Breast cancer in Pregnancy (BCP)
Prospective and Retrospective Registry Study of the German Breast Group (GBG)
for Diagnosis and Treatment of Breast Cancer in Pregnancy compared to young non-pregnant women

GBG 29

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Contents

Summary:

Breast cancer complicating pregnancy is a rare coexistence. Breast cancer is the common malignancy in pregnancy after the age of 25.. Little is known about the incidence in Germany and Western Europe. It seems that it has become the most common malignancy during pregnancy since the decline of cervical cancer. We have initiated a registry for breast cancer during pregnancy, which has led to some interesting findings. The primary endpoint is the foetal outcome 4 weeks after delivery. Secondary endpoints will include maternal outcome, pregnancy outcome, diagnostic procedures used and the biology of the tumour. A flow sheet for the treatment is given and the acceptance of these guidelines will be evaluated. The primary endpoint and some secondary endpoints had been evaluated. But will still remain in the focus as treatment of primary breast cancer has changed. Tertiary endpoints have become the investigation of biomaterial collected from the breast cancer as well as the placenta. We start to build a non-pregnant control cohort (clinical data and biomaterial) with women who were diagnosed with breast cancer below the age of 45 years to match them to the pregnant breast cancer patients in order to have controls treated in everydays clinical practice.
The trial was initiated in the German Breast Group and could be extended throughout Europe (Breast International Group) and worldwide.

Introduction:

Breast cancer is the most common cancer malignancy in women of childbearing age after the age of 25 years.[1]U p to the age of 25 lymphomas is the most common malignancy.[2] About 11% of breast cancer patients are younger than 40 years and about 3% of all breast cancers are diagnosed during pregnancy. The median age of first pregnancy in Germany is 30 years. Since the incidence of breast cancer under the age of 40 is increasing and women tend to

delay pregnancy into later reproductive years the coincidence of pregnancy and breast cancer is increasing.

Therefore the incidence of breast cancer diagnosed during pregnancy is increasing. About 1 in 1,000 pregnancies is complicated by breast cancer.[3] Pregnancy has a dual effect on the risk of breast cancer: it transiently increases the risk after childbirth but reduces the risk in later years[4]. However, little is known about the incidence in Germany/Europe as well as the right therapy for mother and the unborn child.

The patients diagnose more than 90% of the breast tumours in pregnancy. Because of the hypervascularisation and the breast enlargement tumours are often undiagnosed. But even during pregnancy lumps of uncertain dignity need to be investigated. Due to a change in radiographic density, the sensitivity of mammography in detecting breast cancer in pregnant women is about 68%, while that of ultrasound is about 93%.[5] Diagnosis should be made with core cut biopsy under local anaesthesia. A pregnant women has a 2.5fold increased risk presenting with advanced disease than a non-pregnant women and a lower chance of being diagnosed in stage I.[6] The strategies for therapeutic management are depending on the stage. In stage I and II breast cancer modified radical mastectomy is recommended. Radiotherapy should be delayed until after delivery in order to avoid adverse effects on the foetus. Adjuvant and neoadjuvant chemotherapy should not be administered during the first trimester. Trastuzumab as well as endocrine therapy should be given after delivery. The MD Anderson Cancer Centre developed a protocol for the management of breast cancer in pregnancy and demonstrated that it is safe to treat them according to the current standard. During a period of eight years they treated 24 patients according to that predefined protocol.[7] We developed the first guideline on treatment for breast cancer during pregnancy.[8] Based on these first initiatives the registry for breast cancer during pregnancy was build. First results have recently been published.[10] We could demonstrate that breast cancer can and is been treated mostly according to women with non-pregnant breast cancer. Chemotherapy can be given

during pregnancy mostly without additional risks. However, we observed that children exposed to chemotherapy in utero are generally lighter, although this seems to have no consequence.

