Practical Prediction Model for Ovarian Insufficiency after Radiation

Abstract

Objective  The present study aimed to develop a useful mathematical model that predicts the age at which premature ovarian insufficiency might occur after teletherapy radiation. A diagnosis of premature or early menopause has physical and psychological consequences, so women may need support and long-term medical follow-up.

Methods  To correlate ovarian radiation dose with ovarian function, we used the formula described by Wallace et al.: \( \sqrt{g(z)} = 10^{(2-0.15z)} \), where “\( g(z) \)” and “\( z \)” represent oocyte survival rate and the radiation dose (in Gray), respectively. By simulating different ages and doses, we observed a pattern that could be used to simplify the relationship between radiation dose and remaining time of ovarian function.

Results  We obtained a linear function between ovarian radiation dose and loss of ovarian function (LOF) that is the percentage of decrease in the time to the ovarian failure compared with the time expected for a woman at the same age without irradiation exposition. For patients < 40 years old and with ovarian radiation doses < 5 Gy, the equation LOF = 2.70 + (11.08 x Dose) can be applied to estimate the decrease in time to premature ovarian insufficiency.
Introduction

Radiation is an integral component of therapy for a variety of tumors that may affect young people. Most of these tumors are associated with high cure rates; therefore, treatment results in potential risk for survivorship issues.\(^1\) For young women, premature ovarian insufficiency and decreased reproductive potential are important risks related to this treatment, with consequences regarding bone and cardiovascular health.\(^4\) Total body craniospinal axis, whole abdominal, or pelvic irradiation potentially expose the ovaries to irradiation.\(^7\) Radiotherapy is now a well-known cause of ovarian damage. The amount of injury is related to several variables, including the total radiation dose, the fractionation schedule, and age at the time of treatment.\(^10\)

The human ovary contains a limited number of primordial oocytes that reaches a peak at 5 months after conception and declines with increasing age in a biexponential fashion. This decline culminates in the menopause, when the number of oocytes is < 1,000, at an average age of 51 years old.\(^11\) The ovaries are highly radiosensitive organs. Some authors have suggested that doses > 6 Gy in total body irradiation in young women induce premature ovarian insufficiency, whereas prepubertal women can tolerate even higher radiation doses.\(^2\) In a large cohort of childhood cancer survivors, 215 cases (6.3%) developed premature ovarian insufficiency. Radiotherapy to the ovaries was the most significant risk factor for premature ovarian insufficiency, especially at doses ≥ 1,000 Gy, and exposure to the alkylating agents procarbazine and cyclophosphamide, at older ages.\(^12\) Presumably, this reflects the number of oocytes at the time of exposure: a younger patient has more oocytes and, therefore, a wider fertility window.

Wallace et al.\(^{13}\) created a mechanism to predict ovarian insufficiency according to the age of the patient and to the fractionated radiation dose received by the ovaries. In that model, they reported sterilizing dose of radiation for a known age at treatment and the age of ovarian insufficiency for total body radiation maximum dose of 3, 6, 9, and 12 Gy. This is the first model to predict with reliability the age at which ovarian insufficiency will supervene for any patient after treatment with a known dose of radiotherapy received by the ovaries. However, the described model does not allow an accessible evaluation of the decrease of the time for ovarian insufficiency for other doses and has limited use in clinical practice. Therefore, the present study aimed to review the model created by Wallace et al. and to develop a mathematical model to facilitate the prediction of ovarian insufficiency in the era of modern computed tomography (CT) radiotherapy planning.

Conclusion The present study reports a practicable theoretical method to estimate the loss of ovarian function. These findings can potentially improve the management and counseling of young women patients submitted to radiotherapy during their reproductive years.
Methods

The present study was approved by the Ethics Committee of the involved institutions (CAAE number: 77681317.3.0000.5128). To correlate ovarian radiation dose with ovarian function, we used the formula described by Wallace et al.:\textsuperscript{13} \( g(z) = 10^{0.210.14} \) where “\( g(z) \)” and “\( z \)” represent oocyte survival rate and the radiation dose (in Gray), respectively. To solve the differential equation, we applied the fourth order of Runge-Kutta method using a Matlab algorithm and obtained the number of oocytes at a given age and calculated the residual number after irradiation at any dose.\textsuperscript{14} The Runge-Kutta is an iterative method used in temporal discretization for the approximate solutions of ordinary differential equations. It has enabled a more accurate estimate of the radiosensitivity of the human oocyte. We considered 701,200 the initial number of oocytes at birth and 1,000 the number necessary at menopause.\textsuperscript{15}

For the statistical analysis, R software, version 3.4.2 (R Foundation, Vienna, Austria) was used. The loss of ovarian function (LOF) was defined as the percentage of decrease in the time to ovarian insufficiency compared with the time expected for a woman at the same age without irradiation exposition. Assuming that oocyte decay after irradiation was the same as that for nonirradiated oocytes, we simulated the remaining time for women aged between 10 and 50 years old for exposure to 0.5 Gy to doses that cause immediate ovarian insufficiency. From these remaining times, we could obtain a simple equation relating dose and time until menopause.

