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REVIEW

Considerations in radiation therapy for pregnant women with malignancy

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Abstract Treatment of pregnant women with cancer with radiation presents medical, technical, and ethical challenges. Cancer during pregnancy occurs in 1 out of 1000 cases. The most common cancers are those that are common in females of childbearing age, including breast cancer, cervical cancer, melanoma, Hodgkin lymphoma, and leukemia. The in utero radiation exposure of a developing fetus through diagnostic radiology/nuclear medicine and radiation therapy is always a concern for healthcare providers and parents. Radiation exposure to the fetus seems to be associated with increased incidences of childhood cancer at any fetal dose. However, there also seem to be threshold doses for non-cancer adverse outcomes such as intellectual disability, organ malformation, and fetal death. The fetal radiation exposure from diagnostic radiology and nuclear medicine studies is far smaller than these threshold levels. On the other hand, fetal doses from radiation therapy for treatment of maternal cancers depend largely on gestational age and distance of fetus from the treatment field. Treatment of cancers in head and neck or extremities is relatively safe, while that of pelvic organs, such as cervical cancer, is not compatible with pregnancy. It is important to note that the "threshold" doses were calculated based on observational data and therefore should be used with careful considerations in individual clinical scenarios. Ultimately, it is the frank discussion between the pregnant mother and her family with the entire medical team, including her oncologist, the obstetrician, the neonatologist, the psychologist, and the social worker, that will lead to the best individualized management plan.

Keywords Pregnancy · Radiation · Malignancy · Complications · Fetal risk

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Introduction

Cancer complicates in 1 out of 1000 pregnancies [1, 2]. The most common cancers are those that are common in females of childbearing age, including breast cancer, cervical cancer, melanoma, Hodgkin lymphoma, and leukemia [2]. The in utero radiation exposure of a developing fetus through diagnostic radiology/nuclear medicine and radiation therapy is always a concern for healthcare providers. The potential adverse effects of radiation on the fetus include death, organ malformation, microcephaly, growth and intellectual disability, and childhood cancers. Such effects largely depend on the gestational age and the dose of radiation exposed. This review article intends to assist patients, families, and providers in evaluating fetal risk associated with ionizing radiation during diagnostic and therapeutic measures for pregnant patients.

Adverse effects of radiation on the fetus

The adverse effects of fetal radiation exposure depend largely on the gestational age (GA), as detailed in Table 1. Gestational

Table 1 Most common fetal effects of radiation exposure

Gestational age (weeks after LMP)	Most common effect	Threshold dose in mGy	Comments
2–3	Prenatal death	100 [4]	All-or-none phenomenon
5–10	Organ malformations	100 [1]	Small head size is most common
10–17	Mental retardation	60 [5] 100 [6]	25–31 points of IQ reduction per 1000 mGy above 100 mGy [6]
18–27	Mental retardation	280 [5] 700 [3]	13–21 points of IQ reduction per 1000 mGy above 700 mGy [3]
0–Delivery	Childhood cancer (Table 2)	No threshold	Risk highest during the first trimester [7] Leukemia is the most common [8]

Adapted from Centers for Disease Control and Prevention. Radiation and pregnancy: a fact sheet for clinicians [3]

age is defined as the number of weeks since the first day of last menstrual period (LMP), which is approximately 2 weeks earlier than the date of ovulation/conception. Implantation of the conceptus occurs between 2 and 3-week GA [9]. During this period, the effect of radiation on the fetus is an all-or-none phenomenon; that is, if the embryo survives the insult, it will likely suffer no other adverse effects except the increased risk for childhood cancers. Organogenesis coincides with a GA of approximately 5 to 10 weeks. An insult during this period results in organ malformations, among which microcephaly is the most common [1].

Interestingly, although the development of neural tissue begins around 4-week GA, no cases of severe intellectual disability (formerly mental retardation) were seen in the children exposed during 5–10-week GA period by atomic bomb explosions in Hiroshima and Nagasaki [1]. Severe intellectual disability is a main risk with radiation administered after 10-week GA. The risk per gray (Gy) from exposure between 10 and 17-week GA is four times higher than that for exposure between 18 and 27-week GA (Table 1). The former group also has a lower threshold dose for severe intellectual disability. The severity of intellectual disability increases with the amount of radiation exposure, with 25–31 points and 12–21 points of intelligence quotient reduction per 1 Gy above the thresholds for 10–17-week GA and 18–27-week GA, respectively, suggesting that the brain may be most sensitive to radiation damage in the early second trimester (Table 1).