Notwithstanding the fact that breast cancer in pregnancy is generally of higher risk, it does not have a bad prognosis.[11] The 5-year survival rate of patients with negative axillary lymph nodes is 82% in both pregnant and non-pregnant women and 59% in node-positive patients.[12] Overall, metastases in placenta are rare but were observed in advanced breast cancer cases more often than in the cervical carcinoma ones . The post-birth histological examination of the placenta should always be performed.[13]

Adjuvant chemotherapy can cause amenorrhea.[14] Younger patients present higher probabilities to menstruate after chemotherapy and thus to become pregnant again. Gelber et al. evaluated the impact of subsequent pregnancy on the prognosis of patients with early breast cancer. The results revealed that subsequent pregnancy does not adversely affect the prognosis. The superior survival seen was considered consistent with an anti-tumour effect of pregnancy.[15],[16] If women with breast cancer during pregnancy become pregnant again is unknown.

Protocol:

1. Endpoint

Primary endpoint:

- Foetal outcome 4 weeks after delivery.

Secondary endpoint:

- Maternal outcome of pregnancy.
- Stage of and biological characteristics of breast cancer.

- Breast cancer therapy (treatment, response to chemotherapy in the neoadjuvant setting, type of surgery.
- Sensitivity and specifity of diagnostic procedures (palpation, US, mammogramme).
- Adverse events/side effects in BCP patients receiving chemotherapy compared to non-pregnant young women receiving chemotherapy.
- Outcome of the newborn after therapy.
- Outcome of breast cancer after diagnosis.
- Rate of pregnancies after breast cancer
- Biology of the tumour of pregnant breast cancer patients measured with standard immunohistochemistry as well as next generation sequencing compared to young non-pregnant women.
- All parameters will be compared to young non-pregnant women

2. Inclusion criteria:

- Patients with histological confirmed breast cancer who are pregnant.
- Patients < 40 years with histological confirmed breast cancer who are not pregnant (patients who have been pregnant recently can also be collected into this cohort)
- Informed consent for data collection (for prospective participants) and biomaterial collection. For retrospective participants an informed consent is not required as long as the data are anonymously captured.

3. Study performance

3.1 Prospective Registry

Every pregnant patient with histological confirmed breast cancer should be informed about the registry and after written informed consent for data and biomaterial collection has been given; the registration form should be filled completely and sent to GBG. The registry is

independent of the treatment of the patients during pregnancy. Patients who have been diagnosed during pregnancy but not treated during pregnancy can be registered as well. In addition women younger than 40 years of age with breast cancer and are non-pregnant can be collected.

The anonymous data will be collected in a database.

3.2. Retrospective Registry:

A retrospective collection of already treated patients should be done as well

3.3 Translational Research

Tumour specimen and placenta tissue (paraffin embedded tissue) from patients with breast cancer during pregnancy and tumour specimen from young non-pregnant breast cancer patients should be collected after given written informed consent.

4. Therapy

A flow sheet of diagnosis and treatment is provided as a suggestion to guide the investigator but it is not compulsory to apply it.

5. Project-Management, Data-management

The GBG performs the Project-management of this trial. The central data collecion and the statistical analysis is done by the GBG.

6. Statistics

Data should be analysed in a descriptive way.

7. Funding

Funding will be guaranteed by the German Breast Group. Additional projects such as translational research will be funded within collaborative research such as DKTK and other grants.

8. Participants

All the hospitals/clinics and doctors interested in participating, located inside and outside Germany.

9. Publication

Publication will be performed according to the SOPs of the GBG.

Appendix:

