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COMMENTARY

Challenges and opportunities for proton therapy during pregnancy

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Abstract

During pregnancy, the use of radiation therapy for cancer treatment is often considered impossible due to the assumed associated fetal risks. However, suboptimal treatment of pregnant cancer patients and unjustifiable delay in radiation therapy until after delivery can be harmful for both patient and child. In non-pregnant patients, proton-radiation therapy is increasingly administered because of its favorable dosimetric properties compared with photon-radiation therapy. Although data on the use of pencil beam scanning proton-radiation therapy during pregnancy are scarce, different case reports and dosimetric studies have indicated a more than 10-fold reduction in fetal radiation exposure compared with photon-radiation therapy. Nonetheless, the implementation of proton-radiation therapy during pregnancy requires complex fetal dosimetry for the neutron-dominated out-of-field radiation dose and faces a lack of clinical guidelines. Further exploration and standardization of proton-radiation therapy during pregnancy will be necessary to improve radiotherapeutic management of pregnant women with cancer and further reduce risks for their offspring.

KEYWORDS
cancer, fetal radiation, pregnancy, proton therapy, radiation therapy

1 | INTRODUCTION

With growing evidence on its fetal safety, chemotherapy is increasingly administered to pregnant women with cancer, resulting in more live births and less prematurity.[1] Nowadays, chemotherapy during pregnancy is administered to about half of pregnant patients. However, a decreasing trend has been observed for the use of radiation therapy (RT) during pregnancy, currently only administered to 2% of pregnant cancer patients. Indeed, the safety of RT during pregnancy is probably the least investigated, with most data on fetal safety being derived from small cohorts as well as pregnant survivors of atomic bombs and nuclear accidents.[2,3]

Following current consensus, RT can be administered during pregnancy when the fetal radiation exposure is kept below 100 mSv, which is being considered a safe threshold for deterministic effects during all stages of pregnancy.[2–4] On the other hand, the probability of stochastic effects, such as cancer and genetic effects, is considered linearly proportional to the fetal radiation dose without a

Abbreviations: MC, Monte Carlo; MU, monitor units; PBS, pencil beam scanning; RBE, relative biological effectiveness; RT, radiation therapy; WENDI, wide-energy neutron detection instrument.

threshold. For instance, based on in utero atomic bomb fallout and radiographic exposure, the excess relative risk for childhood cancer is estimated to be 2%–4% per mSv of fetal radiation exposure.[4,5] For this reason, ALARA (As Low As Reasonably Achievable) remains the guiding principle for fetal radiation exposure when applying RT during pregnancy.[2,3]

Still, in current clinical practice RT is often postponed postpartum in favor of chemotherapeutic treatment during pregnancy. However, postponing RT is particularly problematic when it is essential for the primary treatment. Moreover, when chemotherapy or surgery is performed early in pregnancy, a potential gap exists between the end of treatment and fetal maturity at 37 weeks' gestational age. With more early detections of cancers, such as lymphomas, through noninvasive prenatal testing,[6] delay of RT until after delivery may be undesirable. Besides, as chemotherapy can only be administered after the first trimester of pregnancy, RT might provide an initial treatment opportunity for tumors detected early in pregnancy.

Practical guidelines exist for the use of photon-RT during pregnancy,[2] being the most common RT modality. Here, the fetal dose is dependent on a combination of parameters (Figure 1A), such as the distance between target and fetus, the prescribed dose and the number of monitor units (MU) used. With fetal dose contributions from treatment head leakage and collimator scatter relating to the number of MU used, it is important to minimize the amount of MU during treatment planning. However, modern techniques such as intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT) require more MU[3] than conformal RT. Therefore, treatment plan conformality is often sacrificed to reduce the fetal radiation exposure. Further fetal dose reductions can be achieved by placing 5- to 7-cm lead shielding over the abdomen and limiting beam angles to directions where shielding can be applied. To consider all these factors, careful preparations and expert knowledge are required.

Key message

Based on a few cases, proton therapy for pregnant cancer patients can reduce the fetal radiation dose over a 10-fold compared with state-of-the-art photon therapy. However, its implementation is still faced with dosimetric challenges and a lack of guidelines.

