MODERN RADIOTHERAPY IN CANCER TREATMENT DURING PREGNANCY

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Abstract

Breast cancer, gynecological malignancies and lymphomas are the most frequently diagnosed tumors in pregnant women. The feasibility of radiotherapy during pregnancy remains a subject of debate and clinicians continue to hesitate on this approach, trying to avoid radiotherapy in most cases. Since the 1990s, several technological advances, including intensity modulated and image guided radiation delivery, have been implemented in radiation oncology to improve the radiation treatment in terms of effectiveness and tolerability. It remains uncertain which short- and long-term health effects the radiation exposure of the fetus may have through advanced radiotherapy techniques. The present systematic literature review aims to summarize the limited current evidences of the feasibility and clinical results of "modern" radiotherapy procedures for the treatment of the most frequently diagnosed tumors in pregnant women.

Introduction

The incidence of cancer during pregnancy is a rare event and affects 0.07-0.1% of all pregnancies[1]. Breast cancer followed by gynecological malignancies and lymphomas are the most frequently diagnosed tumors in pregnant women[1]. For each of these oncologic diseases, radiation therapy (RT) is a cornerstone in the multidisciplinary treatment strategy and has a positive impact on long-term survival of non-pregnant women[2-8]. While the treatment of cancer by RT in pregnant patients is aimed at improving the survival of the mother, special considerations are necessary to maximally reduce possible health impairments of the fetus. Since the 1990s, technological and technical improvements in modern RT, such as 3D-conformal RT (3DCRT), intensity modulated RT (IMRT) or volumetric modulated arc therapy (VMAT), have been introduced into clinical practice. These advanced radiation techniques pursue the goal of delivering high doses to the tumor, while sparing the surrounding tissues or organs at risk in order to improve RT in terms of effectiveness and tolerability[10-13]. Furthermore, image-guided RT techniques using on-board cone-beam computed tomography (CBCT) have been developed to ensure a precise dose delivery[9]. Modulated-RT does not necessarily result in exposure to a higher dose, because these RT-approaches are designed to limit the high dose to a more restricted volume. On the other hand, the disadvantage of modulated therapies remains the exposure of a larger volume to low doses. Starting from this background, the adoption of advanced RT techniques in pregnant women affected by cancer could increase the probability of short and long-term adverse events for the fetus and, thus, during pregnancy, modulated RT has been cautiously used only in strictly selected cases.

The present systematic literature review aims to summarize the current clinical evidences of the feasibility and clinical results of "modern" radiotherapy procedures for the treatment of the most frequently diagnosed tumors in pregnant women.

Fetal exposure and health effects from ionizing radiation during pregnancy

Fetal adverse events

Gestational age (weeks of amenorrhea) does not correspond to embryonal age (weeks or days from fertilization). Adverse events following fetal irradiation vary according to post-implantation week and dose of irradiation. Specifically, during the organogenesis phase (i.e. weeks 2-7) the main effect is the occurrence of gross malformation and small head size (SHS) without mental retardation. Increased risk of growth retardation and SHS was reported for doses superior to 0.5 Gy[15,16]. Normally, the brain develops between weeks 8 and 15 (first trimester of gestation), thus, in this phase, the main potential effects could be SHS and mental retardation. Mental functioning seems not to be impaired for doses below 0.1 Gy, while doses higher than 0.3 Gy might affect its functioning. The incidence of mental retardation for doses between 0.1 and 0.49 Gy is estimated for 6% of the cases[17].

The effects of irradiation in the second trimester (weeks 16-25) are similar to those of the previous trimester. In particular, the main risks include mental and growth retardation, SHS, cataracts, sterility and secondary malignancies. The incidence of mental retardation is 2% for doses below 0.5 Gy[18]. The risk of sterility and neurological diseases is smaller than for irradiations during the previous trimester[19]. Finally, for exposures during the third trimester (weeks>25) the risk of mental and growth retardation and SHS seems low. Nevertheless, evidence for these adverse events were reported for exposures<0.5 Gy[20,21].

Table 1 summarizes the main adverse events following fetal irradiation according to the post-conception time.

