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Integrating Research on Thyroid Cancer after Chernobyl — the Chernobyl Tissue Bank

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Abstract

The only unequivocal radiological effect of the Chernobyl accident on human health is the increase in thyroid cancer in those exposed in childhood or early adolescence. In response to the scientific interest in studying the molecular biology of thyroid cancer after Chernobyl, the Chernobyl Tissue Bank was established. The project is supported by the governments of Ukraine and Russia, and financially supported (in total around US\$3million) by the European Commission, the National Cancer Institute of the USA and the Sasakawa Memorial Health Foundation of Japan. The project began collecting a variety of biological samples from patients on 1 October 1988, and has supplied material to 21 research projects in Japan, the USA and Europe. The establishment of the Chernobyl Tissue Bank has facilitated cooperation between these research projects and the combination of clinical and research data provides a paradigm for cancer research in the molecular biological age.

Keywords

Chernobyl; radiation; research; thyroid cancer

Introduction (A head)

Thyroid cancer comprises about 2% of all malignancies in women and 0.62% in men, but its incidence is rising in a number of developed countries, including the USA [1]. Thyroid cancer in those who are under 14 years of age at diagnosis is even rarer, of the order of 0.5–1 per million per year [2]. In most populations, there is a bell-shaped relationship between frequency of thyroid cancer and age at diagnosis (Fig. 1). The exposure of the population in what is now southern Belarus, northern Ukraine and the regions of Russia that border these two countries, to radioiodine in fallout from the Chernobyl accident in 1986, resulted in a sharp increase in those who were young children at the time of the accident [3]. As the normal frequency of thyroid cancer in children is so low, the sudden increase in thyroid cancer in the population exposed to fallout provided an opportunity to study not only the relationship between radiation exposure and the risk of thyroid cancer in the population using epidemiological methods, but also to correlate the molecular biology of thyroid cancer with exposure to radiation. The Chernobyl Tissue Bank (CTB) was established in 1998, 6

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years after the first publications indicating that there was a rise in childhood thyroid cancer [4,5]. It is the first international co-operation that seeks to establish a collection of biological samples from patients for whom the aetiology of their disease is known — exposure to radioiodine in childhood. The project has the full support of the governments of the Russian Federation and Ukraine. The European Commission, the National Cancer Institute of the USA and the Sasakawa Memorial Health Foundation of Japan co-operate to support the project financially. Thyroid cancers in young people are small, and ethically only material that is surplus to that required for diagnosis can be used for research. Therefore, in order to maximise the use of this precious resource, the CTB does not supply pieces of tissue to researchers, but extracted nucleic acids and tissue sections. This allows multiple analyses on individual samples from the same piece of tumour, facilitating a ‘systems biology’ approach to cancer research. In addition, multiple blocks are collected from the same tumour to facilitate investigation of the heterogeneity within a given tumour — a factor that may prove very important in the future design of therapeutic strategies. The CTB aims to provide not only material for study by the current generation of scientists, but also the next, who may be in a position to benefit from a much more detailed analysis carried out on paraffin-embedded sections in addition to the current molecular biological approaches that use frozen material.

Management of the Chernobyl Tissue Bank Project (A head)

The day-to-day management of the project is carried out from the Coordinating Centre, currently located in Imperial College, London, UK. The institutes in Ukraine and Russia are responsible for the collection, documentation and storage of biological samples after consent of the patients who fit the criteria for inclusion in the study (see below). Clinico-pathological data on each patient are entered into the project database, which is located on secure servers at Imperial College London. The database contains no patient identifiers, but each patient is identified by a unique alphanumeric identifier. Suffixes to this alphanumeric identifier enable identification of the type of sample stored.

In addition to supplying equipment pertinent to the collection and storage of biological samples to the two participating institutions in Ukraine and Russia, fully equipped molecular biology laboratories have also been provided by the project to enable extraction of nucleic acids from blood and tissue to be carried out in Ukraine and Russia. Staff from both institutes have received training at the Coordinating Centre at Imperial College, and return at regular intervals for further training as new protocols are introduced.

The project is overseen by a Scientific Advisory Board, and a Steering Committee. The latter comprises representation from each of the funding bodies and from Ukraine and Russia. A panel of international experts in pathology provide a consensus diagnosis for each case included in the CTB.

