Int. J. Radiation Oncology Biol. Phys., Vol. 62, No. 3, pp. 738–744, 2005

0360-3016/05/$–see front matter

doi:10.1016/j.ijrobp.2004.11.038

CLINICAL INVESTIGATION **Ovary**

PREDICTING AGE OF OVARIAN FAILURE AFTER RADIATION TO A FIELD THAT INCLUDES THE OVARIES

W. Hamish B. Wallace, M.D., F.R.C.P.C.H.,* Angela B. Thomson, B.Sc., M.R.C.P.C.H., M.D.,[†] Frank Saran, M.D., F.R.C.R.,[‡] and Tom W. Kelsey, B.Sc., M.Sc., Ph.D.[§]

*Section of Child Life and Health, Department of Reproductive and Developmental Sciences, University of Edinburgh, Edinburgh, Scotland, United Kingdom; [†]Royal Hospital for Sick Children, Yorkhill, Glasgow, Scotland, United Kingdom; [‡]Royal Marsden NHS Trust Foundation, Sutton, United Kingdom; [§]School of Computer Science, University of St. Andrews, St. Andrews, Scotland, United Kingdom

Purpose: To predict the age at which ovarian failure is likely to develop after radiation to a field that includes the ovary in women treated for cancer.
Methods and Materials: Modern computed tomography radiotherapy planning allows determination of the effective dose of radiation received by the ovaries. Together with our recent assessment of the radiosensitivity of the human oocyte, the effective surviving fraction of primordial oocytes can be determined and the age of ovarian failure, with 95% confidence limits, predicted for any given dose of radiotherapy.
Results: The effective sterilizing dose (ESD: dose of fractionated radiotherapy [Gy] at which premature ovarian failure occurs immediately after treatment in 97.5% of patients) decreases with increasing age at treatment. ESD at birth is 20.3 Gy; at 10 years 18.4 Gy, at 20 years 16.5 Gy, and at 30 years 14.3 Gy. We have calculated 95% confidence limits for age at premature ovarian failure for estimated radiation doses to the ovary from 1 Gy to the ESD from birth to 50 years.
Conclusions: We report the first model to reliably predict the age of ovarian failure after treatment with a known dose of radiotherapy. Clinical application of this model will enable physicians to counsel women on their reproductive potential following successful treatment.

Ovarian failure, Radiotherapy, Fertility, Oocytes.

INTRODUCTION

As survival rates for children and adolescents treated for cancer continue to improve, a population of young women of reproductive age emerges for whom issues of fertile potential are paramount. Impaired fecundity and premature ovarian failure are recognized potential late sequelae of radiotherapy to the ovaries.

The human ovary contains a fixed pool of primordial oocytes, maximal at 5 months of gestational age, which declines with increasing age in a biexponential fashion, culminating in the menopause at an average age of 50–51 years. For any given age, the size of the oocyte pool can be estimated based on a mathematical model of decline (1, 2). The rate of oocyte decline represents an instantaneous rate of temporal change determined by the remaining population pool, which increases around age 37 years when approximately 25,000 primordial oocytes remain, and precedes the menopause by 12–14 years (3). Reproductive aging in women is due to ovarian oocyte depletion with approximately 1,000 oocytes remaining at the menopause (4). Assessment of ovarian reserve and reproductive age in healthy women remains a challenge, but the recent application of our solution to the Faddy-Gosden model of ovarian primordial oocyte decline may allow an accurate assessment of ovarian reserve by measurement of ovarian volume (5).

Radiotherapy may be used either alone or in combination with surgery and chemotherapy to provide local disease control for solid tumors. Because of its established late sequelae on immature and developing tissues, irradiation is used cautiously, especially in children and adolescents. Total body, craniospinal axis, whole abdominal, or pelvic irradiation potentially expose the ovaries to irradiation, and may cause premature ovarian failure. The degree of impairment is related to the volume treated, total radiation dose, fractionation schedule, and age at time of treatment (2, 6–8). The number of primordial oocytes present at the time of treatment, together with the biologic dose of radiotherapy received by the ovaries, will determine the fertile "window" and influence the age at premature ovarian failure.

Reprint requests to: W. Hamish B. Wallace, M.D., F.R.C.P.C.H., Department of Haematology/Oncology, Royal Hospital for Sick Children, 17 Millerfield Place, Edinburgh, EH9 1LW, Scotland, UK; Tel: (+44) 131-536-0420; Fax: (+44) 131-536-0430; E-mail: Hamish.Wallace@ed.ac.uk
Received Oct 20, 2004. Accepted for publication Nov 29, 2004.

Assessing the extent of radiation-induced damage of the primordial oocytes and predicting the impact on fertile potential has been challenging. An understanding of ovarian follicle dynamics has allowed us to determine the radiosensitivity of the human oocyte to be <2 Gy (2). Application of this estimate has made it possible to determine the surviving fraction of the primordial oocyte pool for a given dose of radiotherapy and therefore predict the age (with confidence intervals) of premature ovarian failure by applying a mathematical model of decay.

METHODS AND MATERIALS

Radiosensitivity of the human oocyte

Faddy and Gosden provide a model for natural follicle decline in healthy women (1). The model is obtained by incorporating age at menopause data into a least squares analysis of four histologic studies, (3, 9–11) and a large study of ages at menopause (12). The result is the differential equation:

$$dy/\text{day}\ x = -y\left[0.0595 + 3,716\ /\ (11,780 + y)\right]$$

where x denotes age, $y(x)$ is population at age x, and with initial value y (0) = 701,200. The initial value denotes population at birth.

