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Breast cancer radiotherapy in pregnancy

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Summary

Adjuvant radiotherapy for breast cancer reduces the risk of locoregional recurrence, distant disease and improves the survival of breast cancer patients. The incidence of breast cancer in pregnancy is constantly increasing, and it is expected that an increasing number of pregnant breast cancer patients will require radiation. Ionizing radiation can have a harmful effect on the fetus, which depends on the radiation dose and the gestational age of the fetus at the time of exposure to ionizing radiation. Pregnancy is not an absolute contraindication to radiotherapy for breast cancer, provided that radiation is carefully planned and appropriate protection is used.

KEYWORDS: *breast cancer, radiotherapy, breast cancer in pregnancy*

INTRODUCTION

Adjuvant radiotherapy for breast cancer reduces the risk of locoregional recurrence, the occurrence of metastases, and prolongs the overall survival of patients with breast cancer. Clearly, the effect is not the same for all subgroups of patients. In principle, it is always performed after a sparing procedure and in the presence of metastases in the axillary lymph nodes. It is performed after surgery and after chemotherapy and concurrently with hormonal therapy and anti-HER2 therapy. Radiation should start within 12 weeks of surgery and within 6 weeks of the end of chemotherapy(1).

Breast cancer in pregnancy is defined as cancer diagnosed during pregnancy and within a year of delivery, and is relatively rare. According to literature data, breast cancer occurs in one in 3000 to 10,000 pregnancies(2). The observed increase in the incidence of breast cancer in pregnancy over the past few decades is probably a combination of an increase in the incidence of breast cancer at a younger age and the postponement of pregnancy, i.e., pregnancy at a later age(1,2).

HARMFUL EFFECTS OF IONIZING RADIATION ON THE FETUS

Pregnant women should avoid any form of radiation, diagnostic or curative, due to the harmful effects of the radiation itself on the fetus. Ionizing radiation causes the formation of free radicals and cell damage, which ultimately leads to mutations in the genome. In the absence of the results of prospective studies on the effect of radiation of pregnant women on the fetus, we rely on the results of animal tests, retrospective analyzes of the effects of radiation used for diagnostic purposes on the morbidity of children, and data on malformations, tumors and mortality of children who

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were exposed to radiation in utero during incidents such as the nuclear disaster in Chernobyl and the detonations of atomic bombs in Japan. However, many of the congenital malformations observed in animal studies were not observed in Japanese atomic bomb victims who were exposed to ionizing radiation in utero(3).

The effects of radiation are divided into deterministic and stochastic. The severity of deterministic effects depends on the radiation dose, and there is a threshold for their occurrence below which they do not occur. Examples of deterministic effects in an unborn child are congenital malformations, mental retardation, and fetal death. Stochastic effects are those for which there is no dose threshold because even small doses of radiation can cause these effects, although the probability of their occurrence is lower at lower doses. Here, we can take the development of a malignant disease several years after exposure to radiation as an example. The probability of the occurrence of a malignant disease increases with the total radiation dose, but there is no threshold below which the risk is zero(4).

Among the most important effects of radiation in unborn children are various physical malformations such as growth retardation, organ malformations, mental retardation, germ cell mutations, and death. It is important to note that radiation in utero can induce the development of malignant diseases later in childhood, such as leukemia(4,5).

The effect of radiation on the fetus, in addition to the radiation dose, depends on the stage of pregnancy in which the radiation was administered. If the exposure occurred in the earliest stages of development (up to the 2nd week), it may lead to the inability of the fetus to implant and to a lethal outcome. The fetus is most sensitive to radiation during the organogenesis phase (weeks 2-8). Even at doses of 0.2 Gy, there is a possibility of malformations of developing organs and growth retardation. In the period from the 8th to the 25th week after conception, the central nervous system is particularly sensitive to the effects of radiation, and a dose of 0.1 Gy can cause a decrease in intelligence quotient. With exposure to a dose greater than 1 Gy, the risk of severe mental retardation is about 40%(6).