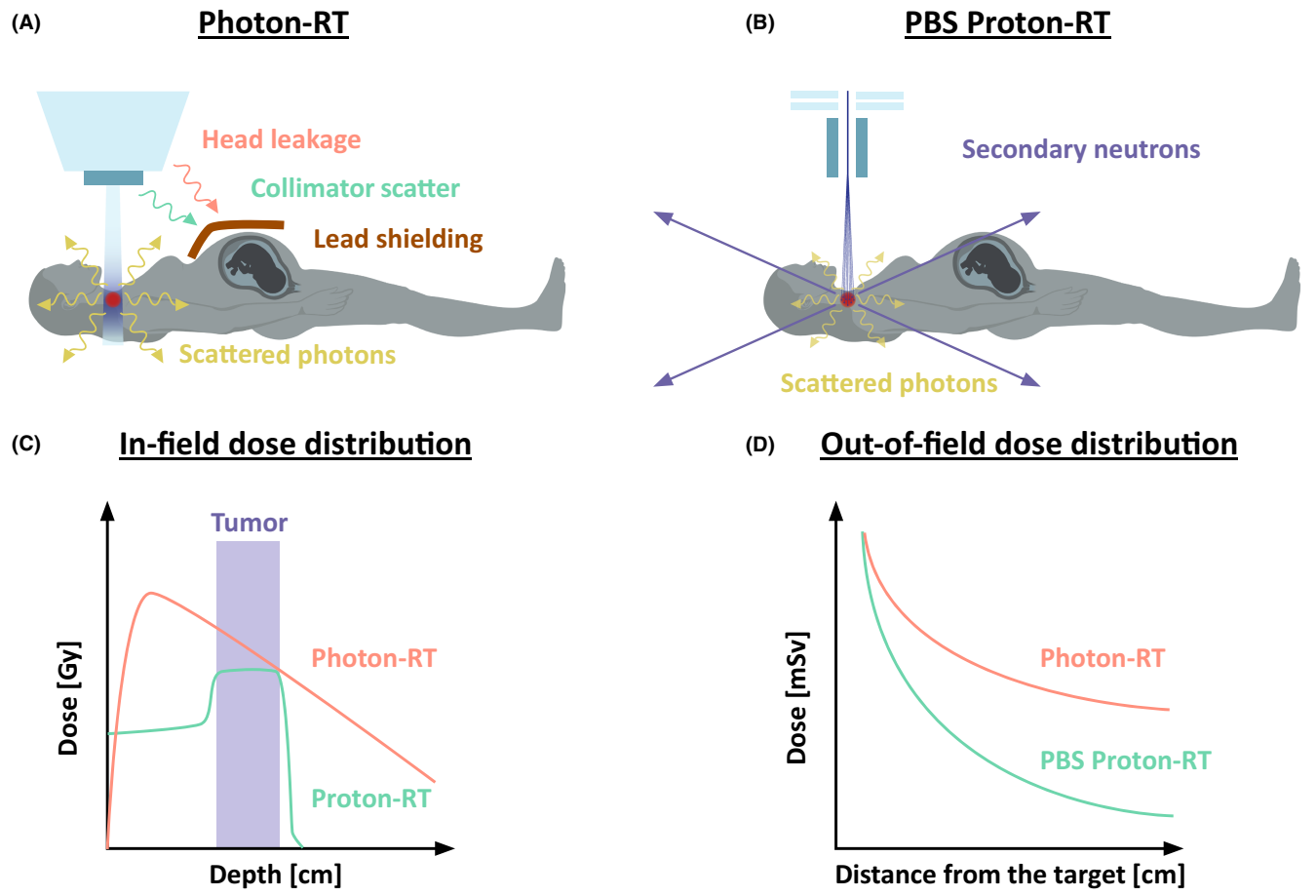

FIGURE 1 Contributions of fetal dose during photon-radiation therapy (RT) and proton-RT. (A,B) Schematic overview of the major contributions to the fetal dose, during photon-RT and PBS proton-RT, respectively. (C,D) Schematic comparison of the in-field (C) and out-of-field (D) dose-distribution of photon-RT and proton-RT.

In non-pregnant cancer patients, proton-RT is increasingly being used due to its favorable dosimetric properties compared with photon-RT, most notably with no exit dose (Figure 1C),[7] often improving treatment conformality and reducing normal tissue complications. Nowadays, pencil beam scanning (PBS) is the most versatile form of proton-RT, with an expected reduction in out-of-field doses compared with passive scattering proton-RT and photon-RT[8] creating new opportunities for the treatment of cancer during pregnancy. Nevertheless, proton-RT generates a secondary radiation field dominated by neutrons, creating several dosimetric challenges. The fear concerning the impact of the fetal neutron dose is still today the main factor in hesitancy to apply proton-RT for pregnant patients.

