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Case Report

Proposal for Radiotherapy Dose Constraint Predicting Uterus Fertility Sparing: Successful Pregnancy Case Report after Curative Chemoradiotherapy for Rectal Cancer

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Abstract

Introduction: Curative sphincter sparing radiotherapy is treatment option for early rectal cancer in patients who are not candidates for a radical surgery. There are many methods developed for fertility preservation in young patients. Pregnancy rates after pelvic radiotherapy are dependent on the radiation dose to ovaries and uterus.

Case Presentation: A 32-year old female was irradiated for anorectal adenocarcinoma T2 N0 M0 with curative chemo-radiotherapy to the total dose of 58, 6 Gy in 2003. The total mean dose was 16 Gy to the uterus and 35 Gy to the uterine cervix. The patient underwent laparoscopic lateral cranial ovarian transposition before radiotherapy. Although a spontaneous conception was not successful, the patient underwent an in vitro fertilisation procedure with donor eggs and conceived twins 10 years after the radiotherapy treatment. She reached a full-term pregnancy and delivered two healthy babies by caesarean section in gestational age of 38 weeks, weighing 2420g and 2220g.

Conclusions: We report a case of full-term delivery of twins after curative radiotherapy for anorectal carcinoma. To our knowledge, this is the first case report of successful pregnancy following sphincter sparing curative pelvic radiation to the total dose 58, 6 Gy. The mean dose to the uterus was 16 Gy and to the uterine cervix 35 Gy. These doses allowed to maintain uterine function for pregnancy after pelvic radiotherapy and we accepted this dose as uterus and uterine cervix for treatment planning constraint.

Keywords: Rectal adenocarcinoma; Radiotherapy; Dose constraints; Uterus; Fertility sparing

Introduction

Radiation therapy in young women has long-term effects on fertility depending on age, radiation dose and site of radiotherapy. Human oocytes are very sensitive to radiation and the estimated median Lethal Dose (LD50) is less than 2 Gy [1]. The radiation exposure leads to premature ovarian failure. The radiotherapy effect is dependent on patient's age and the mean dose of fractionated radiotherapy to the ovarian tissue and uterus. The effective sterilizing dose (which leads to premature ovarian failure in 97.5% of patients) decreases with increasing age of patient. It is 20.3 Gy at the time of birth, 18.4 Gy at 10 years, 16.5 Gy at 20 years, 14.3 Gy at 30 years and only 6 Gy in women beyond 40 years of age [2].

Women after pelvic radiation have not only an increased risk of premature ovarian failure, but suffer also from uterine dysfunction associated with miscarriages, placental abnormalities, preterm labour and low birth weight. Uterine growth is complete around the age of 20 [3]. Radiation exposure of the uterus leads to reduced vascularity, myometrium fibrotic changes and hormone dependent endometrial insufficiency, which decreases subsequent reproductive outcomes due to smaller uterine volumes and atrophic endometrium. In adults, the uterus exposure of 12-14 Gy is associated with significant uterine damage. Childhood exposure to uterine doses of >25 Gy leads to irreversible damage [4]. The highest risk of infertility, miscarriages, preterm labours, intra-uterine growth retardation and low birth weight occurs within one year after radiotherapy [5,6]. Some authors recommend that patients receiving >45 Gy during adulthood and >25 Gy in childhood should avoid attempting pregnancy [7].

The clarity on the radiation dose to the uterus, above which a pregnancy would not be sustainable, is lacking. An evidence of successful pregnancies can be found in the literature like, for example, a report of IVF assisted conception and full-term delivery 14 years after a high-dose chemotherapy and 54 Gy of pelvic irradiation for Ewing's sarcoma (dose to the uterus was not specified) [8]. Herein, we are first to report a case of full-term delivery of twins following a curative radiotherapy for anorectal carcinoma.

Case Presentation

A 32-years old female without comorbidities opted for a curative sphincter sparing radiotherapy over radical abdominoperineal

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resection for distal rectal adenocarcinoma T2 N0 M0. She underwent laparoscopic lateral cranial ovarian transposition 14 days before radiotherapy. Radiotherapy was delivered in prone position with empty bladder using 3D conformal radiotherapy technique. The patient received external beam radiotherapy 48, 6 Gy in 27 fractions combined with concurrent continuous 5-fluorouracil chemotherapy combined with 10 Gy in 2 fractions interstitial anal canal brachytherapy boost (the primary tumour total dose 58, 6 Gy). The mean total dose to uterus was 16 Gy and 35 Gy to the uterine cervix. The dose to transposed ovaries was estimated in the range of 10-12 Gy, as the ovaries were not marked with a contrast clip and were indistinguishable from bowel loops. Spontaneous conception was not successful and the patient underwent an *in vitro* fertilisation with donor eggs 10 years later at the age of 42 years resulting in a full-term delivery with two healthy babies by caesarean section in gestational age of 38+0 weeks. The babies weighed 2420 g (girl) and 2220 g (boy).

