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Comparative retrospective study on the modalities of biopsying peripheral neuroblastic tumors: a report from the Italian Pediatric Surgical Oncology Group (GICOP)

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Abstract

Background: Peripheral neuroblastic tumors are the most common extracranial solid neoplasms in children. Early and adequate tissue sampling may speed up the diagnostic process and ensure a prompt start of optimal treatment whenever needed. Different biopsy techniques have been described. The purpose of this multi-center study is to evaluate the accuracy and safety of the various examined techniques and to determine whether a preferential procedure exists.

Methods: All children who underwent a biopsy, from January 2010 to December 2014, as a result of being diagnosed with a peripheral neuroblastic tumor, were retrospectively reviewed. Data collected included patients' demographics, clinical presentation, intraoperative technical details, postoperative parameters, complications, and histology reports. The Mann–Whitney *U* and Fisher's exact tests were used for statistical analysis.

Results: The cohort included 100 patients, 32 of whom underwent an incisional biopsy (performed through open or minimally invasive access) (Group A), and the remaining 68 underwent multiple needle-core biopsies (either imaging-guided or laparoscopy/thoracoscopy-assisted) (Group B). Comparing the two groups revealed that Group A patients had a higher rate of complications, a greater need for postoperative analgesia, and required red blood cell transfusion more often. Overall adequacy rate was 94%, without significant differences between the two groups (100% vs. 91.2% for Group A and Group B, respectively, $P = 0.0933$).

Conclusions: Both incision and needle-core biopsying methods provided sub-optimal to optimal sampling adequacy rates in children affected by peripheral neuroblastic tumors. However, the former method was associated with a higher risk of both intraoperative and postoperative complications compared with the latter.

KEYWORDS

biopsy, imaging-guided needle-core biopsy, minimally invasive surgery, neuroblastoma, pathology, pediatric

1 | INTRODUCTION

Peripheral neuroblastic tumors (NB) are the most common extracranial solid tumors in children and account for nearly 8% of all pediatric malignancies. They are responsible for at least 15% of all oncological deaths in children. NB derive from primitive neuroectodermal cells of

Abbreviations: GICOP, Italian Group of Oncological Pediatric Surgery; IDRFs, image-defined risk factors; INPC, International Neuroblastoma Pathology Classification; INRG, International Neuroblastoma Risk Group; INRGSS, International Neuroblastoma Risk Group Staging System; MKI, mitosis-karyorrhexis index; NB, peripheral neuroblastic tumors

the sympathetic nervous system and can be located in the neck, chest, abdomen, or pelvis. Prognosis is determined by the age of the patient, the extent of the disease (stage), and by histopathology and biological characterization of the neoplasm. Thus, early and adequate tissue sampling at diagnosis is mandatory in order to ensure optimal treatment.[1,2] The diagnosis may be confirmed through bone marrow sampling when the disease is present at this site, or alternatively by sampling the primary tumor.[3,4]

Different biopsy techniques have been described and have provided good results in skilled hands.[5–7] Surgical biopsy has been considered for a long time the cornerstone in the diagnosis of NB, although comparable results have been demonstrated with imaging-guided percutaneous biopsies.[5–7] Moreover, the introduction of minimally invasive techniques in the field of pediatric oncology may offer safe and effective alternatives to the more traditional techniques.[7–11]

Previous studies on this topic have been based on single-center experiences. This underscores the need for larger, multi-center series in order to further clarify any statistical differences among the various diagnostic techniques.[5–7]

The aim of this multi-center study is to assess the type, accuracy, and safety of the methods used to biopsy patients affected by NB. The ultimate goal of this study is to determine whether there is one biopsy method that should be considered a "first choice."

2 | METHODS

2.1 | Patients

For the purpose of this study, an electronic data collection form was sent to all the centers of the Italian Group of Oncological Pediatric Surgery (GICOP). The GICOP is a cooperative study group dedicated to advancing the surgical aspects in pediatric oncology. At least 20 pediatric surgical units all around Italy are active in the GICOP. All six tertiary centers dedicated to the diagnosis and treatment of NB participated in the survey.

