Pregnancy and Radiotherapy: Protecting Fetuses from the Effects of Radiation

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Abstract

Some pregnant women have cancer and need to receive radiotherapy treatment. However, radiotherapy can be dangerous, especially for the fetus. Radiation exposure can cause many harmful effects on the fetus, including potential death, growth impairments, and many neurological effects like mental retardation, severe intellectual disability, brain injury, loss of IQ points, and more. Such symptoms can hinder the offspring's ability to succeed later on in life after birth. Pregnant women who require radiotherapy often have to compromise between their health and the health of their child. Making radiotherapy safer and finding ways to treat already existing radiation exposure symptoms in fetuses is extremely important. Pregnant patients should feel confident in the safety and effectiveness of their treatment and should not have to choose between their health and the health of their child. The objective of the research is to find methods to increase the safety of radiotherapy, especially when it comes to protecting the fetus from the effects of radiation exposure, and also find ways to treat already existing symptoms of radiotherapy.

Introduction

Imagine someone is going to be a mother. Imagine someone is pregnant and is expecting a child. However, they also have cancer and need to receive radiotherapy treatment for it. A radiation dose of one Grey (Gy), which is defined as absorption of 1 joule of radiation energy per kilogram of matter, can kill 50% of embryos, and a dose of five Gy can kill 100% of embryos within 18 weeks. Such a small amount of radiation can be fatal to developing fetuses, and radiotherapy is a type of cancer treatment that relies on ionizing radiation. Even if radiotherapy does not result in the death of embryos, it still has many side effects that hinder the development of future individuals. Some of the side effects include mental retardation, impaired visual function, neurological injury, and loss of IQ points. A decrease in IQ points increases the risk of severe intellectual disability. The mother is torn between choosing her health or the well-being of her future offspring. What if she could have both? What if professionals could refine radiotherapy so it is safer for the patient's future child? Radiotherapy can be improved by utilizing particular devices and treatments, implementing aspects of other treatments into radiotherapy, creating strict regulations for radiotherapy procedures, and tailoring treatment for pregnant individuals. The purpose of the paper is to inform the reader how radiotherapy can be improved when treating pregnant patients to prevent harmful effects on the fetus. The paper will discuss how each of these ideas will upgrade the safety of radiotherapy.

Devices and Treatments

Professionals can use various medical devices and treatments during radiotherapy to protect the patient and the fetus from radiation or cure radiation-induced injury. One device is the Scale Mail

Armor for Radiation Therapy (SMART). SMART armor is made up of scale mail, which reduces radiation exposure to the breast area during radiotherapy for breast cancer (Butson, 2017). Macinely Butson, the inventor, created the device by interweaving scales with copper because she found it more effective than lead for shielding. The use of SMART armor demonstrated a reduction in radiation exposure by up to 80% (Butson, 2017). The Food and Drug Administration (FDA) approved the invention, meaning that it fits the standard of being safe and effective. Professionals can remodel SMART armor for pregnant patients to protect the region of the fetus. The use of SMART armor will reduce the amount of exposure the fetus receives during treatment. Another medical procedure that can benefit the fetus is the intranasal administration of human mesenchymal stem cells (hMSCs). An experiment conducted on mice reveals that hMSCs effectively repair brain injury and improve brain function without posing risks to the lives of mice with glioma, a malignant tumor of the glial tissue of the nervous system. It also protects against inflammation, oxidative stress, and neuronal loss (Soria et al., 2019). Because the hMSCs are effective in mice, they will likely benefit humans since mice are genetically similar to humans. Professionals can administer hMSCs to newborn babies that were affected by radiotherapy exposure. Doing so will treat any neurological injuries and will reduce the chances of the baby growing up with any mental disabilities. hMSCs should exist in the treatment room as a backup in case the fetus experiences neurological harm from radiotherapy treatment. Another backup treatment is hyperbaric oxygen treatment (HBOT). A study exploring the effects of HBOT revealed that the symptoms of all the tested patients were either improved or stabilized after the experiment (Chuba et al., 2000). Although the patients exhibited no severe side effects related to HBOT, four patients ended up dying because of tumor progression. Even though HBOT is not perfect for treating neurological symptoms, it demonstrated improvement in the patient's condition. Volumetric modulated arc therapy (VMAT) and image-guided radiotherapy serve a benefit also. Techniques like VMAT arcs and image-guided radiotherapy provide precise dose conformation to target volumes while minimizing radiation exposure to surrounding healthy tissues (Sergieva et al., 2023). The techniques contribute to reduced toxicity and improved long-term cure rates. VMAT arcs and image-guided radiotherapy enable personalized treatments based on clinical and anatomical parameters, thus contributing to higher survival rates and improved quality of life for patients (Sergieva et al., 2023). Using these techniques will make radiotherapy treatment safer for the pregnant patient and the fetus.

