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05 March 2015

Minutes ExPO-r-Net 3rd biannual Meeting

Very Rare Tumour Workshop

Venue: Meeting Room 'Aula Magna', Department of Child's and Mother's Health, Via Giustiniani 3, 35122 Padova

Host: Azienda Ospedaliera di Padova (AOPD), Padova, Italy

Very Rare Tumour Workshop 13:00 – 17:45

Welcome by Giuseppe Basso (Head of Azienda Ospedaliera di Padova, AOPD), Ruth Ladenstein (Children´s Cancer Research Institute Vienna) and Gianni Bisogno (AOPD), introduction of all participant.

Ruth explains that ExPO-r-Net intends to create a visible Paediatric Oncology European Reference Network (PO-ERN), starting with very rare tumours (VRT). To this end ExPO-r-Net needs to collaborate closely with its partners to identify hubs of coordination until the end of 2015 for application of a first PO-ERN in the upcoming call from the European Commission, DG-SANCO (details on the 06.03.2015).

Gianni is very pleased that VRT-experts are now meeting for the first time in Europe and hopes that this workshop will clarify what is going on in Europe including possibilities for collaboration. For this, ExPO-r-Net is a key project to support and establish new models of cooperation.

Very Rare Tumor: the EXPERT initiative **Andrea Ferrari**, Istituto Nazionale dei Tumori Milano, **Gianni Bisogno,** Azienda Ospedaliera di Padova	13:20-13:40

Since unfortunately Andrea Ferrari could not come, Gianni Bisogno represents him. He opens with the saying: *"If you work on frequent cancers, do randomized trials! If you work on rare cancers –FIND FRIENDS"* from Andrea. In general, all cancers are rare in childhood, but treatment was much improved in the last years. However, children with very rare tumours. (less than 2 cases per million) have not benefitted to the same extent as adults. Some VRT are rare at any age (pleuro-pilmonary blastoma, pancreatoblastoma), others are rare in childhood, but common in adults (e.g. carcinomas, melanoma). All rare paediatric tumours are orphan diseases (little information available, no dedicated organization to support clinical management and research, difficult/impossible to conduct trials, limited financial resources). In the last century only very few people were researching on VRT but this started to change in the new millennium with the launch of several comprehensive projects dedicated specifically to rare pediatric tumors. For example, TREP (tumori rari in eta Pediatrica) developed epidemiologic and strategic criteria for a long and growing list of VRT. Within TREP experts for each VRT are identified, networks and frameworks are built, research is performed and practical clinical guidelines/advisory service is given. Another network is the German Paediatric Rare Tumour Group (GPOH, Dominik Schneider, Ines Brecht). Various rare tumours had already dedicated studies so the main aims of the project was to establish a

collaborative framework involving people interested in VRT and create guidelines for tumours up to that time ignored. In a publication from Ines Brecht et al. it was shown that though most of the GCCR-registered patients with rare malignant tumours are treated within GPOH trials, there is a considerable number of patients that have been diagnosed and treated outside the structures of the GPOH. These patients will now be reported to the German Paediatric Rare Tumour Registry (STEP). The Polish Paediatric Rare Tumours Study is also active in a list of VRT. Then there is the CCLG Rare Tumour Group UK, which works differently: Their main aim was to produce guidelines and cases are registered in the National UK Childhood Cancer Registry but they do not actively recruit patients with rare tumours that may not be viewed by paediatric oncologist centres. France has the group FRAnCaise des TUmeurs Rares de l´Enfant (FRACTURE, Daniel Orbach) for VRT. The list of tumours is similar to other VRT-groups, but minor differences exist. This means that research and prospective studies are feasible for VRT but the number of patients with a given tumour type recruitable in national-scale protocols will never suffice for the purposes of randomized clinical trials. Therefore, there is a need to go a step further and create larger, international, prospective cooperative projects to improve the quality of the studies which is done by EXPeRT (European Cooperative Study for Pediatric Rare Tumours). At the beginning EXPeRT began with a retrospective data exchange and analysis on various tumour types to developing harmonized, internationally recognized diagnostic and therapeutic guidelines for pancreatoblastoma, followed by pleuro-pulmonary blastoma and ovarian Sertoli Leydig cell tumour. They also started international consultation by email for difficult cases. The US established a similar network (Children´s Oncology Group, Rare Tumours Committee).