Donor Population and Ethics (A head)

Patients attending thyroid clinics at the Institute of Endocrinology and Metabolism in Kiev, Ukraine and the Medical Radiological Research Centre in Obninsk (or one of its sister clinics at the Regional Radiological Dispensary in Bryansk) for intended surgery for a thyroid tumour are asked to participate in this study. Patients are resident in the regions of Ukraine and Russia most heavily contaminated by fallout from the Chernobyl accident. The specific aim of the CTB project is to collect biological specimens from those who were aged under 19 years (i.e. born after 26 April 1967) at the time of the Chernobyl accident. The reason for this is two-fold. Because thyroid cancer is rare in this age group, and because they were subjected to a specific radiological carcinogen that is known to lead to thyroid cancer, a large proportion of the tumours collected can be attributed to exposure to radioiodine in

fallout from the Chernobyl accident. The evidence to date suggests that this is the most susceptible cohort to the effects of radiation exposure. This may be due to a number of factors: this age group may have received a larger dose of radioiodine to the thyroid, and the thyroid in young children may be particularly susceptible to the carcinogenic action of radionuclides. Those who were born after 1 January 1987 represent a cohort of the population who were not exposed to radioiodine in fallout and have developed 'sporadic' thyroid cancer at a young age. The relatively short half-life (8.01 days) of ¹³¹I, the major isotope of iodine released from the accident, means that the radioiodine level in the environment fell quickly after emissions from the reactor ceased. This 'non-exposed' cohort represents the most closely matched cohort in terms of age and residency for studies that focus on the radiobiological aspects of germline genetics or molecular biology of thyroid cancer.

The patients are under the control and management of the local physicians/surgeons and health care system, for which the project has no responsibility. The diagnosis/treatment of a patient is not altered in any way because of the project, i.e. surgery and phlebotomy are carried out whether or not this project exists, and tissue and blood are taken and withdrawn, respectively, independent of the project. There is little potential risk to the patient other than that usually associated with thyroid surgery or withdrawal of a blood sample as part of the patient's normal preparation for surgery. It will already have been decided that there is a clinical need for thyroid surgery before any patient is approached for inclusion in this project. At no time will the patients be subjected to a more extensive operation than is clinically necessary. The clinical care of the patient rests entirely with the physician in day-to-day charge of the patient.

At the time of its inception, the CTB was established according to National Cancer Institute guidelines, which were, at the time, more stringent than those operating in most of Europe. The project is reviewed annually by the institutional review boards (IRB; ethics committees) at the Institute of Endocrinology and Metabolism, Medical Radiological Research Centre and the Coordinating Centre (Imperial College Research Ethics Committee). Annual review of the entire project is also made by the IRB of the National Cancer Institute in the USA.

Informed consent will be obtained from patients (or their guardians) by his or her physician at the time when either the patient attends an out-patient clinic before thyroid surgery, or during consultation with a doctor, if the decision has already been taken for surgery for that particular patient. Informed consent is documented by signature of informed consent forms approved by the relevant IRBs (the institute IRBs and the IRB of Imperial College London). The IRBs have also received approval from the Office of Human Research Protection at the National Cancer Institute of the USA. The consent form states that the doctor has informed the patient that they need to have all or part of their thyroid removed for the benefit of their health. It also states that a sample of blood will be taken from the patient's arm and that this is normal procedure for all patients entering hospital. In addition, the patient is asked a few simple questions about themselves (their date of birth, gender and the oblast where they were living at the time of the Chernobyl accident). Patients are informed that a small sample of their operative specimen and blood will be taken and kept in a safe place as part of this project. The aim of the project is to use this material to learn more about thyroid cancer. As a result of participation in the project, their diagnosis is checked by a panel of experts in thyroid disease. If, as a result of this review, something that could affect the patient's health or well-being is reported, this information would be passed to the doctor in charge of their treatment. The patient is informed that their identity is only known to the doctor in day-to-day charge of their care, as the samples of blood and tissue they donate to the project are identified only by a code number. Their participation in the project does not involve any extra tests or treatment, except for a little extra blood being taken and a small amount of

time for answering questions. The patients are also informed that they are unlikely to benefit individually from most of the research studies that use their tissue and blood. It is more likely that the results of their participation will lead to a better understanding of thyroid diseases and how to treat them, and perhaps better treatments for others in the future. The patients are assured that whether or not they agree to participate in the project, their treatment will be the same and that if they wish to withdraw their consent at a later date, they may do so. Information sheets/consent forms are provided in the local language.