The study retrospectively analyzed data from a five-year period between January 2010 and December 2014. It included the records of all the patients aged 0–18 years with a post-treatment confirmed diagnosis of NB (neuroblastoma, with related grade of differentiation and mitosis-karyorrhexis index [MKI] status, ganglioneuroblastoma intermixed, ganglioneuroma, or nodular ganglioneuroblastoma, according to the International Neuroblastoma Pathology Classification [INPC][3,12,13]) in which an initial biopsy was performed (whichever technique and independently from the result of the biopsy) due to the presence of one or more image defined risk factors (IDRFs)[14,15] contraindicating primary surgery (namely International Neuroblastoma Risk Group Staging System [INRGSS] stage L2).[1] Patients who underwent primary surgical tumor resection (namely INRGSS stage L1, i.e., without IDRFs, or INRGSS stage L2, contravening International Neuroblastoma Risk Group [INRG] surgical indications) and/or patients diagnosed through bone marrow aspirates were not eligible for inclusion in the study.

Primary tumor sites included the neck, thorax, abdomen, and pelvis. Biopsies of solitary central nervous system lesions, excision biopsies of skin, or superficial subcutaneous metastatic lesions (nodes, bone, or soft tissues) were not eligible for inclusion in the study.

Prior to biopsy, patients with suspected NB underwent the following investigations: serology (consisting of a complete blood count, lactate dehydrogenase, ferritin, and neuron specific enolase), urinary catecholamine levels (homovanillic acid and vanillylmandelic acid), metaiodobenzylguanidine scan, and bone marrow aspirates (the latter generally performed under general anesthesia concurrently with other invasive procedures, such as central venous catheter insertion and/or tumor biopsy).

Data collected included patients' demographics, clinical and radiological presentation (location and size of the mass, IDRFs), technical intraoperative details (see the next section "Biopsies"), postoperative parameters (length of hospital stay, level of required analgesia, time interval from biopsy to initiation of treatment), any documented complications, and outcome data (qualitative and quantitative adequacy of the sampling, number and reasons for re-biopsy, histological diagnosis, and any additional treatment). The levels of required analgesia were categorized as "severe," "moderate," and "mild" depending on the analgesic requirement in the immediate postoperative course (morphine, non-steroidal anti-inflammatory drugs, and paracetamol, respectively).

2.2 | Biopsies

A number of techniques were recorded. These were categorized into two groups: incision biopsies (Group A) and needle-core biopsies (Group B). Incision biopsies included specimens obtained either through a traditional "open" approach or through a minimally invasive approach, namely thoracoscopy or laparoscopy. Moreover, radiological imaging (ultrasound or computerized tomography) and minimally invasive surgery (thoracoscopy/laparoscopy-assistance) were both considered as possible guidance methods to correctly direct the needle (16 or 14 gauges) towards the tumor.[16] For each procedure, data regarding the number of withdrawn samples, the duration of the procedure, the need for conversion to a different procedure, and the type of postoperative analgesia were collected.

2.3 | Tissue adequacy

Specimens obtained in each procedure were examined by the local consultant pathologist and then reviewed by the consultant pathologist of the coordinating center and member of the Italian Neuroblastoma Group. These were assessed in order to obtain a histological diagnosis according to the INPC classification. Furthermore, whenever applicable and/or possible, MYCN gene status and other biological and cytogenetic studies such as numerical chromosomal aberrations and segmental chromosomal aberrations were determined.

Tissue inadequacy was defined as the inability to classify the tumor according to the INPC categories, and/or the inability to assess MYCN status, or the above-mentioned biological tumoral features, due to the insufficient quality or quantity of sampled tissue.

