Radioprotection 2019, 54(3), 181–185
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https://doi.org/10.1051/radiopro/2019025

Available online at:
www.radioprotection.org

ARTICLE

Exposure of children with neuroblastoma to ionizing radiation during computed tomography and nuclear medicine imaging – a single centre experience

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Received: 16 August 2018 / Accepted: 5 June 2019

Abstract – *Purpose:* To calculate cumulative doses of ionizing radiation absorbed by children with neuroblastoma during diagnostic CT and NM scans. *Method:* Retrospective analysis of 267 CT and NM scans performed in 21 children treated in 2009–2015. *Results:* The cumulative effective dose absorbed per child ranged from 58 to 536 mSv and was highest in infants under 3 years. *Conclusion:* Children with suspected neuroblastoma may be exposed to significant doses of radiation during the whole period of diagnosis and monitoring the progress of treatment.

Keywords: effective dose / diagnostic imaging / exposure / cumulative dose

1 Introduction

Neuroblastoma (NB) most often occurs in paediatric patients. The mean age at diagnosis is 2 years, and the majority of patients are diagnosed before the age of 10 years. Children, even those with advanced NB diagnosed in infancy, have the best prognosis and in many cases a 100% cure rate is achieved. In older children, disease progression often cannot be stopped despite intensive and advanced treatment. A worse prognosis occurs in patients with NB stage IV, metastases, chromosomal aberrations and poorly differentiated histopathological structure of the tumour. Patient with any of these features are assigned to the group of high risk of treatment failure, which represents about 50% of all cases. Studies conducted to date have emphasized the high value of initial imaging of the neuroblastoma, which is an important factor in risk stratification and the choice of the right therapy (Mueller *et al.*, 2013; Pfluger and Piccardo, 2017).

Patients with a history of cancer may be at risk of relapse, metastases and additional functional disorders or chronic diseases associated with NB and its treatment. Therefore, it is extremely important to monitor patients for possible late adverse effects (Ward *et al.*, 2014).

Standard protocols for a newly diagnosed case of NB recommend tumour imaging with CT (computed tomography), MRI (magnetic resonance imaging), or SPECT (single photon computed tomography). These procedures are performed to detect the primary tumour, identify the disease stage, assign the patient to a relevant group based on the criteria of INRGSS (International neuroblastoma risk group staging system) (Monclair *et al.*, 2009), and to assess response to treatment. Disease advancement and the location of the primary tumour and metastases to other organs are also diagnosed with scintigraphy using MIBG (metaiodobenzylguanidine) labelled with radioactive iodine I-131 or I-123. The procedure has about 90% sensitivity and specificity. Regular imagining during treatment allows for the assessment of treatment outcome, including the completeness of tumour resection and efficacy of chemotherapy. Information obtained during imaging is increasingly often linked with predicting the effectiveness of treatment. After completed therapy, most protocols recommend follow-up imaging for at least two consecutive years (Owens *et al.*, 2016).

Treatments for neuroblastoma, such as radiotherapy and chemotherapy, may be associated with a risk of developing secondary malignancies (Owens *et al.*, 2016). A number of reports also indicate that the cumulative dose of ionizing

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radiation after multiple exposures during imaging of cancer patients may induce the development of secondary malignancies. Increased vulnerability to ionizing radiation and longer life expectancy of children may indicate a higher risk of secondary cancers compared to adult patients (ICRP, 1991).

This article presents information on the doses of ionizing radiation absorbed by children with neuroblastoma as a result of diagnostic CT (computed tomography) and NM (nuclear medicine) scans. We draw attention to the problem of a large number of scans performed in children by using ionizing radiation. The presented information aims at stimulating a debate on the consideration of alternative imaging modalities, whenever possible, when planning further diagnostic procedures.

2 Material and methods

The analysed material were values of DLP (dose-length product) obtained for the CT acquisition protocol and activities of radioisotope administered to patients for the purpose of whole-body scintigraphy. A retrospective analysis of post-study reports, forms and medical files of patients was carried out.