Aspects of Other Treatments

Another way radiotherapy can be made safer is by implementing aspects of other types of treatments into radiotherapy. One of those treatments is Tumor Treating Fields. Tumor Treating Fields use low-intensity electric fields to treat cancer. Electric fields differ from electric currents, ionizing radiation, or magnetism and act as a force on objects with electrical charges (Doyle, 2012). In cancer, the fields interfere with the division of rapidly multiplying cells by stopping the formation of vital protein chains. Tumor Treating Fields pass through transducers attached to a field generator that creates an artificial electrical field around cancer cells, and the procedure disrupts the division process and kills or ceases the formation of unhealthy daughter cells. The fields do not affect normal non-dividing cells. Tumor Treating Fields are incredibly efficient in treating cancer. A study reveals how a patient with Glioblastoma multiforme (GBM) experienced tumor regression and longer life expectancy due to Tumor Treating Fields therapy. Also, clinical trials proved that Tumor Treating Fields can extend survival without the side effects caused by chemotherapy (Doyle, 2012). Not only are tumor treatment fields effective, but they are also much safer than standard chemotherapy and radiotherapy treatments. If professionals use low-intensity electric fields during radiotherapy treatment, the fetus will be less likely to develop the harmful side effects of regular radiotherapy. Also, doctors can administer various chemotherapy drugs after organogenesis, a phase of embryonic development, for up to three weeks before the patient gives birth (Schwab et al., 2023). Although chemotherapy itself as a treatment can be harmful to the patient, not to mention the fetus, administering some chemotherapy drugs during a specific phase of pregnancy decreases the chance of the drugs harming the fetus.

Regulations for Radiotherapy

It is also vital that there are strict regulations put in place for radiotherapy treatment procedures to ensure the safety of both the patient and the fetus. Professionals should apply the principles of “Time-Distance-Shielding” to reduce exposure (Lakhwani et al., 2018). The principles are: reduction of exposure time, increased distance from the radiation source, and proper shielding from radiation. Medical doctors treating pregnant radiotherapy patients should strictly follow “Time-Distance-Shielding” principles so that the treatment is as safe as possible. Furthermore, organs like the thyroid, breasts, and gonads should be protected during treatment (Lakhwani et al., 2018). Not only is it crucial to provide shielding, but professionals must ensure the protection of vital organs to avoid damage. The belly should especially be protected, considering that is where the fetus is. Regulations should be in place requiring essential areas to be covered. In addition, doctors need to ensure that the protection devices they use shield the patient and the fetus effectively from radiation. Unfortunately, there may be cases where such precautions might not successfully protect the fetus from radiation. There is no one-size-fits-all approach, and some fetuses might be more vulnerable to radiation-induced harm than others. In these instances, professionals should conduct radiotherapy treatment post-delivery (Schwab et al., 2023). Radiotherapy should be avoided during iatrogenic preterm delivery because it is a significant risk factor for long-term impacts on the child (Schwab et al., 2023). It is best to delay treatment after the patient gives birth and is no longer carrying the child inside of her. If the patient urgently needs to receive radiotherapy and cannot wait until post-delivery, surgery during pregnancy is a possible option, preferably during the second trimester of pregnancy (Schwab et al., 2023). Of course, there should be regulations for that as well. Professionals should closely examine the condition and the fetus and effectively determine the best course of action. If they decide that surgery during pregnancy is the way to go, doctors should make sure they do the surgery adequately and during the appropriate stage of pregnancy. It is also necessary that the regulations are direct and clear so that there is no confusion about how to follow them. Creating and enforcing proper treatment regulations is crucial in ensuring the safety of pregnant patients and their fetuses.