Cancer induction may occur in a person who was exposed to radiation in utero. There is no threshold dose established for this risk, as evidenced by the increase in infant leukemia across Europe due to very low dose fetal exposure to radiation from the Chernobyl accident [10]. The risk does increase with the increased fetal dose (Table 2), and it has been suggested that the risk may be highest during the first trimester [11].

The spontaneous rates of these adverse outcomes in the population should also be considered. Estimated rate of miscarriage rate is 15 to 20 % in women who know they are pregnant [12]. Major birth defects occur at the rate of about 3 %, while intellectual disability is estimated at 1 % of the population [13, 14]. For childhood cancers, the background rate is at 0.3 % (Table 2).

Fetal radiation exposure from diagnostic studies

The fetal radiation exposure from diagnostic radiology studies can vary tenfold within each imaging modality depending on a number of factors including the fetal position from the field of view, the thickness of the patient, the direction of the projection, and the gestational age of the fetus [15]. Table 3 lists the common diagnostic studies and corresponding fetal doses. The data comes from three sources, and the highest reported dose is used for each modality [15–17].

Malignancies occurring during pregnancy

The most significant risk factor for development of maternal malignant neoplasms during pregnancy is patient's age [18]. As childbearing is increasingly postponed in the developed world, the incidence of cancer during pregnancy also has increased [19]. Types of malignancies occurring during pregnancy include breast cancer, cervical cancer, Hodgkin lymphoma, malignant melanoma, and thyroid cancers. With regards to radiation therapy, peripheral doses that are measured in phantoms are accurate for clinical use and can be used to estimate the fetal dose [20].

Radiation therapy for specific cancers during pregnancy

Fetal radiation doses from radiation therapy provoke the highest concerns for both the patient and the healthcare providers. Generally, cancers that are distant from the fetus, especially in the extremities and head and neck area, can be safely treated with careful planning. On the other hand, cancers in the pelvis cannot be adequately treated with radiation without severe consequences to the fetus, and therefore, pregnancy termination has to be considered [21]. Other cancers,

Table 2 Estimated risk for cancer from prenatal radiation exposure

Radiation dose	Estimated childhood cancer incidence[a]
No radiation exposure above background	0.3 %
0–50 mGy	0.3–1 %
50–500 mGy	1–6 %
>500 mGy	>6 %

Adapted from Centers for Disease Control and Prevention. Radiation and pregnancy: a fact sheet for clinicians [3]

[a] Data published by the International Commission on Radiation Protection

such as breast cancer and those in the thorax and mediastinum, carry intermediate risk to the fetus.

Fetal doses depend on a number of factors, the most important being the distance of the fetus from the edge of the radiation field, with the doses increasing significantly as the distance decreases. The leakage of photons from the head of the linear accelerator, scatter from the collimators and modifiers, scatter within the patient, and additional dose from neutron emission (contamination) in higher energy photon beams (>10 MV) all also contribute to the fetal dose.

A literature search for the case reports of different cancers discussed in this article was performed by using PubMed (up to week 1, October, 2015) with a filter for human only and with words "fetal dose," "cancer," and "radiotherapy". "Breast," "Hodgkin's," "Cervical," and "Head and Neck" were added for each cancer. The cases that are missing the type of cancer were excluded.

