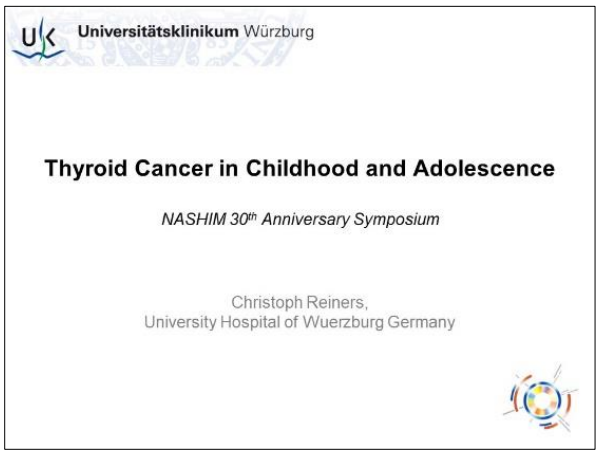
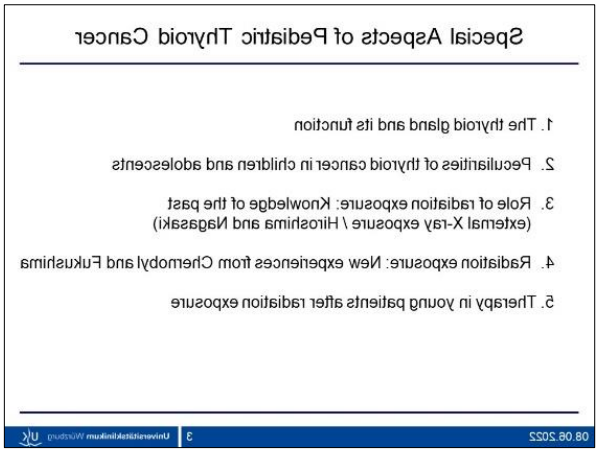
Dear Mr. Chairman Masayuki Morisaki, dear members of NASHIM, dear colleagues and friends,

It is a great honor and pleasure for me, to be invited for a lecture on the occasion of the 30th anniversary of Nagasaki Association for Hibakusha's Medical Care.

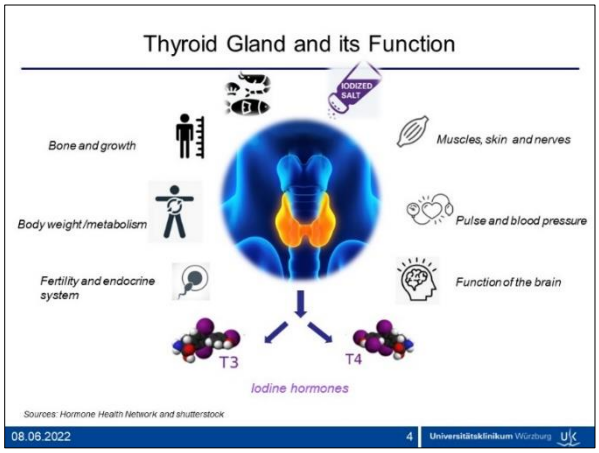



I start with the presentation now.
"Thyroid Cancer in Children and Adolescents" is the title of my presentation.

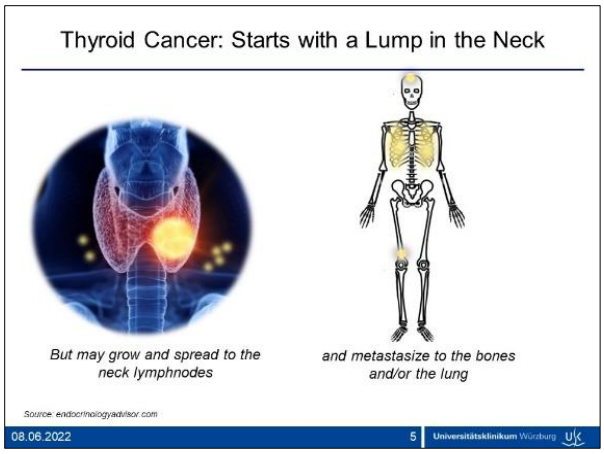

The relations between Würzburg and Nagasaki have a long history.
They started with Dr.Philip Franz von Siebolds, you see just upper left, who journeyed from Würzburg to Nagasaki now appr. 200 years ago.
You see him here in the upper left corner in the uniform of the Durch East India Company.
In 1996 the Medical School of Nagasaki University and the Medical Faculty of Wuerzburg University decided to sign an official partnership agreement.
Since then, more than 100 students and scientists from Nagasaki as well as from Würzburg participated in the exchange program.
The picture on the upper-right side shows Prof. Shunichi Yamashita and me with three Students from Nagasaki who had visited Würzburg in the framework of this program.
The picture in the lower-middle represents an important personal remembrance for me.
It has been taken in 2010 when I had the great honor to receive the Dr. Takashi Nagai Peace Memorial Price as the eight awardee of NASHIM.



