**BEYOND IMAGE DEFINED RISK FACTORS (idrfS): A Delphi survey Highlighting definition of the Surgical Complexity Index (SCI) in Neuroblastoma**

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# RUNNING TITLE

A surgical tool for risk stratification in NB surgery

# KEYWORDS

Neuroblastoma, Surgery, Risk Factors, Delphi Survey

# ABBREVIATIONS

|  |  |
| --- | --- |
| **ABBREVIATION** | **FULL TERM** |
| IDRFs | Image Defined Risk Factors |
| INRGSS | International Neuroblastoma Risk Group Staging System |
| INSFR | International Neuroblastoma Surgical Report Form |
| IPSO | International Society of Pediatric Surgical Oncology |
| NB | Neuroblastoma |
| pre-IDRFs | Preoperative Image Defined Risk Factors |
| SCI | Surgical Complexity Index |
| SIOPEN | International Society of Pediatric Oncology Europe Neuroblastoma Group |

# ABSTRACT

BACKGROUND  
Preoperative evaluation of Image Defined Risk Factors (IDRFs) in neuroblastoma (NB) is crucial for determining suitability for upfront resection or tumor biopsy. IDRFs are linked with a higher potential morbidity at operation and lessen the chance of complete tumor resection. The IDRFs do not all carry the same weight in predicting tumor complexity and surgical risk. In this study we aimed to assess and categorize the degrees of surgical complexity (Surgical Complexity Index, SCI) in NB resection.

 PROCEDURE  
A panel of 15 surgeons was involved in an electronic Delphi consensus survey to identify and score a set of shared items predictive and/or indicative of surgical complexity, including the number of preoperative IDRFs. Risk categories included - (a) Standard risk; (b) Moderate risk; (c) High risk; (d) Very high risk. A shared agreement included the achievement of at least 75% consensus focused on a single category or, alternatively, on the sum between the prevailing category and an immediately closest one.

## RESULTS

After 3 Delphi rounds, agreement was established on 25/27 items (92.6%). A severity score was established for each item ranging from 0 to 3 with an overall SCI range varying from a minimum score of zero to a maximum score of 29 points for any given patient.   
 CONCLUSIONS  
A consensus on a SCI to stratify the risks related to tumor resection was established by the panel experts. This index will now be deployed to critically assign a better severity score to IDRFs involved in NB surgery.

INTRODUCTION  
Peripheral neuroblastic tumors (PNTs) such as neuroblastoma (NB) comprise some 10% of all pediatric solid tumors. NB is derived from primordial neural crest cells and can therefore develop anywhere along the sympathetic nervous system (1). The International Neuroblastoma Risk Group Staging System (INRGSS) stratifies NB into four distinct categories. Localized tumors are staged as L1 or L2 depending on the absence or presence of Image Defined Risk Factors (IDRFs) and metastatic tumors into M (presence of distant metastases) and Ms for metastases limited to the skin, liver, and bone marrow in infants younger than 18 months of age (2). Based on stage, age at onset, biological features and histology, treatment is multimodal. Induction chemotherapy is always performed in high-risk tumors before surgery, whereas in localized non-high-risk tumors, the presence of IDRFs at diagnosis contraindicates upfront resection (3). Following neoadjuvant chemotherapy, preoperative re-evaluation of IDRFs (pre-IDRFs) does not always contraindicate safe surgery (4), although it has been shown that persistence of some pre-IDRFs correlates with surgical outcomes in terms of completeness of resection (4-10). This is linked to the fact that IDRFs are not all equivalent in terms of complexity and surgical risk. Hence in this current report we aimed to assess and categorize the degrees of surgical complexity in NB resection. A Delphi survey was conducted among a surgical panel of experts with the specific aim of defining a novel Surgical Complexity Index (SCI) for more accurate risk stratification in NB surgery. Based on this experience, a future larger cooperative study will be designed to risk stratify each IDRF that perhaps may direct surgical care of the most challenging patients to expert centres.

