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Radiotherapy During Pregnancy: Literature Review

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Abstract:
The diagnosis of cancer during pregnancy is a sensitive and uncommon situation, occurring in approximately 1 out of every 1000 pregnancies. Due to the high vulnerability of the developing embryo and fetus to ionizing radiations, careful consideration should be given to the treatment of these tumors. In this article, we provide a review of existing literature and offer recommendations regarding the use of radiotherapy during pregnancy. The risks associated with radiation exposure depend on the stage of pregnancy at the time of irradiation. The primary risks involve the possibility of malformations, such as microcephaly and mental retardation, in the offspring. There is also a potential risk of radiation-induced cancer in the unborn child. If the irradiation is limited to areas above the diaphragm, radiotherapy can often be administered to pregnant women without posing a risk to the fetus. However, if irradiation below the diaphragm is required, therapeutic termination of the pregnancy may be recommended. In all cases, when radiotherapy is proposed, it is important to estimate the dose delivered to the fetus using a phantom method, which should be confirmed by in vivo measurements. Conformational radiotherapy is the preferred technique because it delivers a lower dose to the fetus, except in tumor locations where other techniques such as intensity modulated radiotherapy treatment are recommended.

Keywords: Radiotherapy, Pregnancy, Fetus, Radiation techniques

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1. Introduction

The identification of cancer during pregnancy is an infrequent event, with a prevalence of approximately one in every 1,000 pregnancies [1]. The likelihood of cancer during pregnancy appears to rise with the mother's age when she has her first pregnancy.

Regarding the estimated occurrences of breast cancer, cervical cancer, and Hodgkin's disease, all of which typically necessitate radiotherapy as part of their treatment, the approximated incidences are as follows: breast cancer ranges from 1 in every 3,000 to 1 in every 10,000 pregnancies, cervical cancer ranges from 1 in every 1,000 to 6,000 pregnancies, and Hodgkin's disease ranges from 1 to 2 in every 10,000 pregnancies [1,2].

2. Risks of radiotherapy on the embryo and fetus:

The risks associated with radiation exposure vary depending on the stage of pregnancy. The available data primarily come from animal studies and observations of individuals who survived atomic or nuclear disasters such as Hiroshima-Nagasaki and Chernobyl. The effects of radiation vary based on the age of the fetus and the dose of radiation received.

2.1 Preimplantation period (within the first week after conception): During this period, known as the "all-or-nothing" law, embryonic cells exhibit a high sensitivity to ionizing radiation, which can result in failed implantation or embryonic death. Studies conducted on rodent fetuses indicate a 1 to 2% risk of embryonic death following exposure to 0.1 Gy of radiation [5].

2.2 Organogenesis (weeks 2-7): Organogenesis refers to the stage of embryonic development during which the formation of organs takes place. The primary risk during this phase is the occurrence of malformations, particularly neurological ones like microcephaly, but without mental retardation [3].

2.3 First trimester (weeks 8-15): During the first trimester, exposure to radiation as low as 0.1 Gy can lead to mental retardation in children aged 10 to 11 years. In addition to microcephaly, mental retardation was observed in cases of exposure [6].

2.4 Second trimester (weeks 16-25): In utero exposure during the second trimester poses risks such as microcephaly, malformations, mental retardation, cataracts, and sterility. However, these risks are relatively lower, with a 2% risk of mental retardation below 0.5 Gy [6].

2.5 Third trimester (weeks 26-delivery): During the third trimester, there is still a risk of mental retardation or malformations when the radiation dose exceeds 0.5 Gy [4]. However, the risk appears to be relatively low, with a prevalence of less than 5% [6].

2.6 Radiation-induced cancers in children: Unlike deterministic effects, the risk of radiation-induced carcinogenesis following in utero exposure is considered a "stochastic" effect. It means that the risk of occurrence is proportional to the dose received, but the severity is independent. Wakeford et al. conducted a review using case-control study data from the Oxford Survey of Childhood Cancers (OSCC) and Japanese cohort studies of survivors of the Hiroshima-Nagasaki atomic bomb [7]. As early as 1956, Stewart et al. reported a connection between in utero irradiation and childhood cancers [8]. The risk of developing cancer after irradiation during the first trimester is higher than the risk during the second and third trimesters (2.5 times higher). Even at a low dose of 0.01 Gy, there is a risk of cancer-related death before the age of 10 years, with a relative risk of 1.5. The majority of radiation-induced cancers in children are leukemia [7,9].

