Nationwide central diagnosis review for childhood solid tumors: From concept to realization of an Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) integrated project

Commentary

Nationwide Central Diagnosis Review for childhood solid tumors: from concept to realization of an Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) integrated project

Spreafico F,[1] Quarello P,[2] Alaggio R,[3,4] Collini P,[5] Haupt R,[6] Mastronuzzi A,[7] Prete A,[8] Rabusin M,[9] Rizzari C,[10] Schumacher F,[11] Zecca M,[12] Pession A,[8] Fagioli F.[2,13]

[1]Pediatric Oncology Unit, Department of Medical Oncology and Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy

[2]Pediatric Onco-Haematology, Stem Cell Transplantation and Cellular Therapy Division, Regina Margherita Children's Hospital, Azienda Ospedaliera-Universitaria Città della Salute e della Scienza, Torino, Italy

[3]Department of Pathology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, U.S.A.

[4]Department of Medicine-DIMED, Padova University Hospital, Padova, Italy

[5]Soft Tissue and Bone Pathology, Histopathology and Pediatric Pathology Unit, Department of Diagnostic Pathology and Laboratory Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy

[6]Epidemiology and Biostatistics Unit, IRCCS Istituto Giannina Gaslini, Genova, Italy

[7]Neuro-Oncology Unit, Department of Pediatric Hematology/Oncology and Cellular and Gene Therapy, Bambino Gesù Children's Hospital, Roma, Italy

[8]Hematology-Oncology Unit, Department of Pediatrics, University of Bologna, Bologna, Italy

[9]Hematology-Oncology Unit, Department of Pediatrics, Institute of Maternal and Child Health, IRCCS Burlo Garofolo, Trieste, Italy

[10]Pediatric Hematology Oncology Unit, Department of Pediatrics, University of Milano-Bicocca, MBBM Foundation, Monza, Italy

[11]Pediatric Hematology Oncology, University Children's Hospital "Ospedale dei Bambini", ASST Spedali Civili, Brescia, Italy

[12]Pediatric Hematology/Oncology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

[13]Università di Torino, Torino, Italy

Corresponding author

Filippo Spreafico, MD

Pediatric Oncology Unit

Fondazione IRCCS Istituto Nazionale dei Tumori

Via G. Venezian 1, 20133 Milano, Italy

filippo.spreafico@istitutotumori.mi.it

Phone: +39 0223902590

Fax: +39 0223902648

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Abbreviations:

CPR, central pathology review

AIEOP, Associazione Italiana Ematologia Oncologia Pediatrica

CDR, central diagnosis review

AxMR®, Advanced eXtended Multicentre Research

UPN, unique patient number

IT, information technology

HTTP, hyper text transfer protocol

SSL, secure sockets layer

Childhood cancer is relatively uncommon: in Europe incidence rates range from 140–170 per million person-years in children younger than 15 years, and from 180–240 per million in those aged 15–19 years.[1] Their prognosis has substantially improved over recent decades, in part because of the assessment and development of their optimal treatment. In this scenario, efforts to improve every single step of cancer cure, including diagnostic accuracy, are becoming significant.

For solid tumors, a correct histopathologic diagnosis is regarded as a cornerstone to implement staging and treatment regimen, and hence potentially influencing final patient outcome. In current practice, despite the clinical relevance of histology at diagnosis, a degree of discordance in the interpretation of morphology or in the integration with ancillary techniques (i.e. immunohistochemistry or molecular pathology) still remains even among experienced pathologists, above all for rare or complex diseases.[2,3] As an example, potentially clinically significant discordances have been documented in childhood renal tumors: 39% of anaplastic cases (which demand intensified therapies as compared to the other histological subgroups) in the National Wilms Tumor Study-5 were not initially recognized by the institutional pathologist, and there were discordances in tumor stage in 19% of these cases.[4] A similar disagreement between local pathologist and secondary specialized review has been recorded in other tumors in both pediatric[2,5] and adult[3,6,7] settings.

Due to their rarity and peculiar characteristics compared to those encountered in adults, tumors in children and adolescents should be submitted for prospective rapid central pathology review (CPR) by pathologists with sub-specialty expertise in pediatric oncologic pathology to review diagnosis and implement tumor staging, especially those registered into clinical trials (CPR is a standardized procedure in most clinical protocols). In rare cancers, CPR is even more relevant and may ensures consistency in the diagnosis, subclassification, and adequate pathological staging.

Until recently, in Italy the submission of childhood tumors for CPR was more based on local hospital enterprise and policy, and only in some circumstances within organized frameworks, especially when

patients had to be registered in controlled clinical trials. In these situations, costs for specimen shipment was heterogeneously covered by private financing, *ad hoc* grants, or local centers resources. With experience of previous and ongoing protocols, it became almost expected and 'accepted' that up to 30% of cases would never be submitted for CPR, undermining the efforts of other health professionals who submit their specimens/data. The overall rate of diagnostic discrepancies encountered during CPR within the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) protocols have never been well assessed.

Within the AIEOP central committee it has become increasingly recognized that there may be benefits from the introduction of a more systematic and nationwide CPR for pediatric tumors throughout Italian pediatric oncology centers. Extrapolation of literature data[2] has suggested us that in the absence of CPR, potentially > 150 patients per year treated at AIEOP institutions (out of 1,500-1,700 newly diagnosed cases) could receive inappropriate therapy, based on incomplete or inaccurate pathologic information.

AIEOP first identified needs, priorities, and areas for potential improvement in this field (also basing on an *ad hoc* survey addressed to Italian pediatric pathologists), such as increasing the rate of cases submitted to reference pathologists for CPR; linking the CPR diagnosis with demographic/clinical patient existing records of AIEOP central database; improving feedback communication to treating clinicians, especially when diagnostic discrepancies may affect clinical patient management.

