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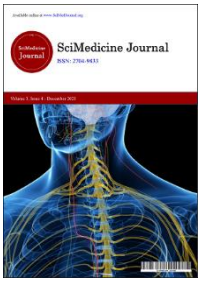

Cancer Morbidity and Computed Tomography: "After" and "Due to" Challenge

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Abstract

The article discusses the problem of carcinogenic risk assessment in the context of relationship with diagnostic radiation resulted from Computed Tomography (CT). The study aimed to evaluate the possible long-term carcinogenic effects after the exposure to a low dose of diagnostic radiation, appeared within a decade after the 1st CT scan. Information on patients examined using CT in the District Hospital of Kasli (KDH) has been derived from the CT archives since 2009 when the first CT examinations has been performed in the KDH. The data were linked to local Cancer registry, the Death registry, and the "CT Registry" database (CTDB) to obtain the information on vital status, the cause of death, cancer morbidity and CT examinations outside KDH, respectively. 275 CT examinations of 246 patients have been recorded to the data file (KDH cluster). To the end of the study, 46 cases of malignant tumours (MT) have been accumulated in the study group. The average observation time was 6.5 years (90% CI 6.2-6.8). The distribution of cancers among patients exposed to CT has been shown retrospectively through the date of birth of patient to December, 31, 2018. The cases of MT diagnosed prior to 1st CT examination have been excluded from the analyses. Cancer-related conditions stated before the date of 1st CT examination have been accounted. The cumulative cancer incidence after the exposure to CT, adjusted for predisposed conditions in the study group was 4.8%. The study results have been compared with the results of the LSS cohort study to assess the expected excess cancer morbidity. The data obtained in the study provide the information for a comprehensive epidemiological assessment of long-term effects related to diagnostic radiation exposure in the Ozyorsk Computed Tomography Cohort (OCTC study).

Keywords: Computed Tomography; Diagnostic Radiation; Cancer; Risk; Low Dose; LNT; Oncological Effects.

1. Introduction

Radiation carcinogenesis in a low dose area is the issue of special interest for researchers due to stochastic nature of long-term effects of radiation exposure of humans [1]. During the last century, X-ray diagnostic examinations played the significant role among the sources of man-made ionizing radiation [2]. In recent decades, modern diagnostic methods such as Computed Tomography (CT) made a significant contribution to radiation burden of the Earth population [3]. Though the patient's exposure due to CT is actually in a low-dose area, repeated CT

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examinations can lead to significant radiation burden of the patients during lifetime. To make the CT procedure safer, it is necessary to control the radiogenic risk resulted from exposure to diagnostic radiation.

Despite a large number of published research works concerning this issue, the radiation risk in a low dose area is the subject for discussions in the world's scientific community [4]. The absence of specific markers of radiation carcinogenesis and substantial variability of carcinogenic effects depending on various concomitant factors of radiation and non-radiation nature complicates the radiation risk assessment problem. Another challenge in assessing the radiation risk of stochastic effects as a probability of outcome appearance (when no direct relation exists between the risk factor and the endpoint) is "after not due to" issue. This issue is all the more relevant in recent years in the epidemiology of infectious diseases in connection with the problem of assessing the consequences of the Covid-19 pandemic.

According to the results of the epidemiological study which is the gold standard in radiation protection (i.e. Life Span Study, LSS) the significant effects of exposure to ionizing radiation were obtained for the radiation doses above 100 mGy [5] with the significant evident of linearity for the doses above 500 mGy. Based on this fact, the extrapolation of the radiation risk estimates has been proposed to assess the radiation risk in the low-dose area in accordance with the linear non-threshold conception, which assumes the presence of radiation-induced effects at an arbitrarily small radiation dose.

Since this conception still does not have an actual confirmation with the real epidemiological data, there are several alternative viewpoints resulted in the appearance of the hypersensitivity model, sublinear and threshold models, as well as a model of radiation hormesis (Figure 1). Due to its mathematical simplicity, the linear non-threshold model (LNT) is most widely used to describe the radiation effects in a low dose area.

