

NCI-CSPH CHORNOBYL TECHNICAL SUPPORT GROUP

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TRIP SUMMARY 31 MAY -11 JUNE 1998

KYIV, UKRAINE

2 June 1998: The weather is hot, more like southern Spain than Eastern Europe at this time of year. We were met at the airport yesterday by Dr. V. P. Tereshchenko, who arranges for our transfer to the Dnipro Hotel with his usual efficiency. He looks fit and relaxed and not unhappy to see us.



Puzcha-Ozernaya Sanatorium

Although the presentations at the International Conference at the Puzcha-Ozernaya Sanatorium are received with muted enthusiasm, the audience claps politely. Dr. Greenebaum and I meet with Dr. T. Bogdanova and discuss her study of 296 patients with thyroid cancer, which will be formally presented in Cambridge next month. These cases are taken from a group of 80,000 patients throughout the Ukraine that she has been tracking since 1986. She also has 22 cases of thyroid cancer in a Thyroid Cancer Registry culled from the smaller study cohort of 20,000 and over the last several years has been targeting thyroid pathology specifically in the Kyiv, Chernigov, and Zhytomyr oblasts. There are an unusually large number of cases of the solid-follicular variant of papillary cancer, which she has directly correlated with increasing radiation exposure. Dr. I. A.

Likhtaryov. Head of the Dosimetry group, is a co-author of the study and has supplied the dosimetry data.

3 June 1998: The review of clinical operations begins with the dosimetry interviewer, Mykola Chepurny. Either the parent or the patient fills out the dosimetry forms, with default to the parent's answer (which could introduce an ascertainment bias). He feels that patients are "sick and tired" of the screening procedures and need a "motivation" to continue with the project (chairs to sit on would be nice, too). The "no show" rate is at least 25% (probably higher), but these individuals are recontacted and urged to make another appointment. Cohort members and their parents must arrange for time off from either school or work and pay for their own transportation costs, which is no small burden. Blood is obtained at the study center, but urine is brought from home. It does not bother the screeners that the urine could belong to another individual, since "everyone in the family has the same diet" (but may not take the same vitamins or medications). Although the ultrasonogram is done the same day as the initial screening, the FNA biopsy



Dr. V. P. Tereschenko

may not be. Even subjects examined by the mobile teams come to Kyiv for an FNA, since the physicians at the IEM "have the best technique." It is worth noting that the sonographers on the mobile teams are the same ones who will perform this procedure at the Institute and that the Belarussians feel comfortable with the idea of the mobile teams doing FNA biopsies.

Dr. Galina Terekova says that a major problem hampering the study is the slow "turn around" on the laboratory reports (few final endocrine forms have been processed because of this). In all, they have seen 68 (or 72, the numbers vary) patients resettled to Kyiv from

Pripyat and Chornobyl. Among these, 3 had nodules and 2 have had a FNA biopsy (the other will be seen again in 3 months). She feels that in cohort patients “all nodules are suspicious” and should have an FNA done if technically possible “regardless of rules.” By this she means the Operations Manual, which states in section 5.4.1 that in patients over the age of 12, only nodules greater than 1 cm in diameter should be biopsied. The same point is raised by the Belarussians who have also adopted an aggressive stance towards smaller nodules.

Memo: (1). The need for an incentive for subjects to continue with the project is a recurring theme, both in the Ukraine and in Belarus. There are plenty of ideas about gifts (pens, tee shirts, certificates to McDonald’s, etc.), but no agreement on what should be given and whether each subject should get a gift on every visit. A lottery might work, with several cohort members winning a token gift every day. This would keep costs down and interest up; (2). It should be firmly established that the FNA is done the same day as the ultrasonogram, since we could begin losing those patients who cannot return for a follow-up visit; (3). Urine for iodine should be collected at the time of the screening procedure and not brought from home (4). Although it would be best for the mobile teams to do FNA biopsies and obviate the need for subjects to come to Kyiv, convincing the sonographers to do so will be difficult; (5). The delay in processing laboratory specimens is causing distress among the endocrinologists and slowing the completion of the clinical forms; (6). I agree with Dr. Terekova that all “suspicious” nodules regardless of size should have an FNA biopsy at the discretion of the endocrinologist or sonographer. What is “suspicious” could be more clearly defined, but it might best be left “fuzzy” and leave it to discretion of the attending physicians. We could stick to the current protocol, but I suspect that most nodules over 5 mm (the smallest that can be biopsied with our present technology) eventually will be sampled anyway, especially as the sonographers become more proficient and aggressive. Not allowing them to exercise their clinical judgment could result in tension, as the physicians see themselves involved in both a research project and patient care.

