

A virtual consultation system for very rare tumors in children and adolescents – an initiative of the European Cooperative Study Group in Rare Tumors in Children (EXPeRT)

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ABSTRACT

Background: Very rare tumors (VRTs) in children and adolescents are orphan diseases defined by an annual incidence of <2/1000,000. For a long time, VRTs have been outside of clinical and research groups in the field of

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pediatric oncology. As a result, exchange of experience and development of therapeutic standards have not been promoted. After the foundation of several national VRT working groups and the European Cooperative Study Group on Pediatric Rare Tumors (EXPeRT), a virtual consultation system (VCS) has been established, which specifically aimed at facilitating access to clinical consultation in complicated cases of VRTs.

Methods: The VCS has been open to physicians. After initial registration, they can present VRT patients free of charge. Patient consent and data pseudonymization were mandatory. Within the VCS, disease specific interdisciplinary panel discussions with at least three experts from the EXPeRT group and partners have been opened, and at the end of the discussion, a written summary and recommendation was provided.

Results: Between Mai 2017 and March 2023, 160 cases from 27 countries (20 European, 7 non-European) have been discussed in the VCS. The most common diagnoses were adrenocortical carcinoma, malignant skin tumors and malignant ovarian tumors. In a survey three months after panel discussion, more than 90% of requesting physicians evaluated the VCS to be easy to use, helpful and to have a significant impact on patient management.

Conclusion: A VCS may provide significant assistance in the management of children and adolescents with VRTs. Furthermore, it may help to overcome inequalities in access to adequate treatment in countries with lower health care system resources or without established VRT study groups. Therefore, EXPeRT will continue to support the VCS. For this purpose, the VRT panels have been integrated into the Clinical Patient Management System (CPMS) within the European Reference Network Initiative (ERN PAedCan).

1. Introduction

The introduction of multidisciplinary treatment strategies constitutes a major advance in the improvement of the survival of children with cancer. For the most common childhood cancers, multimodal treatment is centrally coordinated by national or multinational cooperative groups and reference centers and international protocols are available to guide care. Most cooperative study groups offer multidisciplinary medical advice to the hospitals participating in the network. This consulting activity is organized in different ways at the national and international level, and it may provide different levels of assistance depending on the available resources and organization [1–3]. It has been shown that consultation in interdisciplinary tumor boards may have a positive impact on patient outcome, especially in specific subgroups of rare tumors [4,5]. Therefore, the constitution of interdisciplinary tumor boards, both at the cancer center and at the national or international study group level, is considered an essential component of excellence in pediatric cancer care. Tumor boards serve to coordinate a broad range of medical experts in different disciplines, allowing for discussions and decisions on how to best care for each single patient with cancer and thereby assuring optimal quality of care.

For a long time, patients with very rare tumors (VRTs) have not benefitted from the clinical and scientific progress achieved in pediatric oncology. The working definition of VRTs considers their extremely low incidence (<2/1.000.000) and their orphan status. Altogether, these tumors contribute to approximately 11% all childhood cancers. Nevertheless, due to the extreme rarity of each diagnostic entity, study groups have been formed until recently and diagnostic reference centers have not been established for many rare tumors. Furthermore, clinical trials have been performed only for a minority of VRTs such as adrenocortical and nasopharyngeal carcinoma [6]. The rarity of some tumors precludes the possibility to have tumor experts for each VRT in a single center. In fact, in most cases, pediatric oncologists may see a specific VRT only once during their lifetime. Therefore, optimal quality of care may require external advice more frequently for VRTs than for the more common cancers where experts can be found in many centers.

Therefore, after the European Cooperative Study Group on Pediatric Rare Tumors (EXPeRT) was founded in 2008, its work focused on two main activities. First, international analyses of specific VRTs were promoted such as pancreatic, ovarian and thymic tumors as well as tumors of the adult age such as malignant melanoma and colorectal cancer [7–9]. Second, there was a broad consensus that an international consultation network had to be established to share experience in the management of VRTs. In the beginning, this consultation network started at a very informal level, e.g., through the exchange of emails. However, it became clear very soon that more formal consultation would be required to increase quality. Thus, structured and detailed

medical information should be provided and there should be the possibility to pseudonymously share medical documents and pictures, while maintaining data safety issues. In addition, the consultation process should be open to collaboration with experts in adult cancers (e.g. carcinomas and melanomas).

