teams from NATO exercise 2015 who received no pre-teaching.

Correlation of clinical dose estimates with HARS severity degrees

The correlation of clinical dose estimates with HARS severity degrees 0-4 followed a pattern found in all 32 teams over the last five years (figure 2):

1. At a dose band of < 1.5 Gy almost all HARS 0-1 developed and both HARS severity degrees could not be discriminated by dose. Also, up to 30% of all HARS 2 developed at this dose band.
2. At a dose > 1.5 only HARS 2-4 developed. These HARS severities require hospitalization.

This pattern corresponded to a certain degree with biodosimetry dose estimates (dicentric chromosomal assay) generated from real case histories (SEARCH), which are not part of this study and were introduced for inter-comparison purposes (figure 2, lower right graph): A dose < 1.5 Gy predicted almost all HARS 0, about 25% of HARS 1 and less than 10% of all HARS 2-3 cases. At a dose > 6 Gy many HARS 3 and almost all HARS 4 developed and in between (at doses between 1.5-6 Gy) predictions towards HARS 0-4 appeared inconclusive.

**Discussion**

Radio-nuclear incidents are potentially mass casualty scenarios and tens of thousands of people could be affected (International Atomic Energy Agency., 1988; Laiakis et al., 2017). The medical management demands early decision making within the first days after exposure to channel hospitalization and therapeutic intervention (Farese et al., 2014). Prodrome (e.g. vomiting, diarrhea and changes in blood cell counts) occur within the first 24-48 h after exposure (Darte and Little, 1967). As that, these symptoms in theory might be applicable for early diagnostic purposes (Gorin et al., 2006). Several software tools were developed under the NATO umbrella. They use prodrome either for dose estimation (BAT, WinFRAT) or prediction of acute health effects (WinFRAT, H-Module). Considering the few experts dealing with diagnosis and therapy of the ARS, the medical management in a RN event will become very challenging. This situation demands education of non-expert to support a triage in order to discriminate unexposed (HARS 0) from low (HARS 1) and high exposed individuals (H2-4) who require early hospitalization and early intensive care. In 2015 we used these tools the first time for a NATO exercise involving eight clinical expert teams (Dörr et al., 2017). A database containing prodrome of 191 cases (either originating from real case histories or being generated following the METREPOL approach) was provided and the teams were asked to identify the HARS severity degree 0-4, to provide recommendations regarding early hospitalization, intensive care and doing a dose estimate based on prodrome. These expert teams performed very well (Dörr et al. 2017) given the fact that prodrome are not specific and up to that time it was unclear how well prodrome support medical management decision making of the ARS. NATO teams on average correctly predicted the HARS severity, ARS and hospitalization requirements in 89.6%, 86.8% and 88.8%, respectively (table 3). From 2016-2019 several initiatives were processed (Masterstudy in Radiobiology and a NATO workshop in 2019) in order to educate teams in the medical management of ARS. Teams typically comprised 2-3 non-experts such as biologists, biotechnologists or physicists (table 1). These pre-educated but non-expert teams exercised the same 191 cases after a short learning phase. To our surprise, these teams on average performed even 10% better in comparison to expert teams from NATO exercise 2015 who received no pre-teaching. Moreover, after pre-teaching an up to 3-times lower variance in correct predictions of HARS severity, ARS and hospital recommendations was observed (figure 1) and on average about two-times more cases per hour were processed by the pre-educated teams. These data highlight the value and the teaching concept realized in the context of the Masterstudy in Radiobiology and the NATO StTARS workshop held in 2019 for the first time. The positive vote of the StTARS participants in favour of another workshop forced us to organize a second NATO StTARS workshop which will take place in the USA in 2020.