The coded information supplied with the biological material (date of birth, date of operation, gender, oblast of residence and the CTB pathology panel diagnosis) is provided by the pathologist or physician (in the case of data supplied with the blood sample) at either Kiev or Obninsk. It is not obtained directly from the patient's records. As the CTB database does not contain any patient identifiers, donors are effectively anonymised to researchers.

If information that might be of value to an individual patient were to become evident from research projects using material from the CTB, the project management has an agreed course of action. In this situation, the researcher is asked to contact the project manager at the Coordinating Centre who will pass the information to the director of the relevant institute where the patient is being treated and subsequently to the physician in charge of that patient's day-to-day care. As noted above, patients are able to withdraw consent at any time. The tracking database used by the CTB identifies whether DNA or RNA has been extracted from the samples and whether they have been issued to researchers. Patients are made aware that if they withdraw their consent a long while after their operation, material from their donation may have already been used in research. In the 13 years (to 2011) that the CTB has been collecting material there have been no requests for withdrawal from the project.

Collection and Documentation of Samples (A head)

Biological samples collected for the CTB comprise samples of blood, from which serum and DNA from lymphocytes are extracted, samples of frozen tumour tissue, samples of frozen normal thyroid, and samples of paraffin-embedded thyroid tumour and normal tissue. With the exception of the paraffin-embedded samples, the biological samples are taken specifically as research samples for the CTB. The paraffin-embedded material is provided from material taken for initial diagnosis by the local pathologist.

Detailed standard operating procedures for the collection, documentation and further processing of samples are available from the CTB website (www.chernobyltissuebank.com) and have been developed jointly with the Wales Cancer Bank (www.walescancerbank.com).

Blood Samples (B head)

A sample of blood (about 17 ml, collected in 2×5.5 ml normal S-monovette tubes and 2×2.7 ml EDTA-containing S-monovettes) is taken preoperatively, before the administration of preoperative therapy. Each tube is labelled with a code that identifies the patient. Serum is separated according to an agreed protocol from the samples collected in normal S-monovettes (this yields about 5×1 ml samples). Serum is stored in tubes labelled with the patient's identifying number in a -20°C freezer. The coordinates for each tube are logged in the computer database.

Blood contained in the two EDTA-containing tubes is stored at -70°C . Extraction of DNA from one of the tubes is carried out according to the agreed protocol using Qiagen midi kits and aliquotted appropriately. The remaining tube remains in the freezer for future use. Quality control using gel electrophoresis is then carried out on each sample of DNA.

Tissue Samples from Operative Specimens (B head)

All resected thyroid tissue from the study cohort is carefully described as a fresh specimen, and numbered samples taken of each separate lesion and of background thyroid for diagnostic purposes (formalin fixed and routine processing), with further samples taken for research purposes. The fresh material is immediately snap frozen and a frozen section taken, photographed and the image stored on the computer, for later addition to the database. Where the size of the tumour permits, three or more samples are taken from the tumour and from normal thyroid. These are numbered to correspond to those taken for diagnosis and the relative positions of these samples are marked on a diagram that is scanned into the database. Each sample is stored at -70°C in separate cryovials until processed further and is given a coordinate to facilitate location at a later date. A digitised image of the haematoxylin and eosin-stained sections from the frozen block is stored to ensure that the specimen is not necrotic and to assess the relative proportions of epithelium and stroma within the lesion. This is important information for molecular biologists who may use aliquots of RNA and DNA extracted from the tissue block.

Pathological Review of Cases for the Chernobyl Tissue Bank (B head)

Pathological review of all cases in the CTB is undertaken by an international pathology panel to provide a consensus diagnosis for the project. Further detail on the process for review and the pathology of the cases stored in the CTB is provided in another paper within this special issue [6].

Further Processing of Samples (B head)

Both RNA and DNA are extracted from individual frozen tissue blocks. Full details can be found from the project website, but briefly frozen tissue is homogenised using a tissue lyser (Qiagen), the lysate is then split and DNA and RNA are extracted using Qiagen column-based systems. RNA is frozen at -80°C in standard aliquots of 5 μg aliquots in 20 μl ; DNA in standard aliquots of 3 μg in 50 μl . This facilitates use to projects and the use of samples from one tissue block in multiple projects. Quality assessment is carried out by a Nanodrop spectrophotometer for both DNA and RNA (260/280, 280/230 ratio) and an Agilent Bioanalyser for RNA. Gel electrophoresis is used to further assess the quality of extracted DNA. A recent audit of 433 samples from Ukraine showed that the median RNA integrity number (RIN) was 7.7 (range 1.2–9.6). A recent study of the effect of storage time as frozen tissue (1–10 years) before extraction showed that this did not adversely affect the RIN value (Mathieson *et al.*, in preparation). Frozen pellets from cell lines are used as a quality control for each extraction — the expected RIN value from these pellets is above 9.0.