We consider this to be the best model currently available. Early models were simple exponential (3, 6), and were superseded by a biexponential model (4), which included accelerated depletion from age 37 years. The Faddy-Gosden model is the only model that takes into account all available histologic data and combines these with known ranges for the age of menopause. We solved this model to revise our estimate of the radiosensitivity of the human oocyte, based on data obtained from young women who developed ovarian failure after total body irradiation (2). We obtained the surviving percentage function for a given dose:

$$\log_{10} g(z) = 2 - 0.15z$$

which decreases exponentially from 100% at zero dosage ($z = 0$). Solving $g(z) = 50$ gives an LD_{50} for the human oocyte of about 2 Gy. It should be noted that this estimate of the LD_{50} is an upper bound and all modeling is based on the average case.

Predicting ovarian failure

Given the solution to the Faddy-Gosden equation and the surviving percentage function, we can predict the age of ovarian failure for a patient given a known dose (z Gy) at a known chronologic age (x_{chron} years). The average age of ovarian failure is 50.4 years (12). Assuming that the patient is close to the average case, her oocyte population before treatment will be $y(x_{chron})$. The surviving fraction after treatment is $g(z)$ / 100. Thus, the oocyte population after treatment is the product of $y(x_{chron})$ and $g(z)$ / 100. This new population corresponds to an age, x_{reprod}, between x_{chron} and 50.4 years; x_{reprod} is the age at which the Faddy-Gosden model gives the posttreatment population. The patient's predicted remaining reproductive life span is simply 50.4 − x_{reprod}. Her predicted age of ovarian failure is x_{chron} + (50.4 − x_{reprod}) years. An example calculation with $x_{chron} = 12$ years and $z = 10$ Gy is given in Fig. 1a.

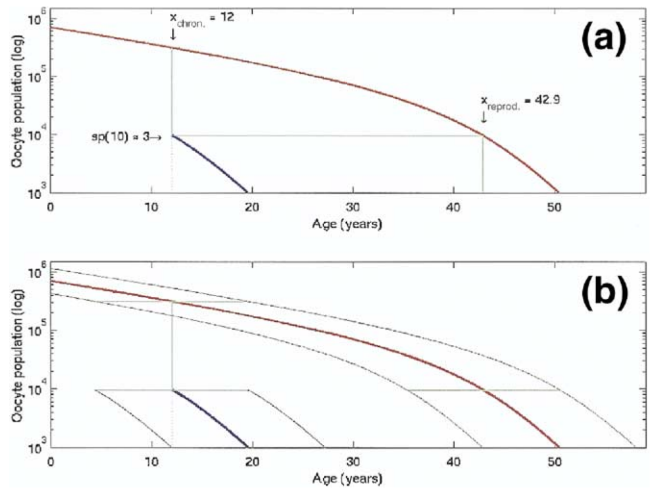

Fig. 1. (a) An example of the method for predicting ovarian failure after treatment. The chronologic age, x_{chron}, is 12 years, and the dose, z, is 10 Gy. The average oocyte population at x_{chron} is 312,000. The surviving percentage after 10 Gy is $\log_{10}$ g (10) = 3.01%, corresponding to a population after treatment of 9,600. This new population is the average population at age 42.9 years, the reproductive age, x_{reprod}, after treatment. The average 42.9-year-old patient is expected to have ovarian failure in 7.5 years, at age 50.4 years. Hence, the 12-year-old patient is expected to experience ovarian failure in 7.5 years, at age 19.5 years. (b) The same example, with confidence intervals included. Average untreated menopause occurs at 50.4 years ± (1.96 × 3.9) years. Average menopause after treatment is the predicted age of menopause (19.5 years) ± (1.96 × 3.9) years.

We next consider a patient having a larger (or smaller) than average follicle population at age of treatment. This corresponds to the case that the patient is likely to have had a later (respectively earlier) than average menopause. In quantitative terms, this means that the patient was toward the upper (respectively lower) limit of the 95% confidence interval for age of menopause: 50.4 years ± (1.96 × 3.9) years (12). The confidence interval used for age of menopause after treatment is the predicted age of ovarian failure ± (1.96 × 3.9) years. This is illustrated in Fig. 1b, again using the example where x_{chron} = 12 years and z = 10 Gy.

Calculating the effective sterilizing dose

Using this model the age of ovarian failure, with 95% confidence intervals, can be predicted given any age from birth to 50 years and any practical dose. The predicted age is based on an estimate of the surviving follicle pool after treatment. We calculate the effective sterilizing dose (ESD) by considering those patients at the upper limit of the 95% confidence interval for follicle population: equivalently, those patients expected to experience menopause at 58 years (50.4 plus 1.96 SD years). The ESD is the dose after which the patients' primordial oocyte population will fall below 1,000. Such a dose will induce immediate ovarian failure in 97.5% of the female population, effectively taking their reproductive age to 58 years. The mean sterilizing dose will induce immediate premature ovarian failure in 50% of women.

Calculating the dose of radiotherapy received by the ovary

Using modern radiotherapy planning methods (computed tomography [CT] planning with or without image fusion) the