SYMPOSIUM

Fertility-sparing Radiation and Chemotherapy

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Keywords: Brachytherapy, Chemotherapy, Fertility preservation, Radiation therapy.
Journal of Postgraduate Medicine Education and Research (2019): 10.5005/jp-journals-10028-1340

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How to cite this article: Kapoor R. Fertility-sparing Radiation and Chemotherapy. J Postgrad Med Edu Res 2019;53(4):168–172.

Source of support: Nil

Conflict of interest: None

Introduction

Owing to the increasing success of oncologists over the past four decades, patients diagnosed with cancer are surviving longer, and care now focuses on improving quality of life and long-term health. Chemotherapy and radiation, the standards of care in cancer treatment, result in significant gonadotoxicity thereby impairing a woman's (and man's) fertility. As a result, cancer patients in their reproductive years are faced with another life crisis in the form of preserving their fertility.

Over 1,00,000 women 45 years of age and younger are annually diagnosed with cancer. Between 1990 and 2008, overall cancer death rates decreased by 23% in men and 15% in women, representing approximately one million lives saved. Approximately 77% of cancer patients diagnosed younger than 45 years. These rates are continuing to improve for the four most serious cancers: lung, colon, breast, and prostate. Gynecologic malignancies account for 1.09 million new cancer cases worldwide consisting of about 12% of tumors affecting female population. About 10% of all female cancer survivors are younger than 40 years of age. Since cancers affecting female genital organs are usually treated by radical surgery, chemotherapy or chemoradiation approaches that induce permanent damage of reproductive functions, the development of strategies for fertility preservation represent one of the most important goals for gynecologic oncology. In this scenario, the newly defined oncofertility discipline acquires increasing interest, offering patients maximal chances to make an adequate decision about future fertility, based on their oncologic diagnosis and prognosis. However, the majority of physicians do not pay particular attention to these issues, even if impressive progresses have been made in this field in the last decades. Possibly, it is due to the lack of strong evidences from clinical trials without an adequate number of cases to establish safety and efficacy of these procedures. In this review I will discuss the most recently debated options for fertility preservation in gynecologic oncology, with radiotherapy techniques and chemotherapy.

Cervical cancer is one of the most common cancers diagnosed in female patients under the age of 40 years.[1] Successful treatment leading to cure is the major concern for most patients. However, for young patients, preservation of fertility and pregnancy related complications after treatment are also of importance. Therefore, if present, the desire to cure the cancer and additionally achieve fertility preservation poses several important considerations both for the patient and the interdisciplinary oncologic team. Due to the trend of delaying child bearing in the interest in fertility preservation might be rising in female cancer patients. For patients with cervical cancer who have to undergo chemo radiation, preservation of ovarian function and preservation of the functionality of endometrial and myometrial structures are of importance but remain a challenge in clinical practice. However bilateral-oophorectomy is not part of uterus to receive nidation and to accommodate normal growth of the foetus to term.[2] The non renewable pool of ovarian primordial follicles declines through atresia with age, from around 2 million at birth to 5,00,000 at menarche. Further decrease of the number of primordial follicles is associated with an increased difficulty of spontaneous conception during lifetime.[3,4] This natural decrease can be aggravated by chemotherapy as well as radiation therapy causing direct DNA damage to follicles. Ovarian tissue is very sensitive to radiation.[5] It was estimated that ≤2 Gy will destroy half of immature oocytes[4,6] and 4 Gy produces infertility in a third of young women and in almost all women over 40 years of age.[7] Childhood Cancer Survivor Study (CCSS) demonstrated that the occurrence of acute ovarian failure was not only associated with older age at diagnosis but also with the conduction of abdominal or pelvic radiation therapy, especially those who received at least 10 Gy to the ovaries.[8] Overcoming these problems would offer selected patients the chance for both, cancer control and preservation of fertility, including nidation of the ovule in their own uterus, e.g., carrying a child to term. Recent interdisciplinary approaches need to be incorporated in the management of young cancer patients desirous of preserving their fertility without comprising on the primary treatment outcome.

Preservation of Ovarian Function, Cryoconservation and Ovarian Transposition

A successful pregnancy is dependent upon a functional hypothalamic-pituitary-ovarian axis and the ability of the preservation of ovarian function is an emerging medical, emotional and quality of life issue for pre-menopausal women affected by