Met the mobile team, which has returned from the Ivankiv raion, where they spent 4 days. There are 6 “specialists” (the endocrinologist who is in charge, a sonographer, nurse, blood technician, and interviewers for both epidemiology and dosimetry) and the van driver. They examined 53 patients (out of 90 invited) and found 12 cases of thyroid pathology (9 diffuse goiters and 3 nodular goiters) and an additional patient with enlarged submandibular lymph nodes and a family history of thyroid cancer. The patients with nodules and the one with adenopathy were referred for FNA at the IEM and all were *benign*. The 12 “volunteers” who presented themselves for evaluation were given an endocrinologic examination and ultrasonogram, but did not have laboratory tests done. It takes about 60 minutes to complete the entire screening procedure and the feeling is that if volume increases to more than 15 patients a day “quality will suffer” (in actuality, they are capable of seeing about twice this number). Blood is obtained for both thyroid function tests and calcium if the patient is fasting and for thyroid tests alone if they have eaten,

since Dr. Ephstein feels strongly that calcium levels should be done only after an overnight fast.

Memo: It is unreasonable to expect patients to fast all morning and sometimes into the late afternoon waiting for their screening to be completed. Blood should be obtained for calcium whether the subject has eaten or not and an appropriate notation made in the record. At the final plenary session, Dr. Tronko appears to agree with this point of view.

The endocrine surgeons at the IEM have 3 computers and a computerized database of 3390 patients (90% thyroid and 10% adrenal) dating back to the early 1980s. They are eager to link their computers to the DCC, which would give us access to their records (and vice versa). We need to discuss this further.



Dr. E. Greenebaum with Dr. Y. Bozhok's Cytopathology Group

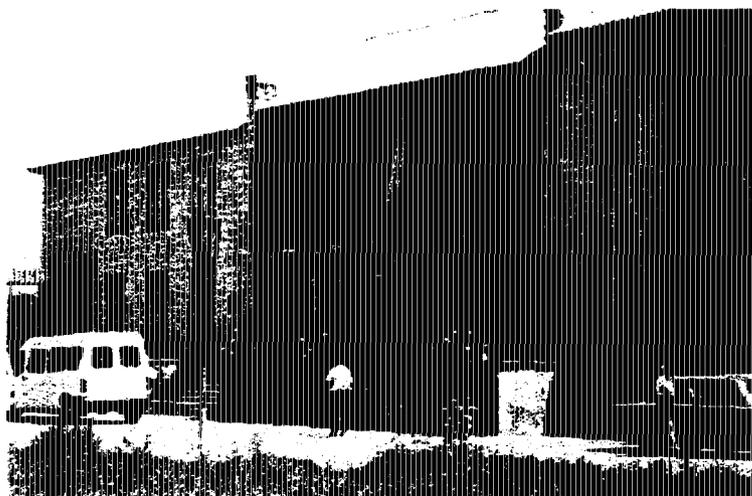
From Dr. Yuri Bozhok, the cytopathologist, we learn that FNA biopsies are done 4 days a week, that about 2000 thyroid biopsies are done every year, and that unstained slides are immediately reviewed to ensure adequate sampling. They are not, however, working with the Cytology Forms. Finally, it turns out that there are 2 different pathology laboratories. Dr. Bogdanova receives specimens from patients under 30 years of age, while a Dr. Cherniv is responsible for the older subjects. Since the oldest cohort members are just now turning 30, Dr. Cherniv could soon begin reviewing pathologic samples from the study.

Memo: Request a meeting with Dr. Cherniv at the time of the next visit to Kyiv.

4 June 1998: Drs. Fink, Greenebaum, and I took a field trip this morning, north along the Dnipro River to Gornostaypol in the Ivankiv raion, where a mobile team headed by Dr.