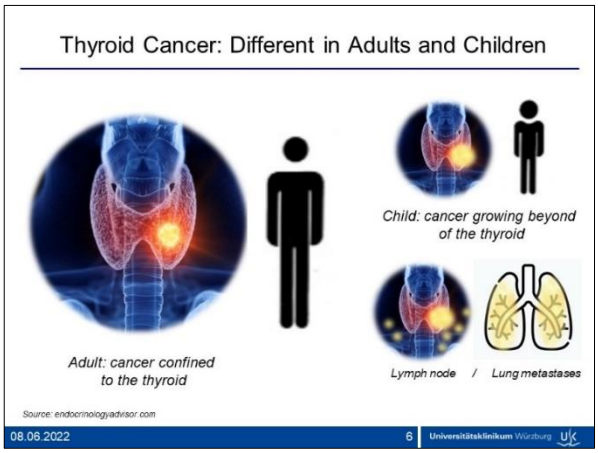

I would like to come now to the outline of my presentation.
First I will explain how the thyroid works and then address some special features related to thyroid cancer in children and adolescents.
The thyroid is known to be very sensitive to radiation.
This is well known since more than 80 years.
Much of this knowledge derives from scientific studies of survivors of the atomic bombing in Hiroshima and Nagasaki.
I personally was involved a lot - together with many scientists from different countries - in studies on thyroid cancer in the aftermath of the Chernobyl accident.
Later on, I participated in meetings which focussed on this issue after the Fukushima accident 2011 too.
Finally, I will report about a humanitarian project which I could organize together with colleagues from Belarus.



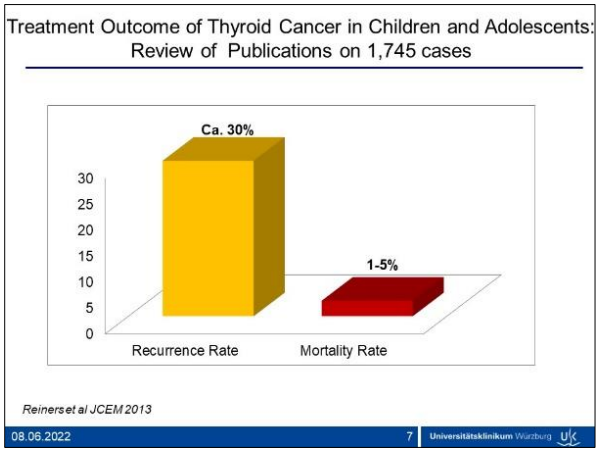

I want to start with a brief description of the thyroid gland and its function.
The thyroid is located in front of the neck just below the voice box.
And, it weighs normally approximately 25g.
To function properly, the thyroid needs iodine.
Its main natural source is seafood and Japanese people get enough iodine with their nutrition.
In Germany, we have to supplement iodine using iodized table salt.
The thyroid uses this iodine to produce thyroid hormones which - a little bit simplifying - can be called T3 and T4.
These hormones are very important for the development of children and nearly all functions of the body, which are shown here on this slide.
To mention these functions briefly:
- Bone and growth,
- body weight and metabolism,
- fertility and the endocrine system,
- the function of muscles, skin and nerves,
- heart rate and blood pressure and
- function of the brain.



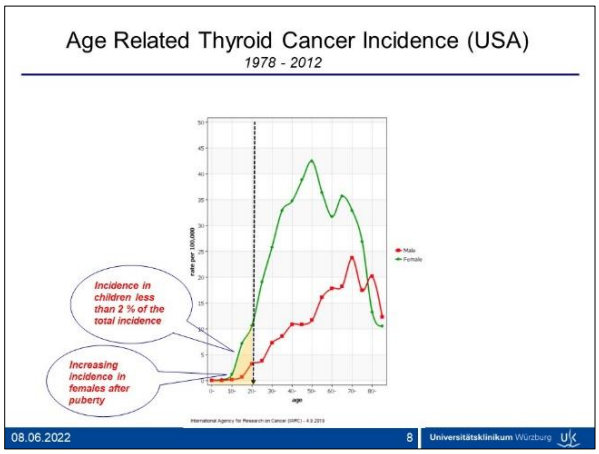

So far a brief overview over this small but important organ.
Now I will come to thyroid cancer, which actually is in the focus of my presentation.
The first symptom of thyroid cancer is a node or lump in the neck, which you usually can feel if it is larger than 2 cm in diameter.
Smaller nodules frequently can be diagnosed by ultrasound only.
One typical characteristic of cancer is that it may become larger and larger.
Secondly, it my spread to the regional lymphnodes.
And thirdly in advanced stages, thyroid cancer may produce deposits – which we call metastases – in the bones and/or in the lung.




Thyroid cancers in children show a typical pattern, which is different from adults.
First, in adults many cancers grow, but remain confined to the thyroid gland if the diameter is not larger than 2-3 cm.
In children, a tumor of this size is already so large, that it goes outside of the thyroid gland.
Secondly, lymph nodes are frequently involved in children with thyroid cancer and even metastases to the lungs may develop.
Contrary to adults, in children all these signs not necessarily are indicators of an unfavourable prognoses.
This maybe related to the particular lymphatic system in children, which better can cope with a thyroid cancer.




So the outcome of thyroid cancer in children and adolescents generally is excellent with respect to survival.
This slide shows a summary of the literaure and review on occastions nearly 2,000 cases of thyroid cancer in children and adolescents.
The mortality rate between 1 and 5 percent is very low.
But the recurrence rate is about 30 percent, and considerably higher.
In case of such a recurrence, these lymph node can be attacked with repeated surgery or radioiodine therapy.
I will come to radioiodine therapy later.
To briefly summarize: the course of thyroid cancer in children is different from adults.
And most importantly, in the vast majority of cases, it can be treated successfully.




I owe you still some important informations about the frequency of thyroid cancer which belongs to the rare diseases.

