Total estimated effective doses from radiologic imaging modalities of children with cancer: a single center experience

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Original article

Background: **Recently, awareness of the cumulative radiation exposure for pediatric oncology patients has been increasing, together with increased survival rates and longer life expectancy. The aim of our study was to quantify the amount of ionising radiation from imaging modalities of pediatric oncology patients.**

Methods: **Eighty-eight patients who were diagnosed with childhood cancer and followed up for 5 years between 2004-2014 in our center were included in the study. Patients' medical files were reviewed retrospectively for imaging history in the first 5 years after diagnosis. Total estimated effective doses from radiologic imaging modalities were determined. Also, the basic demographic data, histologic type, stage, and outcomes of disease were collected for all patients.**

Results: **The individual total estimated effective doses ranged from 8.73 to 167 mSv, with a median of 62.92 mSv. Computed tomography was the greatest contributor of total effective doses. The doses ranged 21.45-113.20 mSv (median: 62.92 mSv) in Hodgkin lymphoma, 12.53-167.10 mSv (median: 52 mSv) in non-Hodgkin lymphoma, 4.13-172.98 mSv (median: 52 mSv) in neuroblastoma, 31-149.89 mSv (median: 63.10 mSv) in Wilms' tumor, 11.50-73.72 mSv (median: 36.90 mSv) in germ cell tumor, 26.46-125.86 mSv (median: 80.90 mSv) in other solid tumor and 0.02-13.31 mSv (5.25 mSv) in brain tumor subgroup. Twenty-two children (25%) died with progressive disease during the 5-year follow-up period.**

Conclusions: **Similar to previous studies, the total estimated effective doses in children with cancer have been found various according to diagnosis, stage and clinical course. To clarify the harmfull effects of radiation burden, prospective studies should be conducted in children with cancer.**

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Introduction

The ionizing radiation is defined as a high-energy radiation that is capable of producing ionization in the tissues through which it passes and can be absorbed. It is especially damaging to replicating cells. Children have a proportionally greater percentage of replicating cells than adults, so they are at particularly high risk of injury from ionizing radiation. Since the first description of X-rays in 1895 by Roentgen, the use of ionizing radiation for diagnostic purposes has increased exponentially. It has been reported that the estimated annual number of computed tomography (CT) and positron emission tomography (PET/CT) procedures that were performed for children rose aproximately sevenfold especially in the past two decades.[1-5]

Effective dose is designed to provide a single number that is proportional to the radiobiological "detriment" from a particular, often inhomogeneous, type of radiation exposure-detriment representing a balance between carcinogenesis, life shortening and hereditary effects. Effective dose has been defined and introduced by International Comission of the Radiological Protection (ICRP) for risk management purposes. It is currently the most practical measure available to assess cumulative doses for individuals who are exposed to multiple radiologic modalities involving ionizing radiation and

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expressed in sievert (Sv). The effective dose of imaging procedures, for example, a pediatric chest radiograph may range between 0.01 and 0.02 mSv, a chest CT 2-4 mSv, a gallium scan 25-50 mSv and a PET/CT 20 to 25 mSv.[6-11]

In pediatric oncology practice, imaging studies that use ionizing radiation are essential tools, especially CT, PET and radionuclide bone scans during diagnosis, treatment and surveillance of childhood malignancies. The accurate and timely imaging is very important for contributing survival of childhood cancers as providing detailed information about diagnosis, stage, tumor responsiveness and the risk of recurrence. On the other hand, improved survival rates for childhood cancers together with longer life expectancy raised concerns related to significant cumulative radiation exposure due to increased using imaging modalites in recent years.[7-9]

There is limited study regarding total effective doses from imaging procedures in pediatric oncology patients. The aim of our retrospective study was to quantify the total estimated effective doses from imaging modalities of pediatric oncology patients in the first 5 years after diagnosis and evaluate the patient's demograpic-clinical features, histologic types, stages and prognosis.