Extracts of DNA from sections from formalin-fixed paraffin-embedded (FFPE) blocks, which have subsequently been used for BAC array CGH [7], and our own in-house studies, have indicated that FFPE material from Russia and Ukraine is of a similar quality to that from UK National Health Service archives with respect to amplicon size on multiplex polymerase chain reaction. FFPE sections have also been used for extraction of miRNA and have yielded good results on Agilent miRNA arrays.

Status of the Archive (A head)

The paper by LiVolsi *et al.* [6] in this special issue of *Clinical Oncology* gives full details of the way in which samples are reviewed by the pathology panel. Thus far, 2840 have been entered into the CTB; all have FFPE material available, most have frozen tissue samples available (2223/2840) and 1605 of these also have preoperative blood and serum samples available. Most of the cases come from the regions of Ukraine and Russia exposed to high

levels of radioiodine in fallout from the accident. Full details of the pathology of these cases are provided in the paper by LiVolsi *et al.* [6].

The patient population can be broken down broadly into three categories; those whose birth dates lie between 26 April 1967 and 26 April 1986, and were therefore exposed to the radioiodine between the ages of 0 and 19 years of age; those who were born between 27 April 1986 and 31 December 1986, and therefore carry the likelihood of exposure to radioiodine *in utero*; and those born on or after 1 January 1987. This last group is a very valuable cohort as it represents a population that still reside in the regions contaminated by radiation following the accident but due to the relatively short half-life of ¹³¹I were not exposed to radioiodine. The incidence of thyroid cancer in this latter group is similar to that observed in unexposed populations of this age, which suggests that it is ¹³¹I that is the cause of the increase in thyroid cancer in the exposed areas of Ukraine and Russia, rather than any of the other longer-lived isotopes that were also released, e.g. ¹³⁷Cs.

The total number of cases from each of the cohorts listed above is given in Table 1. The cases are broken down into papillary carcinoma, the most common form of thyroid tumour in this population, other thyroid cancers (which include follicular cancer and medullary carcinoma, plus rarer tumours) and benign tumours (predominantly follicular adenoma).

Access to Samples and Data (A head)

Researchers wishing to have access to materials and data from the CTB are asked to apply in writing. All proposals are then reviewed by an external review panel of experts who score the proposals under four headings: the scientific merits of the proposal, the methods proposed, the preliminary data provided by the researchers to support their application and the quality of the researchers carrying out the work. Full details of the application procedure can be found on the project's website (www.chernobyltissuebank.com/access). Researchers using material from the CTB are not required to have project-specific ethics approval for their project, rather they receive 'deemed ethics' by approval of their project for access. This is permissible as the project obtains generic and enduring consent from patients at the time of donation for the use of their material. Thus, the CTB functions in much the same way as a National Research Ethics Service-approved research tissue bank in the UK. Researchers sign a Material Transfer Agreement, which binds them to acknowledging the provision of material by the CTB, the provision of the consensus diagnosis from the pathology panel, and inclusion of at least one author from the appropriate centre in either Ukraine or Russia that provided the samples for the project. Samples are labelled with a unique identifier that permits traceability by the Coordinating Centre, not only back to the individual patient, but also to the individual block of tissue or sample of blood from which their material was derived. Researchers are also required to return research data to the CTB project using this identifier. This permits the collation of data on different analytes derived from a single sample (e.g. DNA, RNA from a frozen tissue block) or from different samples from a patient (e.g. from SNP analyses on germline DNA and miRNA extracted from FFPE sections of tumour) and provides a platform for a 'systems biology' approach to radiation-induced thyroid cancer.

