Original Report

A Novel Standard for Systematic Reporting of Neuroblastoma Surgery:

The International Neuroblastoma Surgical Report Form (INSRF)

A Joint Initiative by the Pediatric Oncological Cooperative Groups SIOPEN*, COG and GPOH*****

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SHORT RUNNING HEAD:

The INSRF a joint SIOPEN-COG-GPOH initiative

MINI ABSTRACT:

Presentation of the first universal structured reporting tool to document all neuroblastoma surgical procedures and their outcome(s), created by a unique collaboration of three international Pediatric Oncological Cooperative Groups, to facilitate treatment planning, recording of post-operative metrics (Clavien-Dindo) and analysis of the crucial role of surgery in neuroblastoma.

ABSTRACT

Objective: To create the first structured surgical report form for neuroblastoma (NBL) with international consensus, to permit standardized documentation of all NBL-related surgical procedures and their outcomes.

Summary Background Data: NBL, the most common extracranial solid malignant tumor in children, covers a wide spectrum of tumors with significant differences in anatomical localization, organ or vessel involvement and tumor biology. Complete surgical resection of the primary tumor is an important part of NBL treatment, but may be hazardous, prone to complications and its role in high-risk disease remains debated. Various surgical guidelines exist within the protocols of the different cooperative groups, although there is no standardized operative report form to document the surgical treatment of NBL.

Methods: After analyzing the treatment protocols of the SIOPEN, COG and GPOH pediatric cooperative groups, important variables were defined to completely describe surgical biopsy and resection of NBL and their outcomes. All variables were discussed within the Surgical Committees of SIOPEN, COG and GPOH. Thereafter, joint meetings were organized to obtain intercontinental consensus.

Results: The "International Neuroblastoma Surgical Report Form" (INSRF) provides a structured reporting tool for all NBL surgery, in every anatomical region, documenting all Image Defined Risk Factors and structures involved, with obligatory reporting of intraoperative and 30 day-postoperative complications.

Conclusion: The INSRF is the first universal form for the structured and uniform reporting of NBL-related surgical procedures and their outcomes, aiming to facilitate the postoperative communication, treatment planning and analysis of surgical treatment of NBL.

KEYWORDS

Neuroblastoma; surgery; biopsy; resection; tumor; standardization; operation; reporting; high-ris;, postoperative; complication; outcome; quality; Clavien-Dindo Classification

ABBREVIATIONS

COG: Children's Oncology Group

CT: Computed Tomography

GGLN: Ganglioneuroma

GGLNBL: Ganglioneuroblastoma

GPOH: Gesellschaft fuer Paediatrische Onkologie und Haematologie – German Association for Pediatric Oncology and Hematology

Gy: Gray

IDRF: Image Defined Risk Factor

INRG: International Neuroblastoma Risk Group

INRGSS: International Neuroblastoma Risk Group Staging System

INSRF: International Neuroblastoma Surgical Report Form

IVC: Inferior Vena Cava

MIBG: MetaIodoBenzylGuanidine

MRI: Magnetic Resonance Imaging

NBL: Neuroblastoma

NOR: Narrative operation report

NSRF: Neuroblastoma Surgical Report Form

SIOPEN: SIOP Europe International Neuroblastoma Study Group

SOR: Synoptic operation report

SVC: Superior Vena Cava

US: ultrasound

USA: United States of America

INTRODUCTION

Neuroblastoma (NBL), an embryonal sympathetic nervous system tumor, is the most common cancer in infants and the most common extracranial solid malignant tumor in children (1) (2) (3) (4) , with an overall age-standardized incidence rate of 10.2 to 10.9 cases per million children in the USA and Europe respectively. (2) (3) NBL accounts for 6% of all childhood cancers (1) and 12-15% of cancer-related deaths under the age of 15 years. (3, 5) NBL has a broad spectrum of clinical behavior that correlates with a number of clinical and biological features. (6) Following international consensus, NBL is treated multimodally, according to the pretreatment International NBL Risk Group (INRG) classification system. (6) This system identifies four risk categories (very low-, low-, intermediate- and high-risk) taking into account the tumor stage, age at diagnosis, histology, grade, MYCN status, chromosomal aberrations and tumor cell ploidy. (6) To uniformly stage NBL before the initiation of treatment, the INRG-Staging-System (INRGSS) was developed, based upon tumor imaging and on the absence or presence of preoperative “Image-Defined Risk Factors” (IDRFs). (7) These IDRFs describe the various locations where NBL may occur and the vital structures (organs, vascular and neural structures) that may be involved by the tumor. (8)