Methods

The imaging history for the 5 years after diagnosis was retrospectively reviewed for 88 children who presented to our institution between 2004-2014 with new malignancies. The study group was consisted of 7 subgroups: hodgkin lymphoma, non-Hodgkin lymphoma, neuroblastoma, wilms tumor, germ cell tumor, other solid tumor subgroup (consisting of rhabdomyosarcoma, malignant bone tumors, and hepatoblastoma etc), and brain tumor subgroup. Basic demographic data for each patient were noted and also histologic type, stage, and outcomes of disease were collected. The number of radiographic views, computed tomography and nuclear medicine procedures were recorded from patients charts. The imaging datas could not be retrieved from the Picture Archiving and Communication System (PACS), because of unavailability in our center. Also special software programs for standardization (e.g. OLINDA) in nuclear

Table 1. Age-specific effective dose estimates[7]

Examination	Newborn (0-0.5 y)	1 y (0.5-2.5)	5 y (2.5-7.5)	10 y (7.5-12.5)	15 y (>12.5)
CT, mSv per study					
Head, 1 phase	4.2	3.6	2.4	2	1.4
Head, 2 phases	9.1	7.1	4.8	4	2.9
Sinuses	NA	0.3	0.3	0.2	0.2
Chest	2.8	3.4	3.7	4.1	2.8
Neck/chest/abdomen/pelvis			11.8	13.3	7.2
Chest/abdomen/pelvis	8	10.5	9.4	11.2	6.7
Abdomen/pelvis	13.1	11.1	8.4	8.9	5.9
Plain radiography, single view, msv per view					
Chest	0.016	0.016	0.016	0.016	0.02
Abdomen/pelvis	0.015	0.015	0.05	0.05	0.05
Skull/orbits/sinus/nasopharynx	0.008	0.008	0.008	0.008	0.008
Spine (cervical, thoracic, or lumbar)	0.17	0.17	0.17	0.17	0.17
Extremities	0.0005	0.0005	0.0005	0.0005	0.0005
Plain radiography, examination series, mSv per study					
Shunt series*	0.047	0.047	0.082	0.082	0.086
Skeletal survey†	0.716	0.716	0.716	0.716	0.720
Nuclear medicine dose per unit of isotope, mSv/MBq					
Gallium-67 citrate	NA	0.640	0.330	0.200	0.130
Technetium-99m DMSA (renal scan)	NA	0.037	0.021	0.015	0.011
Technetium-99m MDP (bone scan)	NA	0.027	0.014	0.011	0.007
Technetium-99m DTPA (renal scan)	NA	0.016	0.009	0.008	0.006
Technetium-99m red blood cell MUGA	NA	0.039	0.021	0.014	0.009
Nuclear medicine, examination series, mSv per study					
Iodine-123-MIBG	5.3	3.5	3.7	4.3	6.1
Bone mineral densitometry	0.0005	0.0005	0.0005	0.0005	0.0005
Gastrointestinal/genitourinary fluoroscopy, mSV per study					
Voiding cystouretrogram (female)	0.71	0.83	0.72	NA	NA
Voiding cystouretrogram (male)	0.91	0.89	0.64	NA	NA
Upper gastrointestinal series	3.14	NA	NA	3	3
Interventional fluoroscopy, mSv/min					
Chest	0.086	0.104	0.126	0.144	0.25
Abdomen	0.116	0.181	0.193	0.194	0.265
Spine	NA	NA	NA	0.1625	0.1625

NA: not available; DMSA: dimercaptosuccinic acid; MDP: methylen diphosphonate; DTPA: diethylen triamine pentacetic acid;[7] MUGA: multigated acquisition scan/blood pool scan; MIBG: meta-iodobenzylquanidine. *: Shunt series include chest radiograph, abdominal radiograph, and 2 skull views; †: Skeletal survey includes chest radiograph, 2 skull views, 4 spine views, and 8 extremity views.

medicine are not available in our center. All imaging procedures including the nuclear medicine had been performed at different radiology centers. Because it was imposible to obtain individual machine parameters for procedures, effective doses were obtained from published literature for different age categories (newborn, 1, 5, 10 and 15 years) (Table 1).[7,8] Individual radioisotope doses were recorded in megabequerels according to patients weights. The cumulative effective doses estimates were calculated by summing estimated effective doses over each patient's imaging history.

Statistical analysis

Statistical analysis was performed using the SPSS software version 17. Data were summarized with descriptive statistics using median and range for variables. Student t-test was used to compare the total effective doses of patients with stage I/II and III/IV. An overall *P*-value of less than 0.05 was considered as statistically significant.

Table 2. Diagnostic groups and staging

Diagnostic groups		*n*/total number
Hodgkin's lymphoma (*n*=13)		
	Stage I/II	6/13
	Stage III/IV	7/13
Non-Hodgkin's lymphoma (*n*=19)		
	Stage I/II	2/19
	Stage III/IV	17/19
Neuroblastoma (*n*=9)		
	Stage I/II	2/9
	Stage III/IV	7/9
Wilms tumor (*n*=16)		
	Stage I/II	11/16
	Stage III/IV	4/16
	Stage V	1/16
Germ cell tumors (*n*=10)		
	Stage I/II	8/10
	Stage III/IV	2/10
Other solid tumors (*n*=11)		
	Stage I/II	1/11
	Stage III/IV	10/11

Other solid tumors include rhabdomyosarcoma, adrenocortical carcinom, hepatoblastoma, primitive neuroectodermal tumor, osteosarcoma, ewing sarcoma and kondrosarcoma.

