



Does the Incremental Value of ^{123}I -Metaiodobenzylguanidine SPECT/CT over Planar Imaging Justify the Increase in Radiation Exposure?

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Abstract

Purpose Planar scintigraphy with ^{123}I -radiolabeled metaiodobenzylguanidine (^{123}I -mIBG) is an important imaging modality to evaluate neuroblastoma. In recent years, Single Photon Emission Computed Tomography combined with Computed Tomography (SPECT/CT) has revolutionized nuclear medicine. Nevertheless, the addition of the CT has increased the patients' irradiation. We aimed to evaluate the incremental benefits of ^{123}I -mIBG SPECT/CT over conventional planar imaging and to estimate the relative increase of radiation dose.

Methods We retrospectively evaluated the added value of 56 SPECT/CT performed in 40 children in terms of better characterization of the lesion and its locoregional extension, better lymph node staging, detection of new lesions, and elimination of false positives by a paired comparison between the planar images and the SPECT/CT ones. Then, we calculated the percentage contribution of the additional radiation of the CT in this hybrid imagery.

Results In 88% (49 out of 56) of the examinations, SPECT/CT provided additional information, which was crucial in 20% of the cases. It allowed a better characterization of the lesion and its locoregional extension in 44 cases, a better lymph node staging in 28 cases, the detection of 33 new lesions, and the elimination of 9 false positives. The CT effective dose was significantly lower than the SPECT one. The average additional radiation exposure due to CT was 12% (4–23%).

Conclusion ^{123}I -mIBG SPECT/CT has an undeniable added value that improves planar imaging interpretation and impacts patient management. These potential benefits would justify the low additional radiation induced by the CT.

Keywords ^{123}I -mIBG scintigraphy · SPECT/CT · Neuroblastoma · Pediatrics

Introduction

Neuroblastoma is one of the most common early childhood malignancies [1]. Deriving from primitive neuroblasts of the embryonic neural crest, neuroblastoma originates from the adrenal glands in 30–50% of cases and from anywhere along the sympathetic nervous system including the abdomen, chest, neck, and pelvis in the remaining cases [2–4].

At diagnosis, approximately 50% of patients have distant metastases, usually of the bones, liver, lung, and lymph nodes [5, 6]. The 5-year event-free survival rate strongly depends upon the stage of the disease [7]. It ranges from 99% in stage I to about 45% in stage IV [8, 9]. Staging is therefore primordial for appropriate treatment [10]. Diagnostic imaging plays thus a crucial role. Anatomical imagery; computed tomography (CT), magnetic resonance imaging, and ultrasonography; is used to evaluate local disease staging and monitoring [11]. Functional imaging with metaiodobenzylguanidine (mIBG) labeled with either iodine-123 (^{123}I) or iodine-131 (^{131}I) is important for diagnosing neuroblastoma, staging and localizing distant metastases, and evaluating therapeutic response [12, 13]. This is because neuroblastoma cells accumulate mIBG. The latter is a guanethidine derivative resembling, in its chemical structure, the neurotransmitter norepinephrine. The mIBG is absorbed by the cell through a passive diffusion or through the norepinephrine

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transporter. Then, it is stored in the neurosecretory granules of the sympathetic nervous system [14, 15].

The ^{123}I -mIBG scintigraphy routinely consists of acquiring planar images: whole-body images and/or overlapping spot images, depending on the age of the patient. The addition of Single Photon Emission Computed Tomography (SPECT) acquisition improves the diagnostic accuracy and the certainty of lesion detection and anatomic localization. It is especially helpful for the identification of small lesions and physiologic uptake sites [16–18]. Nevertheless and given its functional nature, SPECT remains poor in anatomical landmarks. These last years, hybrid imaging (SPECT/CT) combining SPECT and CT, providing both functional and anatomical information, has increased the performance of scintigraphies. In addition, the CT improves the quality of images by allowing attenuation correction. It has been reported that ^{123}I -mIBG SPECT/CT allowed better correlation with anatomical imagery and detected more functioning lesions than planar imaging [5, 19, 20].

However, the addition of a CT even low dose, sufficient for the anatomic referencing of SPECT lesions and for the attenuation correction, increases the overall delivered dose of radiation. This is of particular concern in young children who are particularly sensitive to ionizing radiation.