This graph shows the age related thyroid cancer incidences in the USA

for females (in green curve) and for males (in red curve).

Incidence means the rate of newly diagnosed cancer cases per year related to a population of 100,000.

The incidences are shown for all age groups from 0 here in the left corner to 80 plus in the right corner.

And you can generally see that the incidences in female peaks at the age of approximately 40 and it's much higher than in males all over the age groups.

Now we should focus on the age group of less than 20 years, the pediatric population.

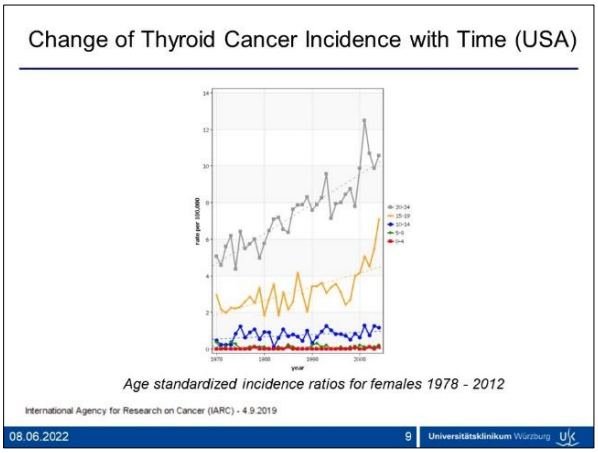
And you can clearly see that in the very young children, the incidence with appr. 0.1 cases per 100,000 in both genders is very low.

Only about 2% of thyroid cancers appear in children below age of 20.

As I already mentioned, that incidences for both sexes are identical below age of 10.

But after puberty, the incidence in females increases much more steeply than in males.

For sex hormones in females have an influence on the development of thyroid cancer.




The next set of curves may appear a little bit crowded, but I will try to extract the relevant information for you.

Again you see the yearly incidences of thyroid cancer as in the graph before but here they are given for girls only and are related to the year of diagnosis from 1978 to 2008 and 2012 here.

The age groups are separated by different colours, with red and green for the youngest age groups below age of 10.

Over time, the incidence in these age groups remain stable. There is no increase.

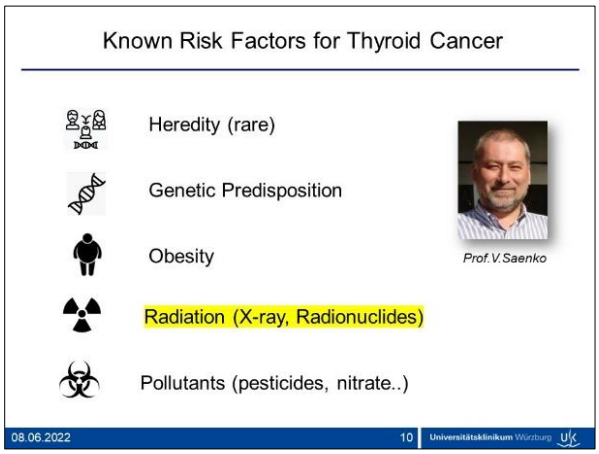
The blue curve characterizes girls before puberty age 10-14, and there is very small increase in this age group.

A much higher increase over time is in the age group 15 to 19.

And the highest increase is in the age group 20 to 24.

The take home message of this slide is: thyroid cancer becomes more frequent from year to year;

And the incidence for girls after puberty doubled approximately over the last 30 years.




What are the reasons for this increase of thyroid cancer incidence?

Some very rare types of thyroid cancer may be directly inherited to the next generation.

More frequent may be the so-called genetic predisposition.

This means that somebody with a corresponding genetic profile may be more prone to develop thyroid cancer when exposed to other risk factors than without this genetic profile.

I will give you an example with the next slide. However, these genetic patterns are under study yet and not well understood.

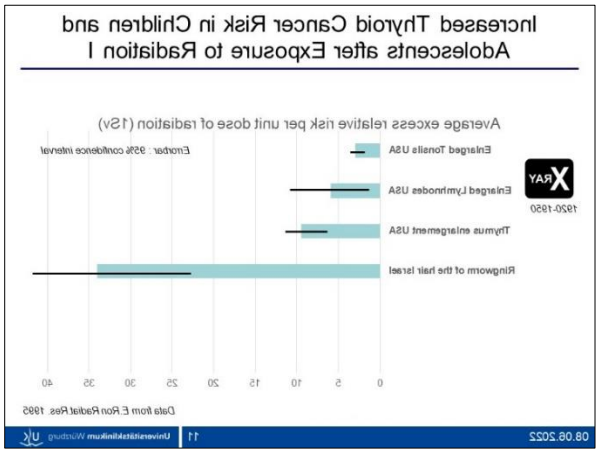
I should mention that Prof. Vladimir Saenko and his group of the Atomic Bomb Disease Institute in Nagasaki contributes a lot to this research.

Contrary to genetic predisposition, obesity is a relatively well known risk factor for thyroid cancer.

Since this condition is increasing over time, it may be at least partially a relevant explanation for the increase of thyroid cancer incidence over the last 30 years.

But we should not forget other risk factors for thyroid cancer, the most important one here highlighted in yellow is exposure to radiation from X-rays or radionuclides.

This kind of ionizing radiation is released in reactor emergencies and with atomic bombing as well.




This slide shows/summarizes the experciences of the past related to radiation exposure as a prominent risk factor for thyroid cancer.

