Study information
Version 4.1.2

OPBC-03 / SAKK 23/16 / IBCSG 57-18 / ABCSG-53: Surgical axillary lymph node removal with the option of "extended surgery" or "radiotherapy" in breast cancer patients with existing axillary lymph node involvement

An open-label, randomized, multicenter phase III study.

(OPBC-03 / SAKK 23/16 / IBCSG 57-18 / ABCSG-53: Tailored Axillary Surgery with or without axillary lymph node dissection followed by radiotherapy in patients with clinically node-positive breast cancer (TAXIS). - A multicenter randomized open labelled phase III trial.)

This study is organized by: University Hospital Basel (USB), Prof. Dr. med. Walter Weber.

Dear Lady, Dear Sir,

We would like to ask you if you would like to participate in a clinical study that would include future medical research on your genetic data as well as your biological material. In the following, this study proposal, including the condition for participation in future research projects, is presented to you: first in a short summary so that you know what is involved, then in a detailed description. You will have enough time to decide whether you want to take part in this clinical study, which involves the further use of your genetic data and biological material for future research projects.

Summary

1	**Aim of the study** We would like to ask you to take part in our clinical trial. The study is looking at the effectiveness of radiotherapy compared to surgical treatment for breast cancer affecting the lymph nodes in the armpit. We are doing this study to find out the most effective treatment with the fewest side effects.
2	**Selection** You suffer from breast cancer with involvement of the lymph nodes in the armpit.
3	**General information about the study** This study is being conducted at many centers in Switzerland and abroad. In total, we include 1500 patients (women and men with breast cancer) over a period of slightly more than 5 years. The total study duration is about 15 years. All patients have a limited number of affected lymph nodes and sentinel nodes removed. Afterwards, the patients are randomly divided into two groups:In one group, the remaining lymph nodes in the armpit are surgically removed.

	This corresponds to the standard treatment, which can effectively prevent recurrences in the armpit. However, about a quarter of patients' experience side effects, some of which are permanent. These include emotional disturbances, chronic pain, restricted movement of the shoulder and swelling of the arm, known as lymphedema. In the other group, the armpit is irradiated without removing the remaining lymph nodes. Radiotherapy to the armpit is given at the same time as radiotherapy to the breast or chest, which is planned for all patients regardless of group allocation. With this study, we now want to investigate whether radiotherapy is also equally effective in your situation and has fewer side effects than surgical removal.
4	**Procedure** If you take part in this study, we will do some additional examinations. You will also be given a questionnaire about your quality of life and physical complaints. The examinations and questionnaires will take place as part of your routine examinations and treatment. No additional imaging procedures are planned, except for an X-ray of the removed lymph nodes after the operation.
5	**Benefit** If you participate in this study, you will be placed in one of two groups depending on the lot (50% of participants each) The first group receives extensive surgical removal of the axillary lymph nodes. This corresponds to the current standard treatment outside of a clinical trial. The second group receives radiation therapy to the armpit instead of surgery. This therapy may be equally effective and cause fewer side effects. If this benefit of radiotherapy is confirmed in this study, it could become the new standard treatment for patients with this disease.
6	**Rights** You decide voluntarily whether you want to take part in the study or not. Your decision has no influence on your medical treatment and you do not have to justify this decision.
7	**Duties** If you participate, we ask you to adhere to certain requirements. As a study participant, you are required to, ▪ Follow the medical instructions of your investigator and adhere to the study plan. ▪ To inform your investigator about the course of the disease and to report new symptoms, new complaints and changes in your condition. This also applies after the end/termination of the study until the symptoms have subsided. ▪ inform your investigator about concurrent treatment and therapies with another doctor and about any medication you are taking. Please list all medicines, including those that you have bought yourself over the counter. Also inform your investigator about all herbal medicines such as herbal teas and tablets/dragées, as well as medicines of alternative medicine (homeopathy, spagyric, etc) that you are taking. Until you have completed the follow-up examinations, which are limited to 10 years, you are required to inform your attending physician of any side effects.