We report a cohort of neuroblastoma patients who have benefited from ^{123}I -mIBG SPECT/CT. The aims of this retrospective study were to evaluate the incremental benefits of ^{123}I -mIBG SPECT/CT over conventional planar imaging and to estimate the relative increase of radiation dose.

Materials and Method

Study Population

We retrospectively studied a series of 40 children followed for neuroblastoma and benefiting from a ^{123}I -mIBG scintigraphy, necessarily including in its protocol at least one SPECT/CT acquisition. A total of 56 SPECT/CT examinations were performed, either for an initial extension assessment or an evaluation after neoadjuvant chemotherapy, or an end treatment evaluation and a diagnosis of recurrence. In order to be able to carry out a dosimetric study, patients were divided in three groups: group A (age ≤ 2.5 years), group B (2.5 years $<$ age ≤ 7.5 years), and group C (7.5 years $<$ age ≤ 12.5 years).

^{123}I -mIBG SPECT/CT Imaging Protocol

Thyroid blockage, which is very important in protecting the thyroid from unnecessary radiation mainly in children, was achieved by orally administering potassium iodide three days prior to ^{123}I -mIBG injection and continuing for an additional

three days after injection. ^{123}I -mIBG was injected intravenously. The injection was slow in order to avoid the potential side effects of mIBG (vomiting, tachycardia, pallor, abdominal pain). The activity injected depended on the age of the patient.

The examination was carried out using a hybrid machine combining a dual-head SPECT unit with a low-energy parallel-hole collimator and an integrated 2-slice CT scanner (Symbia T E-Cam, Siemens Healthcare Erlangen Germany). A series of images was acquired 24 hours later, with the patient supine. The energy window was 159 keV \pm 10%. Static acquisitions were made in anterior and posterior incidences for scanning the whole body. The acquisition/image time was 600 s. The matrix was 256 \times 256. The zoom was adapted to age. The SPECT consisted of the acquisition of 32 projections of 40 s/head, with a total of 64 projections over 360°. The acquisition matrix was 128 \times 128. The energy window was 159 keV \pm 10%. The tomographic image reconstruction used a filtered back projection and the images were smoothed with a Butterworth filter. The CT acquisition immediately followed the SPECT. Its parameters were as follows: tube voltage of 130 kV; tube current of 30–90 mA; 2 \times 2.5 mm collimation; pitch of 1.5; slice thickness of 1 mm; matrix of 512 \times 512; and acquisition time of 2.4 s.

Image Interpretation

Two experienced nuclear medicine physicians who were aware of the patient's clinical history interpreted all planar and SPECT/CT images separately. Positive uptake was based on visual assessment. For both acquisitions, the sites and number of lesions were noted. The study was considered positive if at least one pathological lesion was observed, regardless of the number of foci, while a study containing no abnormal accumulation of ^{123}I -mIBG apart from physiological uptake was considered negative. The added value of SPECT/CT was evaluated by a paired comparison between the planar images and the SPECT/CT ones, using different scenarios including better characterization of the lesion and its locoregional extension, better lymph node staging, detection of new lesions, and elimination of false positives.

Two semiquantitative scoring systems were calculated to provide an objective assessment of the disease load: the Curie score and the International Society of Pediatric Oncology Europe Neuroblastoma (SIOPEN) one [21].

Dosimetric Study

The contribution of the effective dose of ^{123}I -mIBG scintigraphy for each patient was calculated by multiplying the average administered activity for all patients by the conversion factors [22] listed in the International Commission on Radiological Protection (ICRP) [23]. The effective dose

from the CT portion of the examination was calculated from the product of the dose length product (DLP) and a body-region-specific conversion factor k ($\text{mSv} \cdot \text{mGy}^{-1} \cdot \text{cm}^{-1}$) [24]. DLP is a value given, for each patient, by the machine's acquisition station. It depends on the scan length and the acquisition parameters.

The total effective dose of SPECT/CT ($E_{\text{SPECT/CT}}$) is the sum of the effective doses E_{SPECT} and E_{CT} [22].

The percentage contribution of the additional radiation of the CT ($\%E_{\text{CT}}$) is given by the following equation:

$$\%E_{\text{CT}} = \frac{E_{\text{CT}}}{E_{\text{SPECT/CT}}} \times 100$$

Statistical Analysis

Quantitative variables were expressed using means \pm standard deviation. For qualitative variables, an evaluation of frequencies was used. Means were compared by using the Student test. A p value of less than 0.05 was considered statistically significant.