These experiences have been made relativlye early after the invention of the X-Rays by W.C.Röntgen here in Würzburg University in 1895.

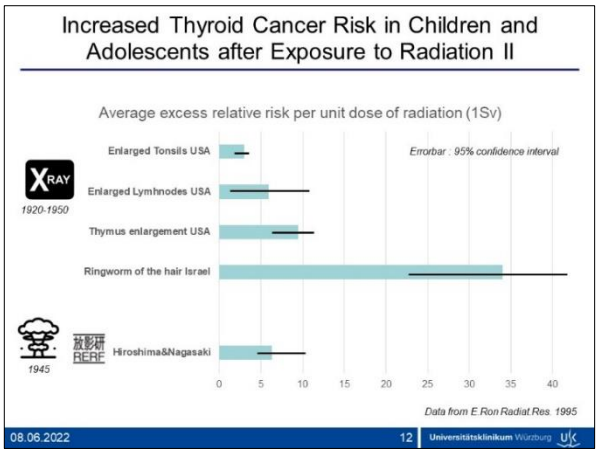
Already in the 1920 ´s, X-rays were used to treat children for benign, non-severe conditions as enlargement of the tonsils you see here, lymphnodes or the thymus.

And it was found that between 3%, 10%, 15% of the children develop later thyroid cancer because of this exposure to radiation.

The highest effect has been found in jewish immigrants to the USA who had been irradiated for ringworm of hair or scalp, a contagious disease where radiation eradicated the ringworm effectively.

However, in this group the risk for consecutive thyroid cancer with more than 30% was considerably higher than in the other populations.

This can be interpreted as an example of an increased genetic predisposition, as I mentiond before, for thyroid cancer in a specific ethnicity.




Finally, the by far most important data about the effects of radiation on the risk of thyroid cancer have been derived from survivors of atomic bombing in Hiroshima and Nagasaki. They are shown here.

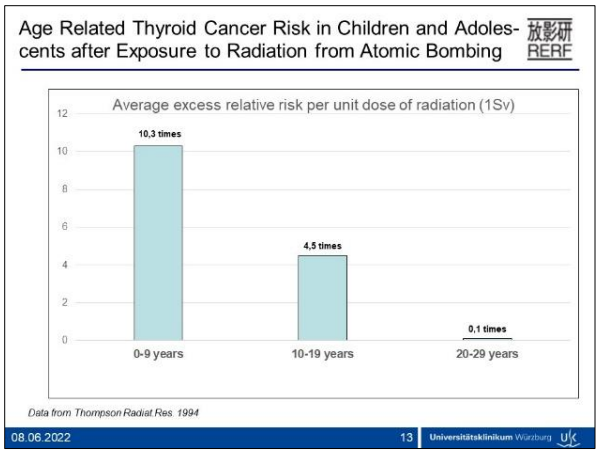
The Radiation Effects Research Foundation (RERF) in both cities conducted the „Life-Span Study“ in more than 80,000 survivors.

Perhaps some of the members of NASHIM still being alive have participated in the Life-Span Study.

The results of this research are until today the main source of knowledge for any kind of radiation induced cancer and non-cancerous disease.

And so it’s very important for science and for the practical use of radiation medicine.

Thanks to all the people from Japan who participated in this kind of studies.




One example of the menaningfulness of the Life-Span Study is shown here in this graph.

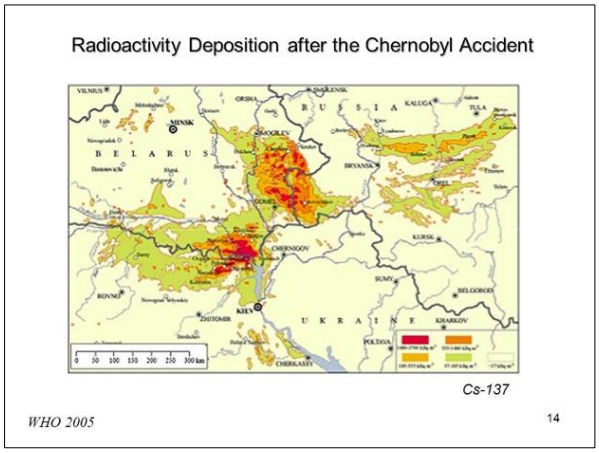
It demonstrates and proves the strong influence of age at the time of exposure for the risk of thyroid cancer.

You can see that this radiation related risk per unit dose of radiation is approximately 10 times higher in young children at the age of 0 to 9 years

As compared to the age group of 10 to 19 years that is appr. 5 times higher than normal.

And in the age group 20 to 29 years, there is no more increase of throid cancer risks.

So the most vulnerable group after radiation exposure to develop thyroid cancer are young children.




The exposure by atomic bombing resulted mainly from external radiation out of the cloud and from fall-out.

The map shows the situation after the Chernobyl reactor accident in 1986.

This is an example for a scenario where incorporation of released radionuclides played the dominant role.

This map shows as an example the deposition of radioactive Cesium in the three countries affected by the accident.

Most heavily affected was the country of Belarus, in this part of the map here.