The lower threshold of a potentially safe dose is not clearly defined, and the fetus is more sensitive to the effects of radiation in the earlier stages of pregnancy/embryonic development. The dose at which radiation effects on fetal development can be expected to occur is considered to be between 0.1 Gy and 0.5 Gy during the first 14 weeks of pregnancy and at least 0.5 Gy after the 14th week of pregnancy.

After the 25th week of pregnancy, no such significant effect of radiation on development has been reported; however, exposure is still not recommended due to the risk of premature birth and stillbirth(5,6).

In addition to the effects of radiation that are evident very early, it is worth mentioning the effects that may appear years later. Due to direct and indirect damage to DNA in cells and the consequent occurrence of mutations, children exposed to radiation in utero are more likely to develop malignant diseases in childhood than children who were not exposed. These include leukemia, lymphoma, and tumors of the central nervous system. The incidence is 2-3 cases per 1000; a radiation dose to the fetus of 0.01 Gy increases the risk of tumor formation by about 40%. An increased risk of childhood tumors has also been observed with the use of diagnostic tests during pregnancy; the risk increases by 6% per Gray. The lifetime risk of developing a fatal tumor caused by radiation at a dose of 0.01 Gy is approximately 1 in 1700. Without radiation, the lifetime risk of developing a fatal tumor is about 1 in 5(7,8).

Finally, radiation can lead to the aforementioned germ cell mutation that can manifest itself in the next generation(7,8).

BREAST CANCER RADIATION DURING PREGNANCY

In women of childbearing age, radiotherapy is most often used in the radical treatment of breast tumors, cervical tumors, and lymphoma(6).

The sensitivity of fetal tissues to radiation and the risk of the aforementioned radiation effects depend on the radiation dose received by the fetus, its intensity and distribution, as well as the stage of pregnancy/gestational age of the fetus(5).

In adjuvant radiation for breast cancer, the target radiation volume is the breast/chest wall

with or without lymphatic drainage – supraclavicular fossa, axilla, nodes along the internal mammary artery. The usual prescribed dose to the breast is 46 – 60 Gy with conventional fractionation at a daily dose of 2 Gy per day or equivalent using daily doses greater than 2 Gy. Since the radiation intensity decreases with the square of the distance from the source, it should also be kept in mind that during pregnancy, the fetus moves closer to the diaphragm, or the target radiation volume – the breast, due to growth. In the first trimester of pregnancy, it is estimated that with breast radiation at a dose of 50 Gy, the fetus receives 0.04 Gy to 0.15 Gy. If radiation is carried out in the third trimester of pregnancy, the total dose to the fetus can reach 2 Gy, with a note that the risk of congenital defects as a result of radiation at this gestational age is minor(7).

The radiation risk to the fetus is therefore determined by the radiation parameters and the stage of pregnancy. The radiation dose received by the fetus depends on the distance of the fetus from the target volume and the size and location of the target radiation volume. The dose received by the fetus is a consequence of internal scattered radiation, scattered radiation from collimators and blocks, and radiation leakage from the accelerator head. Internal scattered radiation depends on the radiation source, the size of the radiation field, and the distance of the radiation field from the fetus(9). An accurate estimate of the dose to the fetus in locoregional radiotherapy is possible using radiation parameters and gestational age, but it also depends on the patient's physical constitution. Thus, the radiation dose to the fetus will be lowest in tall and slim patients and highest in obese and short patients(10). In principle, the fetal dose should not exceed 0.1 Gy, which is considered acceptable during the first half of pregnancy. This dose can still be reduced by using additional protection of the pelvic/abdominal area and can be reduced to half or even a quarter by using protection, e.g., 4-5 HVL (*half-value layer*) of lead around the patient's abdomen(10,11).

Radiation effects such as mental retardation and organ malformations occur at fetal doses higher than 0.1 – 0.2 Gy, which are generally not achieved with radiation during pregnancy if the target volume of radiation is far from the fetus and protective measures are taken against radiation that *leaks* from the collimator head and scattered radiation. These protective measures also reduce the risk of childhood tumors(12).

A valuable option is ultra-hypofractionated radiation with a dose of 36 Gy in 5 fractions administered over a week. The total radiation dose is lower compared to conventional fractionation and is administered within a week, which allows for safer delivery of radiation concerning gestational age compared to radiation that would last 3 or 5 weeks(13).