EXPeRT´s next goals are i) to encourage other European countries to join in, ii) to set up joint international prospective case registries with harmonized data documentation sheets, iii) to develop prospective studies and basic science projects. To reach these goals, financial resources, cooperation with other ventures, adult oncologists and the ITCC is needed.

see presentation ExPO-r-Net VRT_Ferrari_Bisogno.pdf

Discussion:

Ruth Ladenstein is impressed by what the VRT group has already created. David Walker confirms that it is important to work with adult oncologists and share expertise. Ruth agrees and informs that there is also close cooperation with parents and survivors, who are increasingly active in the field

The ExPO-r-NeT project: **WP8** **Gianni Bisogno**, Azienda Ospedaliera di Padova	13:40-14:00

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Gianni Bisogno then explains how ExPO-r-Net can support VRT as indicated in his WP8: Integrating very rare tumours and soft tissue sarcomas into a European reference network through the identification and connection of paediatric oncology centres and cooperative groups with the necessary expertise with the aim to the provide accurate diagnosis and evidence-based treatment to children with VRT in Europe (and worldwide. This work is done in cooperation with the Istituto Nazionale dei Tumori, Milan, Italy, Klinik fur Kinder und Jugendmedizin, Dortmund, Germany, Consorzio Interuniversitario – CINECA, Bologna, Italy and several collaborating partner s of ExPO-r-Net.

The milestone "Establishment of VRT network tumour board and working group on rare STS in collaboration with EpSSG" has already been established in autumn 2014, and an advisory desk has been opened since October 2014. Gianni outlines the fact that the VRT are completely different from each other, therefore a coordinating group is needed containing experts in different fields, which will be covered by EXPeRT.

It is also planned to establish a website, together with the dissemination experts from SIOPE and, finally, in March 2016 a European meeting to reach consensus on guidelines for VRT and rare soft tissue sarcomas is planned. The priority list if tumours is: i) pleuro-pulmonary blastoma, ii) pancreatoblastoma, and iii) Sertoli-Leydig tumours, followed by infantile fibrosarcoma and embryonal sarcoma of the liver.

EXPeRT has made a survey on the existence and activity of cooperative groups in favour of children with VRT. They received 26 answers from 34 countries. In 38,4% of the answers dedicated groups for VRT do exist in the respective countries. If not, the reason for 12,5% was no interest, 12,5% stated that VRT were included in other protocols and for 75% there were other reasons like too small country, lack of time, no trained staff and others.

Nevertheless, several European VRT groups were identified in Hungary, UK and Ireland, Italy, Poland, Germany, Austria and Switzerland, France, Spain, Netherlands and Croatia with other countries planning to join. The VRT survey showed that 54% of the European population are covered by VRT groups, 13% are in registries and 33% are not covered. With this Gianni comes to the conclusion that VRTs are still an "orphan" disease in large part of Europe and the limited number of cases greatly justifies an international collaboration (especially for "small" countries). He thinks that EXPeRT can be the model for common VRT definitions, common structures etc. and EXPORNET can help to create tools (website, tumour board database,..). A first indirect result of ExPO-r-Net is the creation of 2 "new" VRT Groups and the attention of many interested people.

See presentation ExPO-r-Net VRT_Bisogno.pdf

Discussion:

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The VRT website is briefly discussed, which is already quite mature and details can be presented at any time.

Very rare Tumors in children and adolescents in Europe: **Croatia** **Jelena Roganovic**, University Children's Hospital Rijeka	14:00-14:20

Jelena Roganovic informs that there is a long lasting and close cooperation between Padova and Rijeka. She explains that there are 990.000 children in Croatian and 4 paediatric oncology centres with 90 beds as well as 2 bone marrow transplant (1 auto, 1 allo) units. In 2014 the prevalence of new paediatric cancer cases was 144. "6 were registered last year, for example in case of lymphoma out of 10 cases 6 were registered, even less in other cancers. In 2013 3 and in 2014 5 cases of very rare tumours occurred. Until recently, there was no national sub/group for VRTs and no dedicated activities. Oncologists were in principal unfamiliar with the management of such tumours, therefore most paediatric VRT are passed to adult oncologists, which means that Croatia has to improve its clinical standard by increasing the knowledge, practising more disciplined collaboration and participating in national and international trials. When Croatia affiliated to EXPeRT, the work to establish and participate in VRT groups has started and we are looking forward to organise the next EXPeRT meeting.