The opportunity to build such a network came with the EU funded ExPO-r-NeT (European Expert Pediatric Cancers Reference Networks for Diagnostics and Treatment, <https://www.expornet.eu>) a pilot project to establish a European Reference Network in pediatric oncology. A survey showed that interdisciplinary tumor boards have been established in most pediatric cancer centers, but that national or international virtual tumor boards (VTBs) have rarely been established [10,11]. This results in significant inequalities in childhood cancer care, especially in countries with fewer health system resources. Therefore, the implementation of a virtual consultation system (VCS) has been recognized as an issue of utmost importance by the EU community. This endeavor has been included in the EU Directive 2011/24/EU of patients' rights in cross-border healthcare as a tool to increase the capacity of healthcare providers and fundamental to create a European Reference Network. Considering the limited infrastructure for VRTs, the establishment of a VCS specifically dedicated to VRTs in the pediatric age (0–18 years) has been integrated into the ExPO-r-NeT working packages (Fig. 1).

Within this working package, the structures and the organization of the VCS should be defined, and standard operative procedures for inquiries and responses to clinical questions had to be developed. The VCS should be accessible to pediatric oncologists from all EU member states. In the long perspective, the VCS should be the first step to build a database of experience based on cases discussed through the VTB.

2. Methods

A virtual tumor board (VTB) was constructed as a virtual consultation platform with protected access to physicians. The website was programmed by CINECA (vrt.cineca.it). The consultation procedure involved several steps (Fig. 2): The VCS could be contacted by the national VRT coordinator or by physicians primarily in charge of the patient. Parents, patients or other not professionals were invited to submit their requests only through the responsible physician. This restriction was required to assure reliable source data and thus, a meaningful consultation process. Requesting physicians were asked to provide their affiliation, and their identity was checked by the project coordinator (DTS). Prior to registration of the case, physicians were required to obtain patients' consent for pseudonymized presentation of clinical information. After presentation of the case, completeness of information and the appropriateness of the clinical consultation were reviewed by the coordinator. Then the discussion was opened to a disease specific tumor consultation board. In these tumor boards, at least three

for feedback, and 42 physicians replied (Table 2). All but one physician replied that they followed the panel’s advice, either partially (n = 6) or completely (n = 35). Thirty-nine users replied that they felt the panel discussion had an impact on patient management. Thirty-eight users considered the panel’s advice essential (n = 3), very helpful (n = 27), helpful (n = 8), and three found the advice only partially helpful and one not helpful at all. The effect of the consultation was summarized that it confirmed a decision already considered in 27 cases, that it changed a clinical decision already taken in 4 cases, and that in 10 cases, it supported in unclear situation where no decision had been taken before. Only one user took a decision different from the panel’s recommendation. On a scale from one to five, 23 users scored the system with five and 17 with four points. Finally, all users considered a VCS advisable for public support.

4. Discussion

Within childhood cancer, there are several inequalities that may have a significant impact on the quality of care of children with very rare tumors. First, the economic resources dedicated to pediatric oncology are unequally distributed between countries – even in EU countries, which would be considered comparably rich at a global perspective. Second, the clinical and scientific structures available for diagnostic assessment and therapy of childhood cancer may vary significantly

Table 1
Distribution of consultation requests by a) time and b) country.

a)		b)	
Year	Patients (n)	Country	Patients (n)
2017 (5–12)	6	Poland	27
2018	27	Greece	25
2019	26	Germany	22
2020	40	France	11
2021	19	Portugal	8
2022	25	Other European countries	50
2023 (1–3)	7	Non-European countries	17
Sum	160	Sum	160

between countries. In this context, it should be noted that a significant proportion of requests were sent from countries without a national tumor board specifically designated to VRTs. Last, the focus within pediatric oncology has long been on the more frequent cancer diagnoses such as leukemias, lymphomas, brain and embryonal tumors. With the establishment of the first national VRT working groups and with the foundation of EXPeRT, more attention has been drawn to VRTs. The project of a VCS specifically dedicated to VRTs now aims to overcome some of these major obstacles in the care of children with VRTs. Experience in the care of VRTs can be shared between national VRT working groups, both within and outside Europe. In addition, physicians from countries without dedicated VRT working groups may benefit from