2.7 Maternal fertility risks: The ovary is an organ that exhibits a heightened sensitivity to ionizing radiation. The degree of sensitivity depends on the age of exposure, with increased sensitivity observed at older ages coupled with lower ovarian reserve. Studies have shown that the LD50 (lethal dose for 50% of cells) for ovocytes is below 2 Gy [10]. The probability of fertility declining below 1 to 2 Gy is directly proportional to the ovarian reserve. In cases where only supradiaphragmatic irradiation is administered, fertility is typically not compromised if there is an adequate ovarian reserve and no systemic treatment given that affects the gonads. However, if subdiaphragmatic irradiation is required, an assessment of the radiation dose received by the ovaries becomes necessary. If a patient desire to conceive in the future, it is recommended to consult a fertility-sparing team before undergoing radiation therapy.

3. Radiotherapy and pregnancy:

The development of human embryos and fetuses is highly sensitive to ionizing radiation. Abnormalities can occur when the fetus receives doses exceeding 0.2 Gy. Therefore, it is recommended to limit the dose received by the embryo or fetus to not exceed 0.1 Gy when a pregnant woman requires radiation treatment. The fetal dose primarily depends on internal scattered radiation, which is influenced by factors such as the total delivered dose, number of monitor units (MUs), beam size, distance between the uterus and beam edge, specific characteristics of the radiation machine, and radiation transmitted by collimators, filters, blocks, or other accessories. The use of additional protection measures can reduce transmitted radiation by two-fold or four-fold [11].

Several studies on irradiation for breast, head and neck cancers, and Hodgkin's lymphoma specifically in the supra-diaphragmatic region during pregnancy have reported acceptable fetal doses when all necessary precautions are taken [12]. In all cases, the recommended treatment should be discussed in a multidisciplinary consultation panel involving a gynecologist-obstetrician. Additionally, the decision of continuing or terminating the pregnancy should be considered based on the gestational age and prognosis of the disease.

3.1. Characteristics specific to cancer types during pregnancy

3.1.1. Breast cancer

Breast cancer diagnosed during pregnancy often tends to be detected at a later stage and, consequently, at a more advanced stage due to pregnancy-related changes in breast morphology such as enlargement and engorgement [13]. Furthermore, as the age of women conceiving increases, the incidence of breast cancer diagnosed during pregnancy is on the rise, currently estimated at one in 3000 pregnancies [14,15]. However, the prognosis for breast cancer during pregnancy is not worse than that for breast cancer diagnosed in non-pregnant women, and therefore patients are encouraged to continue their pregnancy to full term [13,14].

Typically, radiotherapy is administered after surgery and adjuvant chemotherapy, which can be given during the second and third trimesters. In cases where surgery and chemotherapy are necessary, radiotherapy can usually be postponed until after childbirth. However, the administration of radiotherapy during pregnancy becomes a concern when chemotherapy is not recommended and waiting until after delivery is not feasible due to the time elapsed since surgery. It has been estimated that if a dosage of 50 Gy is prescribed to the chest wall, the fetus will receive a dose of 0.05 to 0.15 Gy [16], which still falls below the recommended thresholds. However, at an advanced gestational age, this dosage can be increased to 2 Gy (Fig. 1) and should therefore be evaluated prior to radiation treatment.

3.1.2. Cervical cancer

Cervical cancer is the most commonly diagnosed gynecological cancer during pregnancy, with an incidence ranging from 1 per 10,000 to 4 per 100,000 pregnancies [2,17]. Standard treatment for locally advanced cervical tumors involves pelvic irradiation, which is not compatible with carrying the pregnancy to full term. Therefore, gynecological cancers during pregnancy should always be managed at specialized centers, where the available treatment options can be carefully evaluated on an individual basis, taking into consideration both the stage of the disease and the stage of the pregnancy, while ensuring the best possible cancer prognosis.

3.1.3. Hodgkin's and non-Hodgkin's lymphomas

Hodgkin's and non-Hodgkin's lymphomas represent approximately 6% and 5% of cancer cases diagnosed during pregnancy [18]. If the disease is limited to the supradiaphragmatic region, consolidation radiotherapy may be considered following chemotherapy, taking into account prognostic factors and a prior assessment of fetal radiation dose. In the majority of cases, prescribed doses of 20 to 30 Gy are deemed safe for continuing the pregnancy [19]. In cases of subdiaphragmatic lymphomas, radiotherapy is contraindicated during pregnancy, and the decision to terminate the pregnancy should be carefully considered on an individual basis, taking into account the necessity of radiotherapy administration.

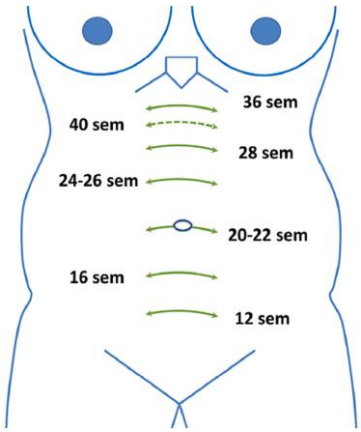

Figure 1 Fetal growth according to gestational age (Sem: weeks).