Head and neck cancers

The large distance from the head and neck to the fetus makes the treatment for these cancers most likely to result in the lowest fetal dose compared with those in the torso. Ten representative cases from the literature are reported in Table 4. Fetal doses range from 19.9 to 110 mGy. The case with the highest fetal dose is reported by Magné et al. in the patient who had a metastatic lesion in the right occipital lobe, with a primary lung lesion that was treated 15 months earlier with lobectomy and radiotherapy [22]. The patient was at 24-week GA at the beginning of the treatment for the metastatic lesion. Two lateral beams were used to radiate the whole brain to 30 Gy, and 2-cm-thick lead screens were used as shields on both sides of the patient. The patient's neck was hyperextended on the edge of the concrete block containing 2.3 % FeO_2. The patient delivered a healthy boy who was free of adverse outcomes at age 3. The only case to report an adverse outcome in brain

Table 3 Common diagnostic studies and estimated fetal doses

Diagnostic modalities	Fetal dose in mGy
Cervical spine (AP, lat)	<0.001
Extremities	<0.01
Chest (PA, lat)	<0.1
KUB	0.01–0.59
Thoracic spine (AP, lat)	<0.85
Abdomen (AP)	1–3
Lumbar spine (AP, lat)	3.46–6.2
IVP (four abdominopelvic images)	3.58–13.98
Barium enema	7–39.86
CT head	<0.5
CT chest	1–4.5
CT coronary angiography	0.1
CT abdomen	2.4–26
CT abdomen + pelvis	7.3–46
CT aorta angiography (chest + abdomen + pelvis)	34
CT lumbar spine	35
PET scan whole body	<12 weeks, 15; >12 weeks, 10
Thyroid scan (iodine 123)	<12 weeks, 0.2; >12 weeks, 0.1

Highest reported dose is used for each modality. Adapted from McCollough et al. [15], Williams et al. [16], and Osei et al. [17]

Table 4 Cases of selected cancers during pregnancy treated with radiation therapy, their management, and outcome

Tumor and location	Tumor dose (Gy)	Fraction	Distance from fetus (cm)	Machine	Fetal dose (mGy)	Gestational age at the beginning of therapy	Outcome	Shield	Ref.
Head and neck metastasis (right occipital lobe)	30 (whole brain radiation	10	N/A	N/A	110 at midline of fetus	24 weeks	Healthy boy without any adverse outcome at age 3	2-cm-thick lead screens on both sides, concrete blocks containing 2.3 % FeO_2 under the neck	[22]
Head and neck squamous cell carcinoma (tongue)	64	25	31	6 MV, 9 MeV	<90	22 weeks	Healthy boy at delivery	Six 1.5-cm-thick cerrobend alloy plates on top of 1.28-cm lead apron	[23]
Head and neck atypical ependymoma	68	65	N/A	6 MV	60	27.4 weeks	Healthy girl at age 2.5	None	[24]
Head and neck anaplastic astrocytoma	78.18	77	N/A	6 MV	30	28 weeks	Health girl at age 1.5	None	[24]
Head and neck pituitary microadenoma	45	45	66	6 MV	19.9	5–6 weeks	N/A	None	[25]
Head and neck squamous cell carcinoma (nasopharynx)	66	N/A	25	6 MV, 9 MeV, 12 MeV	<35	20 weeks at diagnosis	N/A	5-cm lead	[26]
Head and neck (rhinopharynx)	68	34	47	6 MV	49	27 weeks	N/A	6-cm lead	[27]
Head and neck synovial sarcoma (left cheek/ gingiva)	66 (48 at delivery)	33 (24 at deliv- ery)	30	6 MV	85 (fundus)	29 weeks	Healthy boy without any a verse outcome at 8 months	0.6-cm lead	[28]
Head and neck mali gnant Schwannoma (cervical plexus)	60	N/A	N/A	N/A	36	17 weeks	No adverse outcome reported	Yes	[29]
Head and neck high-grade astrocytoma	54	30	N/A	6 MeV	2.7	20 weeks	Died in utero	75-mm-thick lead	[30]
Breast cancer (left breast)	46	20	29	6 MV	39	2 weeks	Healthy boy	None	[31]
Breast cancer (left breast)	50	25	N/A	6 MV	140–180	15 weeks at diagnosis	Elective C-section at GA 33 weeks after radiation treatment. Born in good condition. Respiratory distress due to prematurity and jaundice later.	9-mm lead	[32]

Table 4 (continued)