Bolshova, Chief of Pediatric Endocrinology at the IEM, is set up in the regional hospital. The personnel return to Kyiv every night, while the equipment remains on site. Although they planned to see only 50 patients during their 3 day visit, on the day of our visit there were 34 scheduled patients and 1 “walk in”, all brought in by the van.

We are able to directly observe the screening process, following a young woman through the entire procedure. No bar codes are used on the dosimetry forms (“paper is too expensive”) and, according to Dr. Bolshova, the Medical Interview Form lacks adequate space for a complete past medical history, hospitalizations, and surgeries. Dr. Yavnyuk, the sonographer, sees no need to recalibrate the ultrasound machine after moving it from the IEM, since “it is automatic.” Even though he does several hundred FNA biopsies every year, he feels “uncomfortable” doing the procedure in the field.



Gornostaypol Regional Hospital

Memo: This was a very worthwhile junket. The members of the team are friendly and enthusiastic and the patients do not seem uncomfortable with their experience. The screening process appears to be working as planned. Such trips should be done periodically, both in the Ukraine and in Belarus. Randy Brill needs to comment on the recalibration of the ultrasonogram instrument after it is moved into the field.

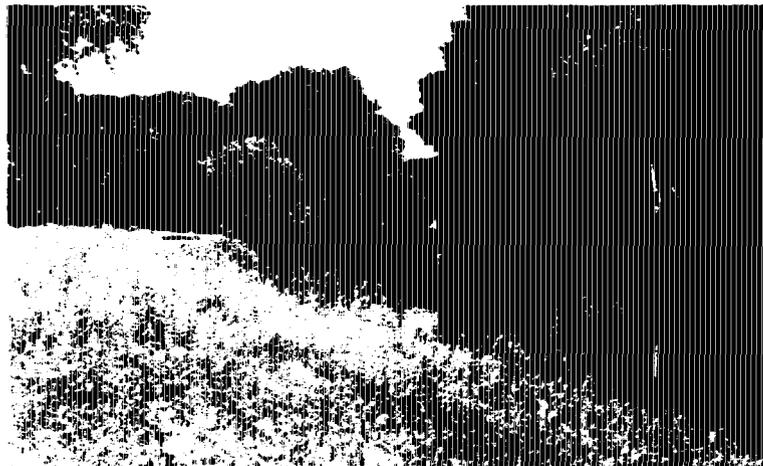
At the Plenary Session, we learn from Dr. Tronko that 145 patients have been examined in the Ivankiv raion and that operations will finish there at the end of the month. On June 15, screening will begin in the Kozelets raion of the Chernihiv oblast. When Dr. Wachholz raises a point about “cross-specialty communication,” Dr. Tronko gets a bit defensive, stating that it is the norm to do so “in difficult cases,” which effectively ends the discussion. Although Dr. Ephstein sees no reason to do thyroglobulin measurements on all patients, after some discussion it is resolved that the final decision be “left to the USA group.” Dr. Bogdanova has information of 33 thyroid cases from the last quarter,

including 9 cases of cancer, but none are in the cohort. Although she is collecting data “according to the Operations Manual, she is unable to transfer data to the DCC, since she does not have the proper computer equipment. Furthermore, she is surprised that we do not have the “final” pathology form agreed to during the February visit (she was to have sent a copy to Dr. Chestvoy for comment, but he did not receive it until we gave him an English translation during our meeting in Minsk). From Dr. Markov, we learn that Dr. Oliynyk reviews “all the (clinical) forms”, makes suggestions, and gives advice “for the future.”

Conclusions: Although considerable progress has been made since our last visit in February and a respectable number of cohort subjects has been identified, the “no show” rate is quite high and the delay in processing laboratory specimens is a drag on progress. If it is decided to sanction biopsy of nodules larger than 5 mm in all patients regardless of age, section 5.4.1 of the Operations Manual will need to be amended. A decision about thyroglobulin assays will be needed by the next visit.

MINSK, BELARUS

8 June 1998: During the agenda session, we learn from Dr. Stezhko that Dr. Yuri Dimidchik has assumed the post formerly occupied by his father as head of the Thyroid Surgery Center at the Minsk Medical Institute. The senior Dimidchik, now retired from surgery, is heading the Tissue Registry at the Institute of Radiation Medicine and Endocrinology.