See presentation ExPO-r-Net VRT_Roganovic.pdf

Discussion:

Ruth congratulates to the initiative and mentions that the first step on a journey is always the most difficult one. Jelena agrees and is happy to start. She emphasizes that already before the patients were not badly treated, whenever a new VRT patient came, she contacted the respective international expert for advice. However, with EXPeRT instructions are clearer and better structured.

Ruth asks if Jelena feels comfortable to leave the patient in his home country with cross-border advice or if she would prefer to send the patient to another country. Jelena says that if the clinical surrounding is good she agrees to keep the patient at home. Merely genetic studies are doe abroad but without costs for Croatian clinics. She informs that the consultation is a lot of work, but it is manageable. For example, Croatia nasopharyngeal tumour patients are treated with the help of Salzburg, Austria. Children with VRT benefit better in countries with good economy because of the better organisation. Ruth explains that the goal of ExPO-r-Net was to the organisation and advice to enable the patient to stay in the homeland with equal quality of care and move only if specific intervention is needed. The second goal of ExPO-r-Net was to identify clusters of experts on a field to establish a roadmap, which shows reference people with tumour board scenarios to be addressed.

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Gianni wonders about the reason why the numbers of patients were higher than those registered and Jelena explains that those are lost, as soon as the patient comes to an adult oncologist.

Very rare Tumors in children and adolescents in Europe: **Spain** **Ricardo Lopez**, Spanish Society of Pediatric Hematology and Oncology	14:20-14:40

Ricardo Lopez informs that there are 17 different health services in Spain and 44 paediatric oncology units linked with SEHOP. Some of those treat patients until 15 and some until 18 years. Since May 2005 Spain has a Rare Tumours and Vascular Tumours Committee with 5 paediatric oncologists and 1 paediatric surgeon. The aims of the working group are i) to improve knowledge and ensure homogeneous clinical management, ii) to develop therapeutic guidelines starting with vascular tumours, iii) to ensure rapid and effective response to the consulting physicians, iv) to collaborate with other Spanish groups related with these tumours, v) to get into contact with consolidated expert groups and to vi) centralize.
However, also the Spanish group faced some difficulties as there were: i) few members for many different groups of tumours and little “free time”, ii) no individual cases registered in the group, iii) no economic support, iv) no data management and v) often no centralized histological review. Rare tumour registries do exist in Spain, for example for hepatocarcinoma und pleuro-pulmonary tumours and a tumour classification list is available. Ricardo also shows a pie chart about the incidence of paediatric cancer in Spain from 2000 to 2012 (11.309 cases in total). Of those, a certain amount of VRT was expected and observed as displayed in a list in Ricardo´s presentation, for some tumours the number was big enough to perform studies. There is also the vascular tumour committee with 4 paediatric oncologists, 1 paediatric surgeon, 1 dermatologist and 1 pathologist. They cooperate with other societies and developed national therapeutic guidelines. Guidelines are also available for gonadal sex cord stromal tumours, adrenocortical tumours, thyroid carcinomas, phaeochromocytomas and paragangliomas, nasopharyngeal carcinomas, paediatric GIST etc. and recommendations for other VRT. In case of paediatric melanomas, guidelines were developed with adult dermatologists for treatment with Vemurafenib, Iplilimumab (BRIM-P-study).

See presentation ExPO-r-Net VRT_Lopez.pdf

Discussion:

Ruth Ladenstein finds this overview from Spain very impressive and asks about the numbers which Ricardo presented. He informs that Spain has a national PO-registry, therefore all cancer data are accessible. However, endocrine tumours are not included because they have a different registry. Since Ricardo showed that there was in part a discrepancy between the numbers of cases expected and the actual numbers, Gianni informs that it is a common experience that more patients register than expected.