Tumor and location	Tumor dose (Gy)	Fraction	Distance from fetus (cm)	Machine	Fetal dose (mGy)	Gestational age at the beginning of therapy	Outcome	Shield	Ref.
Breast cancer (left breast)	50	N/A	24	10 MV	160	24 weeks	Healthy boy at delivery	4-cm lead shield	[33]
Hodgkin's lymphoma (mediastinum)	42.5	20	N/A	N/A	50–180	7.4 weeks	Meets developmental milestones; weight and length at fifth percentile and head circumference at third percentile at the age of 2	None	[34, [-3-5]
Hodgkin's lymphoma (above diaphragm)	35	20	N/A	10 MV	<100	23 weeks	Healthy infant at term	5-cm lead sheet on top of 1.25-cm aluminum plate	[36]
Hodgkin's lymphoma nodular sclerosing (left neck and mediastinum)	(19 at delivery)	(12 at delivery)	10	6 MV	<420	27 weeks	Planned delivery by C-section. Healthy and adverse effect free at 8 years of age	Six 1.5-cm-thick cerrobend alloy plates	[23]
Hodgkin's (above and below diaphragm)	40, 36, 36 ξ	N/A	N/A	6 and 10 MV; 25 MV Ψ	2800–5000	Conception estimated at 9–10 days after the end of supradiaphragmatic irradiation; 4 weeks at the beginning of subdiaphragmatic irradiation	Healthy boy at age 3	None	[37]
Hodgkin's lymphoma (neck)	36.75	20	N/A	6 MV	46	25 weeks	Healthy female at age 9	N/A	[30]
Hodgkin's lymphoma (neck)	36	20	N/A	6 MV	50	24 weeks	Healthy female at age 11	N/A	[30]

ξ 40 Gy for mediastinum, 36 Gy for supraclavicular, and 36 Gy for subdiaphragmatic lesions; Ψ 6 and 10 MV for lesions above the diaphragm, 25 MV for lesions below the diaphragm

Table 5 Fetal doses at different gestational ages during breast cancer radiation

GA (weeks)	Minimum distance from fetus to field center (cm)	Maximum dose (cGy) in fetus for target dose of 5000 cGy (6–25 MV)
10	40	3
14	34	5
18	29	8
22	24	12
26	20	20
30	16	40
34	13	73
38	9	143

Adapted from Van der Giessen (1997) [33]

cancer is by Luis et al. who described a 20-week GA patient with a left frontal astrocytoma [30]. Three linear beams were used to radiate the patient to 54 Gy, and her abdomen was covered in a 75-mm-thick lead shield. The radiotherapy proceeded without complication, but at routine 38-week fetal ultrasound, no heart sounds were detected. The fetal autopsy demonstrated inferior vena cava thrombus that likely occurred around full term given the fetus's size. In three of the other cases reported in Table 4, there was no information about the fetal outcome, but the fetal doses were 19.9, <35, and 49 mGy, all well below the threshold doses for non-cancer adverse outcomes. All other cases reported no adverse outcomes. Jie-Hua et al. reported four cases of nasopharyngeal carcinoma with no adverse outcomes (fetal doses are missing, and therefore, cases were not reported in Table 4) [38]. These cases illustrate that the radiation therapy can be used fairly safely in the cancers of the head and neck. On the other hand, watchful waiting has also been utilized in slow-growing tumors. Haba et al. reported a case in which a 20-week GA patient with glioma was managed conservatively until delivery after serial MRIs showed no progression during pregnancy [39].

Breast cancer

After malignant melanoma and Hodgkin lymphoma, breast cancer is the most common cancer during pregnancy with an incidence of 1 in 3000–10,000 [2]. Breast cancer during pregnancy is generally defined as one that arises during concurrent pregnancy or within 1 year after delivery. The incidence of breast cancer during concurrent pregnancy, however, was 34 out of 100,000 maternities in a population-based study in Australia [40]. Table 5 lists the maximum fetal doses by gestational age, demonstrating a significant increase in fetal dose as the fetus grows—from only 3 cGy at 10-week GA to 143 cGy at 38-week GA. However, one should note that as the gestational age increases, the fetus is more likely to be in cephalic position, reducing the risk of radiation to the fetal brain.