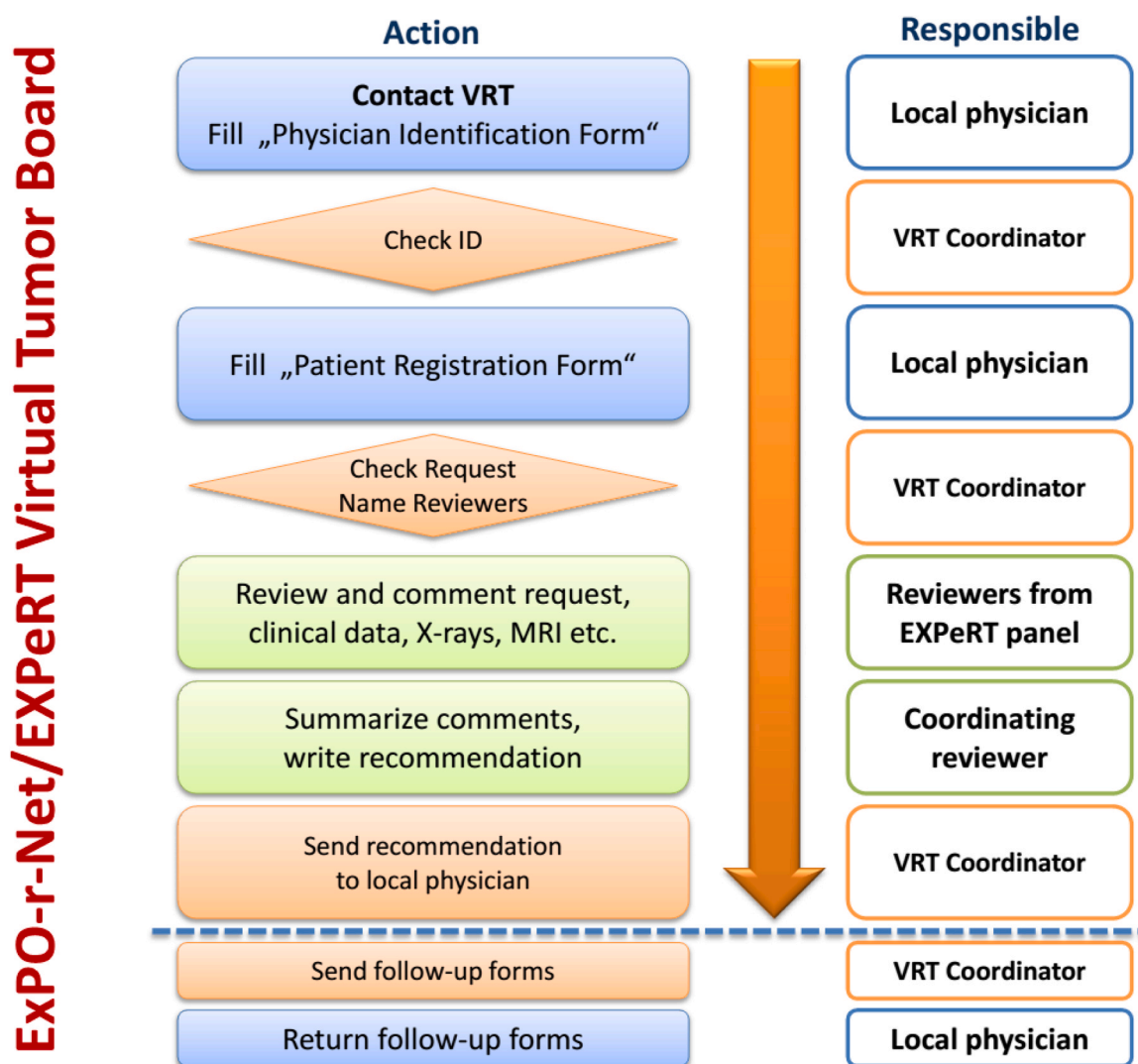


Fig. 2. VRT virtual consultation system: action and responsibilities.