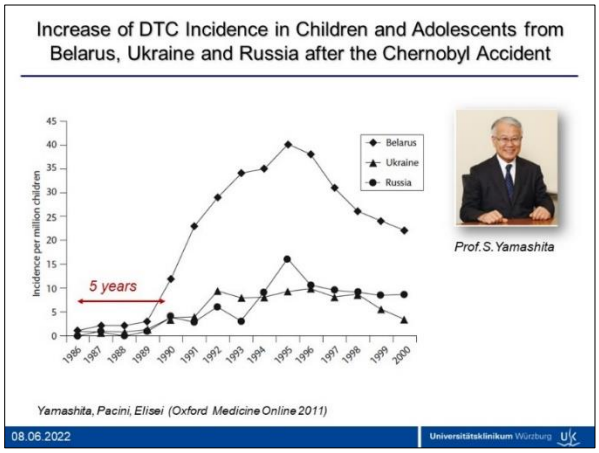
Concerning the health effects, the continous release of radioactive iodine over a whole week was more relevant than that of cesium.

The reason is that the thyroids of the people exposed took up this radionuclide.

And the radiation doses related to radioiodine were very high

because no countermeasures were taken, like withdrawal of contaminated food and milk as well as evacuation or

distribution of iodine tablets for thyroid blocking were undertaken in time.




So approximately five years after the Chernobyl accident the incidence of childhood thyroid cancer increased in Belarus (upper curve)

And in the other parts of the former Soviet Union where the contaminations were not so high like Ukraine and Russia, the increase was not so XXX, and this was not so expressed(impressive?) as in Belarus.

Please remember that there was a lag time of approximately ~5 years until thyroid cancer incidence increased in Belarus and that the maximum was reached after appr. 10 years.

This is important to correctly understand what happened after the Fukushima accident.

In this context I want to mention Prof. Shunichi Yamshita from Nagasaki who was involved in many positions with the reactor accidents, both accidents of Chernobyl and Fukushima.

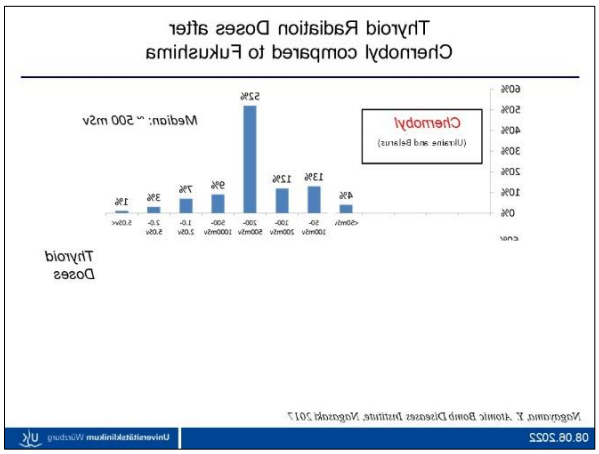
He did this as a member of Nagasaki University, an expert of WHO in Geneva, the vice-president of Fukushima Medical University, and nowadays as the Director General of the National Institute for Radiological Sciences in Chiba.

Prof. Yamashita very frequently visited Belarus and the other countries affected by the Chernobyl accident.

He organized many scientifc meetings on the consequences of the Chernobyl and Fukushima reactor accidents.

He published more than 400 papers mainly about that. It is a plesaure for me that we could publish together 10 of those.

I appreciate Shunichi Yamashita as an open minded, friendly and enthusiastic colleague and friend.




Thyroid radiation doses induced by the Chernobyl Accident were remarkably high, the median as a measure of the average dose being appr. 500 mSv.

The unit “Sievert” for radiation dose is named after the Swedish physicist Rolf Sievert.

For comparison, the median radiation dose to the thyroid after the atomic bombing was less by a factor of 5 with appr. 100 mSv.

Let’s now come to the second most severe reactor emergency was that of Fukushima in 2011.

Happily, thyroid doses were much lower by a factor of appr. 500 with a median of less than 1 mSv.

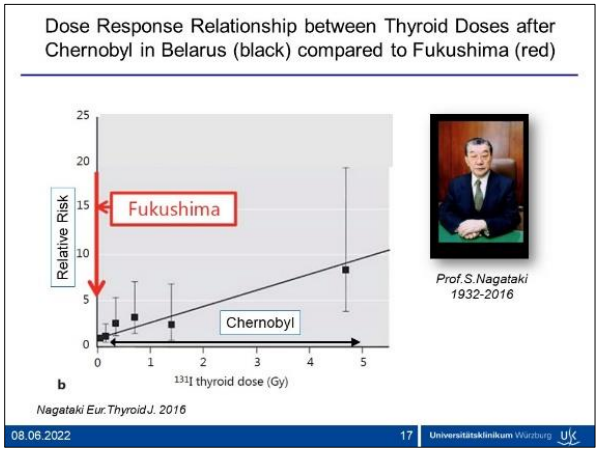
None of the exposed people in the Fukushima population received doses higher than 50 mSv.

The reasons for that were manifold:

During the short-term releases at Fukushima, only about a tenth of the radioactivity of the Chernobyl accident was liberated.

Second, contaminated food and milk were withdrawn systematically.

Third, exposed people were evacuated much earlier in Fukushima as compared to Chernobyl.





