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Review

Müllerian duct anomalies and their effect on the radiotherapeutic management of cervical cancer

Madhup Rastogi[1], Swaroop Revannasiddaiah[2], Pragyat Thakur[1], Priyanka Thakur[1], Manish Gupta[1], Manoj K Gupta[1] and Rajeev K Seam[1]

Abstract

Radiotherapy plays a major role in the treatment of cervical cancer. A successful radiotherapy program integrates both external beam and brachytherapy components. The principles of radiotherapy are strongly based on the anatomy of the organ and patterns of local and nodal spread. However, in patients with distorted anatomy, several practical issues arise in the delivery of optimal radiotherapy, especially with brachytherapy. Müllerian duct anomalies result in congenital malformations of the female genital tract. Though being very commonly studied for their deleterious effects on fertility and pregnancy, they have not been recognized for their potential to interfere with the delivery of radiotherapy among patients with cervical cancer. Here, we discuss the management of cervical cancer among patients with Müllerian duct anomalies and review the very sparse amount of published literature on this topic.

Key words Cancer of the cervix, cervical carcinoma, uterocervical anomalies, Müllerian duct anomalies

Müllerian duct anomalies are a collective set of congenital malformations of the female genital tract, manifesting from abnormalities at any phase of the embryological development involving Müllerian duct genesis, fusion, or septal resorption. Though these anomalies may often remain clinically silent, a number of women develop symptoms such as delayed onset of menstruation, hematocolpos, and dyspareunia[1,2]. The deleterious effects of Müllerian duct anomalies on conception, pregnancy, and labor have been extensively studied[3,4].

Cervical cancer is a major cause of cancer mortality and morbidity among women. Radiotherapy (RT) with concurrent chemotherapy is the current standard treatment for locally advanced cervical cancer. RT is also an equivalent alternative to surgery for early-stage disease[5]. RT for cervical carcinoma includes both external beam RT (EBRT) and intracavitary brachytherapy (ICBT). ICBT is arguably the traditional mainstay of treatment for cervical carcinoma, with EBRT used to deliver doses to target volumes beyond the geometric reach of ICBT and to downsize a tumor for ideal geometry during ICBT[6,7]. Importantly, perfect geometry must be achieved for an acceptable dose distribution in ICBT applications. However, altered anatomy, as is often seen with congenital anomalies of the female genital tract, may impose difficulties in the fulfilment of the rigid rules of the time-tested Manchester system (of gynecologic ICBT).

The intention of this review is to refresh the reader's knowledge regarding normal and abnormal development of the female genital tract, the difficulties that abnormal anatomy impose upon standard RT implementation, and, most importantly, the consequences of missing an anatomical defect prior to RT planning and delivery.

Normal Development of the Female Genitourinary Tract

The embryological development of the female genitourinary tract roughly begins at the sixth week of in-utero life. The main structures involved include the Müllerian (paramesonephric) ducts, Wolffian (mesonephric) ducts, and the genital ridge. In the female embryo, the Wolffian ducts undergo atrophy, whereas the Müllerian ducts persist to undergo further development. At around the third month of intrauterine life, the two Müllerian ducts begin to fuse. The fusion leads to the formation of a septum in the midline, which normally begins to disappear from the caudo-cephalad direction. In the normal

Authors' Affiliations: [1]Department of Radiotherapy & Oncology, Regional Cancer Centre, Shimla, Himachal Pradesh 171001, India; [2]Department of Radiation Oncology, HCG–Bangalore Institute of Oncology, Bengaluru, Karnataka 560027, India.

Corresponding Author: Swaroop Revannasiddaiah, Department of Radiation Oncology, HCG–Bangalore Institute of Oncology, Bengaluru, Karnataka 560027, India. Tel: +91–9805192039; Email: swarooptheone@gmail.com.

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process, the midline septum is completely resorbed, leading to the development of a patent uterine cavity, cervical canal, and the vagina[8,9].

The lateral parts of the ducts remain un-fused, and eventually transform into the fallopian tubes. At the fifth month of intrauterine life, a ring-like constriction appears and represents the position of the uterine cervix. Around the sixth month of intrauterine life, the walls of the uterus begin to thicken[8].

The embryological development of the genital tract and the urinary system is often described together, because of not only the proximity of the developing structures but also the large degree of overlapping origins. Indeed, it is notable that up to 50% of women with Müllerian duct anomalies also have associated renal agenesis[10,11].