TABLE 1 Biopsy techniques in 100 patients with neuroblastic tumors

Total no. of biopsies 100	Group A (incision biopsies) n = 32	Traditional "open" surgery	24
		Minimally invasive surgery (thoracoscopy/laparoscopy)	8
	Group B (needle-core biopsies), n = 68	Ultrasound-guided needle-core biopsy	36
		CT-guided needle-core biopsy	2
		Video-assisted needle-core biopsy	30

CT, computerized tomography.

TABLE 2 Primary tumoral sites in 100 biopsied peripheral neuroblastic tumors

	Group A (incision biopsy)	Group B (needle-core biopsy)	Total
Abdomen	23	56	79
Pelvis	2	4	6
Thorax	1	5	6
Neck	1	0	1
Multicompartment	5	3	8
Total	32	68	100 (100%)

2.4 | Complications

Complications were divided into intraoperative and postoperative (when occurring within 30 days following the procedure). In particular, the need for blood transfusion and the need for surgical re-exploration within 30 days after the procedure were investigated.

2.5 | Statistical analysis

Data are reported in percentages and median values with range. Fischer's exact test and Mann–Whitney *U*-value were employed to assess statistical significance in percentages and median comparisons, respectively. A *P* value <0.05 was considered significant.

3 | RESULTS

A total of 111 forms were returned from six Italian pediatric surgery tertiary centers, all members of the GICOP. Seven forms were excluded from the study because of incomplete data. Among 104 patients included in the study, 32 (30.8%) underwent an incisional biopsy (Group A), 68 (65.4%) a needle-core biopsy (Group B), and the remaining 4 (3.8%) a "combined procedure," that is, experiencing both incision and needle-core biopsies during the same procedure (Table 1). The "combined procedure" set of patients was excluded from the analysis, although it did not show significant differences compared with overall patients (data not shown). The final cohort therefore included 100 patients.

The male to female ratio was 1:1. The median age at surgery was 3 years (range 0–17 years). Primary tumor sites are summarized in Table 2. The median size of the tumors was 7.9 cm (range 3.3–21 cm). A total of 295 IDRFs (median per patient 3, range 1–7) were recorded (Table 3). The most frequently encountered IDRFs were involvement of one or both renal pedicles and/or encasement of the aorta/inferior vena cava, which were described in 76% of patients presenting with an abdomino-pelvic tumor. Encasement of the subclavian/vertebral/carotid arteries and/or tracheal or bronchial compression were the most commonly encountered IDRFs in patients presenting with cervico-thoracic tumors (57%) (data not shown).

All the procedures, including imaging-guided needle-core biopsies, were performed under general anesthesia.

Comparative intraoperative and postoperative data with related statistical analysis are summarized in Table 3. No relevant differences were noted when comparing both median hospitalization and median time interval from biopsy to initiation of treatment. Statistical differences were highlighted when comparing the postoperative level of required analgesia ($P < 0.0001$) and the need for red blood cell transfusion ($P = 0.0307$), both found to be significantly higher in patients undergoing incision biopsies. Needle-core biopsies were associated with a statistically higher number of samples performed compared with incisional biopsies (5.5 vs. 3 specimens obtained per patient, $P < 0.0001$).

No statistical difference in the adequacy rate was found between Group A (100%) and Group B (91.2%) ($P = 0.0933$). Six patients (6%), all of them having experienced a needle-core biopsy, had inadequate sampling, for a variety of reasons. A prevalence of necrotic material in the sampling prevented the diagnosis in three cases, whereas quantitatively and qualitatively inadequate samples were obtained from three other cases. Only one of these patients underwent a repeat biopsy with the same technique, whereas the remaining were diagnosed through concomitant bone marrow aspirate and did not necessitate repetition of the biopsy (Table 3).

Histological diagnoses are reported in Table 4. Risk stratification was further assessed in a significant percentage of evaluable patients—mostly depending on the quality and quantity of sampled tissue—as follows. MYCN status was evaluated in 51 of 71 applicable patients, found to be amplified or gained in 17 of them. DNA aneuploidy was detected in 25 of 40 evaluated patients. Aberration of 11q chromosome was reported in 8 of 22 patients, whereas other cytogenetic anomalies (1p36 chromosome, 17q chromosome, and ALK gene) were detected in 11 of 32 patients.