As NBL originates from developmental anomalies of the neural crest, there is a wide spectrum of locations where the primary tumor may occur, related to the sympathetic nervous system anatomy. (3) The anatomical distribution of NBL can be described by compartmental classification (Figure 1) (4) and most primary tumors arise in the abdominal compartment (adrenal gland 48%, extra-adrenal retroperitoneum 25%). The thoracic location of NBL is less frequent accounting for 16-20%, and the cervical and pelvic compartments account for three to five percent of NBL respectively. (4) Recent studies suggest that the sympathetic anatomical location of NBL may also be relevant as a prognostic factor. (4)

Local control of the primary tumor by complete surgical resection is an important part of NBL treatment. The role of surgical resection in high-risk NBL however remains debated as it is difficult to study, due to the relative rarity of NBL, its different localizations, heterogenous presentations (4) and internationally varying treatment protocols, incorporating postoperative radiation therapy to aid in local control. Especially for high-risk NBL, divergent results have been reported on the role, extent and timing of surgical resection. (9) (10) (11) In addition, the reporting of surgical treatment of NBL is not standardized and may vary considerably. As the surgical reporting of a postoperative residual primary tumor may influence postoperative irradiation planning in future high-risk NBL treatment protocols, the documentation of NBL surgery and its immediate outcomes must be optimized. Improving the quality of surgical reporting will also facilitate the analysis of the role, extent and timing of surgical treatment in NBL. Therefore we aimed to develop a uniform, structured report form to document every NBL-related surgical procedure.

MATERIAL AND METHODS

A working party group within the Surgical Committee of SIOPEN, under the joint leadership of the first and the last author, started in 2014 with the NBL-Surgical Report Form-project. After the approval of the members of the Surgical Committees of the Children's Oncology Group (COG) and of the German Association of Paediatric Oncology and Haematology (GPOH), the surgical guidelines in the different study protocols of SIOPEN, COG and GPOH were analyzed to identify the variables needed to completely describe the mode and impact of surgical interventions (biopsy and resection) for NBL, as well as the outcomes of the surgical intervention. All crucial variables describing the timing, mode, management of IDRFs and the operative results were listed, defined and discussed within the working group of the SIOPEN Surgical Committee.

Thereafter, a first draft of a structured report form was developed, in different steps, discussing each step within the SIOPEN Surgical Committee, until consensus was reached on the Neuroblastoma Surgical Report Form (NSRF). In parallel, the same action was performed within the Surgical Committees of COG and GPOH. Over the years, several joint meetings were organized to discuss and standardize the NSRF draft together with the members of all three Surgical Committees in order to obtain intercontinental consensus. After its conception, the International NSRF was tested and used in clinical practice by the members of the core working party group, confirming its feasibility and completeness,

RESULTS

The International Neuroblastoma Surgical Report Form (INSRF) is the first universal report form to document every NBL-related surgical procedure (biopsy and resection) and contains five sections on five pages, see Figure 2. The first four sections are ideally completed by the surgeon immediately after the surgical intervention.

The first section of the INSRF includes coded patient and treatment protocol details.

The second section involves the type, timing and date of the intervention, the surgical approach (open or minimally invasive surgery) and the extent of the biopsy or resection, including four options, defined with international consensus: "*complete resection*" ; "*minimal residue*" (defined as "less than five cubic centimeter of tumor remaining") ; "*incomplete resection*" (defined as "five or more cubic centimeter residue") or "*other*", for which detailed information is then fully requested.

The localisation of the primary tumor is uniformly reported by the indication of the anatomical compartment(s) (cervical, cervico-thoracic, thoracic, thoraco-abdominal, abdominal/pelvic). Surgical metastatic sites are reported by organ. Preoperative plan discussion at a multidisciplinary tumor board is recorded.