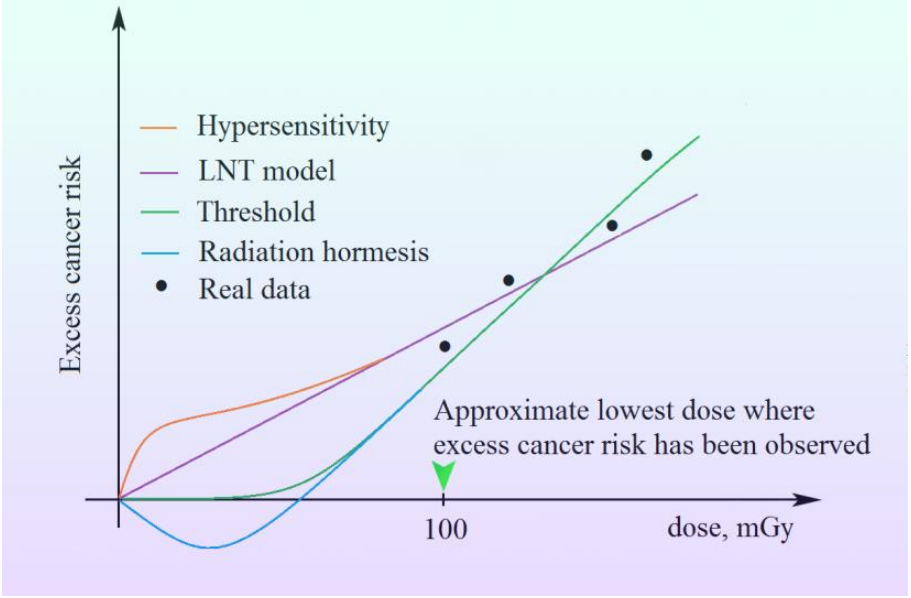

Figure 1. Radiation risk models and the real epidemiological data

The extrapolation of radiation risk estimates in a low dose area according to linear non-threshold conception has been successfully implemented for the radiation protection purposes during the last decades. This approach resulted in establishing the radiation exposure levels for professionals occupationally exposed to ionizing radiation. However, it is unclear whether it can actually protect patients from health disorders caused by the possible impact of low doses of diagnostic radiation resulted from CT scans, and how much.

Although the radiation dose resulted from single CT examination is still in a low dose area [6], the recurrent CT examinations can increase the referent cumulative dose up to 100 mGy, and above [7]. At the same time, the difference between the LSS scenario and the CT diagnostic exposure, differences in the effects of exposure during various diagnostic procedures and related age and health conditions of subjects facilitate the reasoned criticism of the applicability of the LNT for radiation protection of patients [8].

In order to ensure the reliability of the radiation risk coefficients obtained using LNT for the radiation protection of patients, the retrospective epidemiological study using cohort methodology is required to assess the long-term stochastic (cancer) effects taking into account the influence of possible confounding factors [9]. Comparison of the baseline cancer incidence in the population before the diagnostic CT starts, and the cumulative cancer incidence since years after (because of latency period of cancer development) will give the opportunity to understand how fair this

extrapolation is. Special emphasis in that study design should be put on the accuracy and completeness of the data collection. Diagnostic exposure of patient realized from different sources and fractionated over protracted period of time (long-term repeated exposure scenario, LTRE) is typical for CT examinations of patients with chronic diseases. Thus, thoroughly collected, each episode of CT exposure can help to reconstruct the individual dose exposure matrix of patients in order to minimize the uncertainties resulted from underestimated radiation burden and, therefore, avoid overestimating the radiation risk.