METHODS  
The study project and Delphi survey were approved by the primary author’s local ethical committee (protocol n.471/2021). Anonymized data were stored on a secure online server and managed according to the European General Data Protection Regulation (11). A panel of 15 pediatric surgeons actively participating in the International Society of Pediatric Oncology Europe Neuroblastoma Group (SIOPEN) and in the International Society of Pediatric Surgical Oncology (IPS0) was involved in an electronic Delphi consensus survey aiming at identifying shared items predictive and/or indicative of the surgical complexity dealing with NB (5). Surgeons were asked to attribute a grade of risk stratification to each item based on their own experiences and perspectives. Risk categories were scaled and defined as follows: (a) *Standard risk*, for those items which were not considered to lead to an increase in the degree of risk beyond the general surgical risk; (b) *Moderate risk*, for those items thought to limitedly increase the degree of risk beyond the standard risk; (c) *High risk*, for those items thought to significantly increase the degree of risk beyond the standard risk; (d) *Very high risk*, for those items thought to most severely increase the degree of risk beyond the standard risk.

A shared agreement with the surgical panel was then considered adequate and reached with the achievement of at least 75% consensus focused on a single answer or, alternatively, the simultaneous fulfillment of the following conditions: (1) at least 60% consensus focused on the prevailing risk category; (2) at least 75% consensus in the sum between the prevailing category and an immediately closest category (12). At the end of each Delphi round consultation, responses to each outcome were summarized and returned anonymously to the panel within the subsequent rounds. Participants were invited to consider the views of others before score re-rating and, when appropriate, change their individual responses based on the feedback from previous Delphi rounds. Based on the consensus, each item was then scored from 0 (“standard risk”) to 3 (“very high risk”) depending on the grade of agreed perceived risk.

# RESULTS

Among a list of 18 items possibly predictive and/or indicative of surgical risk in NB, the panel agreed upon 11 of them and gathered them in three domains, including pre-operative, intra-operative, and post-operative. Each item, where relevant, was divided into sub-categories for a better specification of the surgical risks, thus ending with a total of 27 issues to be analyzed with the Delphi survey (Table 1). Three Delphi rounds were needed to reach agreement on 25/27 items (92.6%). All experts completed the first two rounds, while 87% of surgeon members completed the final third round (Figures 1, 2, 3). Though thought to somehow increase surgical risk, two items, namely metastatic status and intraoperative complications involving organ, vessel, and/or nerve injury with normal residual function, did not reach a consensus among the surgical panel of experts on the degree / amount of their impact on surgery and were therefore excluded from the final SCI list. The absence (namely L1 stage) and the presence of four or more pre-IDRFs were judged nearly unanimously (87% of consensus) as related to “standard” and “very high risk” respectively. Based on the survey results, a severity score was then established for each item ranging from 0 (standard risk) to 3 (very high risk), with an overall SCI score ranging from a minimum of 0 to a maximum of 29 points for any given patient (Table 2). Among many preoperative items, preoperative radiotherapy/metabolic therapy, and the presence of 4 or more pre-IDRFs received the highest severity score. A two-body compartment surgical approach, massive blood loss, and intraoperative death were notably considered indicative of very complex surgery. Postoperatively, a macroscopic tumor residue estimated to be more than 5 ml in volume as well as complications graded as Clavien-Dindo 4 or 5 were similarly attributed to high-risk surgery.

DISCUSSION  
The ability to better define and stratify surgical risks is of vital importance in the surgical planning of NB resection. IDRFs have been initially elaborated as objective imaging characteristics that might be associated with surgical complications to avoid upfront risky surgery and propose neoadjuvant chemotherapy in localized disease (2,13). The recent introduction of the International Neuroblastoma Surgical Report Form (INSRF) as a systematic integration of the NB surgical report, stimulates surgeons to focus on IDRFs and their correlation with intra and postoperative complications (14). Their presence at pre-surgical evaluation was indeed shown to be correlated to the likelihood of developing surgical complications (4,15,16). IDRFs are a cornerstone in the INRGSS and have also been adopted to inform surgical decisions for children with low-risk neuroblastoma in the Japan Children's Cancer Group Neuroblastoma Committee (2,17). They were also used to guide indication for minimally invasive surgical approach (18-21). IDRFs have then been analysed through their modifications following adjuvant chemotherapy (4,9,22), showing that 60% to 70% of IDRFs persist after neoadjuvant chemotherapy and that quality of resection is significantly associated with the decrease in the number of IDRFs along with chemotherapy.