Specialized Treatment

As mentioned before, there is no one-size-fits-all approach to radiotherapy treatment, especially during pregnancy. Radiotherapy treatment should be tailored for pregnant patients to benefit the mother and the fetus. Professionals should adjust it by regulating the radiation dosage and treatment based on the patient's condition. Professionals can minimize the dose by delaying radiotherapy treatment until a later stage of pregnancy, calculating the needed dosage before the patient undergoes treatment, and modifying the treatment plan to ensure the fetus receives less radiation exposure (IAEA, 2023). Medical professionals should regulate such factors depending on the urgency of treatment and the sensitivity of the mother and the fetus. The type of cancer, its stage, biology, and timing of diagnosis are critical factors to consider (Schwab et al., 2023). Each type of cancer varies in severity and treatment needs, so doctors should adjust treatment plans based on the type of cancer diagnosis of the patient. Doctors should manage cancer treatment during pregnancy to benefit the overall well-being of the mother and the offspring (Ring et al., 2005). Doctors should find a method of cancer treatment that does not require sacrificing an individual's health for the health of their child. Radiotherapy treatment must be safe and beneficial for both the patient and her fetus. Visual assessments are a good way for professionals to decide the treatment plan for pregnant individuals. One study concludes that recognizing visual impairments is crucial for early intervention programs to protect or improve the visual and developmental outcomes of preterm infants (Ramenghi et al., 2010). Visual assessments help recognize visual impairments of fetuses. Analyzing a fetus' current brain health will help decide the optimal treatment procedure. Visual assessments will aid doctors in determining the sensitivity of the fetus. If the fetus is in bad condition before the treatment, professionals will know that they need to further restrict the amount of radiation exposure. Knowing the sensitivity will also help patients decide how long they should wait to receive treatment or if they should receive it all based on their needs. Analyzing visual assessments and neuroimaging in newborns provides valuable information regarding the relationship between brain structure and function in early life, which is necessary for cognitive development. (Ramenghi et al., 2010). Visual assessments are beneficial in providing insightful information on a fetus' or newborn's brain health. Furthermore, they are advantageous in analyzing the neurological development of fetuses, thus helping to determine the amount of sensitivity regarding radiation exposure. Radiotherapy treatment must be specialized for each patient with the help of visual assessments and other methods to ensure the best possible outcome for the patient and her child.

Primary Research and Analysis

Although the literature review provided insight into ways to improve radiotherapy safety for fetuses, primary research was necessary to build off the data and analyze more intricate effects of radiotherapy-related treatments. The sources included literature review only offered summaries of studies, whereas a more thorough analysis would allow for a deeper glimpse into more specific and exact data. An in-depth primary analysis would reveal the specific conditions for a particular result, variations among experimental outcomes, and other factors. For primary research, four articles were reviewed for a meta-analysis. Each of the data tables from the articles are located in the appendix. The articles used for the primary meta-analysis are “WHO Framework for strengthening and scaling-up services for the management of invasive cervical cancer," “Radioprotectors and Radiomitigators for Improving Radiation Therapy: The Small Business Innovation Research (SBIR) Gateway for Accelerating Clinical Translation,” “Brochure for Physicians: Prenatal Radiation Exposure,” and “Advances in Radiotherapy.” The data from each of the articles is recorded in Table 1, Table 2, Table 3, and Table 4, respectively. The overall findings from each table are recorded in Table 5. Although the articles each focus on different aspects of radiotherapy, they all reveal crucial information about making radiotherapy safer. A meta-analysis was the most appropriate form of primary research since there was no access to lab equipment or radiotherapy-related drugs or devices to conduct an experiment and analyze detailed observations. However, using previously existing data from past experiments has allowed for the observation of various radiotherapy treatments without needing to run an experiment. The data from Table 4 demonstrates that radiotherapy is vital for treating various types of cancer and is effective. The table includes data on various cancer treatments for different kinds of cancer. The table also records the results of each

Summary of radiotherapy interventions in the management of cervical cancer

Intervention	Abbreviation	Procedure	Intent/advantage	Associated risks/ adverse events
External beam radiotherapy	EBRT	Radiotherapy delivered from a distance.	> Curative for small to large lesions in combination with BT and chemotherapy. > Palliative to control bleeding and/or pain.	> Infertility > Menopause > Vaginal dryness > Bowel, urinary, haematological and skin toxicity
Brachytherapy	BT	Radiotherapy delivered from a sealed radioactive source placed inside the vagina and uterus, close to the tumour.	> Curative for small to large lesions in combination with EBRT.	> Vaginal stenosis; vaginal dryness > Radiation proctitis > Bowel and bladder toxicity > May require anaesthesia
Adjuvant radiotherapy	aRT	EBRT and/or BT administered after surgery.	> Eradication of any microscopic disease in the irradiated area.	> Bowel, urinary, haematological and skin toxicity

Table 1. Summary of radiotherapy interventions in the management of cervical cancer (From WHO Report (2020), [14]).