Childhood and adult cancer risk after in-utero exposure

No new phantom models studies exists for radiation in pregnancy using new RT-techniques. For this reason, we will focus this section on medical exposures from diagnostic x-rays rather than therapeutic radiation exposures.

Deterministic effects describe a cause and effect relationship between radiation and certain side-effects. They are also called non-stochastic effects and have a threshold, below which the effect does not occur. The stochastic effects may occur by chance without any threshold level of dose, whose probability is proportional to the dose and whose severity is independent of the dose. In the context of radiation protection, the main stochastic effect is cancer induction[21].

A relationship between childhood malignancy and pre-natal diagnostic X-ray irradiation of the child was first reported by Stewart[22,23] in the large Oxford survey of childhood cancers (OSCC). The dependence of the risk on the number of films exposed was highly significant and adequately described by a linear relationship[24]. Wakeford and Little[25] summarized the efforts to derive the fetal doses and obtained an excess relative risk of around 50 Gy^{-1} for childhood cancer below the age of 15 years, leading to an excess absolute risk coefficient for incident cases of about 8% Gy^{-1}. They cautioned that the uncertainties related to these estimates were appreciable, and there were reasons to believe that this coefficient could be a systematic overestimate. The great majority of the intrauterine exposures occurred during the third trimester of pregnancy for obstetric reasons. Nevertheless, the relative risk of childhood cancer associated with exposure during the first trimester was found to be a statistically significant ~2.5 times greater

than that for the third trimester, implying an increased sensitivity to radiation-induced childhood cancer early in pregnancy. While the OSCC is the largest and most comprehensive study for medical exposures from diagnostic X-rays, many other case-control studies are consistent with an increased risk of childhood cancer and leukemia[26,27].

However, in the atomic bomb survivors of Hiroshima and Nagasaki, by far the largest cohort study of intrauterine exposures, only 2 cases of childhood cancer in the first 14 years of life were observed among 1630 children exposed in utero, and no case of leukemia[28]. Since background cancer rates are very small, single cases can have a large influence on risk estimates. Boice and Miller[29] reviewed the arguments for a causal association of intrauterine radiation exposure and subsequent cancer risk. A comparison of the risk estimates between the OSCC and the atomic bomb survivors concluded that the risk estimates of both studies are compatible when taking the uncertainties into account[25]. In summary, the evidence of increased childhood leukemia and solid cancer risk after intrauterine exposure is convincing, however, the uncertainties about the magnitude of risk are significant.

The same atomic bomb survivors constitute the most significant source of information on adult cancer risk after intrauterine exposure. Delongchamp and colleagues[30] analyzed solid cancer and leukemia mortality over the age range 17-46 years. Among the 807 in utero survivors with doses over 10 mSv, eight deaths from solid cancers and two cases from leukemia were recorded. The risk for solid cancer was statistically significant with an excess relative risk (ERR) of 2.4 Sv^{-1} (95%CI: 0.3; 6.7). The magnitude of this excess did not substantially differ from that of those exposed during the first 6 years of life with ERR=1.4 Sv^{-1} (95%CI: 0.4; 3.1). Subsequently, Preston and collaborators analyzed the incidence of solid cancer in the atomic bomb survivors with seven additional years of

follow-up for persons with a range of 12-55 years[31]. Ninety-four cancers were observed among 2452 survivors in utero at the time of bombing. The statistically significant risk was ERR=1.3 Sv^{-1} (95%CI: 0.2; 2.8). Risk for exposure during childhood was somewhat higher with ERR=2.0 Sv^{-1} (95%CI: 1.4; 2.8), however, the difference between these estimates was not statistically significant. The analysis suggested a decrease of relative risk with increasing age, both for individuals exposed in utero and during childhood, and the decrease was more marked for those exposed in utero than as children. No variation in the ERR by trimester of exposure was observed for those exposed in utero, and the risk estimates were identical.

In summary, adult cancer risk was found to increase statistically significant with radiation exposure of the uterus. Risk estimates were similar for intrauterine exposures and for exposures during early childhood. There was no clear evidence for a difference of risk on the trimester of exposure. Compared to childhood cancer risk after intrauterine exposures, the lower relative risk estimates and the decrease of risk with age indicate that adult lifetime cancer risk is likely to be considerably less than projections based on relative risks derived from childhood cancer studies.