To define the relationship between loss of ovarian function and dose, a linear regression was fitted.\textsuperscript{16} To verify the performance of the model, a cross-validation was performed with the leave-one-out method. At the end of the cross-validation process, the root-mean-square error (RMSE) was calculated.

Results

The numerical solution of the differential equation obtained from the Matlab algorithm is shown in Figure 1. The blue curve represents the number of oocytes in a healthy woman at a given age. The green curve shows oocyte decay in a 20-year-old patient who received a 4-Gy dose to the ovaries. The red curve shows the same simulation with an 8-Gy dose. From these simulations, it is clear that the radiation dose greatly affects the remaining time until ovarian insufficiency.

Figure 2 shows the remaining time of ovarian function for ages between 10 and 50 years old for doses ranging from zero to those that cause ovarian insufficiency. The first proposed model (Figure 3) included the entire database but did not represent a satisfactory adjustment (RMSE = 15.22; \( R^2 = 55.7\% \)), as the ovarian function loss for women >40 years old revealed a distinct pattern. Therefore, we readjusted the model excluding women >40 years old. This new model, represented in Figure 4, obtained the equation \( \text{LOF} = 2.70 + (11.08 \times \text{Dose}) \) with an RMSE of 3.05, indicating that the value generated by the formula can range from -6 to +6 years (3.05 × 1.96) with a 95% confidence interval (CI).

Discussion

The equation proposed in the present study can be considered a readily accessible way to predict ovarian insufficiency at an early age.

---

Fig. 1 The influence of aging and fractionated radiation on oocyte number. Blue curve: healthy women; Green curve: woman who received 4 Gy in ovaries at 20 years old; Red curve: woman who received 8 Gy in ovaries at 20 years old.

Fig. 2 Expected time of ovarian function remaining after a certain radiation dose for different ages.

Fig. 3 Relationship between loss of ovarian function and ovarian radiation dose for the complete database.

Fig. 4 Relationship between loss of ovarian function and ovarian radiation dose for women aged 10 to 40 years.
The first model to predict the age of ovarian insufficiency after treatment with a known dose of radiotherapy. In their publication, they provided a table with the predicted age of onset of ovarian insufficiency for ages of treatment from 0 to 30 years old for fixed doses of 3, 6, 9, and 12 Gy.13 Our mathematical model has a sharp CI and yields similar results to those of the table developed by Wallace et al. We observed by our model that the pattern of oocyte/ovarian function loss occurs with different patterns for women younger or older than 40 years old. This can be explained by an increased rate of oocyte loss that occurs around the age of 37 years old, when ~ 25,000 follicles remain.21,22

It is important to note that we did not consider the ovaries receiving different doses, and the results can only be applied to both ovaries receiving the same radiation dose. We acknowledge that this is a predictive model based on preclinical work and that it does not take into account the current use of combined modality treatments. The results do not contemplate the chemotherapy impact on oocytes damage. Radiotherapy is frequently used in combination with chemotherapy for the treatment of cancer. Potentially gonadotoxic chemotherapy may be a contributory factor to the development of premature menopause. It is also important to consider the effect of radiation towards the uterus in terms of fertility. Radiation towards the uterus reduces the size of the organ, makes it less elastic, and, therefore, enhances the risk of spontaneous abortion and premature birth.3,4,23

**Conclusion**

In summary, the present study enables counseling women on their reproductive potential following the successful treatment of their cancer. We have constructed a mathematical model that could be used to quickly estimate ovarian insufficiency after radiotherapy. More studies with clinical outcomes and follow-up of the patients are needed to validate and optimize the proposed model.

**Conflict of Interests**

The authors have no conflict of interests to declare.
References

15. Wallace WH, Kelsey TW. Ovarian reserve and reproductive age may be determined from. Doi: 10.1093/humrep/deh285