The analysis comprised 21 children with neuroblastoma (9 girls and 12 boys) aged from 1 month to 16 years who were diagnosed at Independent Public Clinical Hospital No. 1 of the Pomeranian Medical University in Szczecin between 2009 and 2015.

CT scans in children were performed using a Siemens Sensation Cardiac 64 (in 2009–2012) and a Siemens Somatom Definition AS+ scanner (in 2013–2015); one CT study was done on a Philips Brilliance 16 scanner in the Independent Public Specialist Hospital in Szczecin-Zdroje in 2014. Data acquisition protocols included the following regions of the patient's body: head, neck, chest, abdomen and pelvis, and torso. In many cases, the contrast agent was administered after the first phase of the scanning and another CT acquisition was performed.

Scintigraphic studies were carried out with a General Electric Infinia Hawkeye 4 gamma camera. Patients were examined by whole body imaging after the intravenous administration of 131 I-MIBG, except one child, who was given 99mTc-MDP (Tc99m-methylenediphosphonic acid). The radioactivity was 32–74 MBq for 131 I-MIBG and 240–380 MBq for 99mTc-MDP. The effective dose absorbed by the patient during each CT scan was calculated from the equation (Dunn *et al.*, 2005):

$$E_{\mathrm{Eff(CT)}}[\mathrm{mS\upsilon}] = E_{\mathrm{DLP}} \cdot \mathrm{DLP}.$$

DLP was obtained from a CT acquisition protocol and E_{DLP} (normalised values of effective dose per DLP over various body regions and patient ages) from a reference table (Dunn *et al.*, 2005). This reference table contains a set of E_{DLP} coefficients relating to six broad regions (head & neck, head, neck, chest, abdomen and pelvis, trunk) and five standard ages (0, 1, 5, 10 years and adults). Children were assigned age-specific conversion coefficients according to the following scheme: less than 0.5 year → coefficient for "0 y old", from 0.5 to 2.5 years → coefficient for "1 y old", from 2.5 years to 7.5 years → coefficient for "5 y old", from 7.5 to 12.5 years → coefficient for "10 y old", over 12.5 years → coefficient for "Adult" (Owens *et al.*, 2016). All data for children in the reference table were normalized to $CTDI_w$ (weighted CT dose index) measured in the 16-cm diameter CT dosimetry phantom, as recommended for paediatric body CT dosimetry. If the console-displayed DLP estimates were based on the 32-cm phantom, the DLP values were multiplied by a factor of two before applying the age-specific conversion coefficient.

The effective dose for nuclear medicine scans was estimated from the equation (Dunn *et al.*, 2005):

$$E_{\mathrm{Eff(MN)}}[\mathrm{mS\upsilon}] = A \cdot E_{\mathrm{eq}}.$$

Data on patient exposure was acquired from the patient's medical record, and E_{eq} from reference tables (ICRP, 1987) and (Valentin 1999).

In this study, we used the term cumulative effective dose (CED) (Ahmed *et al.*, 2010; Owens *et al.*, 2016), which is the sum of effective doses absorbed by the patient over several years of diagnostic and follow-up scans employing ionizing radiation.

3 Results

The mean age of subjects enrolled in this study was 3.4 years. All patients were diagnosed with neuroblastoma; most of them (57%) were assigned to the high-risk group (HR). Patients received treatment consistent with the protocol for NB. Overall, children from the analysed group were subjected to 267 diagnostic procedures using ionizing radiation, including 155 CT scans and 112 nuclear medicine scans. The median number of scans in the analysed group of patients was 8 for CT (range: 1–15), and 5 for NM (range: 1–10). Arithmetic means of cumulative effective doses absorbed by children were 79.2 mSv for CT (range: 9.7–173.6 mSv) and 157.7 mSv for NM (range: 28.6–369.6 mSv). The estimated cumulative effective dose per patient was from 57.8 to 535.7 mSv (mean: 236.9 mSv).

CEDs and number of scans performed in all patients are presented in Table 1. Of all patients 19% ($n = 4$) were exposed to CED lower than 100 mSv, 29% ($n = 6$) to CED 100–200 mSv, and 52% ($n = 11$) to CED higher than 200 mSv. The highest dose of ionizing radiation was absorbed by a patient for whom CED was 535.7 mSv (number of studies: CT – 13; NM – 10). The highest sum of effective doses per patient per year was 535.7 mSv.