The aim of the work is to provide the results of our own real data based research on the assessment of oncological effects among patients exposed to diagnostic CT over decade after the first examination. The results of the study can bring some light on the "*after or due to*" challenge which is of special interest of epidemiologists, in conjunction with modern concepts of radiation risk in a low dose area. Also, this study provides an additional data for the CT Register database (CTDB) [10] used to conducting multicenter epidemiological study on radiation risk assessment among patients examined using CT (OCTC study).

2. Material and Methods

2.1. The Methodology and the Data Source

The source for the data was the clinical archive of computed tomography department of the Kasli District Hospital (KDH) located in the South Ural of Russian Federation 15 km far from the Ozyorsk city and the "Mayak" Production Association – nuclear weapon production complex in the former USSR. The data collected from the archive journals contained individual records of CT examinations of Ozyorsk District residents. The information collected from the protocols of CT examinations was digitized and entered into the electronic database (KDH cluster). The methodology of data collection and the database development was detailed in our recent study [11].

The epidemiological study was carried out retrospectively using cohort methodology. The cohort included the residents of Ozyorsk District who underwent at least one CT examination in the KDH. The Somatom Spirit scanner (Siemens Healthcare Diagnostics) has been used for routine examinations in the CT department of KDH during the whole follow-up period. The follow-up started in the 2009 when a new method of X-ray diagnostics – computed tomography – has been just implemented into clinical practice of KDH, and ended on 12/31/2018.

The information on the vital status, cause of death and cancer morbidity among the population of Ozyorsk District was obtained from the population registers of Epidemiological Laboratory of Southern Urals Biophysics Institute: local "Death Registry", "Child Registry" and the "Cancer Registry". The study data has been linked to the "CT Registry" database (CTDB) [10] to account all possible episodes of CT examinations of Ozyorsk District residents performed in the Chelyabinsk region but outside KDH.

Cancer incidence according to the age and sex distribution, the anatomic area which was exposed to CT, patient's clinical diagnosis and the radiologist's conclusion after the CT examination, the dose-length product (DLP), and the effective dose (ED) as the characteristics of radiation burden has been analyzed.

The time at risk for each patient has been counted from the date of the first CT examination to the date of first malignant neoplasm diagnosis (ICD-10 codes C00 – C96), or the date of death, or the end of follow-up, whichever the earliest. Residents of Ozyorsk District with no information on the date of death until December, 31, 2018 were treated as alive. Subjects who did not experience an event (diagnosis of cancer) by the end of the study were right-censored.

2.2. Cancer Incidence Calculation

Cancer cases accumulated in the study group to the end of follow-up were divided into two categories in relation to the date of the first CT examination:

- Cancer diagnosed prior to the first CT examination;
- Cancer diagnosed after the first CT examination.

Cancer morbidity was calculated as the number of cancer cases (n) accumulated in the study group, divided to the total number of observed (N). Persons with cancer cases occurred prior to the date of 1st CT examination (n_0) has been treated as not exposed. These oncological effects without the impact of CT could be considered as "background" cases with zero CT dose for the further comparison. Since previous malignancy is an additional risk factor [12] the cases of second malignant tumours has not been used for the analyses even they appeared after the date of CT examination, and the follow-up period ended on the date of first malignancy.

Predisposed conditions has been defined as those when the patient's clinical diagnosis at referral, or the CT conclusion had the information related to cancer process, that makes likely the probability that malignant tumour will be revealed on or after the CT examination. The cancer cases with predisposed conditions (n_1) were treated as not related to CT exposure. According to that, cumulative incidence (CI) was calculated as following (Equation 1):

$$CI = \frac{n-(n0+n1)}{N-(n0+n1)} \quad (1)$$

where n – total number of cancer cases accumulated in the study group since birth to the end of follow-up; n_0 – cancer cases confirmed during or prior to 1st CT examination; n_1 – cancer cases confirmed after the 1st Ct examination with predisposed conditions, stated before the examination; N – total number of patients recruited in the study cohort.