Results

Patients

The mean age was 3.7 years old. A male predominance was noted, with a sex ratio M/F of 1.7.

The primary tumor was in most cases adrenal. Table 1 describes the characteristics of the 40 patients and the

indications of the 56 SPECT/CT. The main indication for the ^{123}I -mIBG scintigraphy was the initial extension assessment.

Curie and SIOPEN Scores

The Curie score ranged from 1 to 30, with an average of 6.7 ± 10.6 .

The SIOPEN score ranged from 0 to 50, with an average of 7.7 ± 17 .

Results of Planar Imaging

Planar scintigraphy was positive in 53 cases and negative in 3 cases. Table 2 gives details about the sites of positive

Table 2 Findings of diagnostic planar ^{123}I -mIBG scintigraphy

Site	Number of lesions
Primary tumor	
Abdomen	44
Head and neck	1
Thorax and mediastinum	3
Locoregional extension: abdominal lymph node metastases	1
Distant metastases	
Osteomedullary	23
Hepatic	9
Pulmonary	3
Cervico-thoracic	3

Table 1 Patient characteristics

Characteristics	Value	Standard deviation/percent
Age		
Mean	3.70 years	2.75 years
Median	3 years	
Range	2 months–11 years	
Sex		
Male	25	62%
Female	15	38%
Site of the primary tumor		
Adrenal	32	80%
Extra-adrenal, intra-abdominal	5	13%
Thorax	3	7%
Indications for the ^{123}I -mIBG scintigraphy		
Initial extension assessment	30	54%
Evaluation after neoadjuvant chemotherapy	10	18%
End treatment evaluation	13	23%
Diagnosis of recurrence	3	5%

lesions. In the 3 cases of cervicothoracic metastases, static studies could not specify its origin.

Results of SPECT/CT

SPECT/CT studies were positive in 50 cases and negative in 6 cases. It detected 33 new metastatic lesions. It changed the report of three examinations from positive to negative. It better characterized the three cervicothoracic lesions visualized by planar imaging and whose origin could not be specified: supraclavicular lymphadenopathy in one case, jugulo-carotid lymphadenopathies with cervical vertebral metastasis in one case, and mediastinal lymph node metastasis in the last case. Table 3 gives details about the sites of positive lesions.

Added Value of SPECT/CT

The paired comparison between the planar images and the SPECT/CT ones revealed that 12% (7 of 56) of the studies were concordant: the three negative cases of planar scintigraphy and four cases of positive scintigraphy. In the latter cases, the SPECT/CT examinations simply confirmed the findings revealed on planar images.

In 88% (49 out of 56) of the examinations, SPECT/CT provided additional information. Table 4 details the additional information obtained. SPECT/CT increased the sensitivity of the study by detecting new lesions. It also increased the specificity of the examination by determining the functional status of lesions on anatomical imaging (false positives). On the other hand, it increased the confidence of the image interpretation thanks to a better characterization of the lesion and its locoregional extension (Fig. 1). It allowed a better lymph node staging and a better distant extension by eliminating distant metastases in 4 cases and by highlighting others in 4 other cases. In 5% (3/56), SPECT/CT changed

Table 3 Findings of diagnostic ^{123}I -mIBG SPECT/CT

Site	Number of lesions
Primary tumor	
Abdomen	44
Head and neck	1
Thorax and mediastinum	3
Locoregional extension: abdominal lymph node metastases	15
Distant metastases	
Osteomedullary	34
Hepatic	11
Pulmonary	3
Cervico-thoracic	3
Others	3

Table 4 Additional information obtained by SPECT/CT

Additional information	Number
Better characterization of the lesion and its locoregional extension	44
Locoregional lymphatic extension	20
Vascular localization	4
Muscle of the wall	2
Root canal	4
Hepatic metastasis	10
Contiguous bone lesion	4
Better lymph node staging	28
Detection of new lesions	
Locoregional lymph nodes	15
Distant metastatic lymph nodes	4
Hepatic metastases	2
Bone metastases	7
Intradural extension	4
Muscular metastasis	1
Elimination of false positives	
Urinary contamination	1
Physiological renal uptake	3
Physiological digestive uptake	2
Non-specific lung uptake	1
Vascular uptake of the left common carotid artery	1
Non-specific inflammation of a limb	1

the diagnosis of planar scintigraphy from a positive to a negative study. In the last 11 cases (20%), the diagnostic information obtained was crucial. Thus, it makes it possible to adapt the therapeutic management of this cancer.