However, over all teams and irrespective of the pre-teaching phase we experienced limitations in the correct prediction of clinical outcomes using prodrome. In particular unexposed individuals could not be discriminated from exposed groups developing a mild degree 1 HARS. Cases suffering from HARS 1 do not require hospitalization, but surveillance should be increased, since late health effects are to be expected. From this perspective it would be preferable discriminating them. Other approaches such as radiation-induced changes in gene expression seem to allow this discrimination (Lacombe et al., 2018; O’Brien et al., 2018; M Port et al., 2016; Matthias Port et al., 2016). Clearly, a combination of different diagnostic approaches has to be employed for successful medical management decision making and pros and cons of each diagnostic approach have to be analysed carefully in order to develop and employ a concerted battery of diagnostic approaches. Based on prodrome, cases developing a HARS 2-3 degree were difficult to discriminate, but almost all HARS 4 cases were consistently identified by all teams (table 2). Considering clinical implications it is more important identifying cases in need of hospitalization as early as possible. Therefore, misclassifications such as HARS 2 to be HARS 3 or the other way around are tolerable and don´t interfere with medical management decision making.

After pre-teaching on average two-times more cases could be processed per hour than without pre-teaching (table 3, figure 1). This again emphasizes the value of pre-teaching. For instance, participants were guided how to deal with the wealth of data they received per case (e.g. delete those information/variables which are not required to gain an overview). They were also introduced into a strategy by identifying the HARS severity first and from there to deduce about ARS and hospitalization. Interesting, the on average two-fold increased number of processed cases per hour showed a variance, which was even higher after pre-teaching, although the correct decisions appeared comparable among all pre-teached teams. This is partly caused by the team’s intention to prefer discussions over high speed (personal communication during the StTARS workshop 2019). On the other hand it is caused by certain diagnostic “shortcuts” employed by participants. For instance, changes in lymphocyte counts received a high weight and this variable was used as a diagnostic to identify HARS 0-1 cases at first. Given that 134 from 191 cases did fall in this category, a throughput of 118 cases/h or about 2 cases per minute by teams employing this approach appears logic.

The dose dependency of prodrome such as vomiting or diarrhoea (biomarker of exposure) is known for long and used as a triage tool (Goans and Waselenko, 2005; International Atomic Energy Agency. and World Health Organization., 1998). As a prerequisite it was always assumed that prodrome are caused by radiation exposure irregardless of psychological causes that would be present in real-case scenarios where the knowledge about a potential exposure will lead to psychological reactions in unexposed individuals (Sorenson, 1986). This certainly represents a limitation of our exercise. Nevertheless, using prodrome for prediction of the HARS severity persistently over all teams reflected a pattern where H0-1 and up to 30% of all HARS 2 developed after an exposure < 1.5 Gy, while almost all clinically relevant HARS2-4 severity degrees developed at doses > 1.5 Gy (figure 2). Although not ideal this threshold of 1.5 Gy with diagnostic limitations below 1.5 Gy strongly supports the medical management decision making at > 1.5 Gy. This highlights the significance of dose estimates based on prodrome using the software tools WinFRAT and BAT. Interesting, BARDA launched a project for research support of high-throughput tools to discriminate between exposures below and over 2 Gy (LIT). Our data are in support of this approach. However, absorbed dose given as a measure of ionizing radiation exposure and meant as a surrogate for effect prediction is insufficient as long as other exposure features such as dose rate, partial versus whole body exposure, fractionated versus single exposure are not defined (Port et al…). Of note, when using dose estimates based on changes in dicentric chromosomes the pattern appeared slightly different (figure 2, right graph in second row): In analogy with dose estimates based on prodrome at < 1.5 Gy lower (HARS 0-1) and higher (HARS 2-3) were observed, and at > 6 Gy mostly HARS 3-4 developed, but in the dose range between 1.5-6 Gy it was impossible to discriminate HARS 1 (no immediate clinical implications required) from HARS 2-4 with strong immediate clinical implications. The precision of the gold-standard in dosimetry (DIC assay) causes problems in discriminating HARS 1 from HARS 2-3 clinical outcomes, which is not seen when using prodrome for dose estimation. For clinical outcome prediction it might be of advantage employing the less precise and more crude dose estimates based on prodrome. However, it must be considered that prodrome are not specifically occurring after radiation exposure which is true for the DIC assay (Lit).