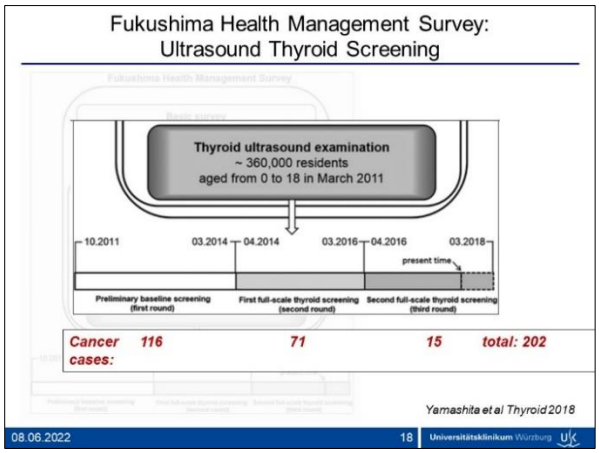

Prof.S.Nagataki
1932-2016

This issue of low radiation doses to the thyroid in Fukushima as compared to Chernobyl has been addressed very clearly in a paper by the late Prof. Shigenobu Nagataki in 2016 from Nagasaki University briefly before he deceased.

With this graph he showed the wide range of thyroid doses and the corresponding risk of thyroid cancer after Chernobyl as compared to the very low doses and low risks of the Fukushima accident.

To be precise, zero risk after Fukushima accident.

I remember – and will never forget - Prof.Nagataki as a great scientist and fatherly colleague.



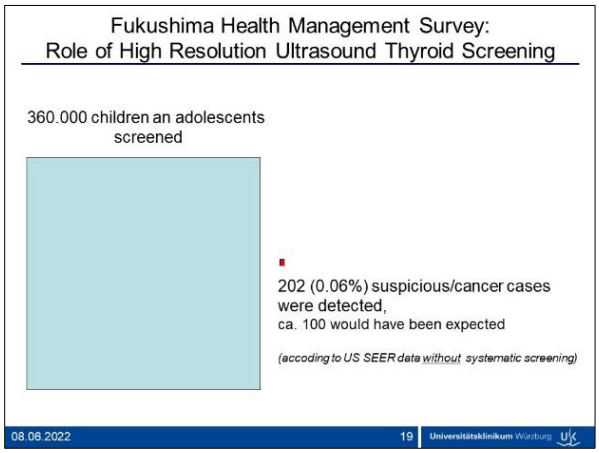

Nevertheless, the Japanese government decided to organize a systematic Health Mangement Survey with a focus on ultrasound examinations of the thyroid in the large number of 360,000 residents aged from 0 to 18 years at the time of the accident.

As a result, among many benign thyroid nodules and cysts, during the three rounds of ultrasound screening from October 2011 to March 2018, totally 202 cases of thyroid cancer cases have been detected.

Interestingly the number of cancers decreased at each round from 116 over 71 to 15.

This observation is called a „Harvesting Effect“ typical for such screening campagnes, if between the first and last round of screening the risk decreases and no new cancers develop.

The considerably decreasing number of thyroid cancers detected is a strong indicator against radiation as the cause of the cancer cases, since we know from Hiroshima & Nagasaki as well as from Belarus after Chernobyl that the risk for thyroid cancer peaks at 10 years and remains elevated for 10 to 30 years.




But we should ask too if the number of 202 cancer cases detected among 360,000 children and adolescents is extraordinarily high.

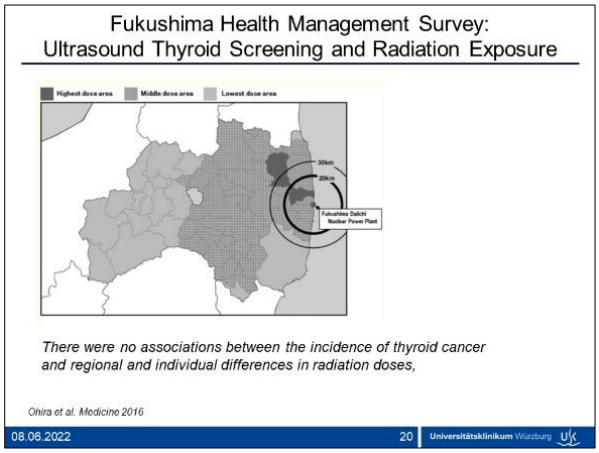
This graph tries to compare the whole screening of 360,000 individuals as an area (in light green) to the 202 cases found (as the tiny red square).

The percentage of cancer cases is 0.06%.

There are no data from Japan about the „natural“ prevalance of thyroid cancer cases in this age group which had to be expected during the screening rounds. But we can take prevalence data from the USA telling us that 100 spontaneously detected thyroid cancer cases had to expected in the group of 360,000 individuals without radiation exposure and a screening campaign.

So it is not so surprising that systematic ultrasound screening alone after the Fukushima accident revealed 102

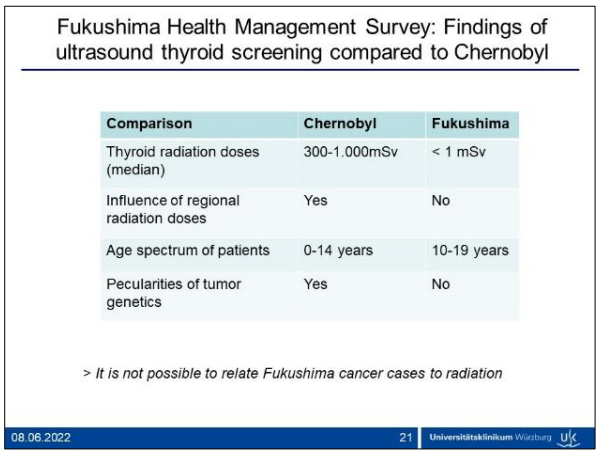
thyroid cancer cases additional to the 100 expected spontaneous cases




Finally, epidemiologists demand for a correlation between the suspected possible cause (in our context radiation doses) with the disease under study (which here is thyroid cancer).