A total of nine patients among the series experienced complications. Seven (21.9%) and two (2.9%) patients belonging to Group A and Group B, respectively, presented at least one intraoperative or postoperative complication, showing a statistically significant difference between the two groups ($P = 0.0044$). Among patients from Group A,

TABLE 3 Characteristics of patients with incision and needle-core biopsies

	Group A (incision biopsies), n = 32	Group B (needle-core biopsies), n = 68	*P* value
Tumor size, median (range)	117.5 (25—210) mm	81 (12–150) mm	0.1074[d]
IDRFs, median (range)	3.5 (1–6)	4 (1–7)	0.603[d]
Number of samples, median (range)	3 (1–4)	5.5 (2–9)	<0.0001[d]
Hospital stay, median (range)	4.5 (0–8) days	4 (0–9) days	0.12114[d]
Postoperative analgesia requirements			
Severe	9	2	<0.0001[e]
Moderate	22	46	
Mild	1	20	
Interval from biopsy to start treatment, median (range)	7 (1–30) days[a]	6 (1–30) days[b]	0.1141[d]
Patients experiencing complications (%)	7 (21.9%)	2 (2.9%)	0.0044[e]
Blood transfusion (%)	3 (9.3%)	0 (0%)	0.0307[e]
Need for surgical re-exploration (%)	1 (3%)	0 (0%)	0.32[e]
Adequacy of biopsy material (%)	32 (100%)	62 (91.2%)	0.1728[e]
Repeated biopsy (%)	0 (0%)	1 (1.5%)[c]	>0.9999[e]

[a]17 patients did not need chemotherapy.
[b]5 patients did not need chemotherapy.
[c]5 out of 6 inadequate patients were diagnosed through bone marrow aspirates.
[d]Mann–Whitney *U*-value.
[e]Fisher's exact test.

intraoperative bleeding occurred in three patients undergoing an open surgical biopsy for abdominal tumors with multiple IDRFs (all managed conservatively, two of them requiring packed red blood cell transfusion). Another patient experienced immediate postoperative abdominal bleeding associated with pleural effusion following an open biopsy for an abdominal tumor with complete encasement of the aorta and the inferior vena cava (this patient required 10 mL/kg of packed red blood cell transfusion, emergency abdominal surgical re-exploration and thoracic drainage, revealing a serous-hemorrhagic effusion). Other reported complications included postoperative peri-tumoral edema causing extubation delay in two patients and an intraoperative duodenal laceration.

Within Group B, one patient developed transient hematuria following a laparoscopically assisted needle-core biopsy of a large suprarenal left mass. Another patient developed transient edema of the external genitalia and of a lower limb following a needle-core laparoscopically assisted procedure in a pelvic tumor.

4 | DISCUSSION

Children affected by NB are currently stratified into different treatment groups (namely very low, low, intermediate, and high risk) depending on different patient-related and disease-related variables, such as age, INRG classification, histology according to the INPC classification, MYCN status, the presence of other chromosomal anomalies, and DNA ploidy.[1,2] It is also well known that tumor architecture and particularly the assessment of the stromal component are crucial in defining the various NB categories (neuroblastoma, ganglioneuroblastoma intermixed, ganglioneuroma, and ganglioneuroblastoma nodular) and related grade of differentiation and MKI status with regard to the neuroblastic component,[3,4,12,13] because a certain degree of intra-tumoral heterogeneity has been described.[17] Efforts and advances in the management of NB are at the present time aimed at reducing intensity of treatment in tumors deemed to have a favorable biology while intensifying chemotherapy regimens in the more unfavorable lesions. Hence, accurate diagnosis and correct risk stratification in NB is of utmost importance.[18] Many authors have described the feasibility and comparison between open surgical biopsies and needle-core biopsies in the diagnosis of other pediatric malignancies.[16,19,20] However, few studies are available in the field of NB and the results provided are not always conclusive.[5–7]