Table 2 presents detailed information on the exposure to radiation for specific regions of the body during CT scans in the studied group of children.

Torso and abdomen/pelvis CT scans were the most frequently performed CT examinations in this group of children. The mean effective dose for the above-mentioned regions was about 12.8 and 10.8 mSv, respectively.

Figure 1 presents the total distribution of doses absorbed during CT and NM scans in particular age groups. The highest exposure was found for children aged 1–3 years, who absorbed over half (53.7%) of all doses. The number of scans performed in subjects aged 1–3 years closely correlated with CED for this group. About 40% of all scans (CT – 62; NM – 45) were

Table 1. Number of studies employing ionizing radiation (CT, NM) and doses absorbed by children, and the number of other imaging studies (US and MRI) performed in children in 2009–2015.

Patient no.	Age of patient[a] (years)	Number of CT examinations	Number of NM examinations	Cumulative effective dose CT (mSv)	Cumulative effective dose NM (mSv)	The highest sum of effective doses (CT + NM) absorbed per year (mSv)	Number of US/MRI examinations
1	0.3	12	5	127.2	200.2	327.4	11/–
2	0.8	3	3	80.2	118.8	199.0	–/–
3	0.1	3	4	39.3	160.6	199.9	7/–
4	0.1	13	8	173.6	315.5	489.1	4/–
5	3	8	6	76.3	151.1	227.4	6/1
6	5	15	9	92.6	190.2	282.8	15/–
7	0.4	1	1	20.8	40.7	61.5	4/–
8	8	9	8	111.5	116.8	228.3	2/1
9	1	13	10	166.1	369.6	535.8	9/2
10	2	11	8	139.0	245.2	384.1	3/–
11	1	3	3	36.0	121.0	157.0	9/–
12	1	2	1	21.5	36.3	57.8	–/1
13	10	9	6	58.8	102.8	161.6	10/1
14	2	6	4	67.1	159.5	226.6	9/–
15	0.7	11	9	92.5	321.2	413.7	2/–
16	0.3	3	3	11.8	115.5	127.3	8/–
17	7	3	3	28.5	67.1	95.6	2/2
18	0.1	4	2	9.7	75.9	85.6	10/–
19	4	10	9	65.0	202.9	267.9	9/9
20	1	4	5	87.9	172.3	260.2	4/1
21	2	12	5	157.6	28.6	186.2	6/6

[a] Age of patient at the beginning of diagnostic procedures using ionizing radiation.

performed in this age group. The pie chart in Figure 2 presents the mean number of CT and NM scans per child in the analysed group performed in particular years.

Figure 3 shows the comparison of median CED for CT and NM scans. Median CED for CT scans in the analysed group of patients was 76.3 mSv, and was twice lower than the median dose associated with the administration of radioactive isotope I-131.

Table 2. Exposure to radiation for specific regions of the body during CT scans in the studied group of children.

CT scans		Estimated effective dose (mSv) per scan		
Region of body	No. of scans	Min	Max	Mean
Head	20	2.3	13.6	6.4
Neck	6	1.2	1.8	1.4
Chest	22	1.3	20.2	5.5
Abdomen/pelvis	59	1.4	26.6	10.8
Torso	63	2.0	57.9	12.8

4 Discussion

The cumulative doses of ionizing radiation absorbed by children diagnosed and followed-up due to NB in Independent Public Clinical Hospital No. 1 of the Pomeranian Medical University in Szczecin correspond to statistics presented in selected papers (Ahmed *et al.*, 2010; Owens *et al.*, 2016). The significant difference concerns the median CED for scintigraphic diagnostic procedures. In this study, the median CED is significantly higher than that reported in previous works (Owens *et al.*, 2016; Özyörük *et al.*, 2017). The use of a I-131labelled radiopharmaceutical during nuclear medicine scans significantly increases the radiation dose absorbed by children during diagnostic procedures. This proves the importance of choosing the right isotope, especially in the case of scans in children affected by a disease. However, in many cases, the choice is ruled by the availability or price of the radiopharmaceutical.