Results

The subgroup and staging of patients are presented in Table 2. The median age of patients at diagnosis was 7 years (range: 1 months-18 years). Thirty-nine percent of the patients were female (*n*=35) and 61% male (*n*: 53). Twenty-two children (25%) died with progressive disease during the 5-year follow-up period (8 non-Hodgkin lymphoma, 3 neuroblastoma, 1 wilms tumor, 1 primitive neuroectodermal tumor, 1 osteosarcoma, 2 rhabdomyosarcoma, 1 hepatoblastoma, 1 adrenocortical carcinoma and 4 brain tumors). No patient died or relapsed in Hodgkin lymphoma subgroup.

A total of 2060 procedures involving ionising radiation (1187 plain radiographs, 780 CT scans, 93 radionuclide scans) were performed in the first 5 years after diagnosis in the present study, with a median of 14 procedures per patient (range: 1-34 procedures per patient). CT and nuclear medicine (NM) were the greatest contributors of the total cumulative effective doses; CT constituted 38% of procedures but 87.6% of the cumulative effective doses, NM constituted 5% of procedures and 11.8% of the cumulative effective doses. Plain radiographs represented 57% of procedures, but accounted for only 0.6% of the cumulative effective doses.

Each individual received ionizing radiation dose from plain radiography ranged 0.03-3.8 mSv (median: 0.4 mSv). The number of plain radiography ranged 1-33 (median: 14). The exposure ionising radiation from CT ranged 5.9-149 mSv (median: 46 mSv) and number of CT ranged 1-34 (median: 10). The recevied radiation dose from NM imaging ranged 0.03-60.10 mSv (median: 12 mSv), the number of NM imaging ranged 1-6 (median: 2).

Individual total estimated effective dose ranged from 8.73 to 167 mSv, with a median of 62.92 mSv. The rate of patients who received >100 mSv radiation doses was 13.6% (*n*=12), between 50-100 mSv was 37.5% (*n*=33) and <50 mSv was 48.9% (*n*=43), respectively. The numbers of procedures performed and cumulative

Table 3. Numbers of procedures performed and cumulative effective dose estimates according to subgroup and imaging modalities

Subgroups	Plain radiography		Computed tomography		Nuclear medicine	
	No.	Radiation doses (mSv)	No.	Radiation doses (mSv)	No.	Radiation doses(mSv)
HL	16-25 (19)	0.30-0.59 (0.40)	4-18 (9)	17.4-96.5 (42)	1-4 (2)	2-60 (22)
NHL	2-33 (15)	0.03-1.24 (0.24)	2-34 (10)	12.5-149 (46.6)	1-3 (1)	0-17.5 (4.6)
NBL	2-22 (11)	0.43-3.8 (0.84)	0-23 (4)	0-143 (20)	1-5 (3)	2.3-32 (11.1)
Wilms	2-29 (17.5)	0.02-0.46 (0.29)	6-29 (11)	31.5-149.6 (59.4)	1-4 (1)	0-14.4 (7.2)
Germ cell tumor	2-16 (6.5)	0.005-0.29 (0.08)	2-8 (6.5)	8.7-70 (34.4)	1-1 (1)	2.2-4.6 (3.5)
Other solid tumors	2-18 (10)	0.03-0.96 (0.19)	4-19 (11)	19.9-112 (74)	1-6 (3)	3-31 (6)
Brain tumors	1-2 (1)	0.02-0.03 (0.01)	1-3 (1)	4-13 (7)	1-1 (1)	4.6-4.6 (4.6)
Total	1-33 (14)	0.005-3.85 (0.26)	0-34 (7)	0-149.6 (46.7)	1-6 (2)	0.00-60 (6.4)

Data were expressed as min-max (median). HL: Hodgkin's lymphoma; NHL: no-Hodgkin's lymphoma; NBL: neuroblastoma.

