



# Imaging, radiation exposure, and attributable cancer risk for neonates with necrotizing enterocolitis

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## Abstract

**Purpose:** Neonates with necrotizing enterocolitis (NEC) receive numerous radiologic investigations that potentially increase their lifetime cancer mortality risk. We evaluated our radiologic practice pattern for patients with NEC and estimated cumulative radiation exposure and lifetime cancer risk.

**Methods:** Infants with NEC in a tertiary care NICU had patient demographics, imaging, treatments/interventions, and outcomes analyzed over 3 years. The number and type of imaging were recorded, including NEC-related imaging (thoraco-abdominal “babygrams” and abdominal radiographs), and all other imaging modalities. Patients were stratified by birth weight: group 1 (<750 g); group 2 (751–1500 g); and group 3 (>1501 g). Pre-existing normative data were used to calculate radiation exposure, absorption, and attributable cancer risk from NEC-related imaging.

**Results:** Sixty-four neonates with 72 episodes of NEC were identified. Overall survival was 75.0%. When stratified by birth weight, mean abdominal radiographs and babygrams comprised 51%, 60%, and 74% of total imaging, giving median mGy doses of 2.1, 0.4, and 0.2, respectively. Compared to normative data, radiation dosing, and median cumulative cancer lifetime mortality risk increased by an average of 4.3× from baseline, with two cases documenting a 20-fold increase.

**Conclusion:** Neonates with NEC are exposed to significant amounts of radiation directly attributable to disease surveillance. Non-radiologic surveillance methods could significantly reduce radiation exposure and cancer risk in these infants.

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Necrotizing enterocolitis (NEC) is an unpredictable disease in which symptoms can progress and become life-threatening within hours. Radiologic surveillance of infants with NEC is currently used to help guide the management

and treatment of this disease. This traditionally entails the use of serial abdominal imaging in which the radiographic hallmarks of NEC can be evaluated. These include pneumatosis intestinalis, portal venous gas, pneumoperitoneum, fixed bowel loops, and dilated bowel loops. In addition to receiving radiographs for NEC management, prematurity and its concomitant need for ventilatory support often mandate serial radiologic investigations, resulting in

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significant baseline radiation exposure to these patients. This need for constant radiographic surveillance suggests the possibility of radiation risks and the long-term cumulative effects that these serial radiographs could have on these neonates. Previous studies have raised concerns about the effects of radiation on cognition, reproduction, and lifetime cancer mortality risks in children [1,2]. Despite this apprehension, neonatal practices do not always adequately protect against the accumulation of ionizing radiation [3]. Efforts to minimize exposure appear warranted.

Radiation doses have never been quantified for neonates diagnosed with NEC. Our study sought to assess the radiologic practice pattern for the surveillance of patients diagnosed with NEC and to estimate radiation exposure and lifetime cancer mortality risk. The number, type, and timing of investigations were documented. The hypothesis of this study is that neonates diagnosed with NEC are subjected to a significant number of radiologic images.

## 1. Methods

After institutional research ethics board approval, the medical charts and radiologic studies of 70 neonates consecutively diagnosed with necrotizing enterocolitis were investigated. Data for 64 neonates were ultimately used in final data analysis; the six additional charts were examined but were not used for final analysis due to missing information. These neonates were admitted to the Neonatal Intensive Care Unit (NICU) or Pediatric Intensive Care Unit (PICU) of the Montreal Children's Hospital between October 2007 and February 2011. The Montreal Children's Hospital (MCH) has a tertiary-level NICU with full medical and surgical capabilities. It accepts transfers from peripheral NICUs both within and outside the McGill University Health Center. All imaging procedures are performed when deemed clinically appropriate by attendant neonatologists or surgeons; no protocol exists for pre-specified imaging intervals for neonates with NEC.

The chart review examined maternal demographics, patient demographics, medical and surgical treatment strategies and outcomes during the course of primary admission in the NICU/PICU. Radiologic images were individually assessed for number and type, including babygrams (single thoraco-abdominal radiographs), dedicated site radiographs (chest, abdomen, and other), CT scans, fluoroscopic examinations, and non-radiation-emitting investigations (MRIs, nuclear medicine images, and ultrasounds). Thoraco-abdominal radiographs and abdominal radiographs are generally used to help survey disease progression and were therefore defined as being attributable to NEC, whereas chest radiographs are typically employed to manage comorbidities associated with prematurity and were deemed not attributed to NEC. All radiographs were assessed both during the entire hospital admission and during the

acute episode of NEC, defined as the first documentation of the disease until resumption of oral intake. The presence of appropriate radiation-sensitive site shielding was noted. All portable films were taken with a General Electric model AMX4 mobile X-ray machine (Fairfield, Connecticut). Tube–film distance was kept constant at about 36 to 40 inches and exposure and peak kilovoltage were recorded for each examination so that the film density did not vary significantly between studies. Imaging practice patterns were evaluated by grade of NEC both during active disease and over the entire hospital admission. In addition, patients were stratified by birth weight—group 1 (<750 g); group 2 (750–1500 g); and group 3 (>1500 g)—for data analysis.