As a first action, in 2016 AIEOP set up a pre-paid shipping system to ease and logistically support the submission of pathology specimens from 49 accredited AIEOP centers to 9 centralized reference laboratories.

AIEOP subsequently conceived a central diagnosis review (CDR)-platform linked to the exiting web-based AIEOP national database for childhood cancer (known as Mod.1.01 form[9]), based on the IT solution AxMR® (Advanced eXtended Multicentre Research) and developed by Cineca (an Interuniversity Computing Center). Cineca IT infrastructure is certified for data quality procedures

(ISO 27001:2013 certification, https://www.cineca.it/en/content/certifications) and through HTTP and SSL protocols encryption standards.

The CDR-platform provides a secure online database that guarantees compliance to up-to-date high security and quality standards and meets all the requirements set by the European General Data Protection Regulation.

Through this approach, the entire data flow concerning histolopatologic review connects to existing patient demographic and clinical data (diagnostic, protocol, follow-up) and is based on a patient-centric approach (Fig. 1): at diagnosis (of a solid childhood cancer or leukemia) every patient is registered onto Mod.1.01 once, after obtaining informed consent from parents or guardian, and is identified by a Unique Patient Number (UPN). All patient personal data are encrypted for all system users except for responsible clinicians (including reference pathologists, who can examine clinical information relevant for diagnosis). Through the UPN, the patient can then be assigned to the CDR-platform and referred for CPR to a given centralized laboratory depending on his/her primary diagnosis (the AIEOP pathology working group has agreed upon pathologists of reference for each type/family of cancer). The CDR-platform then allows reference pathologists to return their report to the responsible clinicians, and linked to all the remaining patient records available in Mod.1.01. Alert messages guarantee real-time traceable flow of information, from the referring center to the reference laboratory, and forwards. A traffic light system notifies any diagnostic discrepancy, pushing for contact between reference pathologists and physicians in charge of the patient care.

Noteworthy, through integration of reviewed histopathologic diagnosis into comprehensive clinical patient data, AIEOP also aims to improve the quality of data itself.

Routine second review of pathologic material is time consuming, and its value and utility is questioned by hospitals. However, pathologic second review could lower overall care costs by preventing inappropriate therapy (both over- and under-treatment), especially when pathologists with subspecialty expertise are responsible for second review of rare tumors.[10] This subject should be

better defined at national level by appropriate regulation/legislative support making CPR mandatory, and better defining the terms of responsibility of reviewer and local pathologists, respectively.

Whether all types of childhood cancers need to be reviewed is debatable. However, since pathologists themselves consider pediatric oncology a minefield, especially in countries where specific training/specialization on pediatric pathology does not exists, we regard the national review of all cases enrolled into protocols for initiation of cure as an important system of quality control and an error-reduction strategy.

Recognizing timely obtaining the correct diagnosis and treatment plan critical to the outcome for each patient, we hope that in future this project might be supported by the Italian Health Care system as other value-based programs.

The utilization of the system over time will highlight both its strengths and weaknesses, providing inputs as to where develop it further. The AIEOP CPR system provides pathologists with a quality of practice improvement tool for reporting, documenting and tracking centralized diagnosis. The analysis of its use will give us more data about the overall rate of diagnostic discrepancies across Italian pediatric cancers or other quality assurance indicators (which will be monitored overtime), and thus an estimate of the impact of inappropriate treatment on health care costs.

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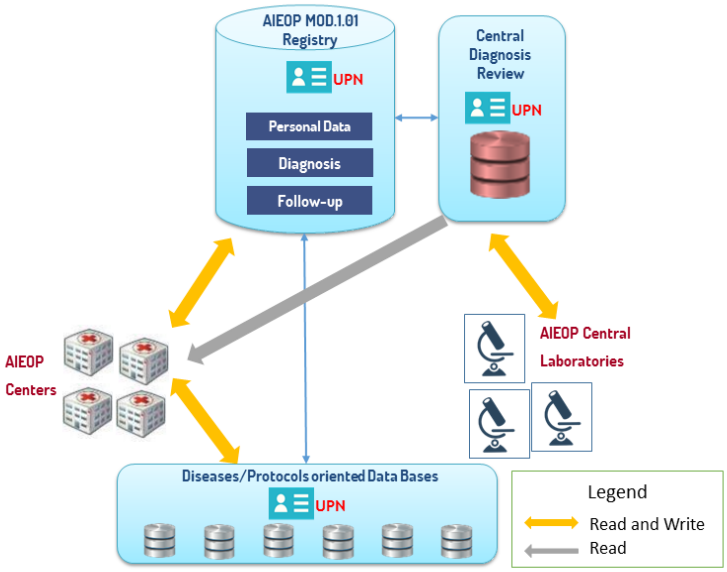

Figure legend

Figure 1. Data flow and access. The cartoon summarizes how the recently introduced Central Diagnosis Review (CDR)-system works, and interacts with the existing nationwide database for children with cancer (named Mod. 1.01). A) AIEOP centers register each patient with newly diagnosed solid tumor or leukemia (identified by a Unique Patient Number, UPN) into Mod. 1.01; B) Mod. 1.01 is a prospective database, containing demographic and clinical data, which in turn is linked to different disease-specific protocol databases; C) to start a central pathology review (CPR) process, AIEOP centers ship pathology specimens to the reference laboratories through a pre-paid courier, while launching the request for CPR for a given patient (identified by UPN) through the dedicated CDR-platform on Mod. 1.01; D) a system of messages notify reference pathologists, who receive

specimens, and upload the reviewed report on Mod. 1.01 patient unique repository; local centers are finally notified when the CPR is complete.