However, a correlation of thyroid doses with thyroid cancer incidence has not been found by Ohira and his colleges when they analyzed the regional distribution of thyroid cancer cases detected by the Fukushima ultrasound screening campaign.

There were no significant differences of thyroid cancer incidence in three areas with high, intermediate and low thyroid doses.




As a summary, this table compares the results of thyroid cancer screening in children adolescents after the reactor accidents of Chernobyl and Fukushima.

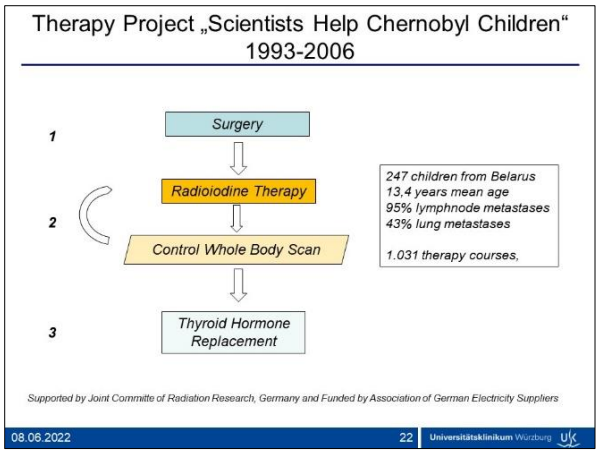
First, the number of 202 Fukushima cases is not unexpectedly high for a systematic screening program in 360.000 individuals which I just mentioned before.

Thyroid radiation doses were higher by a factor of approximately 500 or more in the Chernobyl situation as compared to Fukushima.

In Chernobyl, there was a geographical correlation of thyroid radiation doses with thyroid cancer incidence, which was not found in Fukushima.

Importantly, the mean age of pediatric throid cancer cases detected was clearly below 14 years of age after Chernobyl. This is the most vulnerable age group.Which was not seen in Fukushima, where the mean age of Fukushima was considerably higher between 10 and 19 years.

Finally, a relatively high percentage of genetic tumor variants as possible indicators of radiation induction was found after Chernobyl, but not found after Fukushima.So to summarize, it is not possible to relate Fukushima cancer cases to radiation as the cause.There may be other reasons for the development and findings of cancers which is primarily the screeaning and secondly obesidy or genetic reasons.



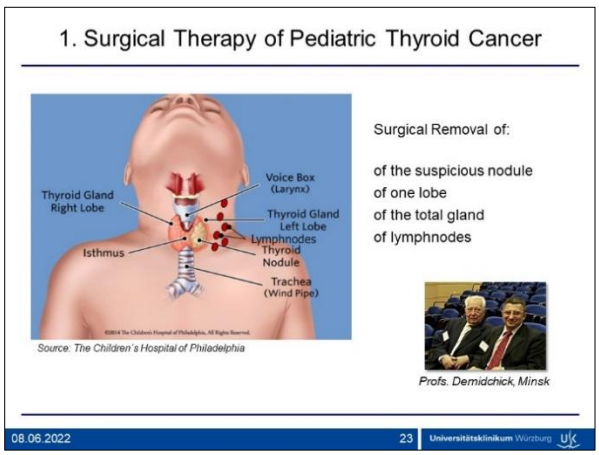

In the last part of my talk, I will address the question how childhood thyroid cancer has to be treated and will present the results of a treatment project of the last 30 years in young patients from Belarus.

With the exception of early stages without local and/or distant metastases, the therapy protocol for thyroid cancer consists of three steps:

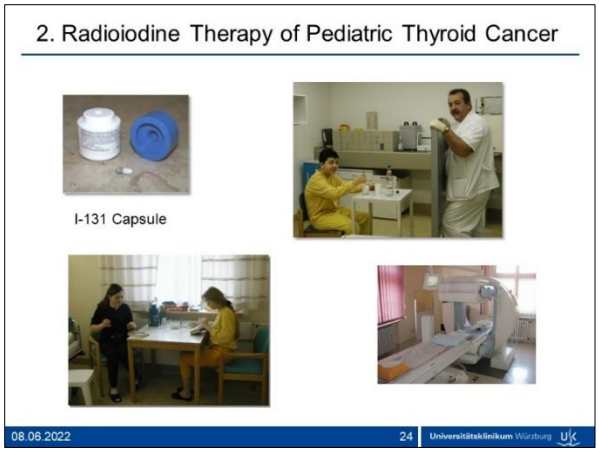
Surgery, radioiodine therapy, then after controls, thyroid hormone replacement finally.

In 1992, I came into contact with physicians from Belarus and

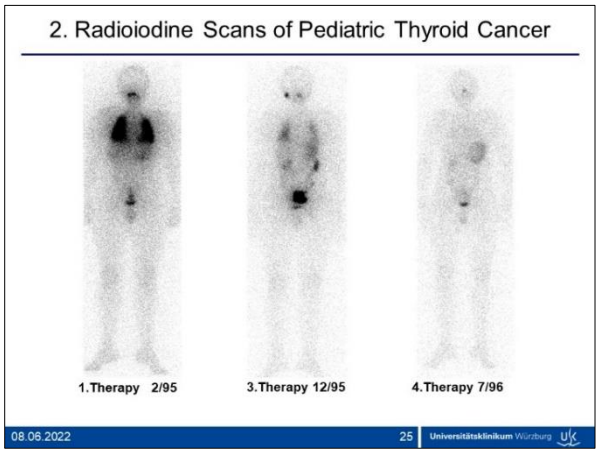
had the opportunity to visit Minsk.
I was frightened to see there many children and adolescents with thyroid cancer who were operated at the Clinic No.1 by Prof. Demidchik and his team.
Since many of them suffered from tumors with local and distant metastases, consecutive internal radiation therapy with radioiodine was indicated,but the facilities for such treatment were missing in Belarus at that time.
Animation 1: So I tried to organize a treatment project for these children which could start some months later.
Between 1993 and 2006, 247 children from Belarus with advanced cancer disease (95 percent with lymphnode metastases, 43 percent percent lung metastases) came for radiation therapy to Germany.
More than 1,000 therapy courses were applied.