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Ruth summarizes that it starts with the awareness and then the patients follow.

Very rare Tumors in children and adolescents in Europe: **Lithuania** **Jelena Rascon**, Vilnius University Hospital	14:40-15:00

Jelena Rascon informs about the situation in Lithuania (number of inhabitants 2,97 Mio, children <18 years 543 00). Lithuania has approximately 100 new childhood cancer cases per year and there are 2 main centres, Vilnius and Kaunas. There is no reference diagnostics for the solid tumours soft tissue sarcoma, osteosarcoma, neuroblastoma and Hodgkin lymphoma. She informs that Lithuania has a constant slow population decrease in the last 13 years including a slightly larger decrease in the number of children. Concomitantly, the number of new childhood cancer cases decreased from 72 in 2000 to 58 in 2014. In this context, Jelena shows two slides with the number of children treated in the Vilnius and Kaunas centres from 1982 or 2000 to 2014 (leukaemias & lymphomas and solid tumours). According to a pie chart indicating the number and type of paediatric cancer there are approximately 3 VRTs per year in Lithuania. The overall survival (OS) of children with VRT is rather constant in the last years with 67%, compared with an increase of the OS in all children with leukaemias, lymphomas and solid tumours. Lithuania has joined international study groups on VRT, e.g. the European Rhabdoid Registry (Europe-wide registration, treatment recommendations) and since Lithuania joined international studies, the event free survival increased significantly. Current activities are scientific multidisciplinary meetings in Lithuania inviting international experts with workshops to learn and improve the knowledge of local clinicians (also from Latvia, Estonia). They also have an institutional tumour board and reference people and it is planned to establish a national reference centre for paediatric rare diseases. Nevertheless, there are still things that could be improved, like registrations, institutional database. The Lithuanian cancer registry is not a real registry. It provides a cancer form to be filled for each patient and the data protection law is causing problems, the transmission of data is illegal. Another issue is the improvement of communication between our 2 centres, which is now tackled by the Horizon 2020 application PICORET with Kathy Prichard-Jones as coordinator. We expect from the European collaboration to i) find the respective reference centre for any kind of VRT, ii) get support to join international studies, iii) get support in clinical management of rare cases, iv) get support to find published data, evidence and v) get support in ICCCC-3 introduction for regular registration. Jelena concludes that international collaboration is essential to optimize management of VRT (Registration studies on VRT, Dissemination (publication) of the recommendations/decisions achieved).

see presentation ExPO-r-Net VRT_Rascon.pdf

Discussion:

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Ruth Ladenstein finds it very interesting to see how Lithuania grows and functions. She wonders if they are already part of a VRT group or if they are yet planning to become one. Jelena informs that there is already close cooperation in ALL and AML and she wants to become the dedicated person for VRT. Therefore, according to Ruth, she will be integrated in ExPO-r-Net as fast as possible. Giannis says that everything which Jelena wants to receive from a European cooperation is actually provided by ExPO-r-Net. David Walker wants to know details about the data protection issue. Jelena says that they are only allowed to share data in case it is a medical trial but not in a clinical trial. David finds this slightly foolish and informs that the UK also has extreme bureaucracy. He wonders if ExPO-r-Net will tackle this problem. Ruth says that our needs were already presented in Brussels and a policy is under development. Therefore data protection is definitely on the agenda and she hopes that the procedures can be simplified in the future.

Coffee break

Very rare Tumors in children and adolescents in Europe: **Slovenia** **Maja Cesen**, University Children Hospital Ljubljana	15:40-16:00

