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Chernobyl-Related Cancer: Re-Evaluation Needed

Çernobil-İlişkili Kanser: Yeniden Değerlendirmek Gerekir

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ABSTRACT

There has been no clearly demonstrated cancer incidence increase that can be attributed to radiation from Chernobyl accident, except for the thyroid carcinoma in the individuals exposed in childhood and adolescence. The drastic increase of thyroid cancer started 4 years after the accident. The solid/follicular subtype of papillary thyroid carcinoma predominated in the early period after the accident. Histopathological diagnosis of cancer in such cases, if no infiltrative growth is visible, is based mainly on the nuclear criteria of papillary carcinoma. Outdated equipment of histopathological laboratories in early 1990s and insufficient quality of histological sections hindered reliable assessment of the nuclear criteria. Access to foreign professional literature has been limited in the former Soviet Union. Appearance of advanced tumors shortly after the accident can be explained by the screening effect with detection of neglected cancers and by the fact that patients were brought from other regions of the former Soviet Union and registered as Chernobyl-related cases. Further evidence in favor of the overestimation of thyroid cancer incidence after Chernobyl accident is discussed. The concluding point is that immunohistochemical and molecular-genetic tests performed within the scope of international studies were partly based on an inadequately selected material, and that supposedly specific features of radiogenic post-Chernobyl cancers characterize, on average, a later stadium of tumor progression. Therefore, some published data on molecular-genetic and other characteristics of post-Chernobyl malignancies require re-evaluation.

Key Words: Thyroid carcinoma, Radiation, Chernobyl, Pediatric pathology

ÖZ

Çernobil kazası sonucu radyasyona bağlanabilen kanser insidansında, çocukluk ve adolesan döneminde maruz kalan bireylerde tiroid karsinomu için olan hariç, açıkça gösterilebilen bir artış olmamıştır. Tiroid kanserlerinin kesin artışı kazadan 4 yıl sonra başlamıştır. Tiroid karsinomunun solid/folliküler subtipi, kazadan sonraki erken dönemde baskın hale gelmiştir. Bu olgularda kanserin histopatolojik tanısı, eğer göze çarpan bir infiltratif büyüme paterni yok ise, temel olarak papiller karsinom hücrelerinin nükleer kriterlerine dayandırılır. 1990'ların başlarında histopatolojik laboratuvarların zaman aşımına uğramış donanımı ve histolojik kesitlerin kalitesinin yetersizliği, hücresel nükleer kriterlerin güvenilir olarak değerlendirilmesine engel olmuştur. Eski Sovyetler Birliğinde yabancı profosyonel literatüre erişim sınırlandırılmıştır. Kazadan hemen sonra ilerlemiş tümörlerin ortaya çıkması, ihmal edilmiş olan kanserlerin saptanması ile birlikte yansıma etkisi olarak ve eski Sovyetler Birliğinin diğer bölgelerinden hastaların getirilmesi ve Çernobil ilişkili olgular olarak kayıt edilmesi gerçeği ile açıklanabilir. Çernobil kazası sonrası tiroid kanser insidansının tahminlerin üzerinde olması yönündeki ileri sürülen kanıtlar tartışılmıştır. Uluslararası çalışmalar kapsamında uygulanan immünohistokimyasal ve moleküler genetik testlerin kısmen yetersiz seçilmiş materyal üzerine dayandırılmış olması kararımızı yönlendiren noktadır ve radyojenik Çernobil sonrası (post- Çernobil) kanserlerin varsayılan spesifik özellikleri, ortalama olarak, tümör progrosyonunun geç dönemini tanımlamaktadır. Dolayısıyla, çernobil sonrası malignitelerin moleküler-genetik ve diğer karakteristikleri üzerine yayınlanan bazı verilerin yeniden gözden geçirilmesi gerekmektedir.