Here, we will discuss current knowledge on the use of proton-RT during pregnancy from out-of-field dosimetry research and clinical cases. Based on current evidence, we will define the potential benefits of proton-RT for radiotherapeutic management of pregnant women with cancer, as well as challenges and knowledge gaps to overcome in further implementing proton-RT during pregnancy (Figure 2).

2 | OUT-OF-FIELD DOSIMETRY DURING PROTON-RT

The generation of secondary neutrons is an unavoidable consequence of proton-RT, creating several challenges when estimating the fetal radiation dose. In this section, we introduce several key aspects to consider when estimating the out-of-field dose for the fetus during proton-RT.

Secondary neutrons in PBS proton-RT are mainly produced in the patient, depositing their energy outside of the irradiated volume (Figure 1B). Indeed, during PBS, a pristine proton pencil beam is magnetically scanned over the target volume without interacting with additional devices, except for range shifters used for shallow target volumes. In contrast, passive scattering proton-RT requires a complex system of scatterers in the treatment nozzle, as well as a field-specific aperture and compensator, leading to the additional creation of neutrons in these components. As a result, PBS proton-RT produces a lower neutron background compared with passive scattering.

Neutrons created during proton-RT have a wide range of energies, ranging from thermal energies (<0.4 eV) up to the maximum proton energy (up to 250 MeV).[9,10] As neutrons are indirectly ionizing, they will deposit energy by creating ionizing secondary particles. These nuclear reaction cross-sections strongly depend on the neutron energy, causing the relative biological effectiveness (RBE) of neutrons to vary greatly for different neutron energies. Furthermore, reports on in vivo and microdosimetric studies observe different RBEs, also depending on cell type and biological endpoint, rendering the use of RBE impractical for neutron dosimetry.[8,11]

The International Commission on Radiological Protection has therefore defined 'dose equivalent' to weigh the dose according to the biological impact of the radiation. In practice, a radiation quality factor Q has been described as a function of energy for neutrons up to 400 MeV and for several materials including human soft tissue.[12] Still, knowledge of the neutron energy spectrum is required to calculate the equivalent neutron dose, which can be obtained only from dedicated experiments or virtual modeling with Monte Carlo (MC) simulations.

Dedicated detector systems, such as ambient neutron monitors, can be used to measure and monitor the out-of-field dose inside proton-RT facilities. The wide-energy neutron detection instrument

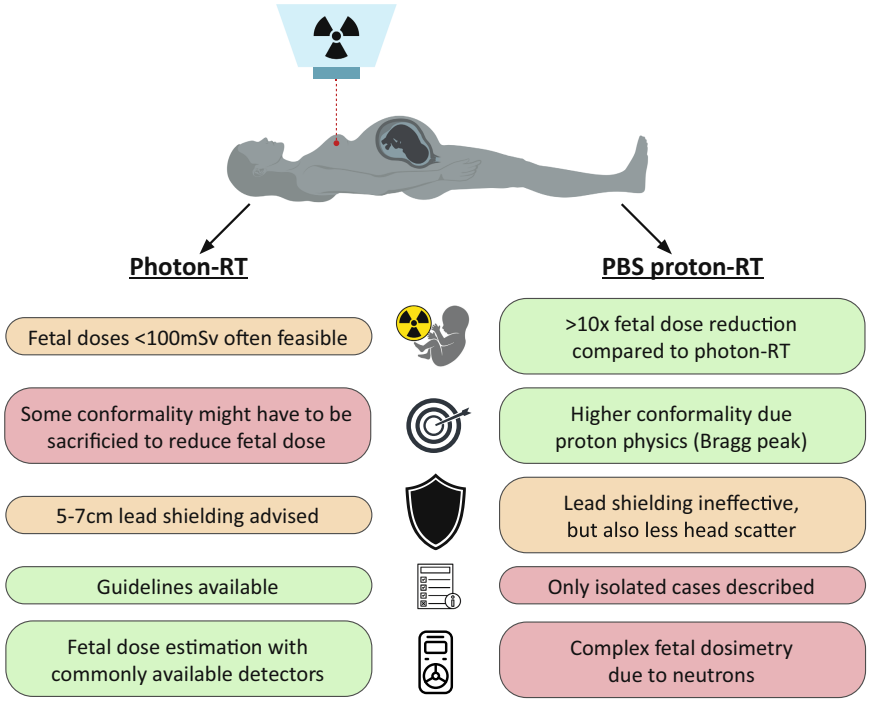

FIGURE 2 Overview of the challenges and opportunities of proton-radiation therapy (RT) during pregnancy, compared with photon-RT.