Classification Müllerian Duct Anomalies

The American Fertility Society (AFS) scheme is most often used to classify the very broad range of Müllerian duct anomalies[12,13]. The scheme includes seven categories (**Figure 1**). Malformations resulting from hypoplasia or agenesis of both Müllerian ducts are categorized as Class I. Malformations arising from incomplete development or absence of a single Müllerian duct are categorized as Class II, and this class covers anomalies such as unicornuate uterus. Malformations arising from complete absence of fusion of the two Müllerian ducts are categorized as Class III. The resultant anomaly for Class III is uterus didelphys, which is characterized by two individual uterine horns—each having its own cervix and

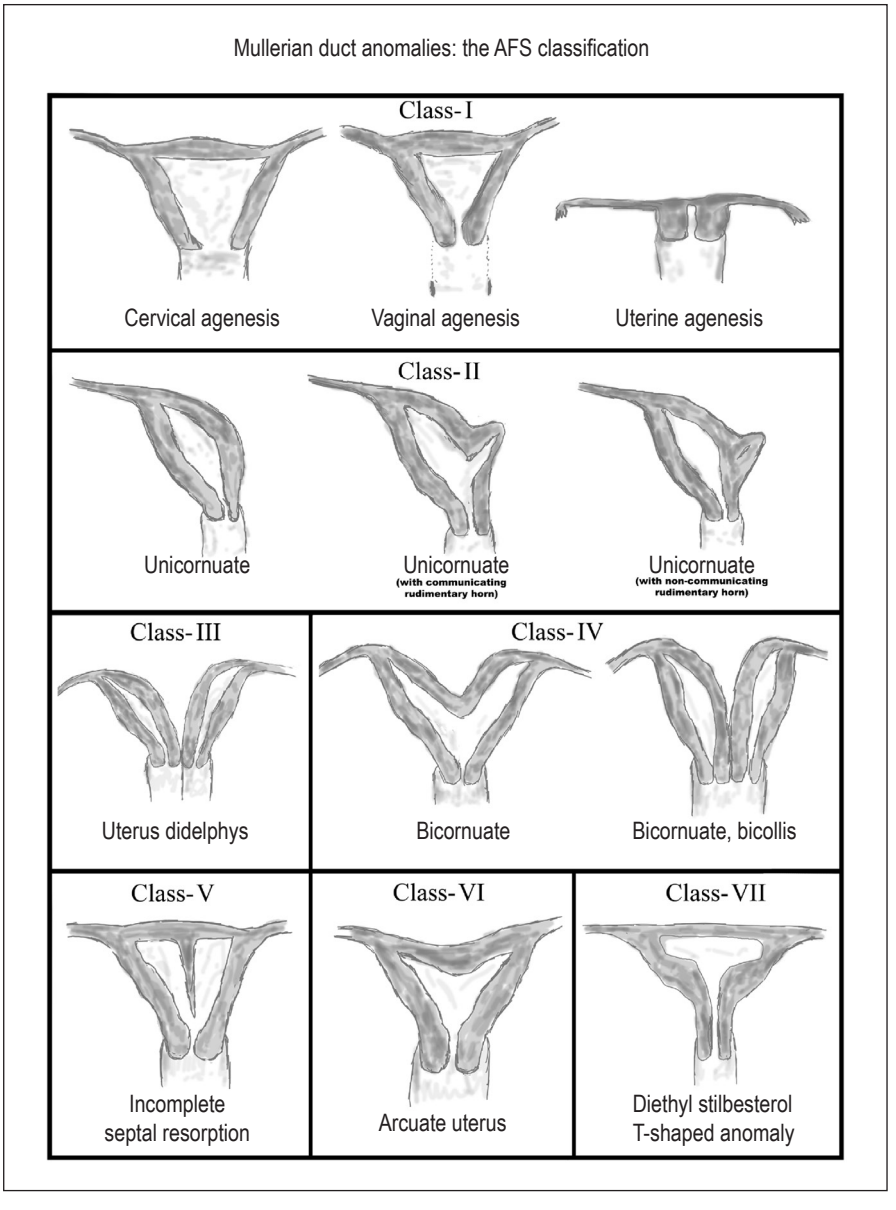

Figure 1. **The variety of possible Müllerian duct anomalies as per the American Fertility Society (AFS) classification scheme.**

vagina. Anomalies arising from the partial fusion of the Müllerian ducts are categorized as Class IV. This class includes lesions such as bicornuate bicollis (two uterine horns and two cervices) and bircornuate unicollis (two uterine horns with a single cervix). Class V includes anomalies arising from a failure in septal resorption after successful fusion of the Müllerian ducts, leading to septate uterus. Class VI anomalies are often clinically insignificant, with the surface of the uterine contour being concave on the outside and resulting in a small uterine cavity, as in arcuate uterus. Class VII is dedicated to rare diethylstilbesterol-related congenital malformations.