Maja Cesen explains that Slovenia is a very small country with only 2 million inhabitants and 400.000 children. It has 1 PO centre and about 60 new cancer patients per year. A cancer registry exists in Slovenia since 1950 and the notification to this registry is prescribed by law. In Ljubljana there is the university children hospital and the university medical centre. The hospital hosts a bone marrow transplant unit since 1991. There is close connection with the institute of oncology Ljubljana, department of cytopathology (flow cytometry and FISH) and paediatric radiotherapy team with weekly meetings. In total, there are 7 full time paediatric haematooncologists, nurses, a psychologist, pharmacologist, dietician, physiotherapist and kindergarden/elementary school teachers. Slovenia is SIOP and SIOPE member and participates in several clinical trial groups. Treatment in Slovenia and abroad (if indicated) is covered entirely by National Health Insurance company with support from the foundation for children with cancer and hematologic diseases, an organization which raises funds for improvement of quality of life and treatment of children with cancer. Slovenia hat 63 patients in 2013, of those only few had VRT according to the definition “any solid malignancy or borderline tumour characterized by an annual incidence < 2/million and/or not already considered in clinical trials”. In case of malignant melanoma there were 55 patients registered between 1984 and 2011, the treatment strategy was developed by the paediatric oncologist and an adult melanoma oncology team with surgery and/or systemic therapy. For thyroid carcinoma there were 77 patients in the same time period. There were only 7 nasopharyngeal carcinoma patients between 1985 and 2014, 18 carcinomas, several patients with various rare mesenchymal tumours, 2 patients with rhabdoid tumours, 16 with hepatoblastoma, and 2 with chordoma.

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If a new VRT is diagnosed, the case presented in the morning sitting round (in-charge physician, past experience), followed by review of literature, protocols for staging, treatment, consultation with national/international experts and discussion of treatment options in a meeting including radiologist, surgeon, radiotherapist, adult oncologist. Slovenia is actively participating in clinical trial groups and study groups like EXPeRT that enables: physician´s access to an established network for expert consultation to assist in clinical decision in VRTs and patients with VRT from Slovenia to be diagnosed and treated according to internationally recognized guidelines.

see presentation ExPO-r-Net VRT_Cesen.pdf

Discussion:

Ruth Ladenstein is pleased to see so much visible effort and good organisation which is exactly what the community wants to achieve. It shows that a major role will fall on the advisory function of tumour boards.

Very rare Tumors in children and adolescents in Europe: **Hungary** **Miklos Garami**, Hungarian Childhood Cancer Registry	16:00-16:20

Miklos Garami presents the Hungarian Paediatric Cancer Registry. Hungary has a population of almost 10 million inhabitants and the Hungarian Paediatric Oncology Network was established in 1971. The activities of the group consisted of: i) registration and follow-up of the patients, ii) treatment by the same protocols nationwide iii) quality control, and iv) postgraduate teaching sessions. It was funded by a $2.33 million grant from the U.S. Agency for International Development (USAID) (1991-1996). Since 2004 there is an internet-based Paediatric Cancer Registration and Communication System for the Hungarian Paediatric Oncology Network. The costs are carried by the compulsory Hungarian health insurance. The network takes care of uniform treatment protocols guidelines and rehabilitation programs according to international standards. It is harmonizing procedures, processes and has long experience with clinical trials. Miklos briefly shows the operating system of the registry (server, application etc.) and explains the methods: the registration is population-based covering about 98%, with partial coverage between 15 and 19 years, computerized access database, an ENCR recommended coding system and international studies. Every centre gets fulltime high-speed internet access and data access. New patients have to be entered by the centres, in case of VRT there is close contact with other experts. In the last 3 years, also a connection with adults was established. Miklos briefly shows how to enter the registry (see presentation), which gives detailed information about the patient. It is also used to address epidemiologic questions like changes of childhood population, relative distribution of disease, age-standardized incidence rates and trends, OS,

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incidence of carcinomas and so on. Therefore in Hungary all VRT are registered, otherwise patients would not get access to therapy. It is updated once a year with international collaborations to ensure innovative treatment.

see presentation ExPO-r-Net VRT_Garami.pdf

Discussion:

Ruth Ladenstein wonders about the re-compensation of this interesting activity. Miklos informs that the system including re-compensation runs since 7 years. Ruth explains that this does not exist in many other countries and is a focus in the Horizon 2020 application PICORET. Miklos says that for common tumours first line treatment should follow international protocols. In case of VRT it is obligatory to contact adult oncologists. Gianni Bisogno asks if there are also data available on treatment on outcome from this registry. Miklos confirms, the data are gathered from protocols.