Pre-existing normative data were then used to calculate attributable cancer risk from NEC-related imaging. We utilized two previously published papers with measured radiation doses (mGy), estimated effective doses ( $\mu$ Sv), and estimated cumulative lifetime mortality risk for cancer in hospitalized neonates to evaluate the radiation risk in our population of neonates [4,5]. Ono et al. [4] feature radiation doses per neonate for different types of imaging based on birth weights. This was used to assign the median radiation doses (mGy) per neonate for babygrams and abdominal radiographs for our three groups based on patient weight. Puch-Kapst et al. [5] demonstrate the effective doses ( $E$  in  $\mu$ Sv) for babygrams and abdominal radiographs and also estimate the associated risk for cancer mortality for these mean effective dose values. This mortality risk was shown to be 1 in 60,000 for hospitalized very-low-birth-weight (VLBW) neonates. Using these normative data, we calculated the median values for radiation doses and effective doses, and estimated the lifetime mortality risk for cancer attributable to NEC imaging in our population.

## 2. Results

Sixty-four neonates with 72 episodes of NEC were identified (31—Bell I, 19—Bell II, 22—Bell III). Table 1 demonstrates basic characteristics for the patient cohort, typical for a series of patients with necrotizing enterocolitis. Overall survival was 75.0%. Table 2 demonstrates patient outcomes stratified by weight.

**Table 1** Patient characteristics of 64 patients with necrotizing enterocolitis.

Gender (M/F)	34/30
Bell grade(1/2/3)	31/19/22
Birth weight (g), mean $\pm$ SD	1577.6 g $\pm$ 1039.0
Groups 1, 2, 3 <sup>a</sup>	14/23/27 <sup>a</sup>
Gestational age (weeks), mean $\pm$ SD	30+5 $\pm$ 4 days
Day of life at diagnosis (days), mean $\pm$ SD	30.3 $\pm$ 35.1

M=male; F=female; SD=standard deviation.

<sup>a</sup> Group 1: <750 g, group 2: 750–1500 g, group 3: >1500 g.

**Table 2** Patient outcomes of 64 patients with necrotizing enterocolitis.

	Survived to DC (Y/N) (% mortality)	30-day survival (Y/N)	Days NPO (mean)	Days on TPN (mean)	Days on ventilator (mean)
Group 1 ( <i>n</i> =14)	10/4 (29%)	13/1	14.1	36.9	34.8
Group 2 ( <i>n</i> =23)	15/8 (35%)	15/7	9.0	20.5	7.4
Group 3 ( <i>n</i> =27)	23/4 (15%)	22/3	7.8	41.0	3.6
Total	49/15 (25%)	50/11	9.7	33.1	11.1

Group 1: <750 g, Group 2: 750–1500 g, Group 3: >1500 g.