Svislach River, Minsk

Almost 800 visits by cohort members have been recorded for the first 5 months of this year, including 69 patients from Bragin and 127 follow-up appointments. A mobile team worked for 4 days and identified 5 patients (2 new) with nodules, but FNA biopsies were

not performed since the older Sigma ultrasound machine could not adequately image the entire gland. Although the subjects were referred to the Aksakovchina Clinic for further evaluation, the 2 patients with new nodules “disappeared,” underscoring the necessity to biopsy nodules when they are discovered and not expect patients to return for another visit.

There is a “data flow problem” between the Dispensary and the DCC which threatens the entire operation. Ultrasound, Palpation, and Preliminary Medical Screening forms are not being sent in a timely fashion and the final medical screening forms are not being sent at all. This has led to considerable tension between Dr. Rzhetsky and Arthur Kuvshinnikov and it soon becomes obvious that they dislike each other intensely. Dr. Stezhko sides with Dr. Rzhetsky, saying that he “needs support”, which translates into: (1). A new copying machine to facilitate the transfer of paper forms to the DCC (It is agreed that the originals should stay at the Dispensary and be available for patient care. Gil Beebe makes the point that “there is too much paper already” and the emphasis should be on electronic data transfers); (2). A second computer operator (even though the one he already has does not work full-time on data entry and devotes some of her time to other clerical matters); (3). The “final” version of the data-entry software (a point forcibly disputed by Kuvshinnikov); (4). A new Tosbee 240 ultrasound machine for the mobile team.

It was pointed out by Dr. Stezhko that “our experience shows that we have many problems with forms” and that “perhaps we should review them more carefully,” even though it was previously agreed to use the forms for a year before discussing changes. Dr. Khlyavich, one of the sonographers, and I subsequently reviewed the Ultrasound Examination Form and the changes he proposed were reasonable. He wished to add a category for “Minimally abnormal thyroid” under section 8 and delete “Slice ID” on the last page, since it is “never used.”

The Dispensary is moving, with a complete transfer of clinical operations to be completed by mid-July. The new facility is located on Makaenka Street, about a kilometer from the nearest metro stop. Screening will continue throughout the summer, with a projected volume of about 30 subjects each day. The laboratory will be relocated after more extensive renovations to the new building, a delay which could further retard an operation which is seriously lagging in processing the specimens already collected.

Dr. N. Litvinova, an Endocrinologist at the Dispensary, tells us that in 757 patient visits (2 were follow-ups) during the first quarter of this year, thyroid abnormalities were found in 97: 11 cancers (4 new), 43 nodular goiters (31 new), 6 chronic thyroiditis “confirmed” (with an additional 10 “suspected”), and 27 diffuse goiters (21 WHO class IB, 5 class II, and 1 class III). FNA biopsy was performed in 9, 22 were referred to the Aksakovchina Clinic for further evaluation, and 6 sent directly to Dr. Y. Dimidchik for surgery (of the 5 operated upon, 4 were cancers and 1 was a benign adenoma).

The relationship among the Dispensary, the Aksakovschina Clinic, and the Thyroid Surgery Center is complex, but is at least partially clarified by Dr. Larissa Danilova. Not every patient with a suspected malignancy is referred to the Clinic, since ones with highly suspicious cytology may be sent for immediate operation. By decree of the Ministry of Health, an "Oncologist" decides which patients go to Aksakovschina for further evaluation. Otherwise, it is implied, more patients would be taken directly to surgery, since the surgeons are "aggressive."

Dr. Y. Dimidchik proposes making changes in the Hospitalization (Surgery) Form to allow addition of a second surgical procedure and multiple doses of radioactive iodine, both of which are appropriate. He also wishes to "link" with the DCC and begin a long-term follow-up of his cases. Although postoperative outcomes are not part of the current study, I feel that much useful information could come of it.