cervical cancer.[9] However, methods of ovarian preservation are often underused (only in 31 out of 108 patients) as demonstrated by Han et al. in a retrospective, single center study.[10] Ovarian function can be preserved either by cryoconservation and re-transplantation of ovarian tissue after oncologic treatment or by ovarian transposition (OT). In current practice a proportion of young cervical cancer patients undergo cryoconservation of unfertilized oocytes after appropriate ovarian stimulation.[11] Another established option which however requires a partner is *in vitro* fertilization (IVF) and cryopreservation of embryos, which is not regulated by legislation in several countries.[9] Alternatively ovarian tissue might be cryopreserved and later be re-implanted, preferably by an orthotropic approach, a procedure which requires no partner and no hormonal stimulation.[12] Whether ovarian suppression through treatment with gonodotropin-releasing hormone (GnRH) agonists or antagonists during chemotherapy might help to maintain fertility is controversially discussed.[13] First live birth after cryopreservation of ovarian tissue followed by transplantation was described in 2004 in a woman with Hodgkin's lymphoma.[12] Literature review suggests that until today the birth of 18 healthy babies has been reported after transplantation of frozen-thawed human ovarian tissue.[14] This promising fertility preservation strategy has also been described in a couple of young women affected by early cervical cancer.[15,16] In order to reduce the dose applied to the ovaries, ovarian transplantation is a surgical procedure to move the ovaries and fallopian tube outside the radiation volume by suturing them within the paracolic gutter as high and lateral as possible (Hwang et al.)[17] demonstrated that fixation more than 1.5 cm above iliac crest was the most important factor for intact ovarian function.[18] Ovarian transplantation can be done during open radical hysterectomy, by laparoscopic approach or more recently used robot-assisted technique.[19,20] Therefore, maintaining of hormonal function can be achieved in 70–93% of women younger than 40 years.[21–26] Successful deliveries after IVF stimulated oocytes retrieval from transposed ovary and transfer to surrogate mothers have been described in patient treated for cervical cancer.[27–29] However, metastases in transposed ovaries also may occur occasionally.[30–32] Data for prevalence of ovarian metastases in patients with cervical cancer in the literature vary between 0% and 15%. Known risk factors for ovarian spread are tumor size, histological type (squamous vs adenocarcinoma), grading, lymphovascular space involvement and hemovascular involvement, all of those having been discussed controversially.[24,33–36]

In case of other pelvic malignancies viz. sarcomas, carcinoma rectum, bone tumors, etc. occurring in young females who are desirous of fertility preservation, it is best to try to keep one or both the ovaries out of the radiation fields if possible depending upon the individual case to case with the help of sophisticated external beam irradiation techniques (intensity modulated radiation therapy [IMRT], volumetric arc therapy and helical tom therapy) offering by means of "dose painting" and sharp dose gradients against normal tissue a considerable dose reduction not only to the transposed ovaries but also to the uterus itself (Figs 1 to 6).

When IMRT should be used to spare healthy uterine tissue, an appropriate management of uterine motion is crucial, as interfractional uterine movement has been well described by others. Besides bladder and rectum filling recommendations we recommend daily soft-tissue imaging with correction for interfractional motion or adaptive replanting if deemed necessary. With the use of MRI guided brachytherapy, the extent of the macroscopic tumor can be exactly determined and the uninvolved corpus uteri should not be part of the target volume.

Chemotherapy-related Ovarian Failure

Another reason of ovarian failure might be the application of chemotherapy in combination with radiation therapy. Most of the available literature on use of chemotherapy and consecutive infertility is limited because of reporting amenorrhea as a surrogate measure of infertility. Generally, a decrease of the total number of primordial follicles could be detected after application of chemotherapeutic drugs and it appears that alkylating agents have the highest risk of permanent amenorrhea, while the risk after cisplatin-containing chemotherapy which is the drug of choice in the treatment of cervical cancer, is considered to be of intermediate risk for infertility.[2,13] Furthermore, it has been described that multi-agent chemotherapy without radiation therapy was not associated with the occurrence and outcome of pregnancies.[37]

Modern Ovarian and Uterine-sparing Techniques in Radiation Oncology

Current prechemoradiation fertility preserving strategies such as cryoconservation of oocytes or ovarian tissue and limitation of the dose applied to the ovaries,[3] ultimately were depending on the use a surrogate mother, as uterine dysfunction after pelvic radiation therapy was assumed to preclude to carry a pregnancy to term. However, due to the availability of newer radiation therapy techniques including IMRT as well as CT and MRT based application of cervical HDR-brachytherapy or even HDR-brachytherapy emulating strategies, e.g., using robotic radio surgery, along with improved fertility preservation methods by reproductive medicine experts, today, the question arises whether fertility can be preserved in young patients with cervical cancer including the ability to carry a pregnancy to term. This would have also forensic implications as third-party reproduction using a gestational carrier is illegal in several European countries. The radio sensitivity of the uterus appears to decrease with advanced age as mentioned above but less data is available from the literature regarding acute and late radiation dose effects on the adult uterus. Milgrom et al.[38] recently described the acute uterine effects after pelvic radiation therapy with a median dose of 50.2 Gy (D95 of the uterus was 30 Gy) in 10 female (7 of which were pre-menopausal) rectal cancer patients who underwent dynamic contrast-enhanced MRI before and 4–7 weeks after radiation therapy. It was found that the median cervical length was reduced after radiation therapy. Interestingly three of the analyzed patients who were initially pre-menopausal underwent ovarian transposition and maintained ovarian function after radiation therapy and three other patients were postmenopausal before radiation therapy. Thus in these six patients radiation induced ovarian failure would not account for the changes in uterine anatomy. Moreover, in pre-menopausal patients the volume transfer constant (Ktrans) and the extracellular extra vascular volume fraction (Ve) were significantly decreased after radiation therapy, suggesting reduced perfusion of the pre-menopausal myometrium after radiation therapy.[38]