8	**Risks** The study is being carried out to prove the effectiveness of radiotherapy compared to surgical removal. It is not excluded that radiotherapy is less effective than surgery. The study is also being done to show that radiotherapy causes fewer side effects than surgical removal. However, it may not be possible to show this superiority of radiotherapy.
9	**Other treatment options** Your doctor will advise you on what other options are available for your treatment.
10	**Results** You will be informed of study results during the study if these results are important for your health. If you do not want this, please inform your investigator. You will be informed of any incidental findings that may help prevent, detect or treat existing or future diseases. If you do not want to be informed, please talk to your investigator.
11	**Confidentiality of data and samples** We comply with all legal rules of data protection and all parties involved are bound by professional secrecy. Your personal and medical data and biological material are used and protected in encrypted form.
12	**Withdrawal** You can withdraw from the study at any time and no longer participate. The data and samples collected up to that point will still be evaluated.
13	**Compensation** You will not receive any compensation.
14	**Liability** The insurance company Chubb Insurance (Switzerland) Ltd, Bärengasse 32, 8001 Zurich is liable for damages within the scope of the study.
15	**Funding** The majority of the study is paid for by: • University Hospital Basel • Company Agendia • SERI • Fond'Action contre le cancer • Rising Tide Foundation for Clinical Cancer Research, • Basel Cancer League • Swiss Cancer Research The USB receives financial support from the State Secretariat for Education, Research and Innovation (SERI), the Swiss Cancer Research Foundation and the Swiss Cancer League.

16	**Contact person:** You will receive information on all your questions at any time. Leader of the study: Prof. Dr. med. Walter Weber Address: Universitätsspital Basel Spitalstrasse 21 4031 Basel Phone: +41 61 328 75 25 24-hour accessibility: +41 61 265 25 25 (Request duty doctor surgery) E-mail: walter.weber@usb.ch

More detailed information

1. Aim of the study

With this study, we want to investigate whether radiation to the axilla is equally effective and causes fewer side effects than surgical removal in patients with breast cancer and affected lymph nodes in the axilla.

2. Selection

All women and men who are older than 18 years and suffer from breast cancer with involvement of the lymph nodes in the armpit can participate. However, persons in whom the successful removal of the tumor-affected lymph node cannot be reliably confirmed in an X-ray image are not allowed to participate. Furthermore, people are not allowed to participate if the removed lymph nodes no longer show tumor involvement after pre-treatment.

3. General information

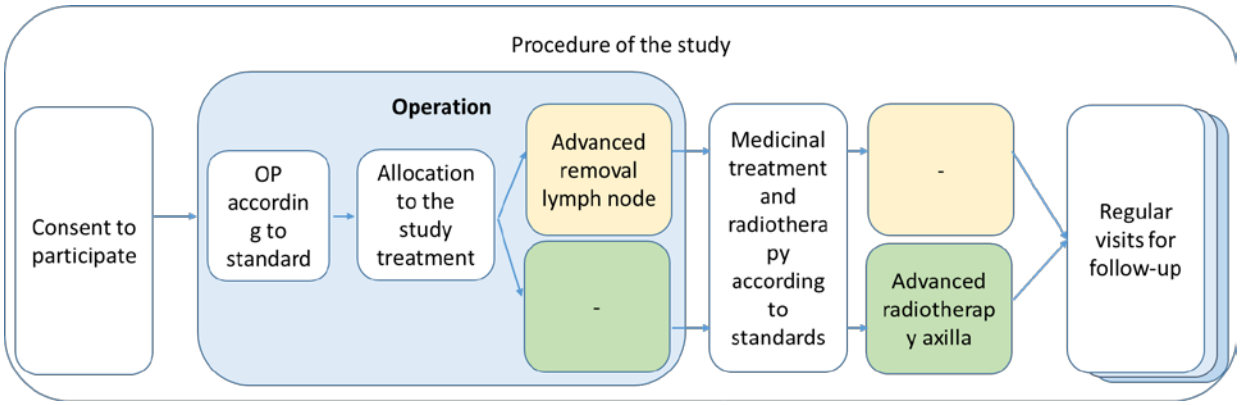
This is an international study that is being conducted at many centers in Switzerland and abroad. A total of 1500 patients are taking part in the study. The aim of the study is to prove that radiotherapy is equally effective and causes fewer side effects. The total duration of the study is about 15 years. All patients will have a limited number of the affected lymph nodes and the sentinel nodes removed. Patients who participate in the study are randomly divided into two groups.