The suggested number of excess cancer cases (ECC) has been calculated using the proportion of excess cancers obtained in the excess relative risk analyses according to the LSS study data [5] (Equation 2):

$$\mathrm{ECC(KDH)} = \frac{ECC(LSS)}{n(LSS)} \times (n-(n0+n1))KDH \quad (2)$$

Procedural frequencies and cumulative radiation exposures were calculated for the entire study group over the 10-year follow-up period. The radiation dose of patients has been counted to the date prior to the first malignancy diagnosed. The ED calculation has been performed using the Nation Radiation Protection Board guidelines. Statistical analyses have been performed using Stata statistical software [13]. The data were processed using generally accepted statistical methods, with the standard deviation indicated for the means. For statistical test of the results obtained, generally accepted significance level of 0.95 was used. The probability value (p) at which the hypothesis h_0 on the absence of a significant influence of the risk factor was rejected, was taken at 0.05.

3. Results

3.1. General Characteristics of the Dataset

275 archive records of 246 patients examined in the department of Computed Tomography of the Kasli District Hospital has been derived from the archive since January, 1, 2009 to December, 31, 2018. In the study group were 113 males (45.9%), and 133 (54.1%) females examined using CT at the age from 8 to 85 years, with the average of 52.5±1.03 years. The proportion of patients examined at the age under 18 was 2.8%. The time under observation for each patient varied from 0 to 10 years (average time 6.5 years). The cumulative person-time in the study group was 291.97 years.

Each CT examination was performed according to strict clinical indications. The number (N) and the proportion (%) of examinations regarding the anatomic area, the dose-length product (DLP) and the effective dose (ED) are shown in Table 1.

Table 1. The proportion of CT examinations by area exposed and the average dose per 1 CT scan

Area exposed to CT	Examinations (*N*)	Proportion (%)	DLP, mGy*cm	ED, mSv
Head*	122	44.4	596.9	1.4
Neck	18	6.5	72.6	1.2
Thorax routine	35	12.7	135.2	4.0
Thoracic spine	19	6.9	130.0	6.0
Abdomen and pelvis	17	6.2	322.2	8.0
Lumbar spine	46	16.7	252.5	6.0
Other**	18	6.5	89.8	5.0
Total	275	100.0	-	-

* Head scans were performed in step mode only

** Including joints, extremities and non-classified areas

The largest part of the examinations has been performed for the brain CT (44.4%). The abdominal area (including lumbar spine) has been exposed in 22.9% of examinations. Thorax region scanning (including thoracic spine) has been performed in 19.6% of examinations. 11.8% of patients underwent multiple CT examinations during the follow-up period (average number 3.5 procedures). Average effective dose per one CT scan was 2.7 mSv (std.er 0.16).

3.2. Vital Status and Cancer Morbidity

The vital status information has been obtained as of December, 2018. To the end of follow-up 36 patients (14.6%) has died, with 55% of malignant tumours (MT) established as a cause of death. The proportion of alive and non-cancer patients in the study group to the end of follow-up was 77.1%. The total number of clinical diagnoses of malignant tumours accumulated in study by the end of follow-up was 46 (18.7%). The structure of cancer morbidity accumulated in the study group to the end of follow-up, including cancer cases diagnosed before the first CT examination, the cumulative number of CT examinations (Σ_{CT}) using the CTDB data [10], and the proportion of CT examinations (Σ_{CT} %) by cancer site is shown in Table 2.