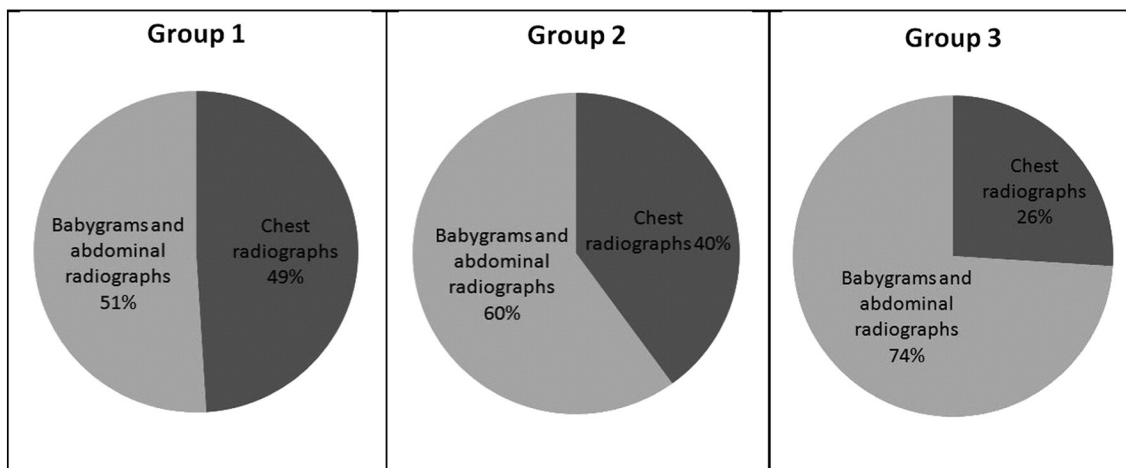
Images stratified by grade of NEC (I–III) yielded no significant differences either during active NEC or during the entire admission. During active NEC, 76.2% of images for infants with grade 1 NEC, 77.0% with grade 2, and 65.4% with grade 3 were composed of abdominal radiographs and babygrams. During the total hospital admission, 63.7% of images performed on neonates with grade 1 NEC, 59.2% of images for neonates with grade 2 NEC, and 58.0% of images with grade 3 NEC were abdominal radiographs or babygrams. Group 1 (<750 g) received the largest number of overall radiographs (mean of 52 images during the complete hospital admission; 27 images during active NEC). Group 2 received 30 radiograph throughout hospital admission and 18 during active NEC episodes. Group 3 received 22 during admission and 16 during active NEC. These included chest radiographs and do not represent the increase in radiation directly attributable to NEC.

Fig. 1 demonstrates the percentage of radiographs directly attributable to NEC surveillance (defined as abdominal and thoraco-abdominal radiographs) during the entire hospital admission. When stratified by birth weight, the mean number of abdominal radiographs and babygrams comprised 50.8%, 60.3% and 73.9% of all radiographs in groups 1, 2, and 3 respectively. The median values of imaging attributable to NEC led to mGy doses of 2.1, 0.4, and 0.2 respectively for groups 1, 2 and 3 (Table 3). Fig. 2 demonstrates the median

estimated lifetime mortality risks for cancer in each group. These were as follows: 1 in 11,000 (group 1), 1 in 21,000 (group 2), and 1 in 14,000 (group 3). Neonates in our cohort had between an increase of 3 and 5.5 times in lifetime mortality risk for cancer when compared to the baseline risk in hospitalized neonates. This risk was estimated to approach 20 times the baseline value in patients who received the most imaging. These estimated risks represent the estimated lifetime risk for cancer that is directly attributable to the surveillance and management of NEC and do not include the additional risk introduced by the numerous chest radiographs taken for each group (26 in group 1, 12 in group 2, 6 in group 3). Nor do these values include the images taken for the surveillance of NEC prior to and following transfer from the Montreal Children's Hospital. Finally, patients underwent a mean of  $0.8 \pm 1.1$  fluoroscopic and  $0.2 \pm 0.5$  CT investigations, increasing the cumulative radiation dose per neonate still further.

### 3. Discussion

Necrotizing enterocolitis is the most common neonatal gastrointestinal emergency, affecting over 5% of preterm infants each year [6]. Despite advances in NICU and surgical



Group 1: <750g, Group 2: 750g-1500g, Group 3: >1500g

**Fig. 1** Percentage of NEC- and non-NEC-related imaging stratified by birth weight.

**Table 3** Imaging, radiation exposure and attributable cancer risk for 64 neonates with necrotizing enterocolitis.

Birth weight	NEC-related X-rays <sup>a</sup> during admission, median (range)	% of total images	Radiation exposure (mGy), median (range)	Radiation dose absorbed (uSV), median (range)	Lifetime mortality risk for cancer/infant, median (range)
Group 1 <750 g (n=14)	20 (0–72)	50.8%	2.1 (0.0–7.1)	383.3 (0.0–1461.6)	1:11,000 (0–1:3000)
Group 2 750–1500 g (n=23)	15 (0–60)	60.3%	0.4 (0.0–4.5)	196.0 (0.0–1284.0)	1:21,000 (0–1:3000)
Group 3 >1500 g (n=27)	16 (3–35)	73.9%	0.2 (0.0–0.6)	285.0 (53.4–671.0)	1:14,000 (1:77,000–1:6000)