Anahtar Sözcükler: Tiroid karsinomu, Radyasyon, Çernobil, Pediatrik patoloji

There has been no clearly demonstrated increase in the incidence of cancers that can be attributed to radiation from Chernobyl accident, except for the increase of thyroid carcinoma (TC) among people exposed during childhood and adolescence (1). Reaction of international scientific community to the drastic increase of TC four years after the accident was skeptical: it was not thought plausible that exposure to radio-isotopes of iodine could lead to such an increase with such a short latency (2). High incidence and the short induction period were designated as unusual in the UNSCEAR 2000 report, where it is also stated that the number of thyroid cancers in children and adolescents exposed to radiation is considerably higher than expected on the basis of previous knowledge. It is assumed that other factors may have influenced the risk (3). Improved diagnostics, registration and reporting were named among

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factors that could have contributed to the increased cancer incidence after the accident (1). It is also noteworthy that exposures to 131I from medical procedures have not demonstrated convincing evidence of an increased thyroid cancer risk (4).

The epidemiologic studies (5-7) constitute the main body of evidence in support of the cause-effect relationship between radiation exposure and TC after the Chernobyl accident (8). The studies (5,6) were based on retrospective estimates of individual doses by means of interviewing on whereabouts and dietary habits during and after the accident. However, questioning years after the accident can provide only approximate information. Besides, a systematic error probably occurred in these studies, which were not blind: both the interviewees and the interviewers knew about TC in the anamnesis. Attitude towards questioning was different in healthy individuals and those operated for TC. Cardis et al. (5) pointed out low participation among the controls, which was obviously caused by weak motivation. On the contrary, some operated patients strived consciously or subconsciously for higher dose estimation to support their status of Chernobyl victims. Registration increase has occurred as some people sought to obtain social benefits (3). Besides, the TC patients probably remembered the facts related to radiation better than healthy individuals, a phenomenon known as a recall bias. These facts can explain the high level of statistical significance of the relationship between a radiation dose and calculated TC risk reported in some studies (5,6). Other non-radiation-related factors and biases could have played their role. In the cohort study by Tronko et al. (7), individual estimates of radiation dose to the thyroid were based both on the interviews and on direct thyroid activity measurements between 10 and 60 days after the accident, before 131I (half-life 8 days) decayed to negligible levels (7). However, a systematic error occurred probably also in this study, based on 45 TC cases found in 13127 screenees. The screening and data collection procedure included, in case of indications, reexaminations and referrals to central clinics in Kiev (7). The screenees knew their doses and, on average, must have been more interested in further examinations, if the dose was relatively high. In the health care system of the former Soviet Union, thoroughness of an examination has sometimes depended on the patient's initiative and persistence. By the small number of cases (45 patients), even a slight observational bias of this kind could have significantly influenced the statistics. The above considerations are, in principle, applicable also to other analogous studies (e.g. 9,10). Moreover, a post hoc logical fallacy can be found in some studies: an unproven cause-effect relationship between elevated radiation background and cancer risk is used as a premise, and e.g. latent periods of malignant tumors are calculated on this basis (11,12). In another study by the same authors, the average annual dose in the studied cohort of nuclear industry workers monitored by dosimeters was 2,4 mSv/year (13). Estimates of radiation cancer risks from yearly exposure to 2,4 mSv were calculated and discussed, although the global average annual dose from the natural background is around 2,4 mSv, being several times higher in some countries (14), so that discussion of cancer risk from 2,4 mSv/year can be compared with prognostication of pressure injuries from 760 mmHg (15). At the same time, such publications create exaggerated impression about consequences of low-dose exposure.

High incidence of pediatric TC after the Chernobyl accident appears doubtful for a pathologist acquainted with diagnostic practice of that time. Ultrasonic thyroid screening was performed, and a large number of thyroid nodules found. Equipment of histopathological laboratories was poor and outdated; excessive thickness of histological sections hindered reliable assessment of diagnostic criteria. Gross dissection ("cutting up") of surgical specimens was often made with blunt autopsy knives, without rinsing the instruments and board for cutting with flowing water, which can result in tissue deformation, contamination by cells and tissue fragments, leading to artifacts hardly distinguishable from malignancy criteria. For example, high frequency of tumor cells found in blood vessel lumina (45 %) was reported in post-Chernobyl pediatric TC (16). In many laboratories celloidin embedding was used, not allowing reliable evaluation of nuclear changes in papillary thyroid carcinoma, in particular, the ground-glass nuclei. Pathologists in Russia, having experience with thyroid tumors from radiocontaminated areas, pointed out the "low quality of histological specimens, impeding assessment of nuclei." (17) The Head pediatric oncologist of Russian Federation prof. Vladimir Poliakov pointed out shortage of cytologists and other qualified medical specialists, especially those having experience with pediatric material (personal communication, 2009).