Clinical Results: fetal exposure and health effects from radiotherapy techniques

Search strategy and selection criteria for clinical studies

We searched PubMed, EMBASE and Cochrane library for articles published in English language between 1 January 1990 and 1 January 2018. Search terms included ("Pregnancy" [MeSH Terms] OR "Pregnancy" [All Fields]) AND ("radiotherapy" [MeSHTerms] OR "radiotherapy"[All Fields] OR ("cancer"[All Fields] AND "radiotherapy"[All Fields]) OR "cancer radiotherapy"[All Fields]).

We identified additional references by doing a manual search of the references of all included articles. Two independent reviewers (VF and MR) identified potential studies and exported them to an electronic reference management software program (Ref Works, version 2.0). VF and MR determined eligibility by first reviewing the title and abstract and then the full article. Disagreements were solved by consensus; if consensus was not achieved, then a third author (RM) provided an assessment of eligibility.

A study was included if it reported on cancer-related RT for breast cancer, gynecological malignancies and lymphomas in pregnant patients. All studies were analyzed for study design, number of patients, age (mean and range), type of RT, radiation dose, gestational phase and outcomes in terms of adverse events for the fetus. Exclusion criteria were: articles with no detailed information regarding clinical outcomes, review articles, editorials, articles not written in English language. Figure 1 depicts the study selection approach.

Breast Cancer

The literature regarding modern breast RT during pregnancy is limited and most experiences come from retrospective case series (see Table 2). The AAPM Task group-36 recommends that a threshold of 50cGy should always be maintained for the fetal dose of RT during pregnancy[15]. Special external abdominal leaf shields have been evaluated to further reduce the fetal dose up to 50-58%[15,32,33]. Taken together, whole breast irradiation is considered as a relatively safe treatment option during the first two trimesters, as the distance between the radiation fields and the fetus is sufficient and fetal doses do not exceed threshold doses associated with organ malformations.

Literature is scarce, but successful treatments with good maternal and fetal outcome using modern RT techniques have been reported during pregnancy. Specifically,

Antypaset al.[34] treated a patient in the first trimester of pregnancy using 6MV photon beam 3D-conformal RT to a total dose of 46Gy in 20 fractions. The fetal dose was estimated to 39mGy using in-vivo and phantom measurements. A report from New South Wales (Australia) described a RT treatment in the second trimester gestation[35]. The patient underwent neoadjuvant RT of the breast and lymphatic pathways with 50Gy in 25 fractions with 6MV photons. With shielding using lead covering and blocks, the fetal dose measured with thermo-luminescent dosimeters was 140-180mGy. Similarly, van der Giessen[36] reported on a case treated during 24-29 weeks of gestation with a fetal dose of 160mGy during breast RT with 50Gy and proper lead shielding. In contrast, Antolaket al.[37] reported a significantly lower fetal dose of 15mGy with abdominal shielding. Of note, this patient suffered from recurrent breast cancer in the area of the mastectomy scar and received chest wall irradiation using electron beams (5-8MeV). In the analysis of cancer during pregnancy by Van Calsteren et al.[38], two breast cancer patients treated with RT in the second trimester are included. They were treated with 46Gy and 50Gy to the chest wall and breast, respectively. Unfortunately, no fetal doses are reported. In terms of fetal outcome of these examples, all pregnancies were carried to term. There was no elective termination of pregnancy or in utero death, and all children were in good health at birth without congenital abnormalities. However, long-term follow-up is missing in most cases. Two children had no evidence of neuro-developmental impairments at 36 and 60 months follow-up, respectively[39,40].