When running the first NATO exercise among expert teams in 2015 each teams used the software tools of their choice. In particular team 3 showed the best results (Dörr et al. 2017). Significant differences in the performance among the teams were interpreted to depend on the combination of software tools. Therefore, from 2016-2018 all teams received another combination of software tools, but all teams after pre-teaching showed very similar performances. In 2019 teams choose the tools by themselves without showing an impact on the performance which was close to 100%. Hence, it is not the combination of software tools used by the teams. Instead, we identified significant performance differences among teams with and without pre-teaching which underscores the value of pre-teaching.

The preferred choice of software tools in 2019 was WinFRAT for dose estimation and H-module for clinical outcome prediction. Merging H-module into WinFRAT or creating a new platform with prodrome used as input data and generating clinical outcome predictions automatically via artificial intelligence that represents future approaches for increasing the througput.

Taken together, prodrome can be successfully used to support early urgent clinical decisions such as hospitalization, ARS prognosis and treatment recommendations in up to 98%. Teaching classes significantly improve the outcome predictions and enable even participants without a medical background to perform comparable to best medical clinical teams. Prodrome based dose estimates > 1.5 Gy seem to support medical management decisions regarding HARS.

**Acknowledgement**

The authors would like to express their gratitude to the participating radiation biology master students of the Technical University of Munich as well as the participants of the NATO 2015 exercise and the NATO StTARS 2019 workshop as their work was the basis for our findings. We are also very thankful to Dr. W.F. Blakely. He kindly shared the algorithm used for WinFRAT so that we could work on a table representing a shortened and condensed version for conversion of prodrome into a dose estimate.

.

**References**

Anno, G.H., Baum, S.J., Rodney Withers, H., Young, R.W., 1989. Symptomatology of acute radiation effects in humans after exposure to doses of 0.5-30 gy. Health Phys. https://doi.org/10.1097/00004032-198906000-00001

Biodosimetry Tools | Uniformed Services University, n.d.

Blakely, W.F., Ossetrova, N.I., Whitnall, M.H., Sandgren, D.J., Krivokrysenko, V.I., Shakhov, A., Feinstein, E., 2010. Multiple parameter radiation injury assessment using a nonhuman primate radiation model-biodosimetry applications. Health Phys. https://doi.org/10.1097/HP.0b013e3181b0306d

Blakely WF, n.d. No Title https://www.usuhs.edu/afrri/biodosimetrytools.

Combs, S.E., Kessel, C., Wilkens, J.J., Multhoff, G., Schmid, T.E., Vaupel, P., Trott, K.-R., Berberat, P., Atkinson, M.J., 2017. Master of Science (MSc) Program in Radiation Biology: An Interdepartmental Course Bridging the Gap between Radiation-Related Preclinical and Clinical Disciplines to Prepare Next-Generation Medical Scientists. Front. Oncol. 7, 226. https://doi.org/10.3389/fonc.2017.00226

Darte, J.M., Little, W.M., 1967. Management of the acute radiation syndrome. Can. Med. Assoc. J. 96, 196–199.

Dörr, H., Abend, M., Blakely, W.F., Bolduc, D.L., Boozer, D., Costeira, T., Dant, T., De Amicis, A., De Sanctis, S., Dondey, M., Drouet, M., Entine, F., Francois, S., Gagna, G., Guitard, N., Hérodin, F., Hoefer, M., Lamkowski, A., La Sala, G., Lista, F., Loiacono, P., Majewski, M., Martigne, P., Métivier, D., Michel, X., Pateux, J., Pejchal, J., Reeves, G., Riccobono, D., Sinkorova, Z., Soyez, L., Stricklin, D., Tichy, A., Valente, M., Woodruff Jr., C.R., Zarybnicka, L., Port, M., 2017. Using Clinical Signs and Symptoms for Medical Management of Radiation Casualties – 2015 NATO Exercise. Radiat. Res. https://doi.org/10.1667/RR14619.1