There have been cases of successful radiation therapy used to treat breast cancer patients with concurrent pregnancies resulting in no adverse outcomes to the fetus [31–33]. All cases occurred in different trimesters during the treatment and showed no abnormalities to the infants. For the tumor doses of 46–50 Gy using 6 and 10 MV photon beams, fetal doses varied from 39 to 180 mGy. In the case with 2-week GA, no shield was used and the fetal dose was less than 100 mGy, the threshold dose for fetal death [31]. Nine millimeter and 4-cm lead shields were used in the other two cases that were over 15-week GA. The fetal doses were also less than the threshold dose for intellectual disability. As with cancers of the head and neck, breast cancers can also be treated with radiation with good fetal outcomes.

Hodgkin's lymphoma

At the incidence of 1 in 1000–6000 pregnancies, Hodgkin's lymphoma is the second most common malignant tumor among pregnant women after malignant melanoma [2]. It has a bimodal age distribution with the first peak in 20s–30s and the second in 50s, explaining the high incidence during the childbearing years. It typically presents in the neck or the mediastinum as painless lymphadenopathy or as an asymptomatic enlarged lymph node on chest X-ray [41]. Depending on the location of the nodes involved, fetal doses can vary. One previous review noted a total of three adverse outcomes in 58 cases of Hodgkin's lymphoma of varying stages, including one perinatal death [30]. Klieger-Grossmann et al. reported an adverse outcome in a case of stage IIA Hodgkin lymphoma in the mediastinum [34]. The patient was found to be pregnant after chemotherapy and radiation therapy. GA was calculated to be 7 weeks and 4 days at the beginning of the radiation treatment. She received 42.5 Gy in 20 fractions, and fetal dose was calculated later to be between 50 and 180 mGy. A healthy baby boy was born at 39-week GA at 10th, 50th, and 20th percentiles for weight, length, and head circumference, respectively. At the age of 2, the boy was healthy and had met developmental milestones. However, his weight and

Table 6 Survival rates of extremely preterm infants with gestational age between 22 and 28 weeks at the time of discharge at 20 US academic centers

Gestation (weeks)	Number	Percent survival	Percent survival without morbidity[a]
22	421	6	0
23	871	26	8
24	1370	55	9
25	1498	72	20
26	1576	84	34
27	1838	88	44
28	2001	92	57
Total	9575	72	37

[a] Morbidities included respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage, periventricular leukomalacia, early onset and late-onset sepsis, necrotizing enterocolitis, infections, patent ductus arteriosus, and retinopathy of prematurity. Adapted from Stoll et al. (2010) [46]

length were at the fifth percentile and his head circumference at the third percentile. His gestational age during the radiotherapy overlapped with the period of organogenesis, potentially explaining his delayed growth, especially the small head size.

On the other hand, Moreau et al. reported a case with a good outcome despite a very high fetal dose [37]. The patient had Hodgkin lymphoma with extensive involvement of both supradiaphragmatic and subdiaphragmatic nodes. She received 40 Gy to the mediastinum and 36 Gy to the neck along with chemotherapy. Radiotherapy for subdiaphragmatic nodes was delayed for 4 weeks during which she became pregnant. Thirty-six gray to the paraaortic nodes was delivered. She was found to be pregnant only after the end of the second course of radiotherapy. Gestational age was calculated to be about 4 weeks at the beginning of the treatment and 8 weeks at the end. The fetal dose was estimated to be between 2.8 and 5 Gy. The option of termination of pregnancy was discussed, but the patient declined. A baby boy was delivered at 41-week GA. At the age of 3, he was healthy and had normal psychomotor development for his age without any hematologic disorders. These two cases demonstrate the unpredictability in adverse outcomes to the fetus from in utero radiation exposure.

Four other cases of Hodgkin lymphoma described in the Table 4 were known pregnancies at the time of treatment. The lesions in all cases were above the diaphragm, and patients also received shielding. The first case was at 23-week GA [36]. The fetus received less than 100 mGy with an outcome of a healthy infant. The second case was at 27-week GA [23]. Before the fetus was delivered through planned C-section, it received less than 420 mGy. The therapy continued after delivery. The child was healthy with no adverse effects at 8 years of age. In the other two cases, the fetuses received 46–50 mGy, and both children were healthy at 9 and 11 years of age, respectively [30]. While most of the cases of Hodgkin lymphoma described above failed to show adverse outcomes, fetal doses have proven to be significantly higher than doses to