Discussion

The radiation exposure of female reproductive organs is an important toxicity issue as almost 50% of cervical cancer, 10% of anal cancer, 5% of colorectal cancer, 2% of uterine or bladder cancer, and number of soft tissue sarcomas occur in women of childbearing potential. The pelvic radiation is often the treatment of choice in management of such cases [7]. Despite low patient numbers of reported successful cases, the published data on fertility outcomes after pelvic radiation serve as a useful indicator of factors impacting chances of fertility preservation.

There have been several methods of fertility preservation developed for these cases: ovarian transposition, gonadal radiotherapy shielding, embryo and oocyte cryopreservation, cryopreservation of ovarian tissue, donor oocytes and gestational surrogacy or ovarian suppression with GnRH analogues or antagonists. The uterine radiation doses of less than 4 Gy seem to have a negligible impact on fertility [9]. The uterine radiation exposure in pre-menarche patients has been more often associated with preterm labour. Thereafter, the radiosensitivity of uterus further decreases with age [10]. Nevertheless, a dose-effect relation has been reported between an increasing uterine exposure and the risk of low birth-weight, with a spontaneous low birth-weight risk of 7, 6% (at a 0 Gy dose level) rising to 25, 5% and 36, 2% at the exposure ranges of 2, 5-5 Gy or >5 Gy, respectively [10].

Data on outcomes of adult Total Body Irradiation (TBI) suggest a pregnancy was possible following 12 Gy TBI, despite elevated rates of preterm deliveries and other complications [7]. Furthermore 14 Gy TBI and bone marrow transplant were noted to lead to ovarian follicular depletion, decreased fertility and impaired uterine growth and blood flow. Pregnancies would terminate in an early pregnancy loss or preterm labour in 50%[11]. The average uterine volume has been reported to decrease to 40% of the normal adult size regardless of oestrogen substitution [12]. Another study evaluating fertility 12 years after a bone marrow transplant have demonstrated an increased risk of spontaneous abortion (37% versus 7%) and preterm delivery (63% versus 18%) of low birth weight children in female TBI recipients compared to the chemotherapy-only group [11]. Oocyte donation represents a treatment option for patients with premature ovarian failure. In a case report of three childhood cancer patients after a bone marrow transplant and TBI, the oocyte donation has resulted in 33% full term delivery rate and 33% risk of miscarriage [13]. Whole abdominal and/or pelvic radiotherapy (20–30 Gy) in childhood has been linked to a shorter uterine length, reduced endometrial thickness and a decreased blood flow later in life, associated with a mid-trimester pregnancy loss [14]. Ultrasound measurements revealed that uterine length in chemotherapy group was 7.3±0.6 cm (mean ±2 SE) versus 4.1±0.8 cm in the group who had received radiotherapy [15]. As for the pelvic irradiation in adolescence or adulthood, the threshold dose for uterine damage remains unknown [7].

A case of a successful pregnancy has been reported in a 25-year-old woman after receiving 30 Gy of pelvic chemo-radiotherapy for anal cancer [16]. Another account has described a successful conception using a donor oocyte program 15 years after irradiation of the right hemi-pelvis for Hodgkin's disease. The pelvic dose has been 36 Gy and the age at irradiation was 16 [17]. Following a higher dose yet and an earlier age of exposure (14y.), a patient irradiated for Ewing sarcoma by 54 Gy and 10 Gy to the left and right hemi-pelvis, respectively, was able to conceive spontaneously and carry the pregnancy to full term [18].

Conclusion

A fertility-sparing pelvic radiotherapy is a feasible treatment option in rectal cancer. Although a precise dose-effect relationship for uterine functional failure has not been established, data from total body irradiation has proven the dose 14 Gy compatible with pregnancy. Some authors point to the similarity of the uterus with other glandular organs (e.g. parotid gland) and recommend to limit the absorbed dose to no more than 20-25 Gy 10, but widely accepted uterus dose constraint is not established and published cases of successful pregnancies in rectal cancer radiotherapy with precisely defined dose are missing. In the current report, we have shown that the mean uterine dose of 16 Gy and the mean cervical dose of 35 Gy were compatible with a full-term twin pregnancy and delivery. We suggest this mean dose could serve as a constraint to maintain uterine function for pregnancy after radiotherapy. The need to address the complexities of fertility-sparing approaches in patients undergoing pelvic radiotherapy underscores the importance of treatment planning in the setting of multidisciplinary oncological teams. Further studies and case reports evaluating uterus dose dependence and associated fertility after pelvic radiotherapy are awaited.

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