There is literature data on the normal outcome of pregnancies after radiotherapy. In one patient, breast irradiation was performed in the third trimester of pregnancy using tangential fields with wedges, photon energy of 6MeV, dose of 50 Gy with lead shielding of 9 mm on the abdomen and a lead block under the breast. The estimated dose to the fetus was 0.14 – 0.18 Gy. In the second patient, radiation was performed in the first trimester of pregnancy with photons of energy 6 MeV in tangential fields without wedges at a dose of 46 Gy. The cumulative dose to the fetus was estimated at 0.039 Gy. In the third patient, radiation was performed for breast cancer in the second trimester at a dose of 50 Gy. Lead shielding of 4 cm thickness was used, and the measured dose to the fetus was 0.16 Gy. Without shielding, it would have been 0.28 Gy.

In principle, radiation therapy can be performed in pregnant women for most tumors located far from the pelvis/abdomen, such as breast, brain, head and neck tumors, and supradiaphragmatic Hodgkin's disease, with careful radiation planning and the use of radiation protection. The use of wedges or lead blocks under the radiation field is not recommended due to possible scattered dose(14).

In non-pregnant patients who have undergone radical radiation, it is recommended to delay pregnancy for one year(1,13).

If breast cancer is diagnosed in the last trimester of pregnancy, it is possible to postpone radiation until after delivery without significantly compromising disease control. It should be noted that radiation also causes changes in the nipple and milk ducts, which can significantly complicate lactation. A study of 2,582 patients showed that bilateral lactation was possible in one in four patients after radiation(15).

PALLIATIVE RADIOTHERAPY IN BREAST CANCER PATIENTS

When deciding on palliative radiation for breast cancer patients, the location of the metastases should be taken into account. For example, metastases in the pelvic or lower abdominal region are too close to the fetus. However, a single dose of 8 Gy can safely irradiate bone metastases, including those located within lumbar vertebrae, in early pregnancy. Later in pregnancy, metastases that are located distant from the fetus, such as in the brain, can be irradiated(6).

STEREOTACTIC RADIOTHERAPY

There is a special group of patients with oligometastatic disease in whom radiotherapy targeted directly toward metastases (metastases-directed radiation therapy) could be performed. In early pregnancy, stereotactic irradiation of liver metastases can be performed(16).

CONCLUSION

In conclusion, radiotherapy for breast cancer during pregnancy is not absolutely contraindicated. In the event that the radiation oncologist considers it to be in the best interest of the patient to perform breast cancer radiation during pregnancy, it is necessary to discuss with the patient the possible risks and harms to both the patient and the developing fetus. If breast cancer is diagnosed in the third trimester of pregnancy, it is recommended to postpone radiation until after delivery.

The use of additional protection can significantly reduce the exposure of the fetus to ionizing radiation. Before the start of the radiation treatment, it is necessary to accurately calculate the radiation dose, taking into account both the patient's anatomy and the effect of additional protection to predict possible side effects and provide information to the parents. The dose to the fetus should be lower than the dose threshold for the occurrence of deterministic effects. In addition to optimizing the radiation technique, close cooperation with medical physicists and the radiation protection team is necessary.

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Sažetak

Radioterapija raka dojke u trudnoći

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Adjuvantna radioterapija raka dojke smanjuje rizik nastanka lokoregionalnog recidiva, udaljene bolesti te poboljšava preživljenje bolesnica s rakom dojke. Incidencija raka dojke u trudnoći je u stalnom porastu te je za očekivati sve veći broj trudnih bolesnica s rakom dojke kod kojih je potrebno provesti zračenje. Ionizirajuće zračenje može imati štetan učinak na plod koji je ovisan o dozi zračenja te gestacijskoj dobi fetusa u vrijeme izloženosti ionizirajućem zračenju. Trudnoća ne predstavlja apsolutnu kontraindikaciju za provođenje radioterapije raka dojke uz pažljivo planiranje zračenja i primjenu odgovarajuće zaštite.

KLJUČNE RIJEČI: *rak dojke, radioterapija, rak dojke u trudnoći*