Table 2. The structure of cancer morbidity depending on cancer site and CT scans

Cancer site	ICD-10	Cancer cases, n	Proportion (%)	Σ_{CT}	Σ_{CT} (%)
Oropharyngeal area	C07-C14	1	2.2	4	4.1
Gastrointestinal	C15-C26	5	10.9	11	11.3
Respiratory	C30-C39	8	17.4	32	33.0
Skin, bone and connective tissue	C40-C49*	7	15.2	8	8.2
Reproductive system, female	C50-C59	3	6.5	7	7.2
Reproductive system, male	C60-C63	5	10.9	9	9.3
Excretory system	C64-C68	3	6.5	3	3.1
Central nervous system	C69-C71	5	10.9	9	9.3
Other and non-specified	C72-C80	6	13.0	9	9.3
Haemopoetic tumours	C81-C96	3	6.5	5	5.2
Total	C00-C96	46	100.0	97	100.0

* Including 3 malignant melanoma cases (C44)

The most proportion of cancer cases (17.4%) revealed among respiratory cancers (8 cases of lung cancer). Positive correlation (R=72.5%) has been observed between the number of cancer cases and the number of CT examinations accumulated within the ICD-10 subgroups. The frequency of cancer examinations (2.1 CT per one malignancy) was approximately 2 times higher than one for non-cancer patients (1.1).

The distribution of cancer cases by date of the first CT examination and the 5-year follow up (t1), as well as 5-year period prior to 1st CT is shown in Figure 2

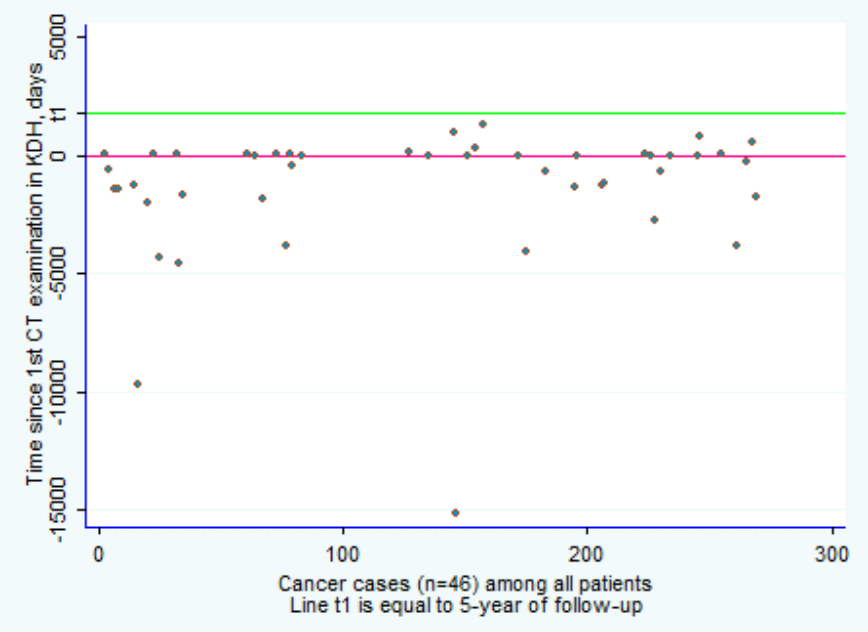

Figure 2. Distribution of cancer cases diagnosed during the follow-up period. The date of the first CT examination in the KDH (0, pink line) and 5-year period (t1, green line) after the 1st CT examination

28 cancer cases in the study group (60.9%) diagnosed prior to the 1st CT examination (t<=0) has been excluded from the comparison (*N* has decreased to 218), among them 17 cancer cases has been diagnosed within 5-year period prior to the 1st CT. To the end of follow-up, 18 newly diagnosed cases of malignant tumours (CI 8.3%) appeared within the 5-year period after the 1st CT examination.

3.3. Predisposed Conditions

Retrospective analyses of cancer registry data shown that in 8 cases diagnosed after the 1st CT examination, clinical signs of cancer or suspected malignancy have been stated on or before 1st CT date. These cases having predisposed conditions has been excluded from the analyses (*N=210*). The number of MT cases diagnosed after the CT examination that could be related to diagnostic radiation in this study group was 10.