Mullassery et al.[5] demonstrated that needle biopsy yields adequate tissue sampling for the diagnosis, risk classification, and staging of NB. Similarly, Hassan et al.[7] concluded that whenever clinical findings allow either needle-core or open biopsy to be safely performed, then needle-core biopsy provides adequate samples for diagnosis with fewer complications. On the other hand, in a less recent series reported by Gupta and co-authors,[6] more than half of the needle-core biopsies for NB yielded insufficient tissue samples to allow for complete histological and molecular classification while the incidence of procedural complications between the two techniques were similar. All these studies agreed on the need for larger cooperative analyses to further delineate possible additional differences between the two biopsy modalities.

Open surgical biopsy of at least 1 cubic centimeter of tumoral tissue has been the cornerstone in the diagnosis of NB for many years. This kind of specimen encompasses enough tissue for histology, biology, and bio-bank storage. It usually preserves the tumoral architecture, thus enabling the pathologist to classify the tumor within the most appropriate histological INPC category. On the other hand, invasiveness is its main intuitive disadvantage.[9,10] Moreover, heterogeneity is a characteristic hallmark of NB, and it has been ascertained that samples taken from different regions of a primary tumor are known to

TABLE 4 Histological diagnoses on 80 centrally reviewed adequate specimens[a] according to INPC classification

Histological classification	Group A n (F-U)[b]	Group B n (F-U)[b]	Total n (F-U)[b]
Neuroblastic tumor, not otherwise specified (NOS)	–	–	–
Neuroblastoma, NOS	1 (0-1)	1 (0-1)	2 (0-2)
Schwannian stroma-poor neuroblastoma			
Undifferentiated	4 (0-4)	4 (0-4)	8 (0-8)
Poorly differentiated	34 (20-14)	14 (4-10)	48 (24-24)
Differentiating	3 (2-1)	1 (1-0)	4 (3-1)
Schwannian stroma-rich Neuroblastoma or Intermixed ganglioneuroblastoma	4 (4-0)	–	4 (4-0)
Schwannian stroma-dominant neuroblastoma or ganglioneuroma			
Maturing	6 (6-0)	4 (4-0)	10 (10-0)
Mature	3 (3-0)	1 (1-0)	4 (4-0)
Neuroblastic tumor compositum or nodular ganglioneuroblastoma	–	–	–
Total	55 (35-20)	25 (10-15)	80 (45-35)

[a]With respect to the initial cohort of 100 biopsies, excluding 6 inadequate specimens, 5 post-chemotherapy biopsies (INPC not applicable), and 9 specimens which were not centrally reviewed.
[b]F = INPC favorable; U = INPC unfavorable.

vary in terms of MYCN, 1p status, their stromal and neuronal components, as well as on their extent of differentiation.[17] To this end, cores taken from multiple sites do have many theoretical advantages over open biopsies in accurately determining the appropriate histological classification.[5,7,21]

Data from our multi-center series confirmed a more demanding peri-operative course (including a greater incidence of red blood cell transfusion, a higher proportion of patients requiring high-to-moderate postoperative analgesia, and a higher complication rate) in patients affected by NB undergoing incisional biopsies. In contrast, the less invasive needle-core biopsies were associated with a lower complication rate, irrespective of which guidance method was used. This advantage was further enhanced when image guidance was employed. One may speculate that patients presenting with tumoral vessel involvement/encasement were intentionally selected for open surgical biopsies and were therefore *a priori* at higher risk of developing complications. However, the incidence and distribution of IDRFs were not different in the two groups (Table 3). Therefore, the most plausible explanation for the higher complication rate observed in patients belonging to Group A is that an incisional biopsy exposes more tumoral surface which is more likely to bleed compared with a relatively narrow tumoral probing which easily seals spontaneously thanks to the pressure of the surrounding tumoral tissue.