In addition, section two incorporates the description of all preoperative post-chemotherapy IDRFs, according to the definitions of terms to describe relationships between primary tumor and vital structures stated in the INRG Guidelines for Imaging and Staging of Neuroblastic Tumors. (8)

The surgical findings are documented in the third section of the INSRF. Here, the surgeon indicates and documents all organs and structures involved, as well as their individual intraoperative management, by the use of agreed-upon and well-defined surgical terminology. To document vessel involvement, the surgeon can differentiate between two types: '*adherence*' is defined as vessel involvement of <50% of the circumference, and

'*encasement*' as 50-100% of the vessel circumference. (12) If a blood vessel was injured, the surgeon specifies how this injury was managed during the surgical intervention and if macroscopic residual tumor remained at this location or not. The side of the vessel is indicated and in case of bilateral involvement, detailed specifications per side can be added as free text. In the same fashion, organ involvement is to be reported. When appropriate, the side of involvement is documented and in case of bilateral involvement detailed specifications per side can be added as free text. The type of organ involvement is stated as '*adherence*' (defined as close contact between tumor and organ but with a distinct plane of dissection) or '*infiltration*' (no distinct dissection plane, necessitating partial (even minimal) organ resection). The surgeon then documents how the organ involvement was treated by the use of one out of three options ("*no organ resection"* – "*partial organ resection"* or "*complete organ resection"*) and whether macroscopic residual tumor was left or not. Liver involvement is described using the segmental classification, as described by Couinaud.(13)

The fourth section of the INSRF documents all intraoperative complications and the management/intervention(s) performed to solve the complication, with enough free text space to add detailed specifications or remarks.

Possible intraoperative deviations from the preoperative plan discussed at a multidisciplinary tumor board can be indicated and described in detail.

The last section of the INSRF is to be completed by the surgeon one month after the operation. This final part describes the postoperative complications, related to the surgery, during the first 30 days after the operation, see Figure 2. To standardize the reporting of postoperative outcomes, the Clavien-Dindo classification was adopted, with space added in the form for free text specifications. (14) (15) In addition, the surgeon is expected to report any unscheduled delay of the postoperative chemotherapy regimen(s) due to the surgery or its complications within the first 30 days after the surgical intervention and to specify how long this delay lasted (in days). (11)

DISCUSSION

We created the first INSRF with intercontinental consensus for the structured and uniform reporting of all NBL-related surgical procedures and their outcomes. Due to the various locations of NBL and frequent encasement or infiltration of vital structures and organs, the surgical treatment of NBL may be highly challenging with important operative morbidity and even mortality.(9) (16) In localized NBL, the impact of surgical resection is well established and surgical resection is an important part in the multimodal treatment protocols. (17) (18) In high-risk NBL and especially in case of distant metastatic disease, the role of surgical resection remains an unsolved issue even after more than 25 years of debate, with many authors favoring complete or gross total resection of the primary tumor (10, 11, 19) (20) (21) (19) (22) (23) (24) - while other authors question the role of aggressive surgical resection for high-risk NBL. (9) (11, 12) (25) The reasons for these contradictory conclusions are linked to differences in protocols, especially indication, dose and field of adjuvant radiotherapy (26) , but also to the subjective appraisal of the completeness of resection, which relies predominantly on the surgeon's report. The assessment of the post-operative residue on imaging is not standardized and differently taken into account across the cooperative protocols. (19, 25, 27)

Postoperative Irradiation has an important role in the multimodal treatment of high-risk NBL but is implicated in numerous late toxicities, including impairment in musculoskeletal growth, fertility, cardiopulmonary function as well as endocrinopathies, bladder dysfunction poor psychosocial health and secondary malignancies. (24) The new SIOPEN HR-NBL2 protocol will randomize patients with macroscopic residual disease to receive a radiation boost of 36 Gray (Gy) on post-operative residue, in addition to the baseline irradiation field of 21 Gy (depending on the preoperative tumor volume). (unpublished data) The patient will be considered to have no macroscopic residue at the time of radiotherapy if, cumulatively:

- the postoperative MRI (or CT scan, if no MRI available) shows no definite residual tumour **and**
- the postoperative metaiodobenzylguanidine (MIBG) scan shows no residual tumour **and**
- the surgical report mentions a complete or minimal residual resection (< 5 cm_3 residual tumour remaining, according to international consensus (unpublished data) agreed upon during joint meetings with the surgeons and oncologists of the SIOPEN, COG and GPOH Surgical Committees (Fig.2).