The cumulative cancer incidence accounted using exposed cases was 4.8%. The Table 3 describes in details the age at exposure, sex, clinical diagnosis (ICD-10) and the cause of death, cumulative number of CT examinations before the diagnosis, accounted using the "CT Registry" data (Σ_{CT}), and the time since the 1st CT exposure (T).

Table 3. Cancer cases diagnosed after the CT examination in distribution by age, sex, maximum number of CT scans (Σ_{CT}), average effective dose (ED), ICD-10 code, stage of MT, cause of death and the observation period (T)

#	Age	Sex	Σ_{CT}	ED, mSv	ICD-10	Stage	Cause of death	T, days
22	77	F	2	1.2	C71.9	-	C71.9	87
32	69	F	1	0.6	C70.0	-	C70.1	33
127	54	F	5	1.4	C25.0	3	Alive	145
145	72	M	1	6.0	C61.0	2	Alive	1014
157	62	F	2	4.0	C43.5	1	Alive	1282
172*	50	M	1	0.4	C07.0	1	I61	1134
245*	62	M	1	5.8	C22.0	3	C22.9	1353
246	60	M	1	6.0	C61.0	2	Alive	825
255	67	M	1	1.4	C20.0	-	C20.0	42
268	69	F	1	4.0	C49.2	1	Alive	609

* According to CTDB data only; - stage undefined or N/A

The male/female ratio in the exposed group of cancer patients was 0.5. The age at the date of the first CT scan varied from 50 to 77 years (average 64.2±2.6 years). All malignant tumors in this group were diagnosed within the first 5 years after the CT examination (average 652±170.5 days, or 1.4±0.48 years). The average cumulative ED taking into account the previous examinations outside the KDH for those 10 cancer cases was 3.1 (min 0.4; max 6.0) mSv. Proportion of cancer survivors in given subgroup was 50%.

3.4. Comparison with the LSS Study Data

The data on cumulative solid cancer incidence in the study group has been compared with the results reported in the LSS study [5]. The results of comparison are shown in Table 4.

Table 4. The results of comparison of KDH cluster data with the LSS cohort study

Parameter	KDH study	Life Span Study (LSS)
N	210	105 447
Follow-up period	10	40
Age at 1st exposure	52.5	30
Number of cancer cases	10	17 448
Cumulative cancer incidence	4.8%	16.5%
Excess cancer cases	0.49**	853*
% excess	-	4.9%

*fitted in the model;

**suggested

The cumulative incidence rate ratio for all solid cancers [KDH:LSS] was 0.29 (95% CI 0.16-0.53); $p<10^{-6}$. Estimated number of excess cancer cases in the KDH group that may be related to radiation exposure will be less than 0.49 cases considering the sample size of N=246 and current follow-up period length.

4. Discussion

The results obtained in the study showed that during the decade of observation period among 246 patients first examined using CT at the age of over 50 years with an average effective radiation dose of 2.7 mSv, 18 new cancer cases (8.3%) has been diagnosed. Of these, 10 cases of malignant tumours diagnosed within 5 years after the first CT examination without cancer-related conditions can be hypothetically associated with the radiation exposure resulted from CT (CI 4.8%).

These findings are consistent with the results of our previous study on assessing the risk of cancer morbidity resulted from repeated CT scans [15]. According to the results reported in the literature, the risk of developing cancer after 1 year from the CT scan with an average follow-up length of 9.5 years and an average ED of 4.5 mSv was 24% higher than in people not exposed to diagnostic CT [16]. Related studies [17-18] reporting that diagnostic CT scans under the age of 21 are statistically significantly associated with an excess risk of brain tumors (ERR 0.023 per 1 mGy), leukemia (ERR 0.036 per 1 mGy), and thyroid cancer.

In our study, no cases of thyroid cancer or leukemia that could be attributed to radiation dose have been found. Four cases of solid cancers diagnosed less than 1 year after CT (see Tab.4) more probably indicate the hypodiagnostics than the association with exposure to diagnostic radiation due to CT. This is consistent with the results of recent study [19] where the radiation dose received as a result of both computed tomography and X-ray procedures did not increase the risk of developing brain tumors in adolescents, as well as results reported in the number of previous works [4].