To minimize risk-exposure, a possible RT strategy is a localized dose escalation using an intraoperative boost to the tumor bed[41]. The European Institute of Oncology, in Italy, evaluated the feasibility of electron beam intraoperative RT (ELIOT) as an anticipated boost using in-vivo dosimetry in fifteen non-pregnant patients[42]. All cases received 21Gy intraoperative RT with electrons using a mobile linear accelerator. Dosimetric

measurements showed a mean dose in utero of 1.7mGy (range 0.6-3.2mGy) with shielding. In 2011 the first pregnant patient was treated at 15th week of gestation. The estimated dose to the fetus was 0.84mGy. Therefore, ELIOT can be considered as a treatment option for anticipated boost therapy during the first or second trimester and postpone whole breast RT after the childbirth. One throwback is the longer time interval between boost delivery and whole breast irradiation, which could increase the risk of local recurrence. Nevertheless, in cases were chemotherapy is administered, this time interval stays within regular time lines[43].

In summary, from the experiences here reported, using the previously described specific precautions, 3DCRT or IORT approaches could be considered in selected cases for breast cancer irradiation during pregnancy. Due to the lacking of clinical data, to date, intensity modulated RT and other modern techniques seem to be not recommended.

Gynecological tumors

Pelvic irradiation during pregnancy is a major challenge because, regardless of the utilized technique, fetal exposure dose is always significant and leads to serious adverse effects for the fetus. With regard to the tumor site, cervical cancer is the most common gynecological cancer during pregnancy, while vulvar, endometrial and ovarian cancer are extremely rare and usually managed with upfront surgery. In contrast, invasive cervical cancer can also be treated with definitive RT or radio-chemotherapy in non-pregnant patients.

Concerning pregnant-patients affected by gynecological cancers, when pelvic RT is performed with the fetus in utero, spontaneous abortion will invariably occur, usually within 3 to 6 weeks[44,45]. If cervical cancer is diagnosed after the 20th week of gestation, a

treatment delay can be considered in the interest of the fetus without significantly affecting the prognosis[46].

According to the inclusion criteria of the present review, a single study was found. Specifically, Soodet al[47] performed a case-control analysis of 26 women with cervical carcinoma who were diagnosed during pregnancy and treated primarily with RT. Patients were treated with external beam 3D-CRT (mean dose, 46.7 Gy) followed by brachytherapy. Two patients with Stage IA2 disease were treated in the third trimester; in these last cases, infants had an uncomplicated neonatal course. On the other hand, seven patients underwent radical hysterectomy due to positive pelvic nodes; thus, abortion of the fetus was performed. Finally, three patients diagnosed during the first trimester were treated with radiation with the fetus in situ, and all had spontaneous abortions 20-24 days after the start of radiation (after a mean dose of 34 Gy). A statistical analysis revealed no differences in terms of overall survival between the pregnant group and the control arm.

In summary, from the few experiences here reported, RT in pregnant patients affected by gynecological malignancies remains contraindicated due to the high risk of abortion and fetal damage.

Hodgkin and Non-Hodgkin Lymphoma

A limited number of experiences have evaluated the role of RT in lymphomas in pregnant women, as described in Table 3. Woo et al.[49] reported on 16 women diagnosed with early stage sclero-nodular HL who received a supra-diaphragmatic radiation treatment of the mediastinal, axillar, cervical lymph node levels or a mantle-field irradiation with a RT dose between 35 and 40 Gy. Four to five half-value layers of lead were used to shield the uterus during RT and the dose to the fetus was estimated in the range from 14 to 55 mGy,

for treatments with 6 MV photons. All pregnancies were carried to term and all children were physically and mentally normal.

Similar results have been published in an investigation focusing on fifty pregnant women diagnosed with HL. Of the fifty pregnancies, there were forty deliveries (two of which were stillbirths), five miscarriages and four therapeutic abortions. Clinical data were collected from 22 cases of 38 live-births. Of the 22 babies who were exposed to multimodal therapy in utero, one was exposed to chemotherapy alone, two babies were exposed to a combination of chemotherapy and RT during and after the first trimester six cases received RT during the first trimester of pregnancy. Finally, seven cases received the treatment after the first trimester. The authors found no differences between the babies born to women with HL when compared to the mother-risk matched controls in terms of birth weight, mean gestational age or method of delivery. In a single case, a malformation of hydrocephaly was observed in a patient who was diagnosed with HL before conception and treated with chemotherapy alone in the first trimester[49].