(WENDI) has been used for this purpose[13] and an intercomparison exercise by the European Radiation Dosimetry Group (EURADOS) of active dosimetry systems in proton-RT found that WENDI-II performed well.[14] However, due to their large size, these detectors cannot be placed inside anthropomorphic phantoms to estimate fetal doses. On the other hand, commonly available small-sized thermoluminescent detectors (TLDs) have limited to no response to neutrons. Alternatively, the use of track etch detectors and bubble detectors has been reported, showing good agreement with each other[15] and compared with MC simulations.[16] Further, though still in its explorative phase, the use of a miniaturized radiation camera (MiniPIX, Advacam) has proven useful to discriminate particle types and energies of the stray radiation field.[17] However, these specialized detectors are not routinely used in a clinical setting.

Besides detector systems, the geometry and tissue of the patient has to be adequately modeled through anthropomorphic phantoms to allow accurate dosimetry for the fetus. While adult female phantoms are commercially available, there are no commercial phantoms modeling pregnant women. Therefore, some research groups have modified anthropomorphic phantoms mimicking a pregnant belly.[18–20] However, using such approaches, it is impractical to model individual patients. Therefore, anthropomorphic phantoms can be used to validate computational methods, which can allow more anatomical variation. Computational phantoms have been developed by researchers both at the University of Florida[21] and at the Helmholtz Zentrum Munich,[22] including different stages of pregnancy. The further development and clinical implementation of these computational phantoms, combined with validated MC simulations, are an essential pathway towards patient-specific fetal dosimetry during proton-RT.

3 | DOSIMETRIC STUDIES

A few dosimetric studies have investigated fetal radiation exposure during proton-RT (Table 1a).

Roy & Sandison[23] performed pioneering experiments using a mono-energetic research beam with a 4-cm spot size to measure the fetal neutron dose in an anthropomorphic phantom using bubble detectors. The measured fetal dose ranged from 0.1 mSv/Gy to a target in the head, to 0.26 mSv/Gy when irradiating the upper abdomen. More recently, Hopfensperger et al.[24] measured the fetal dose to a spherical target in the brain using the WENDI detector and an anthropomorphic phantom. The fetal dose was measured at three representative distances – 47, 39.5 and 32 cm – between the isocenter (ie the central point around which the RT gantry is positioned) and the edge of the WENDI detector. Different aperture set-ups, ie none, static adaptive and dynamic adaptive, were also compared. Estimated fetal doses ranged from 22.5 to 33.2 μSv/Gy, compared with 82–330 mSv/Gy when using volumetric-modulated arc therapy photon-RT. Higher fetal doses during proton-RT were observed at closer distances to the target and when dynamic apertures were used.

MC simulations have also been employed to estimate the fetal radiation dose. Geng et al.[25] used MC simulations to model the fetal dose during irradiation of a $6.5 \times 6.5 \times .4.5\,cm^3$ brain target comparing PBS proton-RT with passive scattering proton-RT and photon-RT at 3, 6 and 9 months of gestation. Equivalent fetal doses during PBS proton-RT increased with gestation from 1.5 to 2.5 μSv/Gy, with photon-RT and passive scattering proton-RT respectively leading to 10 times and 100 times higher fetal doses. Next, De Saint Hubert et al.[26] calculated equivalent doses during PBS proton-RT on a cylindrical brain volume, comparing three computational models of pregnant women in their second trimester, as well as two versions of the Monte Carlo N-Particle® (MCNP) code and two material models. Whereas differences in material composition and MCNP version led to small differences, differences in phantom geometry led to variations in fetal dose of up to 50%. This shows that the estimated fetal dose is highly dependent on the individual geometry of patient and fetus. Finally, Yeom and colleagues[27] used MC simulations to estimate the fetal dose across different stages of pregnancy and for different fetal organs during craniospinal irradiation with PBS proton-RT for a 36-Gy prescribed dose, based on a clinical case by Kalbasi et al.[28] (see below). The total fetal absorbed dose (ie not accounting for RBE) varied between 3.66 and 5.80 mGy, amounting to 26–41 mSv equivalent fetal dose when using a fixed quality factor of Q = 7, with lower doses occurring later in pregnancy as the fetus moves anteriorly. However, individual fetal organ doses were more variable, with the largest variation at 40 weeks' gestation, where the fetal lens received a dose three times higher than the adrenals. This shows that when the target is close to the fetus, the exact fetal dose will be highly dependent on the fetal position within the womb and cannot be considered homogeneous. In such cases, the positioning of the patient and fetus, as well as individual fetal organ doses need to be considered.