This slide shows the surgical approach where the suspicious nodule in earlier cases, only one lobe mostly, the total gland, and lymph nodes have to be removed.
The experienced surgeons performing this kind of operations in Minsk were Prof. Demidchik father and his son which you see here.




This slide shows the therapy capsule with radioiodine and how it is adminstered by Dr.Biko.
Dr.Biko belongs to my team and is a russian speaking physician with a double qualification in pediatrics and in nuclear medicine.
Children had to stay for 5 days in our ward and at the end of their stay, a whole body scan for therapy control was made with this device.
I should mention that our colleagues from Minsk who accompanied the children to Wuerzburg received education and training in radiodine therapy in Wuerzburg.
A separate project funded by the European Commission allowed to install the necessary equipment in Minsk so that since more than 10 years now, radiodine treatment in Wuerzburg is no more necessary and can be carried out in Minsk too.




This is a typical example of three whole body scans which had been made in a 13 years old male patient who received totally 4 therapy courses.

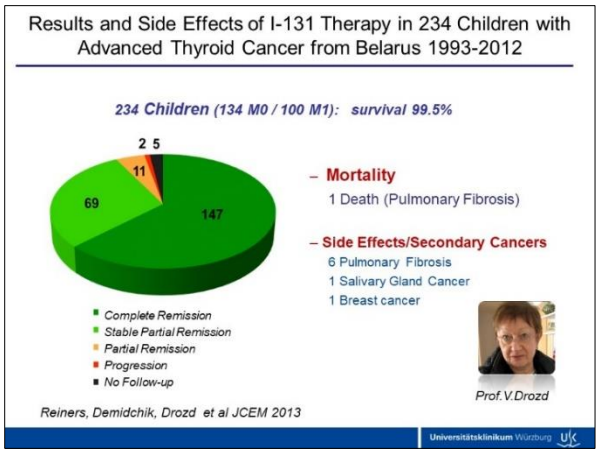
The first scan left shows (this is after first course of therapy) intense uptake in the lung metastases.

After the third therapy, (the scan in the middle) only a faint uptake in the lungs is still visible.

And this is a radioactivity in kidneys and stomach and in urinary bladder, which is normal, and does not mean the cancer deposits in these locations.

After the third therapy, the lungs are totally clear and only the stomach as I mentioned and some uptake in the kidneys and urinary bladder can be seen, and as I already said, it is normal.

Happily, we could register similar responses to radioiodine therapy in about 93% of the patients in this advanced disease.




The survival rate was 99%, is extremely high.

Only one patient died, not of tumor disease but of side effects of treatment which could not be prohibited.

The side-effects were pulmonary fibrosis.

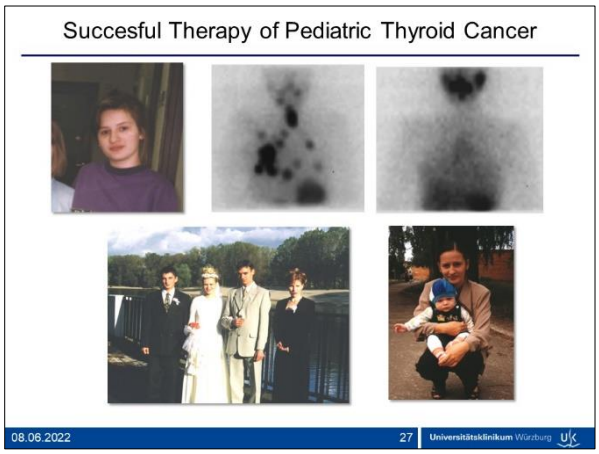
Together with Prof.Valentina Drozd from Minsk, now living in the US, we investigated every kind of side effects of radiation therapy with radioiodine in those 234 children.

Totally six cases of pulmonary fibrosis were found, five of them were not severe XXX.

And the patients are still doing well.

In two cases, a secondary cancer to the salivary gland one case and to the breast cancer one case was found.

But this is not more than expected in this age group without radioiodine therapy.




I want to finish with a case report of an 11 years old girl at the time of diagnosis.

Here you see her just immediately after the surgical operation in Minsk.

She presented with large metastases to the lungs, which can be seen here in this kind of nodules.

This girl received three therapy courses with radioiodine in Germany, which effectively removed all the metastases.

The girl married in 2010 and gave birth to a healthy child in 2011.

She is doing well, I last met here in Minsk in 2017.

I think that this case report symbolizes the potential of radioiodine treatment in children and adolescents with radiation induced thyroid cancer.


So, I want to thank you for your attention.

Last but not least: Congratulations from Würzburg to NASHIM on the occation of its 30th anniversary.

I wish you all the best and succesful continuation of your important work in the interest of Hibakushas!

Thank you very much.