More recently, Evens et al.[50] investigated the effects of chemotherapy, RT or a combination of both in HL and NHL in a series of ninety pregnant women. In this population of study, RT was administrated in four cases with a diagnosis of stage I and IIA with a dose prescription of 25-30 Gy. No spontaneous abortions, neonatal intensive care unit admission or malformations were reported.

In summary, from the experiences here reported, RT in pregnant patients affected by HL and NHL seems to be feasible even if no specific use of modern RT-techniques has been explored.

Discussion

Oncologic treatment of pregnant women is always an interdisciplinary challenge and should be managed by an expert team of radiation-oncologists, gynecologists, neonatologists, medical oncologists, psychologists and others professional figures with the aim to find an individual treatment plan in consensus with the patient/couple. It is well known, that pregnant patients should be treated similarly to non-pregnant cancer patients and that a comparable survival can be achieved[51]. Treatments in hospitals with obstetric high-care units are strongly advocated[52]. It is recognized that an elective pregnancy interruption has not always a beneficial effect on survival[53]. In breast cancer, for example, an international consensus recommendations support a gestation stage-based treatment approach, where the treatment can be postponed until post-partum in near-term patients at more than 37 weeks of gestation[54].

The main aim of the current literature review was to assess the role of RT in the modern era concerning the management of the most frequently diagnosed tumors in pregnant women[1]. Clinical data are very limited and the main experiences since the 1990s derive from retrospective series. Thus, several concerns remain unsolved regarding the potential use of RT in the modern era for cancer treatment during pregnancy. In terms of dose reduction to healthy tissue (and to fetus) advanced techniques seem to be rather contra-productive because of low dose bath by IMRT or RT-rotational approaches. Additionally, image-guided RT does not help to reduce dose to the pregnancy in utero. On board CBCT itself may increase radiation burden. In addition, significant dose contribution for fetus in utero could arise from scattering, for which no valid model exists. Thus, several clinical considerations need to be evaluated. More deeply, concerning the management of breast cancer in pregnancy, modified radical mastectomy or breast conserving surgery with removal of axillary lymph nodes or sentinel node biopsy is safely applicable during all trimesters of pregnancy[55]. The scenario seems to be more

complicated if breast cancer is diagnosed during the first trimester. Besides the option of an induced abortion, surgery and RT are the only treatment options, as chemotherapy is contraindicated. One rationale for mastectomy is to avoid postoperative RT after breast conserving surgery. In cases of breast-conserving surgery, it remains an open question if RT should be administered during pregnancy or should be delayed to after delivery.

In this last clinical scenario, the use of hypo-fractionated breast RT during pregnancy could be a potential option to reduce the overall treatment time. Unfortunately, no clinical data are available in literature.

Looking at the limited current evidences of the feasibility and clinical results of "modern" radiotherapy, the need of RT during pregnancy might be limited to the few patients that will not receive adjuvant chemotherapy. For all the others, chemotherapy during pregnancy allows a safe postponement of RT after delivery.

Some studies focused on the estimation of fetal dose exposure during breast RT using computed dose estimations or phantom measurements. Fetal dose during breast irradiation using a tangential field technique is mainly influenced by patient scatter and out-of-field doses of direct radiation leakage and collimator scattering of the head of the linear accelerator[56,57].

The use of physical wedges in tangential breast irradiation can significantly increase scattered radiation and should therefore be avoided[21]. Physical wedges are commonly used to improve dose uniformity to the target volume[21].

Similarly, the use of intensity-modulated techniques showed a five-fold increase of fetal dose as compared to 3D-CRT, because higher monitor units (MUs) are generally used. MUs represent a measure of the dose delivered by a single beam of ionizing radiations[58].

Finally, during breast irradiation, the most important factors determining the fetal dose are the field size and distance from the radiation field. The absorbed dose by the fetus

increases with gestational stage, as the distance from the radiation field edge to the uterine fundus is narrowing by around a centimeter per week. Thus, it is of great interest to determine the expected change during the course of RT to give an estimate of the fetal dose[59]. The height of the fundus scan be estimated with the help of weekly ultrasound measurement or clinical examinations[32].