These dosimetric studies provide key insights into the potential dose reduction during proton-RT compared with photon-RT, but it is important to note that these simulations use generalized and often simplified models of both patient and tumor. Moreover, MC simulations are most often not validated against physical measurements. Moreover, studies apply different Q-factors to account for the neutrons' RBE, and it is therefore unclear to what extent these simulations are representative for clinical practice.

4 | CASE REPORTS

A few pioneering case studies[28–31] have described the use of proton-RT during pregnancy (Table 1b).

Wang et al.[29] reported on a woman who was diagnosed with a recurrent chordoma at the base of skull and cervical junction at 19 weeks' gestation, who was treated with proton-RT. To minimize the fetal radiation exposure during treatment, the authors iteratively optimized the PBS proton-RT treatment plan for minimal fetal exposure using physical phantom measurements. Most notably, the initial plan included a vertex beam which contributed 85% of the total fetal

TABLE 1 Overview of dosimetric studies and case reports on proton-radiation therapy during pregnancy. Fetal doses are expressed either in absolute terms (mSv) or respectively to the prescribed maternal dose (mSv/Gy).

				Fetal dose estimation during PBS proton-RT			Fetal dose comparison		
Authors	**Target**	**GA at start RT**	**Dose to CTV**	**Method**	**Treatment dose**	**Imaging dose**	**Passive scattering proton-RT**	**Photon therapy**	**Neonatal outcome**
a. Dosimetric studies									
Roy & Sandison (2004)	Monoenergetic beam with 2-cm radius spot at head, chest and upper abdomen			Physical phantom	0.1–0.26 mSv/Gy				N.A.
Geng et al. (2016)[+]	Brain 6.5×6.5×4.5 cm CTV	3, 6 and 9 months	52.2 Gy	MC simulation (TOPAS)	78–130 μSv	18–38 μSv	131–172 μSv/Gy	10–29 μSv/Gy	N.A.
De Saint-Hubert et al. (2021)[+]	Brain cylindrical CTV (r = 3×m, range = 10 cm, modulation = 5 cm)	22, 24 and 27 weeks GA		MC simulation (MCNP)	0.4–0.8 μSv/Gy				N.A.
Yeom et al. (2022)	Craniospinal irradiation (CSI)	10, 12, 17, 22, 27, 32, 37 and 40 weeks GA	36 Gy	MC simulation (TOPAS).	14–21 mSv for Q = 4 25–40 mSv for Q = 7	8.97 mSv			N.A.
Hopfensperger et al. (2023)	Brain, sphere with $r = 3$ cm			Physical phantom	22.5–33.2 μSv/Gy			82–330 mSv/Gy	N.A.
b. Clinical cases									
Wang et al. (2016)	Base of skull chordoma	19 weeks (diagnosis)	70 Gy	Physical phantom	0.35 mSv		70 mSv	±105 mSv	Healthy live birth
Kalbasi et al. (2017)	Atypical teratoid/rhabdoid brain tumor	22–28 weeks	36 Gy CSI + 19.8 Gy boost	Literature based	72 mSv	64 mSv			Healthy live birth at 34 weeks GA (follow-up until 3 year)
Guevelou et al. (2020)	Head/neck	First trimester	64.8 Gy	Physical phantom	0.83 mSv	0.01 mSv			
Heimovaara et al. (2022).	Nasopharyngeal carcinoma	27 weeks	70 Gy (therapeutic CTV) and 54 Gy (prophylactic CTV)	Physical phantom	5.5 mSv	0.21 mSv		185 mSv	Healthy boy at 39 weeks GA. APGAR 9 and 10 at respectively 1 and 5 minutes. Birthweight 3820 g (83rd percentile). Placenta: microscopic fetal vascular malperfusion, but no macroscopic abnormalities. No congenital or neurologic abnormalities. Normal general health, development and growth at 2 months old.

Abbreviations: CTV, clinical target volume; GA, gestational age; MC, Monte Carlo; PBS, pencil beam scanning; RT, radiation therapy.

dose, with the other five beams each contributing 1.7%–3.7%. This shows that one should be careful in using high energy beams aligned towards the fetus. By replacing this vertex field, an estimated fetal dose of 0.35 mSv was achieved, compared with 70 and 105 mSv estimated during passive scattering proton-RT and photon-RT, respectively. After proton-RT, a healthy child was delivered.