1. Flow Chart for Therapy:

Fig 1 a: < 12-14th week of gestation at histological diagnosis

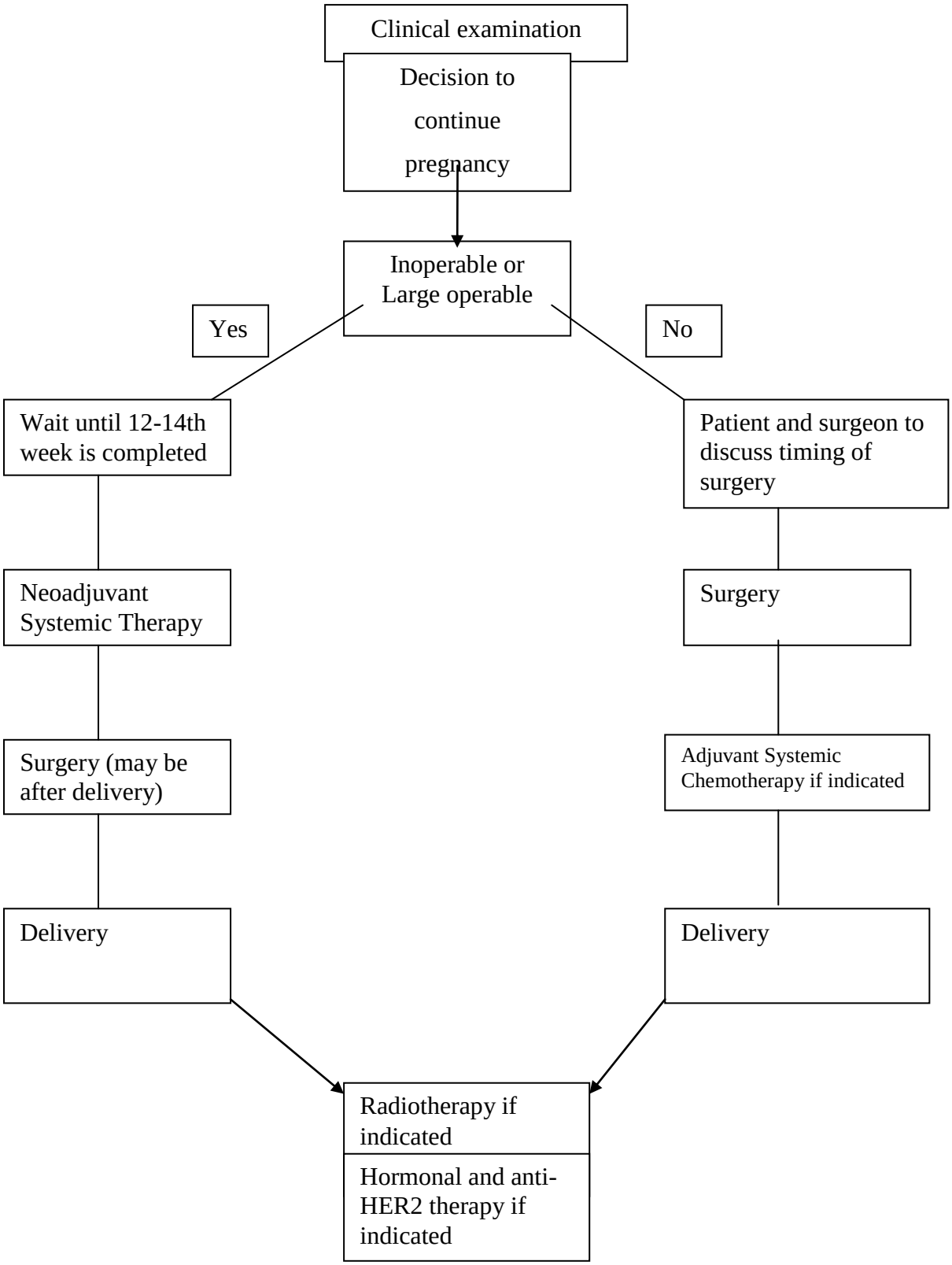

Fig. 1b: 12th -34th week at histological confirmed diagnosis

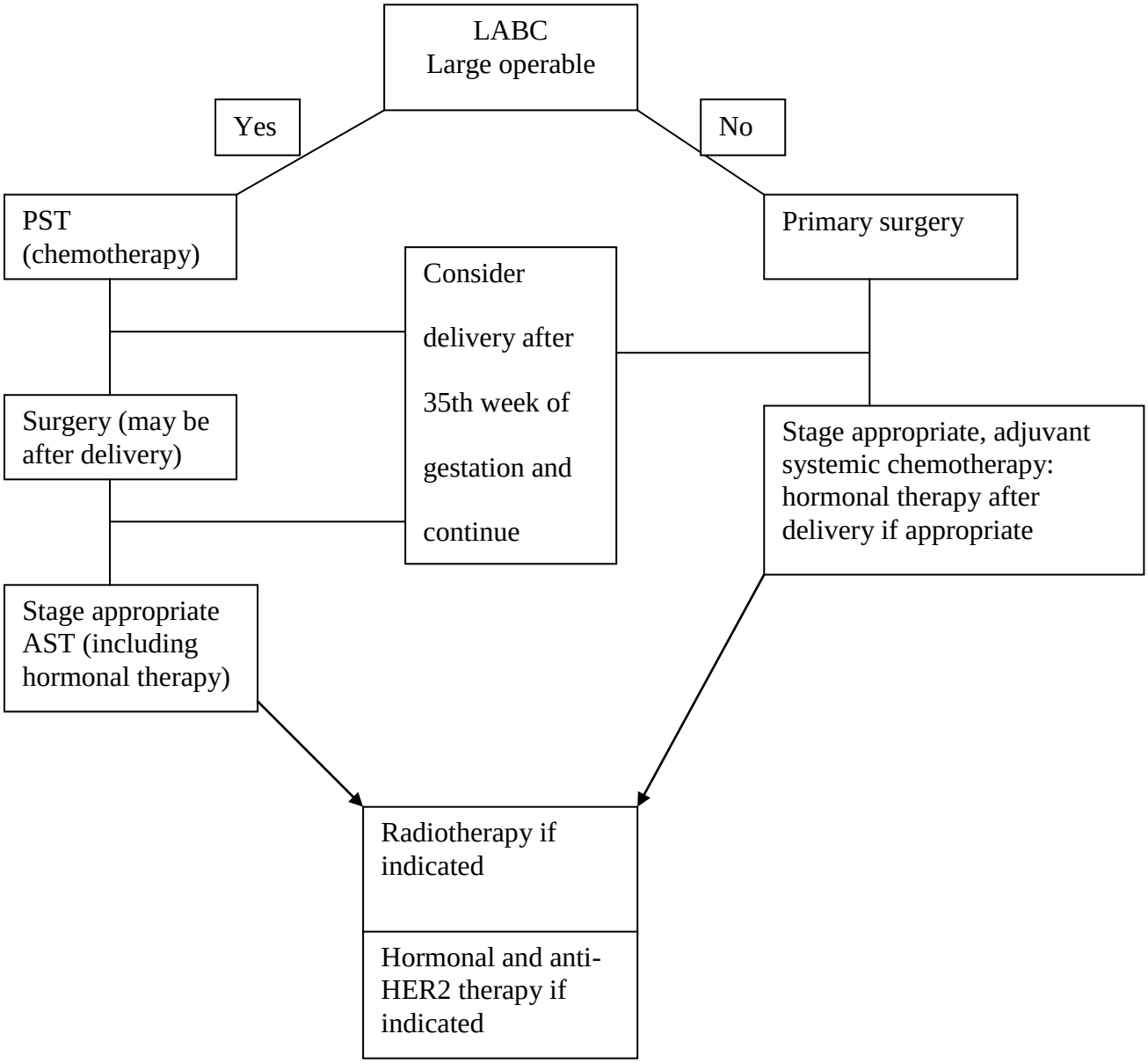

Fig. 1c: 34th week of gestation at histological diagnosis

In case of inflammatory or highly aggressive disease, the delivery should be immediately carried out. Otherwise, plan delivery when fetal maturation is appropriate and begin standard therapy thereafter.

2. Patient Information (Part I Pregnant patients):

Breast cancer in Pregnancy (BCP) Prospective and Retrospective Registry Study of the German Breast Group (GBG) for Diagnosis and Treatment of Breast Cancer in Pregnancy compared to young non-pregnant women

Dear Patient,

During your pregnancy a malignant tumour of the breast was diagnosed. The likelihood of developing breast cancer during pregnancy is very low but it has become more frequent during the last few years. In recent years based on the collection of data in registries such as this one, the knowledge increased and currently it is been recommended to treat as closely as possible according to non-pregnant women. Nevertheless, additional information is needs as treatment changes and because not all questions have been answered. Therefore the registry of "Breast Cancer in Pregnancy" will continue.