treatment depending on what it treated. Many of the treatments used have demonstrated a reduction in the risk of death and other cancer-related effects. Table 1 reveals the advantages of different types of radiotherapy. Some of the benefits are that radiotherapy is curative to small and large lesions, palliative to control bleeding and pain, and can eradicate microscopic diseases in irradiated areas. Professionals cannot completely ignore radiotherapy in cases of pregnancy. Radiotherapy is vital for treating cancer patients. However, the findings from the primary meta-analysis also prove that radiotherapy can pose serious safety and health risks. The same data listing the advantages of different types of radiotherapy also describes the risks of those treatments. Among the potential side effects are skin toxicity, future infertility,

Summary of Activities in the Radioprotectors and Radiomitigators Portfolio

Indication	Drug; company	Award type	Year started	Current status	Model	Aims
Enteritis	DFMO (α-difluoromethylornithine); RxBio Inc., Johnson City, TN	Phase I	2011	Complete	Mouse model of pelvis irradiation; HCT116 and H29 cell lines; and mouse model of colon cancer.	• Evaluate radioprotecting/ radiomitigating effect on gastrointestinal injury. • Evaluate the effect on cancer radiosensitivity.
Enteritis	ABC294640 (sphingosine kinase inhibitor); Apogee Biotechnology Corp., Hummelstown, PA	Phase I	2014	Ongoing	*In vitro* cell lines; mouse model of gastrointestinal acute radiation syndrome.	• Perform proof-of-concept studies to show that drug will reduce GI-ARS following abdominal or pelvic radiation.
Proctitis	PAAG-ployglucosamine; Synedgen, Claremont, CA	Phase I	2014	Ongoing	Rat, acute radiation-induced proctitis.	• Demonstrate efficacy in mitigation of radiation-induced proctitis. • Develop plans to demonstrate that PAAG does not protect cancer cells during radiotherapy.
Mucositis	CBLB502 (TLR-5 agonist); Buffalo Biolabs, Buffalo, NY	Phase I	2012	Complete	Mouse model of head and neck cancer.	• Demonstrate protective effect to skin and oral mucosa after single- and fractionated multiple radiation dose regimens. • Demonstrate safety and efficacy of the drug in combination with radiotherapy.
Mucositis	RLIP76 (proteoliposome); Terapio Inc., Austin, TX	Phase I	2013	Complete	Hamster cheek.	• Develop RLIP as a topical mouthwash. • Test efficacy, systemic absorption and demonstrate no tumor protection.
Mucositis	JVRSOD (gene therapeutic); Colby Pharmaceuticals, Menlo Park, CA	Fast track	2013	Ongoing	Mouse model and patients with head and neck cancer.	• Perform dose- and schedule- optimization studies for protection from radiation-induced oral mucositis. • Identify and qualify a GMP manufacturing site. • Submit an IND application for JVRSOD. • Perform phase I safety and phase II efficacy clinical trials.
Mucositis	BMX-001[a] (metalloporphyrin antioxidant); BioMimetix JV, Engelwood, CO	Phase I	2014	Ongoing	Mouse model of head and neck squamous cell carcinoma.	• Establish optimum dose schedule to reduce xerostomia and mucositis. • Demonstrate that the drug does not interfere with standard of care.
Lung injury	UTL-5g (TNF-α modulator); 21st Century Therapeutics Inc., Detroit, MI	Phase I	2011	Complete	Cell lines and mouse model of lung injury.	• Examine whether the drug reduces tumor cell killing *in vitro*. • Demonstrate efficacy in reducing radiation-induced lung injury *in vivo*. • Demonstrate that the drug does not affect tumor cell killing induced by radiation *in vivo*.

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Indication	Drug; company	Award type	Year started	Current status	Model	Aims
Lung injury	BIO300 (synthetic genistein); Humanetics Corp., Minneapolis, MN	Fast track	2012	Ongoing	Mouse xenograft of NSCLC tumor model and NSCLC patients.	• Perform efficacy studies in mouse model to demonstrate inhibition of tumor growth and mitigation of radiation-induced lung damage. • File IND for the use of BIO300 in patients receiving radiotherapy for NSCLC. • Conduct phase II clinical study to assess safety and effect of BIO300 in improving the morbidity and mortality in patients receiving radiation therapy.
Brain injury	TP508 (biotherapeutic, 23 amino acid peptide); Chrysalis Biotherapeutics, Galveston, TX	Phase I	2011	Transitioned to phase II	Cell lines and mouse xenograft orthotopic model.	• Optimize dose and schedule for vascular protection. • Demonstrate protection to brain tissue from radiotherapy damage. • Determine whether the protection is selective to normal tissue without altering radiation cell killing of cancer cells.
Brain injury	TP508 (biotherapeutic, 23 amino acid peptide); Chrysalis Biotherapeutics, Galveston, TX	Phase II	2013	Ongoing	Mouse orthotopic xenograft model.	• Determine the following: 1. Whether the drug protects also cancer stem cells or whether its protective effects are specific to neuroprogenitor cells; 2. Whether the drug reduces radiotherapy-induced neuronal atrophy and cognitive impairment; and 3. How the drug affects neuroprogenitor cells and generation of new neurons.
Brain injury	Fullerene-based radioprotectors; Luna Innovations Inc., Roanoke, VA	Phase I	2014	Ongoing	Cell lines and animals.	• Perform preclinical studies to demonstrate safety. • Perform preclinical studies to demonstrate effectiveness and improvement in therapeutic ratio.
Thrombocytopenia	CLT009, human allogenic megakaryocyte progenitors	Fast track	2012	Ongoing	*Ex vivo* cell culture expansion.	• Develop culture methods and assays for the expansion, characterization and production of sufficient quantity MKP to initiate and complete IND enabling studies. • Optimize media formulations, growth and culturing conditions and scalability of production of MKP for preclinical efficacy, safety and related IND studies.