The first group receives extensive surgical removal of the axillary lymph nodes. This corresponds to the current standard treatment outside of a clinical trial, and can effectively prevent the recurrences in the armpit. However, about a quarter of patients experience side effects, some of which are permanent. These include sensory disturbances, chronic pain, restricted movement of the shoulder and swelling of the arm, known as lymphedema.
The second group receives radiation therapy to the armpit instead of extensive surgical removal. This therapy can be equally effective and cause fewer side effects. Radiotherapy to the armpit is given at the same time as radiotherapy to the breast or chest, which is given to all patients regardless of group allocation.
If this benefit of radiotherapy is confirmed in this study, this could become the new standard treatment for patients with this disease.

- We do this study as required by the law in Switzerland. We also follow all internationally recognized guidelines. The responsible cantonal ethics committee has reviewed and approved the study.
- A description of this study can also be found on the website of the Federal Office of Public Health: www.kofam.ch.

4. Procedure

Before the removal of the lymph nodes in the armpit, a tumor-infiltrated lymph node is marked with the help of ultrasound and a cannula with a small metal clip. This is done under local anaesthesia before the operation - either in the X-ray department or in your surgeon's consultation.
Your doctor has informed you during the consultation that you will receive limited removal of the affected lymph nodes together with the sentinel lymph nodes. After removal of the lymph nodes, patients are randomly divided into a group with surgical removal of further lymph nodes in the armpit and a group with radiotherapy of the armpit. Radiotherapy of the armpit is performed at the same time as radiotherapy of the breast or chest, which is planned for all patients regardless of group allocation.



The following investigations are specific to this study and will be conducted in addition:

- Marking the lymph node, if not already done routinely.
- The recording of the quality of life as well as the arm function are important parts of this study. Filling out the corresponding questionnaires on these topics takes about 10-15 minutes. The questions are answered before surgery and 1, 9 and 12 months after surgery, then annually for another 4 years. A final questionnaire needs to be completed 10 years after surgery.
- Another important part of the study is the accurate measurement of arm function and circumference. These measurements take place before surgery and 1 and 4 weeks after surgery, then 9 and 12 months, and then annually until 10 years after surgery. Arm circumference measurements are also taken before radiotherapy and annually up to 10 years after surgery. These examinations take place during routine clinical check-ups.
- Once a year, on the occasion of the routine tumor follow-up, an ultrasound examination of the armpit is performed in addition to the routine mammography
- During the operation, an X-ray is taken of the removed lymph nodes to make sure that the metal clip with the lymph node has been removed.
- The removed tumor and lymph node tissue (from the biopsy and surgery) is used for additional laboratory analyses.
- If you are a woman of childbearing age, a pregnancy test will be carried out before the start of the study using a urine or blood sample.

It may be that we cannot carry out the study treatment with you and we have to exclude you again beforehand. This may happen if the X-ray of the lymph node removed during the operation, the small metal clip, cannot be shown and it is therefore not certain that the lymph node with tumor at the beginning was safely removed, or if the removed lymph nodes no longer show any tumor. Your data and samples collected up to this point will still be evaluated.
In this case, you will be finally examined again for your safety and the current standard treatment will be carried out on you, which in most cases corresponds to an extensive surgical removal of the lymph nodes of the armpit.

Your general medical doctor will be informed about your participation in the study.