Diagnosis of Müllerian Duct Anomalies

The majority of patients with Müllerian duct anomalies remain asymptomatic, with a proportion of patients being diagnosed during investigative work-up for infertility or having the condition detected during complications with pregnancy and labor. Some Müllerian anomalies, especially the obstructive types, may be detected at the onset of menarche due to obstructed outflow of menstrual blood, leading to the easily detectable hematocolpos or the more serious hematoperitoneum[1].

The available investigative tools include hysteroscopy, laparoscopy, hysterosalpingography, ultrasonography, and magnetic resonance imaging (MRI). While hysteroscopy allows the visualization of the uterine cavity, it may not be able to assess the thickness of the myometrium or the presence of anomalies outside the accessible cavity, such as a rudimentary horn. Laparoscopy can be used to grossly visualize the uterus and its external structure but would not be able to detect lesions on the inside of the reproductive tract. Hysterosalpingography is a radiological procedure that involves X-ray imaging after the instillation of contrast into the reproductive tract. It allows for delineation of the shape of the uterine cavity but would be insensitive to non-communicating lesions outside the main cavity, as in a rudimentary horn[14].

Hysteroscopy, laparoscopy, and hysterosalpingography may have established diagnostic and therapeutic roles in the evaluation of infertility associated with Müllerian duct anomalies. However, the presence of an obstructive carcinoma in or around the cervical os may preclude the utility of hysteroscopy and hysterosalpingography. Laparoscopy, if resorted to, must be exercised with caution, keeping in mind the morbidity that may arise from the subsequent initiation of RT[15].

The advent of ultrasonography and MRI has made the detection of Müllerian duct anomalies simple and convenient to both the patient and the investigator. Ultrasonography is often the initial imaging modality of choice, owing to its availability and affordability. Endovaginal ultrasonography in combination with transabdominal ultrasonography may provide acceptable sensitivity[16-18].

MRI is the undisputable standard modality for imaging uterine anomalies. Its excellent soft tissue contrast helps in the detection and characterization of lesions in the uterine cavity or the myometrium. If MRI were to be employed in all patients with cervical carcinoma, it would not only help in planning treatment but may also provide information about coexisting congenital malformations of the uterus, in addition to more common lesions like uterine fibroids (leiomyomas)[17,19].

The Prevalence of Müllerian Duct Anomalies among Patients with Cervical Cancer

If cervical carcinoma is superimposed upon the large domain of anatomical variations possible under Müllerian duct anomalies, there are undeniable implications on the planning and delivery of RT. Because the prevalence of Müllerian duct anomalies is estimated to be as high as 5.5%–6.7% among the general female population, it is possible that a similar percentage of women with cervical cancer may have a coexisting Müllerian duct anomaly[20,21].

Given the high incidence of cervical carcinoma in the world, the absolute number of patients with cervical carcinoma and Müllerian duct anomalies can therefore be expected to be very significant, especially in the Asian, African, and South American nations. More importantly, many regions with high incidence of cervical carcinoma are less likely to afford the use of sectional imaging prior to RT, leading to missed diagnosis of anatomical anomalies in the utero-cervical region and consequentially resulting in treatment delivered with no regard to the underlying anatomical abnormality.

An estimated 5% of all cervical cancer patients may have undetected various degrees of malformations, and these patients could receive improper dose distributions attributable to non-recognition of peculiar anatomical configurations. Such possibilities could be the highest in low resource settings where MRI is not used routinely prior to RT. Notably, however, FIGO recommends neither the use of MRI nor CT as mandatory in the staging work-up of cervical cancer[22].

Treatment of Cervical Carcinoma among Patients with Müllerian Duct Anomalies

Cases of cervical carcinoma among women with congenital uterine malformations have been reported at surprisingly low numbers in the published literature. Only 29 cases were recovered on our extensive search of literature indexed in the following databases: MEDLINE, PubMed, Embase, Copernicus, Directory of Open Access Journals (DOAJ), Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Index Medicus. However, of the 29 cases of cervical carcinoma in patients with congenital uterine anomalies reported, the majority of the reports are descriptions of either pathology or treatment with surgery. Only two reports have described the use of RT for treatment, and both were reported after year 2000[23-35].