Additional Radiation of the CT

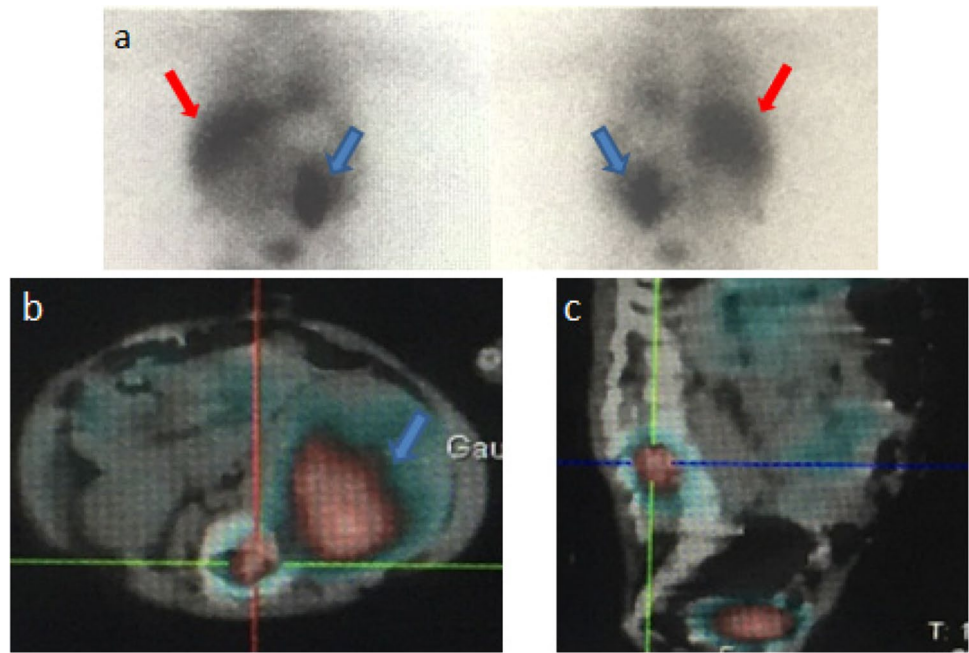
The average effective doses induced by CT, SPECT, and SPECT/CT examinations were 0.65 ± 0.09 mSv, 5.47 ± 1.93 mSv, and 6.11 ± 1.91 mSv, respectively. The CT doses were significantly lower than the radiopharmaceutical administration doses ($p < 0.05$).

The average contribution of CT scans to the total effective dose for SPECT/CT examination was $12 \pm 4\%$, and ranged from 4 to 23%. Table 5 details this contribution for each anatomical region scanned and for each group. The lowest value was for the group A. This contribution increased with age.

Discussion

The results presented in this study demonstrate that the SPECT/CT hybrid imaging improves the performances of planar ^{123}I -mIBG scintigraphy in neuroblastomas. In 88% of our examinations, SPECT/CT provided additional information

Fig. 1 ^{123}I -mIBG scintigraphy for an initial extension assessment in a 2-month-old girl with neuroblastoma. **a** Planar scintigraphy revealed a heterogeneous uptake area of the left flank (blue arrow), liver metastases (red arrow), and a heterogeneous left paramedian uptake of the lumbar spine probably in continuity with the lower part of the primary tumor. Fused SPECT/CT (**b** axial and **c** sagittal) revealed the retroperitoneal mass (blue arrow) with calcifications (corresponding to the primitive tumor) and better characterized the heterogeneous left paramedian uptake of the lumbar spine which corresponded to an intradural extension from L2 to L5.



that improved the diagnostic performances of the ^{123}I -mIBG planar scintigraphy. Indeed, SPECT/CT hybrid imaging combines the advantages of these two imaging methods: high anatomic resolution for the CT and good specificity for the SPECT by providing functional and anatomical fused images.