3.2. Radiation doses and minimizing fetal radiation dose

3.2.1. Source of secondary ionizing radiation:

The majority of radiation dose received by the uterus, in the case of supra-diaphragmatic irradiation, is derived from the peripheral dose, also known as the out-of-field dose. This can be attributed to three factors:

- Accelerator head leakage: Leakage radiation originating from the accelerator head, passing through screens, and interacting outside the treatment field. The amount of leakage radiation depends on the number of monitor units delivered and the modulation factor, which is typically limited to 0.1% of the maximum dose on the central axis.
- Scatter from collimator and beam modifiers: Scatter radiation generated within the accelerator head, passing through the field opening, and interacting with the patient outside the treatment area. This is distinct from the primary beam, which interacts within the treatment area.
- Internal patient scatter: Scatter radiation generated from the treatment beam in regions distant from the treated area inside the patient [20].

The peripheral dose is influenced by several factors, including energy, field size, distance from the uterus to the edge of the radiation field, treatment depth, and the presence of beam modifiers.

3.2.2. Use of additional shielding:

The implementation of additional shielding can enhance fetal protection during radiation therapy. These shields are typically constructed from heavy materials and must be tailored to the beam angles. It is crucial to ensure that they are easy to handle and safe for both staff and patients. However, it is important to note that the use of a lead apron by patients is ineffective due to the high energy of the beams. Examples of shields: Bridge over the patient, Bridge over the patient or Mobile protections [11].

4.Irradiation techniques

4.1. Intensity-modulated conformal radiotherapy (IMRT)

These techniques encompass static and dynamic intensity-modulated conformal radiotherapy (IMRT), as well as volumetric modulated arc therapy (VMAT) and helical tomotherapy. To minimize scattered radiation and its penetration depth, it is recommended to use the lowest energy possible. Employing energies below 10 MV reduces secondary neutron production resulting from interactions in the primary collimator, jaws, or multi-leaf collimator. Compared to three-dimensional conformal radiotherapy, IMRT can yield higher dose gradients at the field edge, but distant doses may be increased due to a higher number of monitor units, contributing to increased head leakage.

In volumetric modulated arc therapy, the issue of out-of-field dose distribution arises due to the increased number of entry ports. However, while a larger volume of out-of-field tissue may be irradiated, the dose itself is not necessarily higher. Helical tomotherapy necessitates a significant number of

monitor units, but extensive head shielding, low-energy beams, and dynamic jaw modes can reduce doses outside of the primary beam [20].

The dose delivered to the fetus is proportional to the number of monitor units. Although IMRT optimizes dose distribution, it requires 1.5 times more monitor units than conformal radiotherapy, making it less suitable for use during pregnancy [21,22].

4.2. Stereotactic treatments

Stereotactic treatments can be administered using a conventional linear accelerator equipped with a multi-leaf or cone collimator, as well as with CyberKnife or Gamma-knife systems. The distribution of off-beam dose varies depending on the specific treatment, particularly when non-coplanar portals are used. In treatments delivered by linear accelerators, out-of-field doses are generally lower due to lower modulation and lower prescribed dose levels compared to CyberKnife treatments. Gamma-knife treatments deliver high doses immediately at the field's edge due to the energy generated by cobalt [20].

4.3. Proton therapy

In proton therapy, the out-of-field dose is primarily composed of neutrons (approximately 90%), with photons contributing only 10%. The doses near the field's edge are lower compared to those delivered by other radiation therapies. Passive scattering proton therapy involves externally-produced neutrons as a significant component of the distant dose. The neutron production increases with energy and depends on the materials encountered and the production line design. Pencil Beam Scanning (PBS) proton therapy results in lower neutron production and consequently a reduced distant dose [23,24].

4.4. MRI-guided radiotherapy

There is a lack of literature data on the use of magnetic resonance imaging (MRI)-guided irradiation in pregnant women. The teratogenic risk of radiofrequency waves on the fetus remains uncertain. However, the recent development of low-field fetal MRI presents an interesting option for fetal imaging compared to ultrasound [25]. Despite this, due to the limited data and precautionary concerns regarding the risk of fetal toxicity associated with MRI, MRI-guided radiotherapy should not be offered to pregnant women.

5. Conclusion

Radiotherapy during pregnancy is technically feasible, a dose of 0.1 Gy to the fetus should not be exceeded. Feasibility should be confirmed using phantom measurements (assessment of the fetal dose). Fetal growth must be taken into account and the technique must be adapted to minimize the dose to the fetus by using: three-dimensional conformal radiotherapy, dynamic filter, image-guided, radiotherapy with low-energy imaging, etc.

Subdiaphragmatic radiotherapy should not be performed during pregnancy so it should be stopped or radiotherapy delayed until after delivery, if possible.

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