The low number of reported cases is likely due to an overall low incidence of cervical carcinoma in developed countries, where the incidence of endometrial carcinoma outnumbers cervical carcinoma. Additionally, it must be acknowledged that a majority of cases from the developing world may go unreported, even if detected.

The presence of Müllerian duct anomalies could possibly complicate, or at times, disallow the attainment of preferred radiation dose distribution to target volumes (**Figure 2**). A brief outline of the issues associated with treatment planning and delivery is summarized in Table 1. Traditionally, ICBT has been considered the main radiation delivery modality to attain suitable dose delivery with techniques and principles that have evolved over decades of observations and experimentation. Indeed, the minimum required dose to *point A* is assumed to be 85 Gy to attain reasonable survival—a dose that cannot be attained by EBRT alone because of the proximity of dose-limiting critical structures[36]. According to our current understanding, both ICBT and EBRT are important, and failure to optimize either could lead to adverse outcomes, not only in the form of treatment failures but also undue toxicities.

In reviewing the only two previously published experiences using RT, we note that both reports used a combination of EBRT and ICBT. The first of the two reports, published by Lee *et al*.[23], described a patient with uterus didelphys with invasive carcinoma (measuring 2.2 cm × 3.3 cm in maximum dimensions) involving both cervices. After initial treatment of the pelvis with a 4-field technique to a dose of 45 Gy in 25 fractions, Lee and colleagues employed brachytherapy with high-dose-rate afterloading using two applicators, one into each cervix. They noticed that the use of point A for dose prescription would require redefinition of point A, in view of the patient having two cervices. In fact, modifying point A to lie 2 cm lateral and superior to each cervical os would have resulted in a very wide prescription isodose surface, which could potentially overdose midline structures. Hence, they set a new prescription point—that is, "the midline between the two intrauterine tubes, 2 cm superior to the mean position of the small metallic flanges located at each of [*sic*] cervix." When they prescribed 6 Gy + 6.5 Gy (in two high-dose-rate treatments) to their customized midline prescription point, they noted that both cervices received 8–9 Gy each treatment. At about 4 years of follow-up, the patient was free of disease and extraordinary toxicity[23].

The second report published by Loo *et al*.[24] described a patient with bicornuate bicollis uterus with carcinoma involving both cervices. The tumor measured 5 cm × 4 cm in maximum dimensions and was bulkier on the right side. After undergoing concurrent chemotherapy (weekly cisplatin at 40 mg/m^2) with external beam RT with 4-field technique to 50 Gy in 25 fractions, the patient underwent ICBT with low-dose-rate Cs-137. Loo and colleagues customized the definition of point A so that each cervix had its own right and left point A without regard to the other cervix. They used two applications, with the applicator inserted into the right uterine canal on the first application and into the left uterine canal on the second application. They also prescribed dose such that both point As received an average low-dose-rate dose of 18 Gy over two applications. At two years after treatment, the patient is free of disease and has manageable side effects including intermittent cystitis, hematuria, and slight rectal bleed. Longer follow-up is not provided[24].

Recent Modalities with Encouraging Prospects

The expense associated with MRI has been progressively decreasing, and in the future, further technologic advancements and cost reductions may occur. Detection and characterization of the tumor and malformation is the first step in optimizing management, and MRI can be used to do both.