Postoperative treatment will therefore rely on the surgeon's estimation and image-based description of the residue.

A recent analysis of the COG A3973 data did not show a statistically significant difference in outcomes based on the extent of prophylactic lymph node irradiation, regardless of the degree of surgical resection. (24) While awaiting the results of the COG phase 3 trial ANBL0532, lowering the volume of postoperative irradiation and adapting an eventual boost on postoperative residue may also become part of upcoming COG NBL trials. (24) (unpublished data, personal communication)

Adequate documentation by the surgeon of the extent of surgical resection and of the volume and localization of postoperative residue, will therefore become essential and will need to rely on uniform, structured reporting, guided by clear-cut, unequivocal definitions. (12)

Recent analysis of 220 patients in the COG A3973 study (evaluating the impact of extent of primary tumor resection on local progression and survival and the assessed concordance between clinical and central imaging review-based assessments of resection extent), revealed however an important discordance (37%) between the operating surgeon's assessment of the extent of resection and imaging-aided assessment. (19) This may be related to the pitfalls of narrative operative reports (NORs) as their content is not

standardized nor regulated and may therefore be of variable quality.(28) (29) In cancer surgery, several authors have recently pointed out that NORs are seldom complete and may be of poor quality (29) (30) (31) (32) (33) (34) suggesting the development and use of standardized operative reports, also known as synoptic operative reports (SORs). Electronic SORs have been developed and implemented with proven benefit and multiple studies proving a gain in time. (35) In addition, structured operative reporting may even be beneficial for surgical education. (36)

The first version of the INSRF presented here is not intended to be a SOR : it is at present a standardized surgical report form, conceived as a structured checklist for the uniform registration of important variables and relevant clinical information on the surgery of NBL and its immediate outcomes. The obligatory standardized registration of intra- and post-operative complications according to the Clavien-Dindo classification (14) (15) will improve the quality of data and facilitate even more the international comparison of different surgical timings, approaches, extents of resection and their outcomes. (19)

As the INSRF incorporates standardized reporting of the preoperative post-chemotherapy IDRFs, it will also aid in the analysis of the role of pre- versus post-chemotherapy IDRFs and tumor volumes. (4) (7) (8, 12) (37) (38)

Furthermore, the INSRF may be used as well for the reporting of surgical interventions of other neuroblastic tumors (i.e. ganglioneuroblastoma, ganglioneuroma,…) - where there is also still controversy on the approach, extent and timing of surgical treatment. (8) (37)

After its use by the members of the core working party group, confirming the feasibility, user-friendliness and completeness of the INSRF, next steps in this joint international collaboration will be the further implementation into clinical practice, by the members of the surgical committees of SIOPEN, COG and GPOH, to collect feedback from the individual

users and further study adherence to the form. Interested pediatric surgical oncologists from other continents are also kindly invited to join this project. Development of an electronic web-based INSRF is highly recommended to allow surgeons to fill out the form immediately after surgery, warranting adherence and the quality of data. The inclusion of an automated reminder to the surgeon 30 days after the operation to complete the registration of postoperative complications will ensure, as it was demonstrated in adult SORs for cancer (39) , higher rates of essential data completeness, intra- and interobserver reliability and faster and more efficient data entry.

The INSRF is highly compatible with different treatment protocols for localized, intermediate and high-risk NBL. Its systematic incorporation in the new upcoming international NBL protocols of all cooperative groups will allow better analysis and definition of the surgical strategy in NBL treatment and comparison of local control modalities between international and cooperative groups.

In conclusion, the INSRF is the first attempt towards a universal operative report form for the structured and uniform reporting of all NBL-related surgical procedures. By documenting important perioperative data and outcomes, the INSRF will facilitate the analysis of the surgical treatment of NBL.

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joint collaboration across all borders, that gave birth to the first standardized INSRF.

LEGENDS FOR FIGURES

Figure 1: Radiogenomics classification of neuroblastoma by anatomical localization of the primary tumor: compartmental versus sympathetic chain classification with respective genomic profile distribution. (4) (with permission of the authors)

Figure 2: The International Neuroblastoma Surgical Report Form (INSRF): paper form on 5 pages.

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