Guidelines for children with very rare tumors **Daniel Orbach**, Institut Curie, France	16:20-16:40

Daniel Orbach informs about the European guidelines for very rare tumours in children: their strengths and weaknesses. The process they are trying to build in EXPeRT and ExPO-r-Net (WP8) are to develop easy to read and easy to use European guidelines to harmonize standard cares around very rare tumours (VRT) and rare soft tissue sarcomas. They have already selected some VRT and rare soft tissue sarcoma like infantile fibrosarcoma, pulmonary pneumoblastoma, Sertoli-Leydig tumors, Pancreatoblastoma, alveolar soft part sarcoma and defined grades of evidence. Grade-I would be retrospective studies, from grade-II on prospective studies and grade-III means that recommendations proposed by experts are developed according to previously-published series, case reports and personal expertise on the topic. However, it also needs to be defined who is an expert (depending on the amount of publications, others?). There are 2 coordinators of each guideline (paediatric oncologist, surgeon and if necessary pathologist, radiotherapist). The validation could be done by a core ExPO-r-Net group, national and international cooperative groups. Guidelines can change over time according to new data and should then be modified. The local clinician remains responsible for the care of his patient. If necessary, medical discussions should be possible via internet.

Daniela shows an example of infantile fibrosarcoma, where no prospective or comparative studies were done yet, but 46 single case reports were published in the last 5 years. The EpssG recommends to start with VA in case of IRS-III tumours, but about VAC there are no recommendations available. This means they have to make choices without much background. What should follow after tumour assessment:

surgery first, neoadjuvant therapy or wait and see strategy?

So far they have already developed grade-III consensus recommendations from EXPeRT/ExPO-r-Net/EpSSG groups concerning guidelines for infantile fibrosarcoma including standards, strategy references and a decision flow chart for therapy. The recommendations always include, that the case should be discussed with an expert group. The document was already validated in France and elsewhere. Next, the same was done with pleuro-pulmonary blastoma (PPB). The recommendations were written by 2 paediatric oncologists and will be evaluated within the expert group, and probably by an external advisor. This will be followed by a decision. In this context Daniel shows 2 cases of PPB (2 male patients, 7 months and 3,5 years) and treatment decisions. He shows a distinct chemosensitivity in type-III PPB, meaning that this therapy could be superior. An EXPeRT report on treatment and prognostic factors in pleuropulmonary blastoma was published in 2014 (Bisogno et al., EJC). A standard is therefore available for PPB with optional recommendations and flow charts for the overall treatment strategy as well as other propositions. It is still not fully clear how to treat newborns and very small infants for example with radiotherapy. Finally, Daniel wonders if they should also prepare guidelines for follow-up (e.g. In case of DICER-1 mutations)

see presentation ExPO-r-Net VRT_Orbach.pdf

Discussion:

Ruth Ladenstein is sure that it is possible to harmonize the field with well described processes including limitations. Tal Ben-Ami points out, that adults with DICER-1 mutation approach her asking about pregnancy, because there is no information available. Daniel recommends clarifying this with a geneticist. Ruth underlines the importance to create evidence and hopes that this will be manageable in the future. Gianni Bisogno is impressed how well the guidelines were done including listing of the problems. He thinks it important to involve EXPeRT as much as possible in the process. He also points out that it is important not to lose information in case an expert is lost (retirement etc.)

Very Rare Tumors: the International consultation desk **Dominik Schneider**, Klinikum Dortmund, Germany	16:40-17:00

Dominik Schneider introduces the international consultation desk for VRT. It started with an EXPeRT and EXPO-r-Net Concept paper, including the facts that an interdisciplinary tumour board (TB) is indispensable for cure of solid tumours and it needs means of quality assurance. However, no TBs are established yet for very rare tumours. The aims of the international consultation desk are to enable the physician to i) draw on experiences from their own patients, ii) discuss with worldwide experts and multidisciplinary experts, iii) explore various therapeutic/diagnostic options, even if they are not available in the centre caring for

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the patient, and iv) continuously expand and refine knowledge. The patients/ parents should also i) benefit from the collective international experience of several specialists, ii) have access to modern treatments , iii) receive treatment locally but with international supervision, iv) be referred to a different centre if particular treatment is needed and not available locally, v) avoid extensive search and travels to find the “right” person and the “best” centre. There were already several activities ongoing for this platform as presented in the last ExPO-r-Net meeting in Valencia and the next steps will be:

- Active (centralized) management of EXPeRT tumor board
  Preparation of consultation, request, consent, data etc.
  Management of tele-conferences
  Management of follow-up
  Coordination in Dortmund (D. Schneider)
- Increase visibility (also via ExPO-r-Net)
- Telecommunication technology: email, ftp-server, video conferences etc.