These functional changes of the uterus could both lead to an impaired implantation of an embryo as well as pregnancy-related complications.[3] The degree of damage has been shown to be dependent on the total radiation dose and it was shown that the pre-pubertal uterus is more vulnerable than

the adult uterus to the effect of pelvic radiation therapy, with doses of 14–30 Gy causing uterine dysfunction.[3,39,40] It has been reported after total body irradiation using 8.5–11.7 Gy total dose[41] or 14.4 Gy total dose (2.40) in young female patients, that uterine growth and blood flow were impaired. Likewise, after whole-abdominal radiation therapy using 20–30 Gy during childhood the uterine length was shorter and endometrial thickness was not increased after hormone replacement suggesting irreversible damage to the uterus.[39] Others have described in a cohort of 340 female cancer survivors that after abdominopelvic radiation therapy the likelihood to have low-birth-weight infants, premature low-birth-weight infants and the parental infant mortality was increased as compared to patients without radiation therapy. These associations were dose

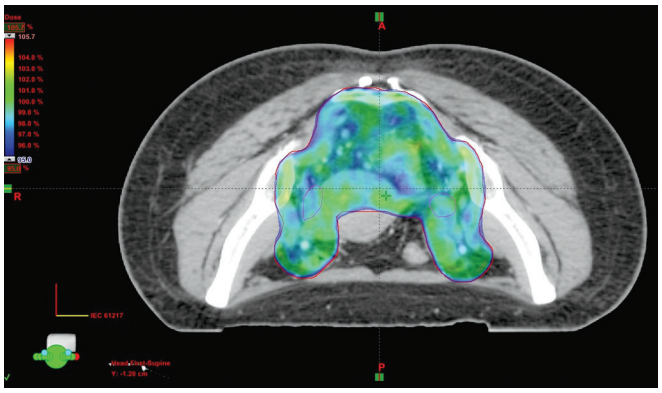

Fig. 1: VMAT plan with color wash

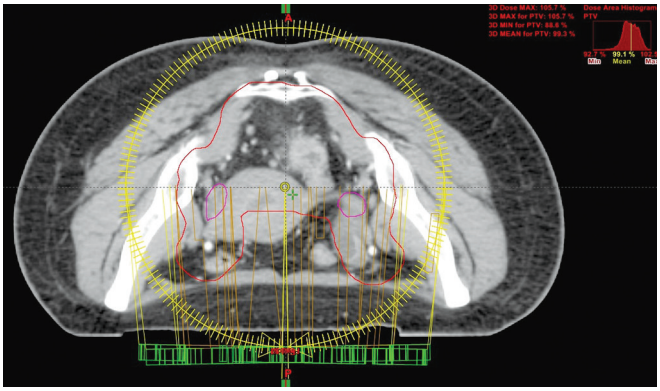

Fig. 2: VMAT plan showing ovarian sparing

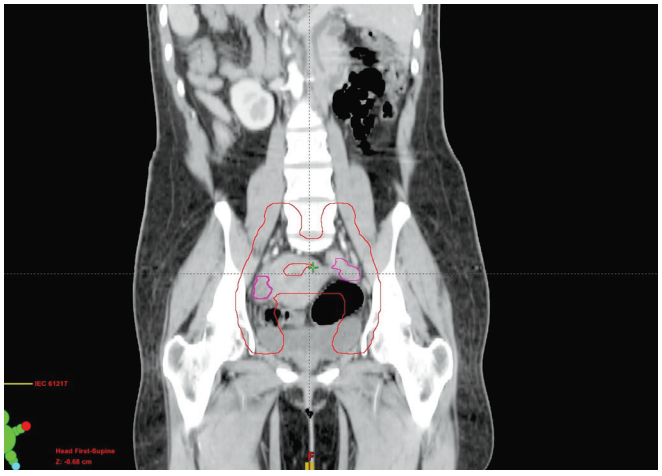

Fig. 3: VMAT plan showing ovarian sparing

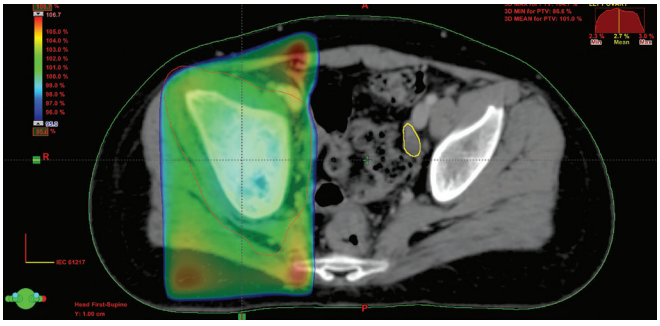

Fig. 4: Dose color wash showing sparing of left ovary

DVH Line	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [Gy]	Max Dose [Gy]	Mean Dose [Gy]
	LEFT OVARY	Unapproved	FINAL	Course1	2.5	100.0	100.3	1.009	1.434	1.211
	PTV boost	Approved	FINAL	Course1						
	PTV	Approved	FINAL	Course1						
	CTV	Approved	FINAL	Course1						
	GTV	Approved	FINAL	Course1						
	BODY	Approved	FINAL	Course1						

Fig. 5: DVH chart showing approved plan

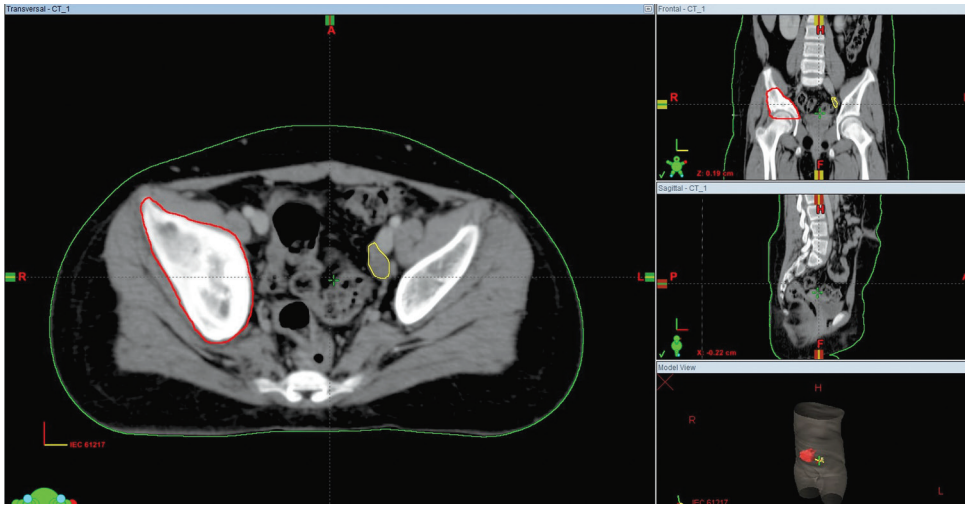

Fig. 6: Showing contouring of GTV of right iliac bone tumor (red) and left ovary (yellow)