Next, Kalbasi et al.[28] described a case of a pregnant woman with an atypical teratoid/rhabdoid brain tumor who, after surgery, was to receive 36 Gy craniospinal irradiation and a 19.8 Gy boost to the tumor bed. Based on the literature, the fetal dose from PBS proton-RT was estimated to be 72 mSv, with an additional 64 mSv from daily kV imaging and computed tomography. Proton-RT was administered in the late second trimester and third trimester, with a healthy boy delivered at 34 weeks' gestation, after which chemotherapy was initiated. Both mother and child were healthy at the 3-year follow-up.

Further, le Guevelou et al.[30] briefly report on a patient undergoing PBS proton-RT of 64.8 Gy for treatment of a head-and-neck tumor during the first trimester of pregnancy. Physical phantom measurements estimated a fetal exposure at 0.83 mSv.

Finally, Heimovaara et al.[31] reported on a pregnant patient with a nasopharyngeal carcinoma who was treated with PBS proton-RT for 70 Gy to the therapeutic volume and 54.25 Gy to the prophylactic volume starting at 27 weeks' gestation. With the fetal position estimated at 20 cm from the caudal border of the clinical target volume, the fetal radiation exposure was estimated at 5.5 mSv during PBS proton-RT, compared with 185 mSv when using photon-RT. At 39 weeks' gestation a healthy boy was delivered (3820 g, APGAR 9/10 at 1/5 minutes, respectively). While microscopic placental examination showed high-grade fetal vascular malperfusion which could not be directly related to the radiation treatment, no other placental or neonatal abnormalities were seen, and the child showed age-adequate growth and motor development at the 2-month follow-up. Three months after the end of treatment, complete remission of the tumor was observed.

5 | DISCUSSION

Notwithstanding the dosimetric challenges and uncertainties in estimating the fetal radiation dose during PBS proton-RT, a small body of literature, consisting of both dosimetric studies and clinical cases, has shown the potential of proton-RT in further reduce the fetal radiation dose during RT. However, the implementation of proton-RT for pregnant cancer patients still faces several challenges.

First, all identified studies applied different measurement techniques to estimate the fetal dose, with physical measurements using different phantoms and detectors, and MC simulations using different physics models and Q-factors. Moreover, these computational and physical models were never validated against each other. For instance, whereas Kalbasi et al. estimated the fetal dose during 36 Gy craniospinal irradiation to be 72 mSv based on the literature, MC simulations by Yeom et al.[27] estimated this dose to only be 26–31 mSv, despite using the same Q-factor. Often, these discrepancies are acceptable, as fetal doses typically remain well below 100 mSv and considering more than the 10-fold dose reduction typically observed compared with photon-RT. However, to better quantify fetal risks during proton-RT, more research is necessary on the conversion of physical to biological doses, as well as the translation of these biological doses in terms of risks for the unborn child.

Secondly, in most radiation oncology centers, MC models for out-of-field dosimetry and compact wide-range neutron detectors are not readily available. More commonly available neutron detectors, such as REM500 and WENDI-II, are large detectors, limiting the accuracy of measurements. Therefore, practical evidence-based guidelines need to be established for fetal dose estimation during proton-RT, using clinically readily available tools, to ensure the quality of the fetal dose estimates.

Thirdly, whereas most studies so far have used routine proton-RT treatment planning for pregnant women, Wang et al.[29] showed that it might be useful to adapt the plan to reduce the fetal radiation exposure further. For instance, it might be advisable to avoid high-energy beams in line with the patient and to minimize neutron scatter by additional components in the beamline such as apertures, compensators and range shifters. However, additional research is necessary to calculate the impact of different planning parameters on the fetal dose to better inform clinical decision-making.

Next, the fetal dose might theoretically be further reduced through abdominal shielding. However, whereas 5- to 7-cm lead shielding is effective for shielding photons, and therefore often useful in reducing fetal radiation exposure during photon-RT, lead is inefficient for shielding neutrons. Indeed, the design of effective compact abdominal shielding for pregnant patients undergoing proton-RT is very challenging. However, since PBS proton-RT, as compared with passive scattering proton-RT and photon-RT, makes fewer contributions to the fetal dose from scatter at the treatment head, abdominal shielding will have less impact. The omission of redundant abdominal shielding during proton-RT will decrease the patient time on-table and will improve patient comfort and safety.