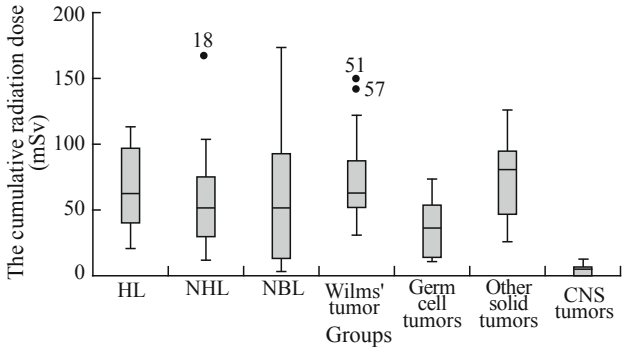

Fig. The cumulative effective doses according to subgroups. HL: Hodgkin's lymphoma; NHL: Non-Hodgkin's lymphoma; NBL: neuroblastoma; CNS: central nervous system.

effective dose estimates according to subgroup and imaging modalities are presented in Table 3. It has been found variability between tumor subgroups regarding cumulative radiation doses (Fig.). For children with Hodgkin lymphoma, the doses ranged from 21.45 to 113.20 mSv and the median effective dose was 62.92 mSv. In non-Hodgkin lymphoma, the doses ranged from 12.53 to 167.10 mSv and the median effective dose was 52 mSv. In neuroblastoma, the doses ranged from 4.13 to 172.98 mSv and the median effective dose was 52 mSv. In the Wilms' tumor subgroup, the doses ranged from 31 to 149.89 mSv and the median effective dose was 63.10 mSv. In germ cell tumor subgroup, the doses ranged from 11.50 to 73.72 mSv and the median effective dose was 36.90 mSv, In other solid tumor group, the doses ranged from 26.46 to 125.86 mSv, and the median effective dose was 80.90 mSv. In the brain tumor subgroup, the doses ranged from 0.02 to 13.31 mSv, and the median effective dose was 5.25 mSv. The highest individual estimated cumulative effective dose (172.98 mSv) was found in the neuroblastoma subgroup, the lowest level (0.02 mSv) was found in the brain tumor subgroup. The total effective doses in patients with early-stage (I/II) (median: 43.59 mSv; range 10.29-121.86 mSv) was statistically different from those in patients with advanced-stage (III/IV) (median: 69.99 mSv; range: 4.13-172.98 mSv) (P<0.05).

Discussion

The National Academies reported the consequences of low-dose radiation exposure as following: 1) A dose as low as 100 mSv is associated with the development of 1 cancer in 100 individuals; the overall lifetime risk of the development of cancer is 42 cases per 100 individuals; 2) Even lower doses, such as that received from one computed tomography (CT) scan (approximately 10 mSv), can be associated with an increased risk of cancer, on the order of one case per 1000 individuals.[5] In addition, the landmarking population-based studies showed a statistical significant connection between radiation exposure from CT and CT-induced cancer. They recommended that future CT scans should be limited to situations where there is a definite clinical indication, with every scan optimised to provide a diagnostic CT image at the lowest possible radiation dose.[12,13] On the other hand, the imaging procedures involving ionizing radiation have been used extensively for diagnosis and monitoring of response and surveillance after therapy for pediatric oncology patients since last decades.[7] Although the radiation exposure from imaging studies is below the exposure in those patients whose treatment includes radiation therapy, these procedures may be the sole source of radiation exposure for many patients with childhood cancer whose treatment does not include therapeutic irradiation. Because it was stated that even low levels of radiation exposure can be harmful, it is really important to evaluate the number and types of imaging studies performed throughout treatment and during the follow-up period.[5] Chong et al[8] reported that the CT and radionuclide scans accounted for 52% of the diagnostic procedures performed but more than 99% of the radiation exposure. In the present study, the CT and radionuclide scans accounted for 43% of the diagnostic procedures but accounted for >99% of the radiation exposure. CT was a major contributor to the total effective dose in our study. The Gallium scintigraphy, PET/CT and bone scintigraphy accounted for 11.8% of the cumulative effective dose in the study group. Particularly, PET/CT is one of the modalities in diagnostic imaging that has the highest radiation exposure. Although, it has become more available and replaced the use of gallium and computed tomography all over the world, the number of PET/CT was 9 and it was not used intensely in our clinic during the study period.

On the basis of the studies specified in Children's Oncology Group (COG) protocols, it has been estimated that cumulative effective doses of 100-150 mSv would be common.[9] The individual estimated cumulative effective doses ranged from 8.73 to 167 mSv, with the median of 62.92 mSv in our study.

Ahmed et al[7] reported that significant variability in the total effective doses received by pediatric oncology patients, both between individuals within a tumor subgroup and between subgroups. Similarly, we determined that significant variabilities between subgroups in the present study. The dose was the lowest in the brain tumor subgroup. Routine use of MRI at initial diagnosis and during the follow-up period

in brain tumors, together with less use of CT, were responsible for this result.