Table 2
Evaluation of user feed-back three months after consultation at the VRT VCS.

The advice was ...	n	%
Essential	3	7
Very helpful	27	64
Helpful	8	19
Partially helpful	3	7
Not helpful	1	2
The received advice was followed	n	%
Yes	35	83
Partially	6	14
No	1	2
The advice has an impact on the patient's treatment	n	%
Yes	39	93
No	3	7
What was the effect of the advice?	n	%
It supported a decision I had already taken	27	64
It completely changed my decision	1	2
It partially changed my decision	3	7
I did not have a clear decision and the advice helped me to make a decision	10	24
In the end, I did not consider the advice	1	2
Sum	42	100%

experience gained in other countries with established VRT groups. Thus, disadvantages caused by both the rarity of the diagnosis or limited health system resources can at least in part be overcome. Consequently, an international VCS has the potential to have a significant impact on the quality of care of children and adolescents with VRTs by promoting international collaboration and driving research in this area.

One key benefit of an international VCS is the ability to connect healthcare professionals from different regions and countries, who may have different levels of expertise and experience in treating pediatric VRTs. By sharing knowledge and expertise, pediatric oncologists can also work together to develop new treatment consensus recommendations, in specific diagnoses even clinical trials that could benefit patients in Europe and all over the world [12–19]. This collaboration may also potentially help to reduce the lag time between the discovery of new treatments and their implementation in clinical practice, through enhancing the exchange of experience.

Another potential benefit of an international VCS is the ability to promote clinical research in this area. In the next step of European collaboration, the PARTNER project, the development of a common data base for VRTs is being promoted, into which information from the VCS could also be integrated [20]. Vice versa, the consultation process within the VCS may also benefit from experience documented in the common data base.

However, there are also some challenges that need to be considered in the implementation of this system. One of the main challenges is ensuring the security and privacy of patient data, as well as complying with various data protection regulations across different countries. This has been ensured by mandatorily requesting patient consent before registration of the request. Another challenge is ensuring that the system is accessible and user-friendly for healthcare professionals with varying levels of technological literacy and resources. To this respect there have unfortunately been some technical obstacles especially during the process of physician registration. On the other hand, the strategy to discuss cases in a chat format that does not require simultaneous presence of the panel participants, and has significantly facilitated access to the panel discussions. However, in some cases, we observed that discussions were fading out, when further questions were raised, and panel partners did not return to the discussion. Thus, stronger guidance of the discussion will be required for such cases. In this context, the response rate of 26% to the anonymous follow-up survey is not satisfactory, probably due to the fact that this survey was not mandatory. However, the overall feedback to the consultation system was positive, urging us to further develop this project. Last, the system should ideally be constructed and continuously maintained so that a long-lasting use is ensured.

Considering these critical issues, the EXPeRT group has decided to move the current VRT VCS to the Clinical Patient Management System (CPMS) already established for other childhood cancers within the ERNPaedCan and for other rare diagnoses [21]. This EU-based system considers all relevant data safety issues and ensures continuous technical support. Of note, the system also includes additional features such as the possibility to include DICOM data from radiological examinations and a safe video conferencing tool, so that the quality and intensity of patient discussion can further be enhanced.

Last, the aspects of resources also need to be addressed. The VCS and the future CPMS may be able to solve technical and legal issues, but it does not resolve the need for continuous coordination of the system. Furthermore, it is also necessary to support the efforts of the experts who must carve out time required to discuss complex cases during their intense daily activity. Therefore, the recently established ERNs should ideally be able to support these initiatives and the personal efforts of the panel leaders and discussants. And this work should find recognition and support from the institutions where the experts operate.

In conclusion, an international VCS has the potential to have a significant impact on the clinical care of children and adolescents with VRTs, promote international collaboration, and drive research in this area.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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