The first studies demonstrating the interest of mIBG SPECT/CT in the management of neuroblastomas were often limited by heterogeneous study populations including a limited number of recruited neuroblastoma patients. The study by Fukuoka et al. including 16 patients (eight pheochromocytomas and eight neuroblastomas) objected that, compared to planar imaging, the ^{123}I -mIBG SPECT/CT provided additional information for 75% of patients [5]. The study by Goswin et al. including 22 patients suspected to have pheochromocytoma objected that ^{123}I -mIBG SPECT/CT is particularly useful for patients at high risk of pheochromocytoma, for the confirmation of a small extra-adrenal pheochromocytoma, and for the detection of local recurrence and multifocal tumors [25].

Few clinical studies have included a homogeneous population of neuroblastomas. The rate of value-added information of our study was higher than that of Nadel (29%) [26], Liu et al. (39%) [27], and Theerakulpisut et al. (41%) [28]. In this last study, including 86 SPECT/CT carried out in 36 patients, SPECT/CT detected additional lesions in 23.2% of cases, helped localize lesions in 21.1% of cases, resolved suspicious findings in 85.7% of cases, determined functional status of lesions on anatomical imaging in 94.4% of cases, and changed diagnosis from a negative to a positive study in 19.5% of cases [28]. However, this latest study used ^{131}I -mIBG as a radiopharmaceutical. For diagnostic imaging, ^{123}I -mIBG is preferred over ^{131}I -mIBG. On the one hand, it has better physical characteristics: its low gamma energy (159 vs 364 keV) is more suited to conventional gamma-cameras with a better target-to background ratio and a better image resolution. On the other hand and particularly in the pediatric population, it presents a better dosimetric profile thanks to its shorter half-life (13 hours vs 8 days) and

Table 5 Percentage contribution of the additional radiation of the CT ($\%E_{\text{CT}}$) by region explored and age group

Explored area	Number of patient	Age group	Average effective dose E_{CT} (mSv)	Average effective dose E_{SPECT} (mSv)	Average effective dose $E_{\text{SPECT}/\text{CT}}$ (mSv)	Percentage contribution of the additional radiation of the CT ($\%E_{\text{CT}}$)
Abdomen and pelvis	22	A	0.62 ± 0.12	7.55	8.17 ± 0.12	$8 \pm 1\%$
Thorax	3	A	0.61 ± 0.08	7.55	8.15 ± 0.08	$7 \pm 1\%$
Abdomen and pelvis	20	B	0.68 ± 0.04	4.11	4.79 ± 0.04	$14 \pm 1\%$
Thorax	3	B	0.62 ± 0.04	4.11	4.73 ± 0.04	$13 \pm 1\%$
Abdomen and pelvis	8	C	0.64 ± 0.09	2.89	3.53 ± 0.09	$18 \pm 2\%$

no beta emission (which locally deposits substantial dose locally but does not contribute to image formation) [29, 30].

In our study, the anatomical data of the SPECT/CT allowed a better characterization of the lesion and its locoregional extension in 44 cases; thus, it increases the confidence of lesion localization. This was particularly useful for the small retroperitoneal foci. Indeed, the retroperitoneum is the sites of both pathologic activity (i.e., nodal disease or residual tumor) and physiologic activity (i.e., adrenal glands and urinary activity) [30]. This allowed us in some cases to solve the problem of patient return for imaging at 48 hours. In addition, we detected 33 new lesions, increasing so the sensitivity of the study. In the majority of cases, they were metastatic lymph nodes: locoregional and distant. This allowed a better lymph node staging and a correct tumor staging. Moreover, by providing correlative anatomic information, SPECT/CT reduced false-positive results and increased the specificity of the examination. It allowed determining the functional status of lesions: three renal and two digestive uptakes. Their characterization by planar imaging was impossible due to a mass effect induced by the large size of the primary tumor, which pushes back or even compresses them. Furthermore, the SPECT/CT revealed three cases of increased uptake caused by non-malignant etiologies interpreted as recurrent disease on planar images: pulmonary, muscular, and vascular (left common carotid artery). Benign entities accumulating the mIBG have been described in the literature: vascular malformations [31, 32], pneumonia [33], atelectasis [34], focal pyelonephritis [35], and focal nodular hyperplasia [36].

Of the additional information provided by our study, 20% were crucial. In three studies, by diagnosing false-positives foci, SPECT/CT changed the diagnosis of planar end-treatment scintigraphy from a positive to a negative, confirming complete remission. It allowed a better distant extension, by eliminating distant metastases in four studies and by highlighting others in four other cases, thus adapting the management of neuroblastoma.