dependent and the likelihood to have low-birth-weight infants and parental infant mortality were higher in patients receiving >25 Gy as compared to total doses below 25 Gy.[42]

Conclusion

Fertility preservation options depend on many factors. The age of the patient will provide insight to her ovarian reserve to contemplate the utility of fertility preservation. The tumor type, stage, and treatment plan determine the time available, if any, to proceed with an emergency IVF cycles.

Younger than age 40 undergoing chemotherapy will experience ovarian failure following treatment. Alkylating agents, particularly the combination of oral cyclophosphamide, methotrexate, and fluorouracil (CMF) have the highest risk of ovarian failure. Post chemotherapy resumption of menses, if applicable, occurs in 6 months but may require up to 2 years. It is important to note that the return of menstrual function does not equate with maintenance of pretreatment biologic ovarian age. Therapy results in the death of primordial ovarian follicles and interrupts follicle recruitment and maturation, resulting in decreasing ovarian reserve. So, the reproductive potential of a woman post chemotherapy can still be impaired despite the return of menstrual cycles as demonstrated by a higher rate of infertility and lower ovarian reserve. Furthermore, even prior to therapy, cancer patients have a lower number of eggs retrieved after gonodotropin stimulation for fertility preservation than age-matched healthy controls.[3] Patients undergoing pelvic and abdominal irradiation are at significant risk for ovarian failure following treatment. The ovarian follicles are remarkably sensitive to DNA damage from ionizing radiation. The most damage is from single-dose total radiation therapy rather from fractionated therapy. A dose above 300 cGy is the threshold for permanent ovarian failure. Most pelvic malignancies and Hodgkin lymphoma require radiation doses over, 1,000 cGy and are associated with the highest risk for permanent loss of ovarian function.

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