Farese, A.M., Brown, C.R., Smith, C.P., Gibbs, A.M., Katz, B.P., Johnson, C.S., Prado, K.L., MacVittie, T.J., 2014. The Ability of Filgrastim to Mitigate Mortality Following LD50/60 Total-body Irradiation Is Administration Time-Dependent. Health Phys. 106, 39–47. https://doi.org/10.1097/HP.0b013e3182a4dd2c

Friesecke, I., Beyrer, K., Fliedner, T.M., 2001. How to cope with radiation accidents: The medical management, British Journal of Radiology. https://doi.org/10.1259/bjr.74.878.740121

Friesecke, I., Beyrer, K., Wedel, R., Reimers, K., Fliedner, T.M., 2000. SEARCH: a system for evaluation and archiving of radiation accidents based on case histories. Radiat. Environ. Biophys. 39, 213–7.

Goans, R.E., Waselenko, J.K., 2005. Medical management of radiological casualties. Health Phys. 89, 505–512.

Gorin, N.-C., Fliedner, T.M., Gourmelon, P., Ganser, A., Meineke, V., Sirohi, B., Powles, R., Apperley, J., 2006. Consensus conference on European preparedness for haematological and other medical management of mass radiation accidents. Ann. Hematol. 85, 671–9. https://doi.org/10.1007/s00277-006-0153-x

International Atomic Energy Agency., 1988. The Radiological accident in Goiânia. International Atomic Energy Agency.

International Atomic Energy Agency., World Health Organization., 2000. The Radiological accident in Lilo. International Atomic Energy Agency.

International Atomic Energy Agency., World Health Organization., 1998. Diagnosis and treatment of radiation injuries. International Atomic Energy Agency.

Lacombe, J., Sima, C., Amundson, S.A., Zenhausern, F., 2018. Candidate gene biodosimetry markers of exposure to external ionizing radiation in human blood: A systematic review. PLoS One. https://doi.org/10.1371/journal.pone.0198851

Laiakis, E.C., Wang, Y.-W., Young, E.F., Harken, A.D., Xu, Y., Smilenov, L., Garty, G.Y., Brenner, D.J., Fornace, A.J., 2017. Metabolic Dysregulation after Neutron Exposures Expected from an Improvised Nuclear Device. Radiat. Res. RR14656.1. https://doi.org/10.1667/RR14656.1

Master program Radiation Biology | TUM Fakultät für Medizin [WWW Document], n.d.

Majewski M, Combs SE, Trott KR, Abend M, Port M. Successful Teaching of Radiobiology Students in the Medical Management of Acute Radiation Effects From Real Case Histories Using Clinical Signs and Symptoms and Taking Advantage of Recently Developed Software Tools. Health Phys. 2018 Jul;115(1):49-56.

O’Brien, G., Cruz-Garcia, L., Majewski, M., Grepl, J., Abend, M., Port, M., Tichý, A., Sirak, I., Malkova, A., Donovan, E., Gothard, L., Boyle, S., Somaiah, N., Ainsbury, E., Ponge, L., Slosarek, K., Miszczyk, L., Widlak, P., Green, E., Patel, N., Kudari, M., Gleeson, F., Vinnikov, V., Starenkiy, V., Artiukh, S., Vasyliev, L., Zaman, A., Badie, C., 2018. FDXR is a biomarker of radiation exposure in vivo. Sci. Rep. https://doi.org/10.1038/s41598-017-19043-w

Port, M., Herodin, F., Valente, M., Drouet, M., Lamkowski, A., Majewski, M., Abend, M., 2016. First Generation Gene Expression Signature for Early Prediction of Late Occurring Hematological Acute Radiation Syndrome in Baboons. Radiat. Res. 186, 39–54. https://doi.org/10.1667/RR14318.1