Dr. N. Litvinova

Dr. Khlyavich tells us that, contrary to the Operations Manual, FNA biopsy is done on most nodules over 5 mm in diameter. He also is of the opinion that FNA can be done by the mobile teams once an appropriate ultrasound machine is obtained (the Tosbee that Dr. Rzhetsky covets). They are having a problem insuring that aspirated specimens are adequate for cytological interpretation, since Dr. E. Gapanovich, a cytopathologist based at the Thyroid Surgery Center, reviews slides only part-time at the Dispensary. Unlike the setup in Kyiv, slides are not reviewed at the time of biopsy, so patients sometimes need to return for another procedure. Color doppler is done on "difficult cases and pathologic glands," but there is no obvious record keeping. The Aksakovschina Clinic also has a color doppler and has been using it for the last few months.

Memo: The sonographers could be taught to review slides, obviating the need for a cytopathologist to be in attendance. This would also be a useful skill for the mobile teams to have, cutting down on the number of referrals to the Dispensary and reducing the need for return visits. It would be necessary for them to receive the proper instruction in slide review and to have a microscope (“Dr. Rzhetsky will not give us one”).

9 June 1998: After Dr. Rzhetsky makes his pitch for a calcium autoanalyzer to take into the field, Dr. Fink points out that Dr. Ephstein found that “the autoanalyzer did not travel well.” The counter-argument is that “the specimens do not travel well” and only stay frozen for 6 hours, too short a time to transport back to the Dispensary. No final decision is reached and the discussion stops here. Dr. Rzhetsky plans to employ 3 endocrinologists full time: 2 at the Dispensary and 1 on the road. If the volume of patients increases (and if funding is available), he would add yet another endocrinologist at the Dispensary and organize a second mobile team. He anticipates that the mobile team will be able to screen 20 patients a day and be away for 10 working days each month. For “walk in volunteers,” he plans to examine them (“it is impossible to refuse”) and either not use the data or check with the DCC to see if the patient can be included in the study.



Dr. Y. Dimidchik

10 June 1998: This morning we had a chance to visit Dr. Yuri Dimidchik at the Thyroid Surgery Center. Although he gets most of the thyroid cancers in Belarus, a “small number” are operated upon in the oblasts (Dr. Cherstvoy claims that Dr. Stezhko has information about how many). Although patients are generally filtered through the Aksakovschina Clinic, those from Mogilev are sent directly for surgery. The Center does almost 1200 thyroid operations a year, for both benign and malignant disease. They run 3 operating rooms (2 tables in each) and have about 60 thyroid cases “in house” at any one

time. There are facilities for FNA, cytopathology (Dr. Gapanovich), pathology (Dr. Siderov), and a storage facility for tissue blocks dating back several years.

After a tea break with Dr. Dimidchik, we were driven across town to see Dr. Cherstvov, who has sufficiently recovered from his stroke to meet with us. He had just received the English translation of the Ukrainian pathology form, faxed to him from the DCC the evening before. His strong feeling was that there were “too many extraneous items not useful for the project.” Although he did not elaborate on this (and I did not feel free to press him for specifics), he did agree to discuss the matter further with Drs. Bogdanova and Virginia LiVolsi in Cambridge. He further proposed that the expert pathology group convene in Minsk, since “it would be simpler.” He reviews the pathology for all patients up to age 20 (and all “complicated” cases regardless of age) and has tissue blocks and frozen sections dating back to 1991 (he would like all pathologic material stored at his facility instead of sharing it with the Thyroid Surgery Center). Unlike Dr. Bogdanova, who is finding a huge increase in the solid-follicular variant of papillary cancer, he finds “no special radiation effect” in his material. He has also reviewed Ukrainian specimens and finds “mistakes.”

At the concluding Plenary Session it is agreed to change the Operations Manual to allow FNA biopsy of all nodules greater than 5 mm in size. It is apparent that translation must be done between the old and new WHO classification of goiters, since Arthur Kuvshinnikov has almost “6000 patients” in his data base according to the old grading system and it seems useful to begin classification according to the new one. It would also be prudent to keep the written description along with the WHO Grade (e.g., Grade 0 = no palpable or visible goiter).

Conclusions: The clinical screening is moving ahead at a steady pace, but a bottleneck has developed in the flow of data between the Dispensary and the DCC. As in the Ukraine, the Operations Manual (section 5.4.1) would need amendment to accommodate biopsy of nodules larger than 5 mm. We should directly observe operations of a mobile team “in the field.” Dr. Y. Dimidchik is establishing himself as an important member of the project and we should develop a good relationship with him.



The Road to Chornobyl