The cumulative effective dose absorbed by a child as a result of scans employing ionizing radiation differed significantly and ranged from 58 to 536 mSv. As many as 52% of patients absorbed CED greater than 200 mSv. Meanwhile, according to the BEIR VII report of the National Research Council of the US National Academies (Health risks from exposure to low levels of ionizing radiation 2006), cumulative effective doses of ionizing radiation higher than 100 mSv can cause adverse health effects. In the present study, the highest effective doses were absorbed by children aged 1 to 3 years, and over 1/3 of all scans using ionizing radiation were performed in infants. Because organs of children aged under

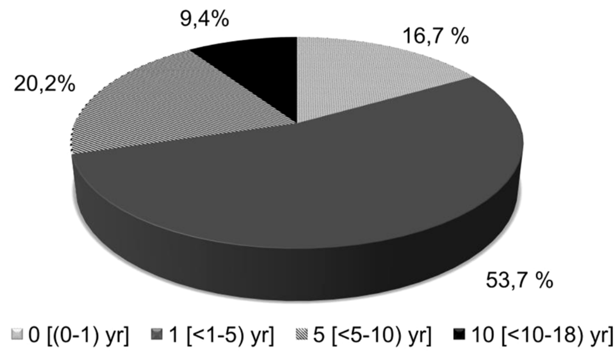

Fig. 1. Percentage distribution of effective doses from CT and NM depending on patient's age.

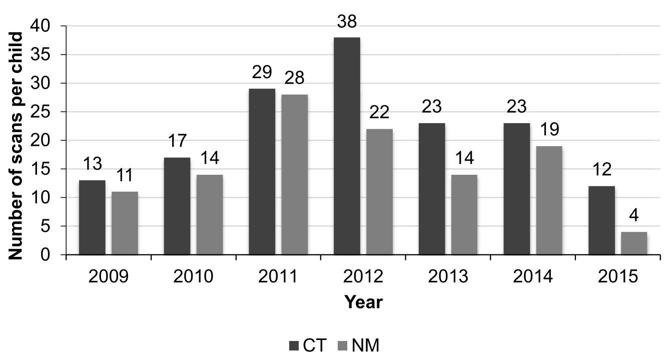

Fig. 2. Number of scans per child in the analysed period.

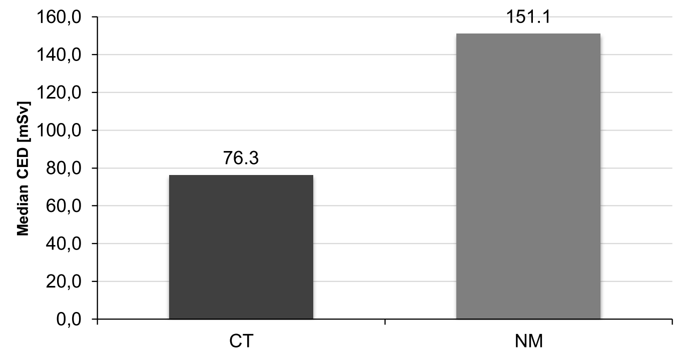

Fig. 3. Cumulative effective dose (CED) estimates for a child with NB.

10 years are several times more vulnerable to ionizing radiation than those of adults (ICRP, 1991), the risk of adverse effects associated with multiple exposures of young children may be even higher. In the present study, the highest estimated dose absorbed in 1 year by a 2-year-old boy was 536 mSv and resulted from 5 CT scans and 5 studies using iodine I-131.