5. Benefit

You will not personally benefit from taking part in the study. The results may be important for others who have the same disease.
If you take part in this study, you have a 50% chance of having extensive surgical removal of the axillary lymph nodes. This is the current standard treatment outside of a clinical trial. However, you also have a 50% chance of receiving radiation therapy to the armpit instead of surgery. This therapy may be equally effective and cause fewer side effects. If this benefit of radiotherapy is confirmed in this trial, it could become the new standard treatment for patients with this disease.

6. Rights

You participate voluntarily. If you do not want to participate or later withdraw your participation, you do not have to justify this. Your medical treatment/care is guaranteed regardless of your decision. You may ask questions about your participation in the study at any time. Please contact the person named at the end of this information.

7. Duties

As a participant it is necessary that you

- Follow the medical requirements of your investigator and adhere to the necessary specifications and requirements of the study through the protocol;
- Inform your investigator about the course of the disease and report new symptoms, new complaints and changes in the way you feel. This also applies after the end/termination of the study until the adverse effect has subsided;
- to inform your investigator about concurrent treatment and therapy with another doctor and about the intake of medicines. Medicines also include any self-purchased, over-the-counter medicines and/or alternative medicine preparations (herbs, plants, homeopathic and spagyric essences, Asian remedies, special foods and vitamins);
- Notify your investigator of any side effects until the completion of the 10-year limited follow-up.

8. Risks and burdens for the participants

If you take part in this study, you have a 50% chance of receiving extensive surgical removal of the lymph nodes of the armpit. Following this, the non-operated parts of the lymphatic drainage pathways will be irradiated. This is the current standard treatment outside of a clinical trial. However, you also have a 50% chance of receiving more extensive radiotherapy including the armpit instead of extensive surgery. Since in this case the area that is irradiated anyway only has to be extended a little, the additional radiation exposure is very low. A comparable efficacy of radiotherapy with better tolerability compared to surgery has already been shown in similar situations. In one study, radiotherapy of the armpit was significantly gentler than surgery, with the same effectiveness. After five years, lymphedema occurred in 11% of patients after radiotherapy and in 23% after surgical removal. However, this has not yet been confirmed for your personal situation. It cannot be ruled out that radiotherapy of the armpit is less effective or causes more side effects. An excerpt of the most important risks and side effects of both surgical removal and radiotherapy are numbness of the upper arm and the side of the chest, chronic pain, restricted movement of the shoulder and swelling of the arm, known as lymphedema. The attending physician is responsible for a complete explanation of the undesirable effects, please contact him.

For women who can become pregnant
In order to prevent damage to the unborn child, study participants must use a reliable method of contraception (condom, diaphragm, IUD) from the beginning of the study until the end of the radiotherapy, or in the case that they receive a therapy with medication according to the valid guidelines. Hormonal methods such as the pill are prohibited, as this hormonal manipulation can promote the disease.
If you still become pregnant during the study, you must inform your investigator immediately. In this case, you will be asked to provide information about the course and outcome of the pregnancy. The investigator will discuss the further procedure with you.

For male participants
Sperm damage cannot be ruled out, so you must use contraceptive methods (condoms) from the beginning of the study until 6 months after radiotherapy. If you are still receiving treatment with medication, you may need to use a reliable contraceptive method for longer than 6 months after radiotherapy, in accordance with the current guidelines. As a study participant, you must inform your partner(s) about your participation in the study and have sexual intercourse only with a condom.
If your partner nevertheless becomes pregnant, you should report this to the investigator in consultation with your partner. Your partner must be given the opportunity to come along to a study visit for information. The investigator will ask your partner for consent to obtain information about the pregnancy and the child.

9. Other treatment options
You do not have to take part in this study. If you do not participate, you will be given the current standard treatment, which in most cases is extensive surgical removal of the axillary lymph nodes.

10. Results from the study
The investigator will inform you during the study of any new findings that may affect the benefit of the study or your safety and therefore your consent to participate in the study. You will receive the information verbally and in writing.
You will be informed in the case of incidental findings that may contribute to the prevention, detection and treatment of existing or future expected diseases in you. If you do not want to be informed, please talk to your investigator.