Currently, Positron Emission Tomography (PET) is becoming the leading functional modality in cancer imaging, thanks to its better image resolution, the shorter duration of its procedure, and its more precise quantification [29]. In the evaluation of neuroblastomas, PET tracers have also proven their usefulness, but their use remains limited to the services which have them. Shahrokhi et al. analyzed and prospectively compared ^{68}Ga -DOTATATE and ^{131}I -mIBG SPECT/CT imaging in small group of 15 neuroblastomas. ^{68}Ga -DOTATATE detected more lesions than ^{131}I -mIBG, especially bone metastases [28]. Piccardo et al. objectified that the sensitivity of ^{18}F -DOPA PET/CT, in staging and in therapeutic assessment of patients with neuroblastoma, was greater than that of ^{123}I -mIBG SPECT/CT [37]. Melzer et al. have shown that ^{18}F -FDG

PET/CT is useful in the event of a discrepancy between morphological imaging and ^{123}I -mIBG SPECT [13].

However, the addition of a CT even low dose, sufficient for the anatomic referencing of SPECT lesions and for the attenuation correction, increases the overall radiation dose delivered. This must be considered, especially in children. These latter represent a population that is particularly sensitive to ionizing radiation. It is therefore necessary to justify the radiation dose and to keep it as low as reasonably achievable (ALARA). In order to estimate the increase of irradiation dose, we firstly calculated and compared the effective doses induced by CT and by SPECT. The CT doses were significantly lower than the radiopharmaceutical administrated ones. Secondly, we calculated the percentage contribution of the additional radiation of the CT in the ^{123}I -mIBG/CT study. We objectified reasonable values, ranging from 4 to 23%, with an average of 12%. These values, which depend on the radiopharmaceutical, were lower than those of other studies in adults: 14% for breast lymphoscintigraphy [38], 60% for $^{99\text{m}}\text{Tc}$ -MDP (methylene diphosphonate), 65% for $^{99\text{m}}\text{Tc}$ -MIBI (MethoxyIsoButylIsonitrile), and 42% for ^{131}I -mIBG [39, 40]. For PET/CT, the region explored by CT often extends from the vertex to mid-thigh. Therefore, the CT additional radiation increases considerably. It reached 66% in the study of Quin et al. [41], 76.7% in the study of Khamwan et al. [42], and 78.2% in the study of Paiva et al. [43].

This study has certain limitations which must be acknowledged. Firstly, the retrospective nature of the study may cause selection bias. The decision whether or not to perform additional SPECT/CT depended mainly on the results of planar imaging. If the results of the latter were positive or suspect, the SPECT/CT was requested. Conversely, in the event of negative results, hybrid imaging was not carried out. This could explain the low number of negative studies and thus overestimate the added value of SPECT/CT. Another limitation is that the performances (sensitivity, specificity, accuracy) of planar and SPECT/CT acquisitions could not be calculated, due to the scarcity of confirmation of the imaging results by a histopathological diagnosis. Despite these limitations, this study presents certain highlights. In fact, the population included is homogeneous having only included neuroblastomas. In addition and to our knowledge, this is the first study in the published literature that has looked at two different areas: clinical study of the added value of ^{123}I -mIBG SPECT/CT in neuroblastomas and dosimetric study of the addition of CT. So by counterbalancing the benefits and disadvantages of SPECT/CT, we can conclude that the potential benefits of this dual-modality imaging justify widely the additional radiation induced by the CT in this pediatric population.

Conclusion

^{123}I -mIBG SPECT/CT hybrid imaging allows in children with neuroblastomas a detection of new lesions, a better characterization of the lesion and its locoregional extension, and a better lymph node staging. This would justify the low additional radiation induced by the CT.

Author Contribution Dorra Ben-Sellem collected the data and wrote the article. Naima Ben-Rejeb did the literature search and analyzed the data.

Data Availability Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Ethics Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the Helsinki declaration as revised in 2013 and its later amendments or comparable ethical standards.

Informed Consent It is a retrospective study that was approved by the hospital ethics committee and that did not require informed consent from patients.

Competing Interests Dorra Ben-Sellem and Naima Ben-Rejeb declare no competing interests.

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