The problem of multiple exposures to radiation during CT and MN scans in children diagnosed and followed up due to cancer has been addressed in scientific reports for several years (Robbins, 2008; Ahmed *et al.*, 2010; Miglioretti *et al.*, 2013; Almohiy, 2014; Federico *et al.*, 2015; Owens *et al.*, 2016). Particularly noteworthy is the study published by Federico *et al.* (2015), who reported that for patients with non-thoracic high-risk neuroblastoma at diagnosis, omission of surveillance chest CT imaging can save up to 42% of the effective dose of the radiation without compromising progression or recurrence detection. Moreover, Miglioretti *et al.* (2013) estimated that in the US about 4870 cancers may be induced within 1 year due to the performance of 4 million CT scans in children. Migloretti *et al.* emphasized that the large spread of doses absorbed by diagnosed and monitored children clearly shows that their exposure can be reduced many times. The elimination of unnecessary scans relying on ionizing radiation, raising the radiological awareness of doctors who refer children for these procedures, and the introduction of standard CT and MN study protocols are measures proposed to achieve a significant reduction in the potential incidence of radiation-induced cancer. Armao and Smith (2014) emphasized that children are often referred for CT imaging for no other reason than routine practice and protocols followed in a given hospital. Doctors do not analyze the history of radiological studies in paediatric patients, and have insufficient knowledge about the potential risk associated with multiple exposures to ionizing radiation during diagnostic procedures. Despite the important beneficial diagnostic role of CT, authoritative sources, including the Radiological Society of North America, suggest that between 20 and 50% of all such scans could be replaced by an alternative imaging procedure, or completely omitted. The authors of the present study advocate a reduction in the number of CT scans, as well as considering alternative procedures to those using ionizing radiation, such as ultrasound imaging or MRI. Another important issue is the possibility of reducing patient exposure through the use of modern CT scanners, often equipped with special tool kits for patient protection, such as: automatic exposure control, iterative reconstruction, safety cut-offs to prevent excessive doses, and (especially important for paediatric patients) prompts for coupling protocols to patient size.

In 2007, the American Society for Paediatric Radiology launched the Image Gently Campaign to raise the awareness of doctors about methods to reduce radiation dose during paediatric medical imaging exams. Good practice in paediatric radiology should rely primarily on optimized study protocols and standardized procedures to ensure the safety of children.

Figure 2 shows a decreasing trend in the number of procedures performed using ionizing radiation per child in the analyzed group, starting from 2012. In papers published in 2010 and 2013 (Ahmed *et al.*, 2010; Miglioretti *et al.*, 2013), the authors reported a clear decline in the number of CT scans used in paediatric patients between 2007 and 2010. One of the many factors contributing to the reduction in the number of diagnostic radiation procedures may be the increasing awareness of physicians' about radiation-related risk associated with multiple exposure of children with compromised health due to disease. Adequate knowledge of oncologists and paediatricians on the radiological history of their patients, as well as awareness of the potential risks associated with CT and MN procedures, are important elements of correct diagnosis and monitoring of patients with cancer.

Currently, there are publications whose authors deny the need for radiological protection of patients subjected to diagnostic procedures using ionizing radiation. The key argument raised by them is the broad criticism of hypotheses on the adverse health effects of even the lowest doses of radiation, the LNT (Linear no-threshold theory) model that is the basis for radiological protection. In 2017, Siegel *et al.* (2017) suggested that the optimization of radiological procedures and the tendency to reduce doses of ionizing radiation may strengthen unjustified radiophobia, both among patients and physicians referring their patients for imaging studies. The only reasonable solution to disputes about the potential harmfulness of multiple radiological exposures is to conduct extensive dosimetry and radiobiological studies in this area.

5 Conclusions

Children with suspected neuroblastoma may be exposed to significant doses of ionizing radiation during the whole period of diagnosis and monitoring the progress of treatment.

Physicians who refer children with cancer for diagnostic radiation procedures should be familiar with the particulars of "radiological history of patients". In cases of paediatric patients with a history of exposure to a significant effective dose of radiation, the possibility of further imaging with magnetic resonance or ultrasonography should be considered.

For all these reasons, there is a need for extensive research on the potential harmful effect of multiple radiological procedures on paediatric patients with cancer.

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Cite this article as: Iwanowski J, Piwowarska-Bilska H, Wawrykow P, Walecka A, Peregud-Pogorzelski J, Birkenfeld B. 2019. Exposure of children with neuroblastoma to ionizing radiation during computed tomography and nuclear medicine imaging – a single centre experience. *Radioprotection* 54(3): 181–185