Tangential radiotherapy and electron beam intraoperative radiotherapy in pregnancy associated breast cancer

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Abstract
Pregnancy-associated breast cancer (PABC) is defined as breast cancer occurring at any time during pregnancy or lactation, or diagnosed within one year post-delivery. The diagnostic procedure should not impact the development of the fetus, but effective therapeutic treatment must take into account the possible effects of the therapy as well as the time required for development of the fetus. A diagnosis of cancer during pregnancy increases the complexity of not only the pregnancy, but also of the cancer treatment. Currently available data does indicate, however, that the pregnant patient diagnosed with breast cancer should receive optimal multidisciplinary treatment. The established therapeutic approach in pregnant women with breast cancer is problematic and not well developed. The main problem is the effect of the drugs on the developing fetus, including the possibility of later complications following exposure to anticancer drugs. Surgical resection is the mainstay of treatment for early breast cancer diagnosed during pregnancy. It is worth noting that breast-sparing surgery is not contraindicated in the first trimester of pregnancy, but because of the potential consequences of delaying radiotherapy, rarely used.

Key words: pregnancy, breast cancer, intraoperative radiotherapy

Introduction
Pregnancy-associated breast cancer (PABC) is defined as breast cancer occurring at any time during pregnancy or lactation, or diagnosed within one year post-delivery. PABC is a challenge in many respects; taken in connection with other issues it presents clinical difficulties. The diagnostic procedure should not impact fetal development, but effective therapeutic treatment must take into account the possible effects of the therapy as well as the time required for fetal development in order to ensure optimal fetal growth and lung maturity. In this way, a diagnosis of cancer during pregnancy increases the complexity of both the pregnancy and the cancer treatment.

The currently available data does indicate, however, that the pregnant patient diagnosed with breast cancer should receive optimal multidisciplinary treatment. Early termination of pregnancy has been found not to improve the outcome of patients with PABC [1].

Approximately 0.2% to 2.6% of all breast cancer cases occur in women during pregnancy (PABC) [1, 2]. Whether or not pregnancy adversely affects the prognosis remains a matter of debate. I still do not have a complete understanding of the relationship between pregnancy and the development of breast cancer. Some studies have shown a worse prognosis for cases of PABC [3-6], while other researchers have found similar survival rates compared to the control group of non-pregnant patients [7-10].

A study was conducted on a large group of 447 pregnant women and 865 non-pregnant women diagnosed with breast cancer. The aim of this study was to compare survival rates between women with PABC and women with breast cancer who were not pregnant. A summary of the results has demonstrated similar survival rates for patients with primary breast cancer diagnosed during pregnancy as compared to non-pregnant female patients with breast cancer, when taking into account known prognostic factors [11].

The therapeutic approach currently considered optimal for cases of pregnant women with breast cancer is problematic and not well developed. The main problem is the effect of the drugs on the developing fetus, including the possibility of later complications from exposure to anticancer drugs. Surgical resection is the mainstay of treatment for early breast cancer diagnosed during pregnancy. Modified radical mastectomy is the standard of care in the first trimester of pregnancy; breast-conserving surgery (with dissection) can be carried out, but preferably in the second and third trimesters [12, 13].

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While breast-conserving surgery is not contraindicated in the first trimester of pregnancy, it is rarely used because of the potential consequences of delaying radiotherapy which is not recommended during pregnancy.

Treatment of breast cancer using two opposing fields is now rarely used as a stand-alone radiotherapy or even as part of the external course of radiotherapy. Measurements of the dose to the fetus resulting from tangential breast radiation fields during pregnancy have been reported [14, 15]. These studies, however, do not provide data for fetal dose estimation because they were focused on the treatment of individual patients. In addition, several studies suggest an assessment of fetal exposure during the whole pregnancy based on information on the doses at the periphery tangential fields [16, 17]. Both sets of studies, however, lack information on the estimation of the dose at different gestational ages. Researchers have been limited by the assumption that the embryo can be represented by a single point. This may be an acceptable practice for estimating the dose to the fetus during the first weeks post-conception when the size of the embryo is minimal; however, in advanced gestational age, growth of the fetus may cause significant variations in the photon doses that are dispersed throughout it [18].