The radiation dose >100 mSv was accepted as a significantly harmful level at the Biological Effects of Ionizing Radiation VII report from the National Academy of Science.[11] In previous study, it was reported that 41% of patients had received total effective doses of >100 mSv, 22% received >200 mSv, and 1.3% received >500 mSv.[7] The rate of patients receiving >100 mSv effective dose was lower in our study compared with previous study. In another study, the median cumulative CT dose of the subgroup of 22 children with cancer was found to be 30-39 mSv by Lee et al.[14] They had calculated by using a dose-length product (DLP) based method estimated effective dose of CT extracted from Digital Imaging and Communications in Medicine (DICOM) files. They concluded that this lower dose might be a result of optimization of pediatric CT protocols at their institution.[14]

The total estimated effective doses in patients with advanced-stage was determined statistically higher than in patients with early-stage. Except for the one patient with anaplastic Wilms' tumor (Stage I), the patients relapsed or died were presented with advanced stage at initial diagnosis. As in our study group, the likelihood of disease recurrence and death was seen higher in patient with advanced stage, therefore the number of the performed radiologic procedures and estimated effective doses seemed to be increased related with poor clinical outcome. There is a generally held belief that patients benefit from close radiological surveillance as early stage detection of a relapse is more frequently detected by clinical history, and physical examination than by routine radiological screening. Also, detection at an early versus late relapse stage did not statistically differ in probability of survival.[15-18] Chong et al[11] found that protocol-required imaging accounted for only 34% of the imaging studies performed, contradicting their postulated hypothesis that the majority of imaging was mandated by study protocol. Of 452 (66%) discretionary investigations; 224 (50%) were directly attributable to management of co-morbid illness, with the remaining 217 (48%) requested for disease surveillance. They estimated that 40% (86/217) surveillance studies were performed when the recurrence risk was low and/or no clear indication was identified within the medical records. Of these 94% (81/86) were CT and radionuclide scans which carry significant radiation burden. They concluded that CT had overused for routine surveillance of patients with HL that usually have excellent overall survival rates.[11] Similarly, no patient relapsed or died with progression in HL subgroup, but their cumulative estimated effective dose was markedly high. Because of the excellent cure rate of HL patients and frequent CT and PET/CT scans have potentially negative long term impact on children, we should use alternative diagnostic tools such as ultrasonography and MRI during follow-up period. Also, it might be beneficial using dose monitoring software like DoseWatch (General Electric) for prospective monitoring of individual and groups of patients.

Children have increased risk because of higher sensitivity to radiation and because of their longer life expectancy, which allows for more time to actually develop cancer. It has been reported that the risk is as 0.016% per mSv for children <10 years old.[7,19] The median estimated cumulative effective dose of our patients was 62.92 mSv and the likelihood of radiation induced cancer was estimated as 1% for children <10 years old.

Our study has several limitations. First, this study was a retrospective study; second, the values of effective doses were calculated as a rough estimation, because our data were not retrieved from the Picture Archiving and Communication System, due to technical insufficiency. The effective dose of each CT was calculated by multiplying the DLP value with specific conversion factors for age, gender, body part, phantom size and tube voltage. Because the all imaging procedures were performed at different radiology centers, it was imposible to obtain the size of computed tomography dose index (CTDI) phantom and DLP values. Therefore, the dose estimation could not be done on the basis of real measured data by the means of dose area product (for plain film and fluoroscopy), dose lenght product (for CT) and applicate activity (for nuclear medicine) multiplied with specific conversion factor for each modality, age and scanner. Third, the radiation doses from contemporary CT scans are likely to be lower than those used in earlier decades in developed countries, but there is still technical difficulties in developing country.

In conclusion, it is well known that both chemotherapy and radiotherapy regimens are significant contributing factors of developing a second malignant neoplasm for cancer survivors. On the other hand, the cumulative radiation doses from diagnostic imaging procedures may have additional risk factor especially for patients who do not have any radiation therapy, therefore alternative diagnostic tools such as ultrasonography and MRI should be used especially during follow-up period. Similar to previous studies, the total estimated effective doses in children with cancer have been found various according to diagnosis, stage and clinical course. Although the dose values of newer scanner generations are less than the values given in previous years, the

radiation dose of each procedure need to be integrated into medical files of patients and tracked by pediatric oncologists. In addition, to clarify the harmfull effects of radiation burden, prospective studies should be conducted in children with cancer.

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