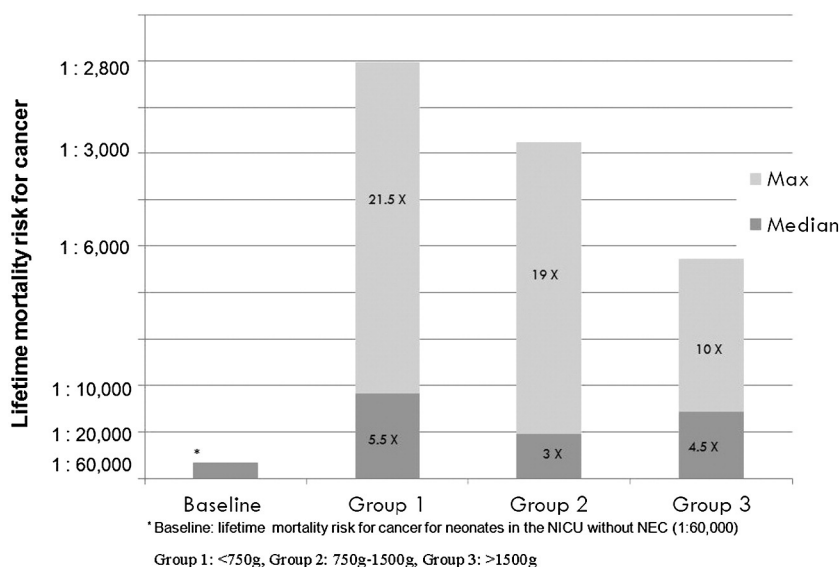
<sup>a</sup> Defined as thoraco-abdominal and dedicated abdominal radiographs.

care, the mortality rate continues to be as high as 16% to 42%, with prematurity the single most significant risk factor [7,8]. Other possible contributing risks factors include intestinal immaturity (digestive ability and motility), abnormal bacterial colonization of the intestine, an exaggerated inflammatory response, immature vascular supply to the intestine, and enteral feeds with formula [9]. Prophylactic measures are currently insufficient to prevent this disease, thus NICU and surgical management remain critical components of ensuring survival and acceptable patient morbidity. The unpredictable nature of disease evolution requires vigilant surveillance, traditionally via clinical signs (abdominal distension, bloody stools), laboratory evaluation (thrombocytopenia, acidosis) and radiographic findings (pneumotosis intestinalis, pneumoperitoneum). Serial imaging of neonates with NEC thus remains important in ensuring that swift and appropriate care is delivered, but this practice likely portends a long-term cost.

Our study demonstrates that neonates diagnosed with NEC are exposed to significant amounts of radiation and are thus very vulnerable to developing radiation-associated cancers. In this study, the smallest neonates underwent the

greatest amount of radiologic images and therefore represent the most vulnerable group of patients. Babygrams and abdominal radiographs directly attributed to NEC surveillance accounted for >50% of imaging in all groups. Compared to normative data, radiation doses and estimated cumulative lifetime mortality risk for cancer increased substantially in our population. In each birth weight group, the maximal values reached 21.5-fold, 19-fold, and 10-fold the baseline lifetime risk for cancer. Due to a lack of data for neonates weighing more than 1500 g, the value for group 3 was calculated using the baseline data in Puch-Kapst et al. for VLBW infants (1 in 60,000). Neonates weighing more at birth tend to have a decreased need for radiographs, thus the true increase in lifetime mortality for cancer due to NEC would likely be higher than this 10-fold value.

No level of radiation has been shown to be safe and the link between radiation exposure and subsequent cancer development is likely [10,11]. Although the risk of developing complications such as cancer from radiation is a random, stochastic event, the probability of these events is proportional to the radiation doses placed on individuals. It is impossible to predict whether or not an individual will



**Fig. 2** Lifetime mortality risk attributable to NEC-related imaging.

experience the consequences of radiation; it is therefore important to try and reduce radiation doses in everyone whenever possible. The best way to approach the issue of radiation doses seems to be the linear, no-threshold model of radiation exposure. This model states that radiation exposure in any amount has the potential for negative consequences. Using this model as an estimate of risk agrees with the ALARA (as low as reasonably achievable) principle, which encourages attempts to reduce radiation doses when possible [12]. Reducing radiation doses by decreasing the need for imaging, imaging only the indicated regions, and shielding radiation-sensitive sites, is especially important in the pediatric population. Children are more sensitive to radiation than adults and their risk of developing a fatal cancer is increased with decreasing patient age [12]. Reasons for this increased susceptibility include high sensitivity of their growing tissues with increased cell division, a higher fractional distribution of radiation-sensitive bone marrow in their skeletons, the greater potential years of life following radiation during which radiation-induced cancers can develop, and the patients' limited ability to cooperate with technicians resulting in multiple exposures [13–15]. While a recent study on neonatal radiation exposure has demonstrated reasonable cumulative relative doses received relative to the overall complexity of typical NICU patients, the study failed to investigate patient subsets at increased risk of excessive radiation [16].