For several cases, such as brain and head/neck tumors, routine planning might often suffice to achieve a fetal dose that is already well below 50 mSv or even below the public limit of 1 mSv. Notwithstanding the dosimetric uncertainties of those fetal dose estimations, this clear reduction might already be enough to apply PBS proton-RT for these patients. On the other hand, proton-RT might also allow for the treatment of more challenging cases such as craniospinal irradiation.[27,28] However, in such cases it is important to account for dosimetric uncertainties as well as uncertainties on the fetal position, in order to ensure fetal doses remain below acceptable threshold levels.

Also, the fetal exposure during imaging procedures should be considered. Whereas in most reports the fetal doses during imaging remained a factor lower than the exposure during proton-RT treatment,[30,31] in the report by Kalbasi et al.[28] imaging procedures led to an additional 64 mSv fetal dose. Accounting for the fetal exposure during imaging becomes especially important in cases where the

imaging field is close to or includes the fetus, or when computed tomography imaging is often repeated for adaptive therapy. Here, site-specific optimization of the image-guided proton-RT protocol is advisable, eg by replacing low-dose computed tomography with planar imaging and/or surface scanning whenever possible.

So far, we have only identified four clinical cases and four dosimetry studies discussing proton-RT during pregnancy. While these studies provide essential information on the feasibility of proton-RT during pregnancy, they discuss isolated and thereby selected cases. More data are necessary to confirm and generalize these findings. To achieve this, it is important to report on known cases of pregnant women undergoing proton-RT and to register them in (inter)national databases such as the INCIP registry (www.cancerinpregnancy.org).[32]

In conclusion, although data are scarce, different case reports and dosimetric studies using PBS proton-RT for pregnant patients have shown a strong reduction in fetal radiation exposure compared with photon-RT, with good health outcomes for the offspring being reported. Nonetheless, the implementation of proton-RT during pregnancy is still faced with the complex fetal dosimetry, including neutrons, and a lack of clinical guidelines. The further implementation and standardization of proton-RT during pregnancy is therefore necessary to improve radiotherapeutic management of pregnant women with cancer with minimal risks for their offspring.

AUTHOR CONTRIBUTIONS

JB, MDSH and ML contributed to the first draft of this paper. All authors were involved in the conceptualization, as well as writing and revising of the final version of the paper.

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CONFLICT OF INTEREST STATEMENT