Port, M., Herodin, F., Valente, M., Drouet, M., Ullmann, R., Doucha-Senf, S., Lamkowski, A., Majewski, M., Abend, M., 2016. MicroRNA expression for early prediction of late occurring hematologic acute radiation syndrome in baboons. PLoS One 11. https://doi.org/10.1371/journal.pone.0165307

Port, M., Majewski, M., Abend, M., 2019. Radiation dose is of limited clinical usefulness in persons with acute radiation syndrome. Radiat. Prot. Dosimetry. https://doi.org/10.1093/rpd/ncz058

Port, M., Pieper, B., Knie, T., Dörr, H., Ganser, A., Graessle, D.H., Meineke, V., Abend, M., 2017. Rapid prediction of haematological acute radiation syndrome in radiation injury patients using peripheral blood cell counts. Radiat. Res.

Sine, R.C., Levine, I.H., Jackson, W.E., Hawley, A.L., Prasanna, P.G., Grace, M.B., Goans, R.E., Greenhill, R.G., Blakely, W.F., 2001. Biodosimety Assessment Tool: a post-exposure software application for management of radiation accidents. Mil. Med. 166, 85–87.

Sorenson, J.A., 1986. Perception of radiation hazards. Semin. Nucl. Med. 16, 158–70.

**Legends**

**Figure 1**

Comparison on the performance of clinical expert teams (NATO exercise 2015) who received no pre-teaching in relation to radiobiology students and participants of a NATO workshop in 2019 who received a teaching class (highlighted by a grey overlay) before doing the exercise. Performance differences were found regarding the correct prediction (in percent) of response categories, RC (A), development of an ARS (B), decision for hospitalization (C) and the number of cases judged per hour (D). Symbols indicate mean values over all teams of a teaching class and error bars represent the standard deviation. Symbols were connected with a fourth-degree linear regression model. Outliers in number of cases/h in 2018 were excluded from the regression model. Inserts reflect normal distribution based on RC, ARS etc. mean values and standard deviations of two groups, namely the group without pre-teaching (NATO exercise 2015, white circles) and the group with pre-teaching (all teams from 2016-2019 combined, black squares).

**Figure 2**

Clinical dose estimates generated from three different representative student teams in 2016-2018 by using the provided software tools were correlated with the known HARS severity degrees 0-4. The last lower graph reflects the same correlation, but using biological dose estimates documented in the SEARCH database and originating from real case histories. These data were generated in another context and are not part of this study, but were incorporated for intercomparison purposes. Symbols (grey circle) represent single measurements and box plots (median, 10%; 25%,75%, 90% percentile) reflect the corresponding estimated distribution of dose estimates per known HARS severity degree.

**Table 1**

The number of teams and members/team as well as their academic background and software tools used during their course is provided in this table. Three to nine teams were built in the context of a NATO exercise (2015) comprising experts dealing with the acute radiation syndrome (ARS), students of a Masterstudy in Radiobiology (2016-2019) and a NATO workshop (StTARS). Abbreviations: METREPOL = **Me**dical **Tre**atment **P**rotoc**ol**s for Radiation Accident Victims; WinFRAT = Windows First-responders Radiological Assessment Triage, BAT = biodosimetry assessment tool, AFRRI = Armed Forces Radiobiology Research Institute.

**Table 2**

The reported response categories (RCs, upper part), reported Acute Radiation Syndrome (ARS, middle part) and reported requirements for hospitalization (lower part) are shown to the left side relative to the true RCs, ARS and hospitalization requirements reflected on the right side of the table. Results from three representative teams out of the 32 teams examined are selected. True RC, ARS and hospitalization decisions and corresponding correctly (expected) reported RC, ARS and hospitalization decisions are highlighted in bold numbers.

**Table 3**

The performance (correct prediction of response categories, RC, acute radiation syndrome, ARS and hospitalization requirements in percent) of the teams in the context of different exercises, classes or a workshop as well as the number of cases examined per hour are shown in this table. Abbreviations: standard deviation (stdev), standard error of mean (sem), \*calculations of descriptive statistic excluding the outlier (team 4) from analysis.