[a] All information provided here and in the text is publicly accessible at http://projectreporter.nih.gov/reporter.cfm, except for funds distributed in 2015. While this information is accessible on the website, http://projectreporter.nih.gov/reporter.cfm, at the end of FY 2015, the company BioMimetix has kindly agreed to publicly release this information in this article.

Table 2. Summary of activities in the Radioprotectors and Radiomitigators Portofolio.From Prasanna et al. (2015) [8].

menopause, vaginal dryness, radiation-induced proctitis, bowel and bladder toxicity, and many others. Not only can those effects hinder a pregnant patient in their ability to sustain their pregnancy and deliver their offspring, but it would likely impact the fetus as well. Also, Table 3

ACUTE RADIATION DOSE* TO THE EMBRYO/FETUS	TIME PRECONCEPTION (UP TO 2ND WEEK)	TIME POSTCONCEPTION (3RD TO 5TH WEEK)	TIME POSTCONCEPTION (6TH to 13TH WEEK)	TIME POSTCONCEPTION (14TH TO 23RD WEEK)	TIME POSTCONCEPTION (24th WEEK TO TERM)
< 0.1 Gy (10 rads)†	Noncancer HEALTH EFFECTS NOT DETECTABLE				
0.1-0.5 Gy (10-50 rads)	Failure to implant may increase slightly, but surviving embryos will probably have no significant (noncancer) health effects.	Growth restriction possible	Growth restriction possible	Noncancer health effects unlikely	
> 0.5 Gy (50 rads) The expectant mother may be experiencing acute radiation syndrome in this range, depending on her whole-body dose.	Failure to implant will likely be high, depending on dose, but surviving embryos will probably have no significant (noncancer) health effects.	•Probability of miscarriage may increase, depending on dose. •Probability of major malformations, such as neurological and motor deficiencies, increases. •Growth restriction is likely.	•Probability of miscarriage may increase, depending on dose. •Growth restriction is likely.	•Probability of miscarriage may increase, depending on dose. •Growth restriction is possible, depending on dose. (Less likely than during the 6th to 13th weeks postconception) •Probability of major malformations may increase.	Miscarriage and neonatal death may occur, depending on dose. §

8th to 25th Weeks Postconception:
The most vulnerable period for intellectual disability is 8th to 15th weeks postconception.
Severe intellectual disability is possible during this period at doses > 0.5 Gy.
Prevalence of intellectual disability (IQ<70) is 40% after an exposure of 1 Gy from 8th to 15th week.
Prevalence of intellectual disability (IQ<70) is 15% after an exposure of 1 Gy from 16th to 25th week.

Note: This table is intended only as a guide. The indicated doses and times post conception are approximations.

* Acute dose: dose delivered in a short time (usually minutes). Fractionated or chronic doses: doses delivered over time. For fractionated or chronic doses, the health effects to the fetus may differ from what is depicted here.
† Both the gray (Gy) and the rad are units of absorbed dose and reflect the amount of energy deposited into a mass of tissue (1 Gy = 100 rads). In this document, the absorbed dose is that dose received by the entire fetus (whole-body fetal dose). The referenced absorbed dose levels in this document are assumed to be from beta, gamma, or x-radiation.
§ For adults, the LD50/60 (the dose necessary to kill 50% of the exposed population in 60 days) is about 3-5 Gy (300-500 rads) and the LD100 (the dose necessary to kill 100% of the exposed population) is around 10 Gy (1000 rads).