In our Delphi consensus survey, the presence and number of IDRFs (L1 or L2) were evaluated in the immediate preoperative setting (independently whether neoadjuvant chemotherapy was administered or not) in a very consistent manner by all active panel members. The increase in the number of pre-IDRFs detected was directly related to the surgeons’ perceived risk. IDRFs may be grouped into categories (vascular, neurological, infiltrative, compressive) and it appears that some IDRF groups are associated with increased risk of surgical complications, but also to some extent to histology, biology, and/or to localized or metastatic status (4,6,7,15,16,23). However, to date, the precise role and weighting of each IDRF has never been critically analysed and quantified, nor has it been fully investigated with the possibility of undertaking surgery with a “limited surgical risk” despite the presence of certain IDRFs. Equally, the possibility that certain IDRFs absolutely contraindicate aggressive upfront surgery - at least at new disease onset – has never been challenged. In other words, the loss of a kidney or a postoperative Horner’s syndrome may be acceptable if the surgery is considered critical for the outcome of the patient, as in high-risk groups where it seems that surgery impacts both event free and overall survival. Conversely, the risk of damaging the small bowel by extensive dissection of an encased superior mesenteric artery in a small child may be not acceptable in a low or intermediate risk tumor (24,25). In an attempt to answer these challenging questions, it is necessary to start at the definition of “surgical risk” and how this may be quantified. There are no defining generic risk stratification scores in neuroblastoma surgery. The only way to attribute a degree of surgical complexity specifically to NB surgery is to engage surgeons well trained in this type of complex surgery and count on their lifetime years of experience, collecting both pre-operative, intra-operative, and postoperative aspects predictive and/or indicative of an increased surgical risk. The Delphi survey method is widely acknowledged for achieving convergence of opinion from experts on the importance of different outcomes in sequential questionnaires (or rounds). It is highly advantageous in that it is an anonymous process, avoiding the effects of dominant individuals and can be circulated to large numbers of participants with wide geographic dispersion (11,26-28). With no direct communication occurring between surgeon participants, this feedback provides a mechanism for reconciling different opinions of experts and is therefore, critical to achieving a consensus (12). However, these aspects are counterbalanced by some weaknesses in the methodology itself. Delphi guidelines are open to different interpretations depending on the purpose of the survey, its reliability is extremely poor (i.e., if two panels of experts received the same question they may not come to the same consensus), it does not allow participant discussion nor opportunity to elaborate on their views, and the existence of a consensus does not necessarily mean that the correct answer, opinion, or judgement has been found. It merely helps to identify areas that one group of participants or experts considers important in relation to that topic (12,26-28). Keeping all these considerations in mind, the definition of the SCI thanks to this Delphi survey has allowed us to retrospectively attribute a degree of surgical risk to neuroblastoma operations. The SCI is not a preoperative score. It aims to analyse objectively how each individual IDRF may correlate with the SCI value for each patient in ongoing collaborative studies. This current study project will thus proceed forward with cooperative retrospective data collection on patients operated on for NB and the precise SCI calculation for each enrolled patient. In a subsequent analytical phase, the calculated SCI will then be correlated to each IDRF preoperatively detected in any given patient. The median SCI value for each IDRF will be calculated for a study cohort NB patient population. Once a SCI median value score has been assigned to each IDRF, these will be sorted according to the decreasing value of median SCI and ultimately, statistically risk scored. In conclusion, this Delphi survey constitutes the preliminary phase of future larger collaborative studies. A consensus on a NB surgical complexity index to better accurately stratify the risk related to tumor resection was reached among oncology surgeons. This will serve to better define indication and extent of resection of NB, considering the tumor risk group, and may potentially facilitate refer the most challenging patients to high volume oncology centres to offset risks of morbidity and mortality.

# CONFLICT OF INTEREST STATEMENT

The Authors declare they have no conflict of interest.

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# FIGURE LEGENDS

Figure 1 – Percentages of consensus among the expert surgical panel after the third Delphi survey round on preoperative items.

Figure 2 – Percentages of consensus among the expert surgical panel after the third Delphi survey round on intraoperative items.

Figure 3 – Percentages of consensus among the expert surgical panel after the third Delphi survey round on postoperative items.