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

REFERENCES

1. de Haan J, Verheecke M, Van Calsteren K, et al. Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. *Lancet Oncol*. 2018;2045:337-346.
2. Stovall M, American Institute of Physics, American Association of Physicists in Medicine. Fetal dose from radiotherapy with photon beams. *AAPM Rep*. 1995;50:63-82.
3. Wong YM, Koh CWY, Lew KS, et al. A review on fetal dose in radiotherapy: a historical to contemporary perspective. *Phys Medica*. 2023;105:102513.
4. ICRP. Biological effects after prenatal irradiation (embryo and fetus). ICRP publication 90. *Ann ICRP*. 2003;33(1–2).
5. Wakeford R, Bithell JF. A review of the types of childhood cancer associated with a medical X-ray examination of the pregnant mother. *Int J Radiat Biol*. 2021;97:571-592.
6. Lenaerts L, Brison N, Maggen C, et al. Comprehensive genome-wide analysis of routine non-invasive test data allows cancer prediction: a single-center retrospective analysis of over 85,000 pregnancies. *EClinicalMedicine*. 2021;35:100856.
7. Newhauser WD, Zhang R. The physics of proton therapy. *Phys Med Biol*. 2015;60:R155-R209.
8. Hälg RA, Schneider U. Neutron dose and its measurement in proton therapy- current State of Knowledge. *Br J Radiol*. 2020;93:20190412.
9. Mares V, Farah J, De Saint-Hubert M, et al. Neutron radiation dose measurements in a scanning proton therapy room: can parents remain near their children during treatment? *Front Oncol*. 2022;12:1-13.
10. Mares V, Romero-Expósito M, Farah J, et al. A comprehensive spectrometry study of a stray neutron radiation field in scanning proton therapy. *Phys Med Biol*. 2016;61:4127-4140.
11. Montgomery L, Lund CM, Landry A, Kildea J. Towards the characterization of neutron carcinogenesis through direct action simulations of clustered DNA damage. *Phys Med Biol*. 2021;66:205011.
12. Romero-Expósito M, Domingo C, Sánchez-Doblado F, Ortega-Gelabert O, Gallego S. Experimental evaluation of neutron dose in radiotherapy patients: which dose? *Med Phys*. 2016;43:360-367.
13. De Smet V, Stichelbaut F, Vanaudenhove T, et al. Neutron H*(10) inside a proton therapy facility: comparison between Monte Carlo simulations and WENDI-2 measurements. *Radiat Prot Dosimetry*. 2014;1(161):417-421.
14. Farah J, Mares V, Romero-Expósito M, et al. Measurement of stray radiation within a scanning proton therapy facility: EURADOS WG9 intercomparison exercise of active dosimetry systems. *Med Phys*. 2015;42:2572-2584.
15. Knežević Ž, Ambrozova I, Domingo C, et al. Comparison of response of passive dosimetry systems in scanning proton radiotherapy—a study using paediatric anthropomorphic phantoms. *Radiat Prot Dosimetry*. 2018;180(1–4):256-260.
16. De Saint-Hubert M, Verbeek N, Bäumer C, et al. Validation of a Monte Carlo framework for out-of-field dose calculations in proton therapy. *Front Oncol*. 2022;12:1-22.
17. Nabha R, De Saint-Hubert M, Van Hoey O, et al. Characterization of the secondary radiation field in proton therapy using a Timepix detector. In: PTCOG. Miami 2022.
18. Labby ZE, Barraclough B, Bayliss RA, Besemer AE, Dunkerley DAP, Howard SP. Radiation treatment planning and delivery strategies for a pregnant brain tumor patient. *J Appl Clin Med Phys*. 2018;19:368-374.
19. Nuyttens J, Prado K, Jenrette J, Williams T. Fetal dose during radiotherapy: clinical implementation and review of the literature. *Cancer/Radiothérapie*. 2002;6:352-357.
20. Mazonakis M, Damilakis J, Varveris H, Theoharopoulos N, Gourtsoyiannis N. A method of estimating fetal dose during brain radiation therapy. *Int J Radiat Oncol*. 1999;44:455-459.
21. Maynard MR, Long NS, Moawad NS, et al. The UF family of hybrid phantoms of the pregnant female for computational radiation dosimetry. *Phys Med Biol*. 2014;59:4325-4343.
22. Becker J, Zankl M, Fill U, Hoeschen C. Katja — the 24 th week of virtual pregnancy for dosimetric calculations. *Polish J Med Phys Eng*. 2008;14:13-20.
23. Roy SC, Sandison GA. Scattered neutron dose equivalent to a fetus from proton therapy of the mother. *Radiat Phys Chem*. 2004;71:997-998.
24. Hopfensperger KM, Li X, Paxton A, et al. Measurements of fetal dose with Mevion S250i proton therapy system with HYPERSCAN. *J Appl Clin Med Phys*. 2023;24:e13957.
25. Geng C, Moteabbed M, Seco J, et al. Dose assessment for the fetus considering scattered and secondary radiation from photon and proton therapy when treating a brain tumor of the mother. *Phys Med Biol*. 2015;61:683-695.
26. De Saint-Hubert M, Tymińska K, Stolarczyk L, Brkić H. Fetus dose calculation during proton therapy of pregnant phantoms using MCNPX and MCNP6.2 codes. *Radiat Meas*. 2021;149: (August). doi:10.1016/j.radmeas.2021.106665

27. Yeom YS, Griffin KT, Mille MM, et al. Fetal dose from proton pencil beam scanning craniospinal irradiation during pregnancy: a Monte Carlo study. *Phys Med Biol*. 2022;67:035003.
28. Kalbasi A, Kirk M, Teo BKK, et al. Proton craniospinal irradiation during the third trimester of pregnancy. *Pract Radiat Oncol*. 2018;8:213-216.
29. Wang X, Poenisch F, Sahoo N, et al. Spot scanning proton therapy minimizes neutron dose in the setting of radiation therapy administered during pregnancy. *J Appl Clin Med Phys*. 2016;17:366-376.
30. Le Guevelou J, Lebars S, Kammerer E, et al. Head and neck cancer during pregnancy. *Head Neck*. 2019;41:3719-3732.
31. Heimovaara JH, Blommaert J, Free J, et al. Proton therapy of a pregnant patient with nasopharyngeal carcinoma. *Clin Transl Radiat Oncol*. 2022;35:33-36.
32. Maggen C, Wolters VERA, Cardonick E, et al. Pregnancy and cancer: the INCIP project. *Curr Oncol Rep*. 2020;22:17.

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