In the 1990s, some diagnostic criteria of TC were hardly known in the former Soviet Union, they were not mentioned by Russian-language handbooks and monographs used at that time (18,19). The minimally-invasive follicular TC and its diagnostic criteria were absent in Russian-language literature. One of the most significant diagnostic criteria of papillary carcinoma - ground-glass or cleared nuclei - was mistranslated as something like "watch-glass nuclei

moulded together" (yadra v vide pritertykh chasovykh stekol) and presented by the most authoritative Russian-language handbook of tumor pathology (19) as a sign not only of papillary, but also of follicular TC, for which it is not characteristic. Nuclear changes, typical of papillary carcinoma, are not visible in the illustrations of this handbook. Even less understandable comparisons with a sand-glass (16) or "crumbled glass" (20), other mistranslations of the term "ground-glass", can be encountered. First time after the Chernobyl accident, among children operated in Ukraine in 1990-95 years, the predominant TC type was the solid/follicular subtype of papillary carcinoma (21,22). A conclusion about malignancy in such cases, if no infiltrative growth is visible, is based mainly on the nuclear criteria of the papillary carcinoma (ground-glass nuclei, nuclear grooves and inclusions). Inadequate evaluation of these criteria can result in false-positive conclusions, for example, in case of well-differentiated tumors of uncertain malignant potential (23) or benign papillary nodules (24). Equipment of histopathological laboratories in the early 1990s was poor (25); excessive thickness of histological sections hindered reliable assessment of the nuclear criteria. Access to foreign professional literature has been limited. Even in the recently edited "Atlas of human tumor pathology" (26) potentially misleading information can be found. The following is stated, for example, about thyroid nodules (p. 204, verbatim from Russian): "In severe dysplasia appear cell groups with clearly visible atypia. Therefore, 3rd grade dysplasia is considered as an obligate pre-cancer, which histologically is hardly distinguishable from carcinoma in situ" (26). Similar statements can be found also in a monograph dedicated to thyroid microcarcinoma (27). Note that nuclear atypia (enlargement, hyperchromatism, pleomorphism) is not regarded in modern literature as a malignancy criterion of follicular and papillary thyroid nodules, and the concepts of dysplasia and carcinoma in situ are not applied to them (28). Cases of false-positive TC diagnosis, caused by misinterpretation of nuclear atypia as a malignancy criterion, are known. It is no surprise that A. Iu. Abrosimov (29) found the following formulations in histopathological reports from radiocontaminated areas, witnessing about false-positivity (verbatim from Russian): "follicular TC without invasion" or "follicular TC in situ" (29).

Remarkable observations about post-Chernobyl attitude to thyroid nodules can be found in Russian-language literature (p. 47, verbatim from Russian): "Practically all nodular thyroid lesions in children, independently of their size, were regarded at that time as potentially malignant neoplasms, requiring urgent surgical operation" or "Aggressiveness of surgeons contributed to the shortening of the minimal latent period." (30) In the circumstances of the poor equipment of laboratories and lack of modern literature, such attitude contributed to overdiagnosis. Data about verification by expert commissions of post-Chernobyl pediatric TC in Russia provided further evidence for false-positivity: "As a result of histopathological verification, diagnosis of TC was confirmed in 79,1 % of cases (federal level of verification - 354 cases) and 77,9 % (international level - 280 cases)" (29). Clearly, false-positive diagnoses remained undisclosed in cases not covered by verification, quite numerous because of missing or poor-quality histological specimens (29).