As far as specimen adequacy is concerned, some observations should be highlighted. The significance of the statistical test employed could have been underestimated due to the relatively small difference between the two groups concerning adequacy rate in a relatively small cohort of patients, as in our series. A hypothetical patient series to definitely prove such a statistical difference could not be reached due to the retrospective nature of the study. The overall accuracy rate was 94%, with a failure to obtain a correct diagnosis in six patients, although only one required a biopsy to be repeated. All these patients underwent a needle-core biopsy, with multiple tumoral sampling. In all these cases, a preponderance of necrotic tissue within a relatively tiny amount of tissue may have influenced the consistency and the integrity of the specimen, thus affecting the diagnostic possibilities. As a general recommendation, it would be reasonable to consider alternative procedures to needle-core sampling whenever preoperative imaging suggests the presence of a significant proportion of necrotic tissue. On the other hand, if preoperative imaging suggests intra-tumoral heterogeneity, then multiple sampling in different areas of the tumor ought to be considered, possibly with imaging-guided needle-core biopsy.

A laparoscopy/thoracoscopy-assisted needle-core biopsy may represent a valid alternative whenever the tumor cannot be safely accessed through an imaging-guided percutaneous approach.[11] This technique provides the possibility to minimally expose the tumor while performing a relatively safe needle-core biopsy under direct vision and enabling the operator to promptly detect and manage any possible complications. Moreover, this technique may allow us to perform an incisional biopsy concomitantly to a needle-core one. "Combined biopsies" did not have different results compared with single open or needle-core biopsies in our series (data not shown).

The decision to perform such a procedure should then rely on preoperative (necrosis, intra-tumoral heterogeneity on preoperative imaging) and intraoperative (quality of specimens) findings. However, even this choice may be influenced by a rate of failure, as was the case in a patient from our series. This patient (not included in the analysis) initially underwent "combined biopsy" (laparoscopic needle-core and incision biopsy) which did not show viable tumor tissue in either sample and was required to undergo a repeat biopsy (with the same technique) to determine the diagnosis.

None of the patients from our series underwent fine needle aspiration biopsies exclusively. Although this may have been performed in a number of patients as a complementary procedure in order to collect intra-tumoral cellularity for analysis, in this particular series these two techniques were not distinguished and the contribution of each one was not evaluated.

Current treatment of patients with NB ranges from "observation only" to maximal multimodal treatment, depending on tumor types and subtypes and consequently on correct tumor classification at diagnosis, a task in which tumor biopsy plays a key role. Currently, there is no standard protocol for determining which method should be used to obtain tissue in NB. Although this study has several limitations (retrospective analysis, possible case-selection bias, different operators, different institutional facilities), some relevant conclusions can be drawn. All the examined techniques proved to be effective and relatively safe. Both incision and needle-core biopsies provide equally sub-optimal to optimal sampling adequacy rates in children affected by NB, although the former are associated with a higher risk of

intraoperative and postoperative complications. It is however reasonable and highly desirable to offer clinicians a choice between biopsies via needle-core versus open surgical methods. The decision-making process should rely on a proper preoperative imaging assessment with accurate IDRF detection, on the operator's confidence with each technique, and on possible concomitant procedures to be performed. A dedicated multidisciplinary team involving the oncologist, the radiologist, the surgeon, the anesthetist, and the pathologist remains crucial in preoperatively assessing the patient. Likewise, effectively communicating with the parents to discuss the available treatment options as well as the odds of success and relative risks of complications is essential. Finally, ensuring appropriate sampling and specimen handling and analysis complete the expert management of patients with NB.

Minimally invasive surgery as well as high-resolution imaging devices will probably continue to develop and be optimized with time.[9] It is reasonable to state that this may progressively change and improve the way tumor biopsies will be obtained in the future, including the amount and quality of tissue required to ensure a diagnosis, aiming at minimizing complications while maintaining the standards for diagnosis and subsequent treatment stratification.[22]

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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