Tumour and placenta specimen (formaline fixed paraffin embedded FFPE) will be collected centrally for further investigations.

All this information will be gathered anonymously in a central database.. Your personal data will naturally not be recorded. Your name or other identifying material will not be made known if the results of this study are published for scientific purpose.

Your decision to take part in the registry study is entirely up to you. You may withdraw from the registry study at any time that you wish without having to give any reason or without having to suffer any consequences. There will be no further investigations conducted and data collected.

3. Patient informed consent:

Breast cancer in Pregnancy (BCP) Prospective and Retrospective Registry Study of the German Breast Group (GBG) for Diagnosis and Treatment of Breast Cancer in Pregnancy compared to young non-pregnant women

Name of Patient: _____
Address: _____

Name of Doctor: _____
Address: _____

I have been informed by my doctor of my disease. I understand that I am pregnant and am suffering from breast cancer. I understand that data shall be gathered concerning my pregnancy and my breast cancer diagnosis and treatment as well as the outcome of my child. I further understand that this data shall be stored anonymously.

I have been informed that I may withdraw from the study at any time without giving any reason and without suffering any consequences as regards to my further medical treatment

I have read and understood all of the information presented to me in this informed consent document.

I agree that blocks of the tumour and the placenta will be collected centrally:

yes☐ **no**☐

I voluntarily agree to participate in this study.

_____ _____
Place, date Signature of Patient

_____ _____
Place, date Signature of Doctor

Patient Information (Part II Non- Pregnant young patients):

Breast cancer in Pregnancy (BCP)
Prospective and Retrospective Registry Study of the German Breast Group (GBG)
for Diagnosis and Treatment of Breast Cancer in Pregnancy compared to young non-pregnant women

Dear Patient,

A malignant tumour of the breast was diagnosed. The likelihood of developing breast cancer during pregnancy is very low but it has become more frequent during the last few years.
In recent years based on the collection of data in registries such as this one, the knowledge increased and currently it is been recommended to treat as closely as possible according to non-pregnant women. Nevertheless, additional information is needs as treatment changes and because not all questions have been answered. Therefore the registry of "Breast Cancer in Pregnancy" will continue.
In parallel we will establish a control cohort of non-pregnant breast cancer patients below the age of 40. This is necessary to compare data and results from breast cancer patients diagnosed and treated during pregnancy with non-pregnant very young breast cancer patients, because the young age has an impact on treatment and outcome.

Tumour specimen (formaline fixed paraffin embedded FFPE) will be collected centrally for further investigations.

All this information will be gathered anonymously in a central database. Your personal data will naturally not be recorded. Your name or other identifying material will not be made known if the results of this study are published for scientific purpose.

Your decision to take part in the registry study is entirely up to you. You may withdraw from the registry study at any time that you wish without having to give any reason or without having to suffer any consequences. There will be no further investigations conducted and data collected.

3. Patient informed consent (Part II Non-Pregnant young patients):

Breast cancer in Pregnancy (BCP)
Prospective and Retrospective Registry Study of the German Breast Group (GBG)
for Diagnosis and Treatment of Breast Cancer in Pregnancy compared to young non-pregnant women

Name of Patient: _____
Address: _____

Name of Doctor: _____
Address: _____

I have been informed by my doctor of my disease. I understand that I am suffering from breast cancer. I understand that data shall be gathered concerning my breast cancer diagnosis and treatment as well as the outcome of it and data regarding previous and future pregnancies. I further understand that this data shall be stored anonymously.

I have been informed that I may withdraw from the study at any time without giving any reason and without suffering any consequences as regards to my further medical treatment

I have read and understood all of the information presented to me in this informed consent document.

I agree that blocks of the tumour will be collected centrally:

yes☐ **no☐**

I voluntarily agree to participate in this study.

_____ _____
Place, date Signature of Patient

_____ _____
Place, date Signature of Doctor

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