Among early post-Chernobyl TC cases were many advanced and metastasizing tumors, which were regarded to be radiation-induced. High percentage of advanced cancers was reported in a study encompassing the period 1986-1991 i.e. immediately after the accident (31): extrathyroidal extension was found in 60.5%, regional lymph node metastases in 74%, and distant metastases in 7% of 92 pediatric TC cases from radiocontaminated areas of Belarus. Another study from the years 1991-1992 (84 children with TC, from Belarus) reported that "microscopically these tumors were usually aggressive, often demonstrating intraglandular tumor dissemination (92%), thyroid capsular and adjacent soft tissue invasion (89%), and cervical lymph node metastases (88%)." (21) Eloquent passages can be found in the recent monograph on TC after Chernobyl (p. 76, verbatim from Russian): "If we assume that all tumors grow with approximately similar speed, those with a longer latency period must be bigger. In reality they were even somewhat smaller" or "Tumors with a shorter latent period show more pronounced intra- and exrtathyroid spread." (20) In a later study (32), the following figures were reported in regard to TNM staging of TC in children younger than 14 years diagnosed in Ukraine (Table I). It can be seen from the table that the stage T4 was diagnosed in about 50 % of all 244 post-Chernobyl pediatric TC cases. During the years 1981-1985 preceding the accident, only 3 TC were diagnosed in children, all T2 stage (32). To grow to a T4 stage, a tumor needs certain time. If no overdiagnosis has taken place, high percentage of T4 cases can be in part explained by the screening effect with detection of old neglected cancers, which had nothing to do with radiation. At the same time, according to UNSCEAR, "aggressiveness of the thyroid cancers found in the Chernobyl area, which is frequently present with periglandular growth and distant metastases, argues against the findings being entirely a result of the screening." (3) Appearance of advanced cancers shortly

Table I: Incidence of Thyroid Carcinoma in Children in Accordance with the TNM Classification System Number of patients (%). An extract from the table 5 from the article (32)

Classification	1981-1985	1986-1990	1991-1995	1996-1996	Total
T1	0	0	4 (2.7)	1 (1.6)	5 (2.0)
T2	3 (100)	9 (31.0)	49 (32.4)	18 (28.6)	79 (32.4)
T3	0	6 (20.7)	27 (18.2)	6 (9.5)	39 (16.0)
T4	0	14 (48.3)	69 (46.3)	38 (60.3)	121 (49.6)
N1	0	9 (31.0)	45 (20.2)	22 (34.9)	77 (31.5)
N2	1(33.3)	9 (31.0)	45 (30.2)	22 (34.9)	77 (31.5)

after the accident was partly caused by the fact that patients were brought from other regions of the former Soviet Union and registered as Chernobyl-related cases. It was known by physicians and general public that diagnostics and treatment of Chernobyl victims were performed by modern equipment with participation of foreign specialists. Children with thyroid lesions were brought from other regions, while the data on the whereabouts during and after the accident were adjusted or confabulated in order to be accepted as Chernobyl victims. In particular, for children with advanced or metastasizing carcinoma, it was seen as an opportunity of access to modern therapy. In advanced cases, incorrect time of the initial diagnosis was sometimes recorded. Retrospectively, such cases were classified as aggressive radiation-related cancers developing after a short latency. Unfortunately, this confounding factor is discussed only now, post factum. There were not so many pediatric TC cases nationwide. A solution must have included the same therapy for all of them, both Chernobyl-related and not, thus eliminating the motives for the patients and their parents to modify the anamnesis. Probably, a solution could have been found in cooperation with foreign aid workers and specialists, who practiced in the former Soviet Union at that time. However, another way was chosen, which means that some immunohistochemical and molecular-genetic tests (e.g., 33,34) were applied to an inadequately selected material, and that some supposedly characteristic features of the "radiogenic" post-Chernobyl cancer may pertain, in fact, to a later stadium of the tumor progression (35). For example, the "marked solid component and more aggressive behavior [which] characterize tumors with shorter latency" (22) were, obviously, the features of older and more advanced cancers. Then it becomes clear why "short latency is associated with tumors with a phenotype that is significantly less structurally differentiated, shows significantly less peritumor fibrosis, and significantly more invasive spread when compared to tumors with a longer latent period" (36). The concluding point is that information on molecular-genetic and immunological characteristics of supposedly radiogenic post-Chernobyl tumors, accumulated as a result of international research, requires re-evaluation and new interpretation.

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