Use of Samples in Research Projects (A head)

The CTB started issuing samples to researchers in July 2001. It has currently supplied samples to a total of 21 projects, with researchers based in the USA, Europe and Japan. The most commonly requested samples are sections from FFPE tissue blocks (6253 sections from cases) and RNA derived from frozen tissue (2138 individual aliquots issued derived from 605 cases). A smaller number of samples has been issued of DNA from frozen tissue (1215 aliquots from 596 cases) and DNA from blood (441 aliquots from 248 cases). A

variety of different biosamples are often requested from a single case, for example FFPE sections, RNA and DNA from frozen tissue. A recent European Union project involving researchers based in four different European Union countries analysed copy number alteration using array CGH and mRNA expression using the Affymetrix 3' platform in DNA and RNA, respectively, extracted from the same individual tissue blocks from 80 patients. Single gene analysis for ret translocation using RNA and BRAF mutation using DNA was also carried out on additional aliquots of RNA and DNA from the same frozen tissue blocks, and miRNA extracted from FFPE sections from the same cases are also currently being analysed on the Agilent miRNA platform. This was complimented by analysis of SNPs in DNA derived from normal tissue from the same cases. Alterations in genes of interest were then confirmed using quantitative reverse transcription polymerase chain reaction on additional aliquots from the same patients for genes altered at the RNA level and fluorescence *in situ* hybridisation on FFPE sections from the same cases for genes showing copy number alterations.

Because of the fact that the CTB issues aliquots of RNA and DNA from frozen tissue rather than a block of tissue itself, a large number of projects can have access to material from the same patient. In some cases, 12 separate projects have used material from a single patient; 316 cases have been used in more than one project. The CTB has currently issued material from only 25% of the patients who have donated material to the project.

Because of the natural clinical course of thyroid cancer in young patients, we would predict that only 30% of these cases will suffer relapse within the next 30 years [8]. Clinical data on relapse, and therefore correlation with molecular predictors of outcome, will require several more years of data collection.

Further information on the types of biological sample available and papers published using these samples is available on the project's website (www.chernobyltissuebank.com).

Integrating the Data to Maximise our Understanding of Radiation-induced Thyroid Cancer (A head)

Understanding the major drivers in tumour growth will depend increasingly on being able to take a pathway approach, rather than an individual gene or analytical platform approach. It is already evident from the literature [9] that a change in copy number at the DNA level does not always result in an increase in RNA expression of all of the genes coded for by the amplified region. Collating all of the research data generated from the samples donated by those affected by the Chernobyl accident is a challenge. By collating the data in a central resource, the CTB will facilitate not only projects that require access to samples alone, but also projects that wish to link their results with data already available. A data warehouse is currently being built at the Coordinating Centre at Imperial College London to house not only de-identified clinical information (pathology, age, gender and outcome data), but also research data collated by the project. A specialised Google-style search facility will be provided to enable researchers to identify cases on which research data are already available. This will be extended over time to provide a platform for bioinformatic projects for mathematicians and computer scientists who require access to data only in order to build models for systems biology that integrate different types of data. Access to data from the CTB project will be governed using similar rules to that already in use for access to biological material. Release of a project's data will only occur after the consent of the principal investigator for that project and acknowledgement of the origin of the data would be mandated in any resultant publication.

Summary (A head)

The accident at the Chernobyl nuclear power plant 25 years ago was a catastrophe for the local population resident in the areas surrounding the power station. However, the support of international agencies has provided an infrastructure that facilitates integration of a variety of molecular biological and pathological studies on a tightly defined cohort. The CTB provides a paradigm for tissue banking for cancer research in the molecular age.

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Fig. 1.
Relationship between age and thyroid cancer in non-exposed populations.
(A) US data from the SEER database (<http://seer.cancer.gov/statfacts/html/thyro.html>); (B)
UK data from Cancer Research UK
(<http://info.cancerresearchuk.org/cancerstats/types/thyroid/incidence/>).

Table 1

Number of cases from Ukraine and Russia included in the Chernobyl Tissue Bank. The patients are divided into three groups: born between 26 April 1967 and 26 April 1986 and therefore exposed to radioiodine in fallout as children or adolescents, born between 26 April 1986 and 31 December 1986 and therefore exposed to radioiodine *in utero*, and those born on or after 1 January 1987 and therefore not exposed to radioiodine in fallout. More detailed information on the pathological subtypes of these cancers, see [6].

	Papillary thyroid carcinoma	Other carcinomas	Benign	Total
Born before 26 April 1986	1473	117	757	2347
<i>In utero</i>	36	4	25	65
Born after 1 January 1987	263	36	129	428
Total	1772	157	911	2840