Here, Dominik shows a flow chart, how the data flow could be stablished starting from the different countries ending at the VRT EXReRT TB. He then shows the so far identified experts for disease specific consultation including non-European partners. Physicians can apply via a specific form including contact data, the questions to the TB and a document uploading function. Currently it is sent to the email-address of the specific expert. In the future it is planned to use the CINECA consultation platform. The platform is considered best for VRT. It offers:

- Web diagnostic image visualization
- Linkage to clinical data
- Expert review forms
- Consensus diagnosis form
- Webconference
- Repository of images
- Storage of images in a certified data centre

There will also be a follow-up evaluation after 3, 12, 24 and 36 months including the patient´s status, the the impact of the recommendation, if further advice is needed and others. Dominik summarizes that it was already achieved to develop the concept paper, find a group of experts, develop an application form, clarify the coordination of the VRT-TB and they had already successful consultations. The next steps will be the installation of the consultation platform with CINECA including a web conference platform, to formalize the consultation and follow-up process and to establish a database.

Dominik points out that there are several VRT groups in Europe who are sometimes different concerning the tumours but in total there is a feasible number of VRT available in whole Europe. In general, 80% are

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treated on a national level, 20% are complicated and have to be discussed in an international board. Therefore the structure of the VRT consultation platform shall take this in consideration.

see presentation ExPO-r-Net VRT_Schneider.pdf

Discussion:

Piotr Czauderna explains that the SIOPEL consultation platform, also developed from CINECA, has a slightly different concept. It does not usually use a teleconference tool because they do not have time for teleconferencing, but web-conference functionality is integrated into the system in case of need. However, everything else can be done via their platform and a moderator summarizes the conclusion. However, a typical TB could be attached. Dominik answers that the SIOPEL platform will definitely be considered as a model for the future VRT platform. It is good that it has an electronic case report for the individual trial experience and a database. Gianni Bisogno agrees that SIOPEL is a good model, but VRT has additional needs and challenges due to the multiple different diseases. It should also be easily usable for countries with little experience in such tools. Dominik explains that they had 5 requests so far and answers will be given only if additional data are available. His experience is that it should still become more formalized. The requesting clinician will receive a summary of answers, not an official report paper for the patient. Enrique Terol asks where the data are stored in the moment and if there are problems for anonymization in rare disease. Dominik answers that data are so far in the firewall-protected hospital server system and will be also save in the CINECA system. Patient images are not (yet) anonymized but kept confidential.

Lars Hjort thinks that the 80%:20% distribution may hold true in large countries but may be very different in small countries.

Ruth Ladenstein points out that a compensation system for such kind of advice has to be developed, because there will be intensive work. This needs policy action for compensation and should become very clear, when the PO-ERN is built. It has to be made clear that we offer a quality assured network, where a request is entered, put in the right direction and answered. She therefore encourages attending VRT experts to perform cost calculations (expert´s effort, IT-infrastructure and maintenance etc.). Finally, it should be done on a routine basis. Adela Cañete adds the importance of harmonization and working in a standard way. Dominik, however, informs that this can be done with more frequent tumours but is difficult for VRT, where the experience is hidden and information is low. Ruth agrees that different tumours have different needs and scenarios. One model may not fit for other diseases. It is therefore very important to get a clear picture of the needs of different tumours including cross-border activities. This can be done by contacting the national tumour groups. She also points out that it has to be clarified if and how to deal with very frequent but highly unstructured parent/patents requests. She reports that some

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patients send up to 20 requests to different hospitals at once. This needs to be guided. Dominik answers that his experience is different meaning that 90% of his requests come from physicians. He then forwards the information about the respective expert(s) (national and international). He gives generalized recommendations but never gives patient-specific advice. Gianni informs that a formalized process is currently created. Dominik considers that an access also for parents could be included and they could get the automatic answers that the request should come from the clinician.