In contrast, it is a major challenge to irradiate the pelvic region for gynecological tumors in pregnant women, as preservation of fetal life is not really possible. In this last clinical scenario, it has to be decided whether the treatment should be postponed until after delivery or whether elective termination of pregnancy should be chosen.

Finally, Hodgkin and Non-Hodgkin Lymphomas are very common haematological diseases in young women. Over the last decades, chemotherapy cycles have been shortened and RT volumes decreased, in order to reduce the risk of late side effects. This last strategy allowed decreasing the possible fetal exposure to ionizing radiation. In fact, the reported risk of mental retardation, growth retardation, secondary tumors and organ malformations in clinical practice seems to be very low. Obviously, the irradiation of supra-diaphragmatic disease represents the best clinical situation with regard to a possible exposure of the fetus to ionizing radiation.

Possible statements, within the present literature review, could derive from limited series (i.e. 22 patients diagnosed with breast cancer in pregnancy and 118 with lymphoma); therefore, there is a quite small fundament for any clinical recommendation. Apart from the crucial role of high-expertise centers in the management of pregnant patients, many efforts are needed to ensure safe RT options. New technologies such as heavy particle therapy could also become a treatment option for pregnant women affected by cancer. Nevertheless, the uncertainties regarding the production of neutrons by heavy ions and the subsequent fetus exposure remain unclear[60]. The available clinical

experiences are scarse[61]. Undoubtedly, future investigations or prospective clinical trials will have to encompass important issues.

In summary, even if technological advances have been introduced into clinical practice, the role of RT during pregnancy in modern era needs specific precautions and it could be still considered only in selected cases of breast cancer and lymphomas. Due to the lacking of clinical data, the potential role of intensity modulated RT and other modern techniques remain uncertain.

In the absence of valuable data, a case-by-case assessment is needed to address concerns about potential risks for the fetus and the impact on the oncological outcome for the patient.

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Table 1. Effects of fetal irradiation according to the postconceptional time.

Post-conceptional week(s)	Embrional period 1	Organogenesis 2-7	First trimester 8-15	Second trimester 16-25	Third trimester >25
Effect					
Death	+++	+	+	-	-
Malformation	-	+++	+	+	-
Growth retardation	-	+++	++	+	+
Mental retardation	-	+	+++	+	-
Small head size	-	++	+++	+	+
Sterility	-	-	+	+	+
Cataracts	-	-	-	+	+
Neurological disease	-	+++	-	+	+
Malignant disease	-	+	+	+	+

- no effect; + demonstrated effect with small incidence; ++ demonstrated effect with average incidence; +++ high incidence.

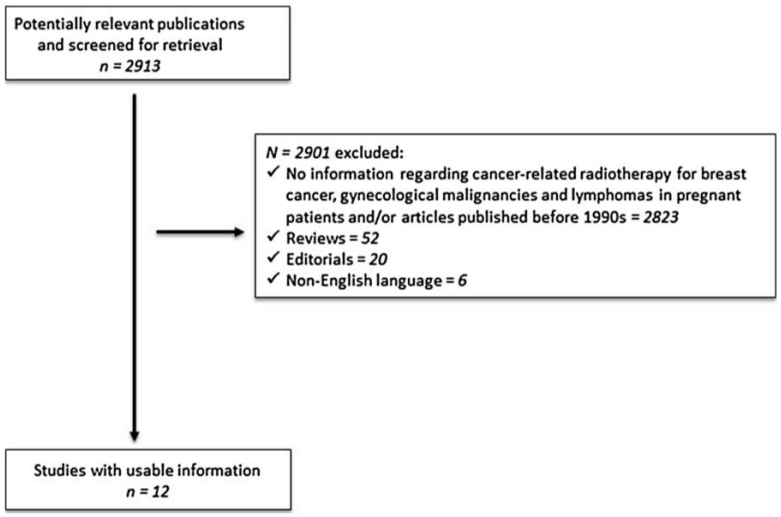

Fig. 1. Search strategy flowchart for the inclusion and exclusion of studies.