Table adapted from Table 1.1 of the National Council on Radiation Protection and Measurements Report No. 174, "Preconception and Prenatal Radiation Exposure: Health Effects and Protective Guidance" [NCRP2013].

Table 3. Potential health effects (other than cancer) of prenatal radiation exposure. From CDC (2024) [3].

reveals that radiation doses between 0.10 Gy and 0.50 Gy can lead to the failure to implant and possible growth restriction depending on how many weeks pass post-conception. The effects are more severe for doses above 0.50 Gy. Such doses can result in side effects such as miscarriage, major malformations, and neonatal death.

Also, some of the methods mentioned in Table 4 require large doses.Sometimes doses must be greater than 60 Gy to treat some cancers. That would require the patient to compromise between their health and the health of their offspring.

Common indications for radiotherapy

Cancer	Role of radiotherapy	Example of indication	Comments	Outcomes
Breast	Adjuvant treatment	Early stage after wide local excisions	In selected cases may be given intraoperatively (mature data awaited)	Reduces first recurrence at 10 years (from 35.0% to 19.3%); reduces 15 year absolute risk of death from breast cancer by 3.8% (from 25.2% to 21.4%) compared with no radiotherapy
		High risk mastectomy patients		Reduces local recurrence at 5 years (from 23% to 6%) and reduces 15 year absolute risk of death from breast cancer by 5.4% (from 60.1% to 54.7%) compared with no radiotherapy
				After breast radiotherapy the hazard ratio for death from heart disease is 1.27 and lung cancer 1.78 compared with no radiotherapy (overall mortality still reduced)
Prostate	Primary treatment	Early stage	Radiotherapy alone (brachytherapy in some cases) as a treatment option rather than surveillance or surgery	Similar outcomes to surgery; 93% prostate specific antigen control with brachytherapy at 7 years in low risk disease
		Locally advanced	EBRT is often used in combination with androgen deprivation therapy	74.1% and 71.4% prostate specific antigen control and overall survival, respectively, at 10 years for inoperable tumours
Lung	Primary treatment	Locally advanced tumours or comorbidity	Optimal outcomes using CHART or chemoradiation; radical high dose treatment for small tumours	Concurrent chemoradiation improves 2 year survival by 8% compared with radiotherapy alone; CHART improves 2 year survival from 20% to 29% compared with conventional radiotherapy
	Stereotactic ablative radiotherapy	Medically inoperable tumours		Mature outcome data awaited
Head and neck	Primary and adjuvant treatment	Can be used in most cancers to aid organ preservation	Often given with cisplatin	5 year survival: 80-90% in stage 1-2 tumours, 60-70% in stage 3-4 tumours
Rectum	Neoadjuvant treatment	To downstage bulky tumours at risk of involved resection margins	Given as short course (5 days) or long course (5 weeks) treatment	Cochrane review shows improved overall survival (by 2%) and local recurrence rates (heterogeneous across trials) compared with no radiotherapy
Gynaecological	Primary and adjuvant treatment	Cervical cancer	Primary chemoradiotherapy is standard of care in all but early stage I cervical cancers	Concurrent cisplatin and radiotherapy improves 5 year survival from 60% to 66%
		Endometrial cancer		Adjuvant EBRT reduces locoregional recurrence from 8.5% to 2.5% compared with surgery alone but has no effect on survival
Brain	Primary and adjuvant	After debulking surgery	Concurrent temozolamide improves survival	At doses above 60 Gy improves median survival from 18 to 42 weeks compared with surgery alone

CHART=continuous hyperfractionated accelerated radiotherapy; EBRT=external beam radiotherapy

Table 4. Common indications for radiotherapy. From Ahmad et al. (2012)[1].

Radiotherapy can be fatal for both the patient and their offspring if not managed safely. It is necessary to find a solution for administering radiotherapy safely and effectively. Although Table 3 lists the consequences of patients receiving different dosages, the effects of a dose greater than 0.50 Gy are probably insignificant among surviving embryos if administered after two weeks post-conception. Health effects are unlikely for doses between 0.10 Gy and 0.50 Gy. Doses under 0.10 Gy have not posed any harmful effects. Keeping the dosage amount low when possible will help ensure the safety of patients and their offspring. Table 2 summarizes various tests conducted on animal models and samples to improve the safety of radiotherapy and reduce its side effects. A few models were used to test certain drugs and determine their safety and effectiveness.The methods mentioned in the study from the article serve as potential ways to improve radiotherapy safety and provide solutions to already existing side effects.