A study has provided reliable data to estimate the dose to the fetus resulting from tangential breast radiation fields in the first, second, and third trimesters of pregnancy [19]. In this study, radiation doses were measured in anthropomorphic phantoms simulating the geometry of pregnant women in the first, second, and third trimesters of pregnancy. Medial and lateral irradiation fields were then generated using a 6-MV X-ray beam. Finally, dose measurements were performed using thermoluminescent dosimeters.

For a course of radiotherapy, delivering 50 Gy to the breast tumor, the dose to the fetus during the first trimester of pregnancy was 2.1-7.6 cGy, depending on the size of the applied field and the distance between the germ and the primary radiation field. The dose to the fetus in the second and third trimesters of pregnancy was 2.2-24.6 cGy and 2.2-58.6 cGy, respectively.

<table>
<thead>
<tr>
<th>Field size (cm²)</th>
<th>First trimester (cGy)</th>
<th>Second trimester (cGy)</th>
<th>Third trimester (cGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.5 × 11.0</td>
<td>2.1-2.9</td>
<td>2.2-7.5</td>
<td>2.2-16.8</td>
</tr>
<tr>
<td>6.0 × 12.5</td>
<td>2.8-3.9</td>
<td>2.9-10.4</td>
<td>3.3-23.8</td>
</tr>
<tr>
<td>8.0 × 14.0</td>
<td>3.5-5.1</td>
<td>3.7-13.9</td>
<td>4.0-34.7</td>
</tr>
<tr>
<td>10.0 × 16.0</td>
<td>4.4-6.2</td>
<td>4.7-18.2</td>
<td>5.0-45.2</td>
</tr>
<tr>
<td>11.5 × 18.0</td>
<td>5.2-7.6</td>
<td>5.9-24.6</td>
<td>6.5-58.6</td>
</tr>
</tbody>
</table>

Total radiation dose to conceptus, resulting from tangential breast irradiation at the first, second, and third trimesters of gestation. Conceptus dose values correspond to a tumor dose of 50 Gy.

Doses for the fetus due to breast radiotherapy using two opposing fields can be estimated with sufficient accuracy for the first, second, and third trimester pregnancy, using the data presented in this paper.

The decision to deliver therapeutic radiation during pregnancy is rare. It is estimated that only 4000 women in the United States are treated annually with radiation therapy during pregnancy for various types of cancers [20].

The International Commission on Radiological Protection (ICRP) considers a dose of radiation to the fetus of less than 1 mGy to be negligible, and that doses of a few mGy are permitted and are not associated with an increased risk of birth defects [21].

**Electron beam intraoperative radiotherapy (ELIOT)**

The use of the full dose (21 Gy by isodose 90%) of ELIOT following breast-conserving surgical treatment delivered to one fraction of postmenopausal women in the context of partial breast irradiation has yielded encouraging clinical results. The procedure eliminates the need for a long course of postoperative RT and drastically reduces the radiation dose to normal tissues and organs. Additionally, treatment under direct visual control in place of the removed tumor improves the topography and eliminates the geographical error [22, 23].

In connection with this promising method of conserving therapy for cases of breast cancer found in the seminal work [24], a study was performed to provide dosimetric data associated with the safety of this procedure in the case of pregnant women.

**Radiotherapy technique**

Four selectable radiation energy levels (Novac 7: 3, 5, 7 or 9 MeV; Liac: 4, 6, 8 or 10 MeV) at high dose (about 10-20 Gy per minute, depending on the size of the beam energy and applicator) were administered during breast-conserving surgery with a mobile linear accelerator installed in the operating room so that the exposure time was 1-2 min. The beam was collimated by a sterile applicator with a cylindrical Plexiglas thickness of 5 mm and a diameter of from 3 to 12 cm. For breast cancer, the size of the applicator selected was typically from 4 to 6 cm in diameter. Source to skin distance of 80 cm for Novac7 and 60 cm for Liac was used. Shields
made of aluminum and lead diameter of 5-8 cm (6-8 mm thick) was placed between the breast and the remainder of the thorax as a shield protecting the internal tissues of the chest wall.