Very rare Tumor: Toward a European reference network Discussion lead by **Gianni Bisogno**, Azienda Ospedaliera di Padova & **Ruth Ladenstein**, Children´s Cancer Research Institute, Vienna	17:00-17:40

Ruth informs that a process is needed to better understand the respective countries and their centres to learn, where patients could be sent within their home country. This will be done by Jerzy Kowalczyk, who will present details on the 06.03.2015. Only some patients with specific needs should go cross-border. Dominik and Gianni repeat that the overall aim should be to share expertise but treat patients locally, except for very specific needs. All agree that a harmonized approach is most important. It is also agreed to evaluate the costs for a consultation. David Walker mentions that in the UK such service is already reimbursed but only on the national level. It might be difficult when you have to go cross-border. Ruth suggests that whenever available, cost calculations from several already existing TBs should be made (e.g. the one from Gabriele Calaminus and others). This should enable ExPO-r-Net to develop a proposal. Nevertheless, according to Dominik it will be complicated because time efforts and costs differ between countries. David informs that the UK decided to reimburse a lump-sum, because it was impossible to harmonize hourly rates. Dominik suggests, that maybe the CINECA system could observe time and effort per person which would help to give an estimate of the costs. However, Piotr points out that being online in a system does not necessarily always have to be active working time.

Enrique Terol says that there are no easy solutions because there are no definitions for the services yet. The human resources will be the cost drivers. The EC will explore that which will be followed by decisions from the member state´s insurance companies. That implies high level decision processes and we have to show a business case. Now there are no prices for telemedicine, only Germany pays lump-sums. The private companies in the UK have price consultants, which is highly complicated. We have to be very careful how to conceptualize everything. There is also the danger that if too much time is spent in VTB and case consultation platforms, the hospital management could close it up. David agrees with this problem, therefore the UK developed an official framework for giving advice to other hospitals. Now they have multidisciplinary teams, before it was only 1 expert opinion.

Bruce Morland informs that the ECCO is anxious to provide detailed costs, especially if there is no indication who is going to pay. Currently his team gives several advices per week without payment. He

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points out that the initiative is so valuable, that it should be kept alive, even if there is no compensation. Ruth counters that the member states have already agreed that cross-border healthcare is compensated and it should be emphasized that a cross-border virtual tumour board is even saving costs by enabling the patient to stay at home. Nevertheless, according to Bruce it is a very complex issue, because different member states want different regulations. Dominik expects that most requests will stay on the national level, but international requests will increase and it would be very valuable to be at least able to fund the infrastructure for IT-platforms.

Gabriele Calaminus informs that big hospitals have national patient´s managements. They prepare consultations which are paid. Therefore recommendations are already available. All disciplines get specific amounts of money that the institution/patient has to pay. Probably virtual tumour boards could profit from it. She also informs that in the system she presented earlier today everything is paid and everyone is remunerated. In this context Enrique makes aware of the problem that despite compensation systems hospitals sometimes do not get their money back. It is not desired that the patient himself has to pay, probably in advance which would cause treatment inequalities. Therefore the social insurance system should be responsible for payment. This debate should be addressed and it is very complicated. It will take time and we need business cases. They need to know what a network is offering at which costs and the EC will approach the networks with specific questions.

Piotr makes aware that if you get a fee for a service you become liable. This should be clarified and avoided. Ruth agrees. She informs that St. Jude´s in the US also charges fees for advice without liability. However, it could be different in Europe.

David Walker shares his experience for a business case: they deal with 70 patients per week in 2h, they dedicate 1min to each adult patient and 4min to each child. Gianni emphasizes that it is not the intention to gain profit but to keep the system sustainable and make sure that the local parent/patient organizations will be held responsible for payment.

Closing remarks by **Gianni Bisogno**	17:40-17:45
End of VRT-workshop	