Article (year)	Purpose of study	Research findings
[1] (2012)	- To analyse different roles of radiotherapy depending on the type of cancer being treated - Records outcomes of the each treatment depending on the indications for each cancer	-For *breast cancer,* adjuvant treatment is used -Examples of indication are early state wide local excisions and high risk mastectomy patients -Reduces (for early stage) first recurrence at 10 years (from 35.0% ro 19.3%), reduces 15 year absolute risk of death by 3.8% (from 25.2% ro 21.4%) compared to no radiotherapy -Reduces (for high risk mastectomy) local recurrence at 5 years (from 23% to 6%) and reduces 15 year absolute risk of death by 5.4% (from 60.1% ro 54.7%) compared with no radiotherapy -After treatment, the hazard ratio for death from heart disease is 1.27 and lung cancer 1.78 compared with no radiotherapy -For *prostate cancer*, primary treatment is used, and identification is early stage and locally advanced -It is used alone rather than with surveillance or surgery -Similar outcomes with surgery -93% prostate specific antigen control with brachytherapy at 7 years low risk disease -ERBT is often used in combination with androgen deprivation therapy and results in 74.1% and 71.4% prostate specific antigen control and overall survival, respectively, at 10 years in inoperable tumors -For *lung cancer*, primary treatment (specially, CHART or chemoradiation) is used, and indication is locally advanced tumors or comorbidity -Stereotactic ablative radiotherapy is also used, and indication is medically inoperable tumors -Need to use a high dose for optimal outcomes when using CHART -CHART improves 2 year survival rate by 8% compared with radiotherapy alone (from 20% to 29% compared with conventional radiotherapy) -No data recorded on the outcome of stereotactic ablative radiotherapy -For *head and neck cancer,* primary and adjuvant treatment is used, and it can be used in most cancers to aid organ preservation (often given with cisplatin) -5 year survival (80-90% in stage 1-2 tumors, and 60-70% in stage 3-4 tumors) -For *rectum cancer*, neoadjuvant treatment is used to downstage bulky tumors at risk of involved resection margins (given as short course of 5 days or long course of 5 weeks treatment) -Improved overall survival by 2% and local recurrence rates compared with no radiotherapy

		-For *gynecological cancer* (cervical and endometrial), primary and adjuvant treatment are used -In cervical cancer, primary treatment is used in all stages except for early stage -In cervical cancer, concurrent cisplatin and radiotherapy improves 5 year survival from 60% to 66% -In endometrial cancer, adjuvant ERBT reduces locoregional recurrence (from 8.5% to 2.5%) compared with surgery alone but has no effect on survival - For *brain cancer,* primary and adjuvant treatment is used after debulking surgery Concurrent temozolomide improves survival -Doses above 60 Gy improves median survival from 18 to 42 weeks compared with surgery alone
[3] (2024)	-Summarizes the potential risks from radiotherapy (not cancer related) -Intended to help physicians advise pregnant women who may have been exposed to radiation -Not a definitive recommendation -Data is approximate	-Less than *0.10 Gy* have not shown any effects *-0.10-0.50 Gy* may increase failure to implant after two weeks post conception (unlikely the effects will be significant) -Growth restriction possible for 3rd to 13th weeks post conception -Health effects unlikely for 14th week post conception to term -*Dosage greater than 0.50 Gy* can make the failure to implant high after two weeks post conception (probably not significant among surviving embryos) -Probability of misscarriage, major malformations, and growth restriction may increase after 3rd to 13th week post conception -Same effects as 3rd to 13th week post conception except the likelihood is lower (14th to 23rd weeks) -Miscarriage and neonatal death may occur 24th week to term