Abdominal radiographs and babygrams are important assessment tools of the severity of NEC and may be obtained several times a day in search of radiological findings associated with NEC. Previous investigations have criticized the excessive use of babygrams for NICU patients due to their increased radiation doses (approximately double compared to a single view chest radiograph), as well as the concentration of radiosensitive body organs involved in these thoraco-abdominal images [17,18]. In the absence of respiratory complications, the use of babygrams should be minimized. Babygrams and abdominal radiographs make up the majority of images taken in this study; reducing their number would therefore significantly reduce the radiation doses placed on these neonates. Unlike chest radiographs, these images are associated with the management of NEC. The possibility of utilizing novel tools for NEC surveillance could reduce the need for frequent babygrams and abdominal radiographs in the management of NEC patients and may reduce the lifetime mortality risk of cancer in these neonates. The use of non-radiation emitting ultrasonography (US) as an imaging modality may aid in reducing overall radiation exposure. The detection of absent bowel wall perfusion through the use of color Doppler US has been shown to be more accurate than the presence of free air on radiography in detecting the presence of bowel necrosis in patients with NEC [19]. Clinical scoring systems such as the metabolic derangement score and the HeRO score may also supplant radiographic investigations in the management of these patients.

The metabolic derangement 7 score (MD7 score) includes physiologic parameters (blood pressure, acidosis, platelet count, neutrophil count, etc.) that signal clinical deterioration in patients with NEC [20]. This composite score has been proposed as a decision-making tool for surgical intervention and may also be appropriate in decisions to escalate medical care or transfer patients to higher acuity NICUs [21]. The Heart Rate Characteristic HeRO score, measures fluctuations in heart rate and has been shown to reduce mortality in very-low-birth-weight infants in the NICU [22]. Detection and treatment of conditions involving inflammatory processes such as NEC may benefit from the monitoring of heart rate characteristics index score and result in better outcomes, although further validation is required. The discovery of new markers associated with the development and progression of NEC could be especially helpful in NEC cases where classic radiographic signs are absent and could lead to earlier and more accurate diagnosis with less reliance on imaging [23]. A combination of the above tools with supplementary radiographs as needed may prove most effective but further studies are needed to clarify optimal surveillance strategies for neonates with NEC.

There are several limitations with this study, most notably its retrospective design. The introduction of bias as a consequence of this methodology is unlikely but not impossible, given that data quantifying the number and type of imaging per neonate are unlikely to be influenced by preconceptions held by data entry personnel. With regard to calculating cancer risk, prospectively assessing the actual risk of cancer development is rarely done due to the difficulty in observing patients for extended periods of time following radiation exposure. We chose to use pre-existing data from prior publications for our estimations. This relies on the accuracy of previous radiation dose measurements as well as on the accurate estimation of lifetime mortality risks for cancer. Values for the estimation of risk for radiation-induced cancer in Puch-Kapst et al. were derived from data supplied by the International Commission on Radiologic Protection and are likely the best available data for our population [24]. Despite this, it is clear that the estimation of radiation exposure and cancer risk is inexact. Furthermore, assumptions were made about the similarity between our patients and infants in other NICUs, as well as the similarity in imaging techniques. The patient demographics and outcomes presented are in keeping with previous publications of NEC patients. The generalizability of our radiographic surveillance of neonates with NEC is dependent on institutional and individual practices, but also falls within standard practice patterns across similar centers. While acknowledging these limitations and potential inconsistencies resulting from our use of normative data, our calculated cancer risk has been performed based on NEC-attributable imaging alone and therefore represents an *under-estimation* of overall risk of subsequent cancer development.

Necrotizing enterocolitis is an unpredictable disease requiring vigilant surveillance to identify opportunities to

intervene and alter disease course. Radiography remains one of the most practical and effective methods of doing so. This study draws attention to the high number of radiographs undergone by neonates affected with NEC and demonstrates the potential benefit of novel tools in the management of these infants. Clinicians are urged to exercise prudence in the use of radiography during NEC surveillance.

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