11. Confidentiality of data and samples
Your personal and medical data will be collected for this study. If you are treated at a branch of a hospital network, copies of your data will be sent to the main centre of that network. Very few professionals will see your unencrypted data, and only to carry out tasks within the study. When data is collected for study purposes, it is encrypted. Encryption means that all reference data that could identify you (name, date of birth) are deleted and replaced by a key. The key list always remains in the institution/hospital. Those persons who do not know the key can therefore not draw any conclusions about your person. In the event of publication, the summarised data cannot therefore be traced back to you as an individual. Your name never appears on the internet or in a publication. Sometimes there is a requirement in a journal for publication that individual data (so-called raw data) must be submitted. If individual data have to be transmitted, then the data are always encrypted and therefore also not traceable to you as an individual. All persons who have access to your data within the framework of the study are subject to the duty of confidentiality. Data protection regulations are observed and you, as a participant, have the right to view your data at any time.

Your data could be important for answering other questions at a later date and could later be sent to and used in another database in Switzerland or abroad for as yet undefined studies (further use). This other database must comply with the same standards as the database for this study. For this further use, we ask you to sign another consent form at the very end of this document. This second consent is independent of participation in this study.

The data and samples may be sent to the USA (Irvine, California) in encrypted form for certain genetic analyses for breast cancer. The unused samples are destroyed The key list remains in the institution and only this institution has access. The sponsor is responsible for ensuring that the same standards are maintained abroad as in Switzerland.

This study may be reviewed by the relevant ethics committee or by the institution that initiated the study. The investigator may have to disclose your personal and medical data for such checks. Similarly, in the event of damage, a representative of the insurance company may also need to look at your data as an exception. All persons must maintain absolute confidentiality.

It is possible that your post-treatment doctor will be contacted to provide information about your state of health.

12. Withdrawal
You can stop and withdraw from the study at any time if you wish. The data and samples collected up to that point will still be evaluated in encrypted form, because otherwise the whole project will lose its value. After the evaluation, your data and samples will be completely anonymised, i.e. your key allocation will be destroyed so that no one can find out afterwards that the data and samples originally came from you. You can contact your investigator if you wish your samples to be destroyed.

13. Compensation for participants
If you participate in this study, you will not receive any compensation. We will reimburse you for expenses such as travel expenses that are only due to participation. Please discuss this point with your investigator if you wish to be reimbursed in this way.
There are no additional costs for you or your health insurance for participating.

14. Liability
The institution (the sponsor) that has arranged the study and is responsible for conducting it is liable for any damage that you may suffer in connection with the research activities (e.g. surgery). The requirements and procedure for this are regulated by law. The USB (Spitalstrasse 21, 4031 Basel) has therefore taken out insurance with Chubb Insurance (Switzerland) Ltd, Bärengasse 32, 8001 Zurich, to cover liability in the event of a possible claim.
If you have suffered any damage, please contact the investigator or the insurance company mentioned above.

15. Funding of the study

The majority of the study is paid for by:

- University Hospital Basel
- Company Agendia
- SERI
- Fond'Action contre le cancer
- Rising Tide Foundation for Clinical Cancer Research,
- Basel Cancer League
- Swiss Cancer Research

The USB receives financial support from the State Secretariat for Education, Research and Innovation (SERI), the Swiss Cancer Research Foundation and the Swiss Cancer League.

16. Contact person(s)

If you have any questions, uncertainties or emergencies that arise during the study or afterwards, you can contact one of these contact persons at any time.

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17. Glossary (terms requiring explanation);

- What does "randomised" mean?
  In many studies, two or more different types of treatment are compared, for example, a real drug and a standard treatment. Two groups of participants are then formed, one receiving the real drug and the other the routine treatment. "Randomisation" then means that a lot is drawn to determine who goes into which group. In such a test, it is therefore a matter of chance whether one receives the real drug or the routine treatment.