[8] (2015)	-Summarizes the activities of radioprotectors and radio mitigators -Looks at tested animals and describes the tests done on them -Models used to test ways to mitigate radiation effects	-*The mouse model of pelvis irradiation* is used for enteritis (indication) -The aims are to evaluate radio protecting/radio mitigating effect on gastrointestinal injury and to evaluate the effect on cancer radiosensitivity -*The mouse model of gastrointestinal acute radiation syndrome* is used for enteritis (indication) -The aims are to perform proof of concept studies to show that a particular drug will reduce GI-ARS following abdominal or pelvic radiation -*The rat for acute radiation induced proctitis* is used for proctitis (indication) -Aims to demonstrate efficacy in mitigation of radiation induced proctitis and to develop plans to demonstrate that PAAG does not protect cancer cells during radiotherapy -*The mouse model of head and neck cancer* is used for mucositis (indication) -Aims to demonstrate protective effect to skin and oral mucosa after single and fractionated multiple radiation dose regimens and demonstrate safety and efficacy of a specific drug in combination with radiotherapy -*The hamster cheek* is used for mucositis (indication) -Aims to develop RLIP as a topical mouthwash and to test efficacy, systemic absorption, and demonstrate no tumor protection -*The mouse model and patients with head and neck cancer* is used for mucositis (indication) -Aims to perform dose and schedule optimization studies for protection from radiation induced oral mucositis, identify and qualify a GMO manufacturing site, submit an IND application for JVRSOD, and perform phase I safety and phase II efficacy clinical trials -*The mouse model of head and neck squamous cell carcinoma* is used for mucositis (indication) -Aims to establish optimum dose schedule to reduce xerostomia and mucositis and to demonstrate that a particular drug does not interfere with standard of care -*The cell lines and mouse model of lung injury* is used for lung injury (indication) -Aims to examine whether a drug reduces tumor cell killing in vitro, demonstrate efficacy in reducing radiation-induced lung injury in vivo, and demonstrate that the drug does not affect tumor cell killing induced by radiation in vivo -*The mouse xenograft of NSCLC tumor model and NSCLC patients* is used for lung injury (indication) -*The cell lines and mouse xenograft orthotopic model* is used for brain injury (indication) -Aims to optimize dose and schedule for vascular protection, demonstrate protection to brain tissue from radiotherapy damage, and determine whether the protection is selective to normal tissue without altering radiation cell killing cancer cells

		-*The mouse orthotopic xenograft model* is used for brain injury (indication) -Aims to determine whether a particular drug protects also cancer stem cells or whether its protective effects are specific to neural progenitor cells, whether the drug reduces radiotherapy-induced neuronal atrophy and cognitive impairment, and how the drug affects neural progenitor cells and generation of new neurons -*The cell lines and animals* are used for brain injury (indication) -Aims to perform preclinical studies to demonstrate safety and effectiveness and improvement in therapeutic ratio -*Ex vivo cell culture expansion* is used for thrombocytopenia (indication) -Aims to develop culture methods and assays for the explanation, characterization and production of sufficient quantity MKP to initiate and complete IND enabling studies and to optimize media formulations, growth and culturing conditions and scalability of production for MKP for preclinical efficacy, safety and related IND studies
[14](2020)	-Summarizes radiotherapy interventions in the management of cervical cancer -Describes the procedures, intents/advantages, and risks of each type of radiotherapy listed in the chart	- *External beam radiotherapy (EBRT)* is to delivered from a distance -The intents/advantages are that is is curative for small to large lesions in combination with BT and chemotherapy, and that it is palliative to control bleeding and/or pain -The risks are infertility, menopause, vaginal dryness, bowel, urinary, hematological and skin toxicity -*Brachytherapy (BT)* is delivered from a sealed radioactive source placed inside the vagina and uterus, close to the tumor -The intent/advantage is that it is curative for small to large lesions in combination with ERBT -Risks are vaginal stenosis, vaginal dryness, radiation proctitis, bowel and bladder toxicity, and that it may require anesthesia -After *adjuvant radiotherapy (aRT)* is administered, EBRT and/or BT are administered after surgery -The intent/advantage is that it eradicates any microscopic disease in the irradiated area -The risks are bowel, urinary, hematological, and skin toxicity

Table 5. Summary of research findings.

Discussion

The findings reveal that radiotherapy is necessary to treat cancer, can cause serious side effects if patients and their offspring are not safely protected, and that various ways to remedy the effects of treatment exist. Such information can be taken into consideration when deciding the best course of action when a pregnant patient needs to receive treatment for cancer. Although the meta-analysis reveals information for combating the issues with radiotherapy, the study has some limitations. The articles used for primary research are not very recent. The oldest article was published in 2012. Also, the data from Table 3 is approximate and not intended to serve as a definite recommendation. In addition, Table 2 does not include the results of the recorded methods. The primary data collection was limited to older data because no resources were available for conducting an experiment and acquiring new observations. However, anyone wishing to conduct further research into the issue of radiotherapy safety could build off the meta-analysis by conducting experiments and recording more exact data. Furthermore, they can replicate the tested methods in Table 4 to analyze the outcomes.

Conclusion

Radiotherapy has many dangerous implications, especially for fetuses. However, it does not have to stay that way. Radiotherapy can be improved by implementing certain devices or treatments during procedures, incorporating aspects of other cancer treatments into radiotherapy, following strict treatment regulations, and individualizing treatment plans for pregnant patients. By doing these things, fetuses exposed to the treatment will not have to suffer the lifelong effects of radiotherapy. Mothers will be able to receive radiotherapy without having to compromise the health of their future son or daughter.

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