**In vivo dosimetry**

Thermoluminescent radiation detectors (TLDs) in the form of microdiod (TLD 100, Harshaw, USA) were used. TLDs were provided in two places on the skin of each patient: subdiaphragmatically on the irradiated side (10-15 cm from the applicator) and at the medial suprapubic position (about 30-40 cm from the applicator). For the uterus, TLDs were placed in a sterile tip thin close-ended flexible catheter (length 30 cm, the outer diameter of 2 mm). The catheter was introduced into the uterus by a gynecologist when the patient was under general anesthesia, immediately in front of the chest. Written informed consent for the procedure was obtained for each patient. A protective apron (equivalent to 2 mm of lead) was placed on the patient’s abdomen in order to block most of the scattered electrons from an accelerator.

Detector TLDs from the entire lot were calibrated with respect to the absorbed dose in water 6 MeV electron beam, generated by a conventional linear accelerator (Clinac 2100, Varian, USA). Twenty-four to forty-eight hours after irradiation, the detectors were analyzed manually by a commercial TLD reader and software (Model 3500 reader and WinREMS W, Saint-Gobain Crystals and Detectors, USA). The readings were converted to absorbed dose calibration using a suitable reader. After radiotherapy the TLDs were sterilized by heating for 1 hr at 400°C, followed by 16 hours at 80°C.

The overall degree of uncertainty of the measurements was estimated to be approximately ± 15% (standard deviation). The analyzed data were scaled to the assigned dose of 21 Gy. The average dose to the subdiaphragmatic skin was 3.7 mGy, (SD ± 2.4 mGy, range 1-8.5 mGy) while the mean dose at the medial suprapubic position was 0.9 mGy, (SD ± 0.5 mGy, the range of 0.3-2 mGy); the average dose in utero applicator was 1.7 mGy, (SD ± 0.8 mGy, range 0.6-3.2 mGy).

The mean ratio of the dose to the surface of the intrauterine subdiaphragmatic was a dose of 0.6 (SD ± 0.4, range 0.16-1.58) and in the two cases (13%), the intrauterine dose was slightly higher than the subdiaphragmatic dose on the surface.

The mean ratio intrauterine dose suprapubic area was 2.08 (SD ± 1.1, range 0.8-3.88), with a slightly lower dose than the dose intrauterine suprapubic area.

These results suggest that the dose may be considered subdiaphragmatic measured on the surface at the upper limit of the dose absorbed by the fetus. In general, doses were measured independent of the irradiated breast quadrant and size applicator.

After 30 weeks, the fetus is much closer to the chest than in the earlier stages, so ELIOT is less secure.

During the first and second trimester of pregnancy, intraoperative radiotherapy with ELIOT may be considered part of a breast-conserving approach. Considering the second term in the initial experiment in young women suggests that the dose of 12 Gy boost intraoperatively may be administered during pregnancy, if the time between the boost and conventional RT whole breast after birth does not exceed 16 weeks [25, 26].

We recognize, however, that this was not a clinical trial in partial breast irradiation in young women during pregnancy, although it may be acceptable under certain conditions (such as during pregnancy and when the tumor is small). The possibility of induced early delivery may be considered, depending on fetal weight and maturity. During the first trimester, when the fetus is in the lower part of the pelvis, a full dose of ELIOT (21 Gy) may be accepted.

**Recommendations** [24]:

- For the 1st trimester: ELIOT full dose (21 Gy),
- 2nd and 3rd trimester: intraoperative boost dose of 12 Gy + conventional whole breast RT later,
- After 30 weeks: conventional RT after parturition.

An informed decision in the best interests of both the mother and the fetus must be made with the active involvement of multidisciplinary patients in all stages of the process. The aim of therapy is to maximize the possibility of a cure for the cancer while minimizing the risk to the fetus.

**References**