Table 7 Postneonatal death rate by gestational age

Gestation (weeks)	Total preterm infants, *n*	Postnatal deaths, *n*	Postneonatal mortality rate, %
25	9783	960	9.81
26	13,735	961	7.00
27	17,208	894	5.20
28	19,769	719	3.64
29	28,571	662	2.32
30	35,112	602	1.71
31	48,956	622	1.27
32	63,752	654	1.03
33	90,249	674	0.75
34	137,886	837	0.61
35	237,125	1179	0.50
36	415,182	1623	0.39
37	770,206	2250	0.29
Total	1,895,350	12,637	0.67

Data from 2001–2005 US birth/infant death database. Adapted from Kamath-Rayne et al. [47]

more distant lesions, particularly in the head and neck region. In addition, involvement of nodes below the diaphragm will likely push fetal doses above threshold.

Cervical cancer

Cervical cancer has an incidence of 1.2 in 10,000 pregnancies [2]. Unfortunately, radiation therapy for cervical cancer cannot be safely administered during pregnancy. Budzinski et al. reported five cases of stage IIb invasive carcinoma of the cervix during pregnancy in which spontaneous abortions/premature labor occurred after 30.6–32 Gy of irradiation was delivered through external beam and brachytherapy [42]. If pregnancy is desired, the risk to the mother from delaying the treatment should be carefully balanced with the risk to the fetus from early delivery to find the optimal gestational age for delivery. For early delivery, the fetus is generally not viable in the first trimester, but viability improves after 23 weeks of gestation. Cautious delay in treatment may be an option if pregnancy is still early and the disease is also in early stage [43]. However, a disastrous outcome to the mother after such a delay has also been reported [44]. The following topic discusses the survival of preterm deliveries. If the treatment is postponed until after delivery, vaginal birth is contraindicated due to the risk of recurrence in episiotomy scars [45].

Considerations in pregnancy management for pregnant women with cancer requiring radiotherapy

When the risk of radiation to fetus is considered, one alternate solution is to consider early delivery. The decision for the delivery should be guided by the risk of mortality and morbidity to the newborn due to prematurity. The data adapted from the study by Stoll et al. (Table 6) shows the survival rate of preterm delivery [46]. This data came from 20 US academic centers across the nation from 2003 to 2007 and studied children born between 22 and 28 weeks of gestation. This study highlights the fact that although greater than 75 % of infants with gestation age over 26 weeks survive, many of those who survive will have morbidities due to prematurity, including respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage, periventricular leukomalacia, early onset and late-onset sepsis, necrotizing enterocolitis, infections, patent ductus arteriosus, and retinopathy of prematurity. These morbidities can have long-term complications and may translate into mortality after discharge. The postneonatal (defined as 29 days to 1 year after delivery) mortality rate for premature infants born before 38.0 weeks of gestation who survived the neonatal period is illustrated in Table 7.

The limitation in using Tables 6 and 7 is that the preterm deliveries in these studies are not specific for those due to medical indication from maternal cancer treatments. In fact, many are due to fetal indications (e.g., distress or abnormality) that may have different mortality risk when compared with maternal indications. Therefore, they should be used with caution when the physician discusses the data with the patient. They are intended to supplement the discussion between the patient and the providers about options for the patient. The patient will ultimately need an expert opinion from a neonatologist and an obstetrician regarding the mortality and morbidity risk due to premature delivery.

Conclusions

Radiation exposure to the fetus is associated with increased incidences of childhood cancer at any fetal dose. However, there seem to be threshold doses for non-cancer adverse outcomes such as intellectual disability, organ malformation, and fetal death. The fetal radiation exposure from diagnostic radiology and nuclear medicine studies is far smaller than the threshold levels. On the other hand, fetal doses from radiation therapy for treatment of maternal cancers depend largely on gestational age and distance of fetus from the treatment field. Treatment of cancers in head and neck or extremities is relatively safe, while that of pelvic organs, such as cervical cancer, is not compatible with pregnancy. Shielding should be used to reduce fetal dose. It is important to note that all data in this paper, collected from several sources, come from observational studies. The “threshold” doses were calculated by studies that are based on the limited number of observational cases and therefore should be used with careful considerations to individual clinical scenarios.

Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest.

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Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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