Finally, in accordance with the recommendations [20-21] and the methodology used to calculate the dose using a 5-year lag period for solid cancers as a group [5], none of the MT accumulated in the KDH study group can be attributed to the radiation dose received during CT examination. Based on this, the excess risk of cancer attributed to diagnostic radiation due to CT examination in this study is currently undetectable. That is consistent with the results of LSS study comparison: the cumulative solid cancer incidence in the KDH study was significantly lower (IRR 0.29) than one in the LSS cohort ($p<1*10^{-6}$), and the number of suggested excess cancer cases is less than one (0.49) excess case per group of 246 KDH patients (see Tab.4). According to the reported 17% decrease in cancer incidence with each decade increase of age at exposure [5], this ratio expected to be much lower in fact. Thus, it is most likely that 10 cancer cases accumulated in the study cohort during the follow-up are the result of other causes rather than exposure to diagnostic radiation resulted from CT. Moreover, based on the target theory, predominantly local irradiation in the case of diagnostic CT should give a lower yield of cancer effects than uniform exposure scenario in the LSS, at the same dose.

However, this comparison is rather arbitrary since it does not take into account the follow-up length, and does not reflect the other characteristics of the compared groups associated with the age at exposure, attained age, different health conditions of the examined persons, different exposure scenarios and the dose, different types of CT scanners, and other. Possible differences in the background cancer incidence and the exposure levels due to conventional radiography also pose a major problem for this comparison.

A short survival period for elderly patients and age-dependent health disorders is another problem that biases the assessment of the carcinogenic effects after the radiation exposure [22]. Since the age-dependent health conditions can reduce the patient's life expectancy, the changes caused by exposure to diagnostic radiation are less likely lead to detect the clinical manifestation of malignant process within the short period after the radiation exposure due to competing causes [23]. Nevertheless, a significant proportion of alive and non-cancer patients in this hospital cohort (77.1%) is of interest in terms of further observation with extended follow-up period to assess the realization of possible long-term carcinogenic effects.

The lack of reliable epidemiological data of radiation risk in a low-dose area is still necessitate the approaches of decreasing the radiation dose of patients [24] in regard to the ICRP recommendations [9]. This could be of special importance in case of presence of other radiation risk factors, such as conventional X-ray procedures and occupational radiation exposure of nuclear workers [25].

5. Conclusion

A retrospective quantitative assessment of carcinogenic effects in a group of 246 residents of Ozyorsk District exposed to low dose of diagnostic radiation resulted from computed tomography (KDH cluster) has been performed. The probability that cancer will be diagnosed within first 5-year period *after* the 1st CT examination not associated with the presence of predisposing conditions was 4.8%. No epidemiological data have been found for the association of these cancer cases with diagnostic radiation exposure *due to* CT. Further follow-up is necessary in relation to lifetime risk assessment taking into account 77.1% of non-cancer survivors in the study group. The results reported in this paper provide an additional data for a complex assessment of radiation risk in the OCTC study.

6. Declarations

6.1. Author Contributions

Conceptualization, M.O.; methodology, M.O.; validation, M.O., V.L. and V.M.; formal analysis, P.D.; investigation, M.O.; data curation, V.L.; writing—original draft preparation, M.O.; writing—review and editing, P.D.; visualization, M.O.; supervision, M.O.; project administration, M.O. All authors have read and agreed to the published version of the manuscript.

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6.3. Acknowledgements

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6.4. Ethical Approval

The manuscript does not contain experiments on animals and humans; hence ethical permission not required.

6.5. Data Availability Statement

Restrictions apply to the availability of these data. Data was obtained from the archive of the Computed Tomography Department of the Kasli District Hospital with the permission of KDH administration.

6.6. Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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