The simultaneous implementation of both intracavitary and

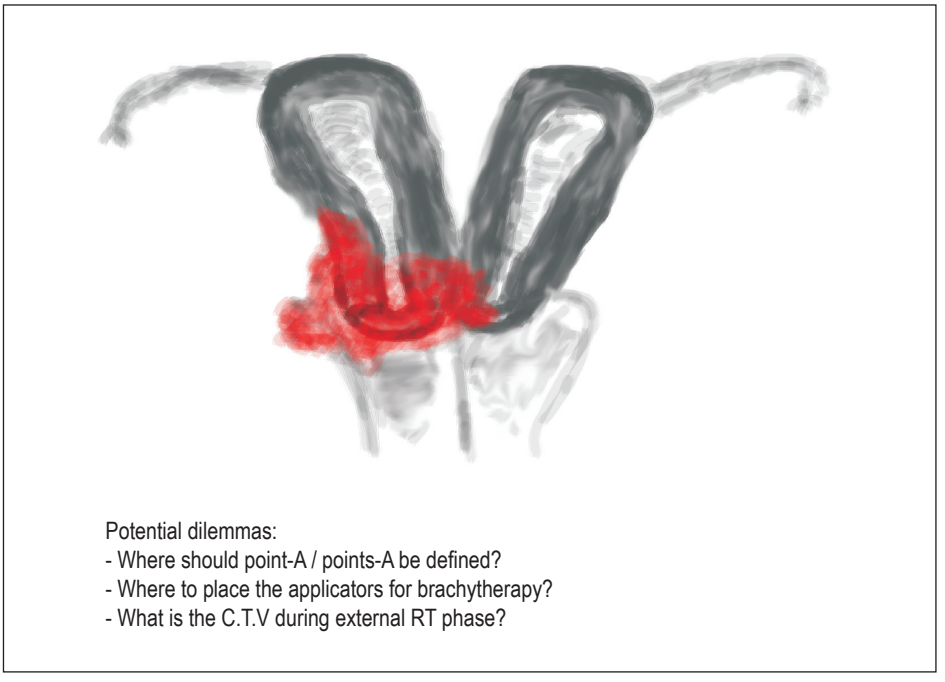

Figure 2. **Ambiguities exist with regard to the use of both brachytherapy and external beam radiotherapy in the treatment of cervical carcinoma, when associated with Müllerian duct anomalies.**

Table 1. A summary of the issues in management of cervical cancer among patients with Müllerian duct anomalies and their potential implications

General issues	• Staging can be ambiguous • Natural history may be altered • Common association with renal agenesis, which could influence the use of potentially nephrotoxic agents, like cisplatin, that are a part of standard chemoradiotherapy • Non-use of sectional imaging prior to radiotherapy may make the clinician totally oblivious to the underlying anomalies
Issues arising in treatment planning	• Decision making needs to be intrepid, in view of the very minimal amount of prior literature on the topic • Treatment volumes for external beam radiotherapy are ambiguous, with no set recommendations regarding the irradiation of aberrant structures • No available literature to describe the lymphatics of the various Müllerian duct anomalies • Time-tested Manchester system cannot be applied for intracavitary brachytherapy (ICBT), especially because of the inability to define a point A in patients with anomalies featuring double cervix and uterus • Altered anatomy of the uterus may not allow for adequate coverage under the characteristic "pear shaped" isodose curves of ICBT • Relationship between point A and the utero-cervical triangle may be lost • Intensity-modulated radiotherapy (IMRT) for cervical carcinoma in general is not established and consensus guidelines are still a work-in-progress. IMRT for cervical carcinoma with Müllerian duct anomalies may need pioneering delineation efforts on a case to case basis
Issues arising in treatment delivery	• Applicator placement for ICBT may be fraught with obstructions • Even the mildest of anomalies, such as the arcuate uterus, may not allow adequate penetration of the central tandem, which may possibly lead to under-dosage of the upper parts of the uterus • Anatomical friability of the uterine cavity may also be associated with risks of perforation • The use of interstitial implants may also be complicated by the altered geometry • Uncertain dose delivery to anomalies such as the rudimentary horn, which may be centimeters away from the uterine tandem

interstitial applicators customized by image-guided adaptive brachytherapy (IGABT) with MRI-compatible applicators for "image-guided dose prescription" may offer an entirely new way to optimize dose distribution. This approach holds great potential in cervical carcinoma and may be of special benefit in cervical cancer patients with Müllerian duct anomalies, for whom customized dose distribution is often a necessity.

Stereotactic body radiotherapy (SBRT) may be an acceptable alternative to brachytherapy, especially when brachytherapy is not feasible. Hsieh *et al*.[37] reported the successful use of helical tomotherapy in a patient with cervical carcinoma in whom large intrauterine leiomyomas precluded the use of standard brachytherapy. A similar approach with either IMRT or SBRT may be very useful when brachytherapy is not possible due to a uterine malformation that impedes ideal applicator placement and thereby precludes an acceptable dose distribution. Even though IMRT cannot be expected to deliver as high as a dose would be possible with ICBT, it would still be a better option than older techniques such as conventional and three-dimensional conformal RT.

Conclusions

Among patients with cervical cancer who have utero-cervical anomalies, radical surgery should be selected over radiotherapy in the early operable stages. When inoperable, concurrent chemoradiotherapy with image guidance for both EBRT and brachytherapy, with suitable optimizations, could lead to acceptable results. When brachytherapy is impossible, newer techniques such as IMRT and SBRT may hold acceptable potential to attain desirable dose distributions.

Going by the adage, "the eyes cannot see what the mind does not know," we can assume that the clinical team, including radiologists, radiation oncologists, and gynecologists, are less likely to visualize a uterine anatomical malformation unless they are open to the possibility of such occurrences.

Additionally, "the mind will not know of what the eyes don't see," meaning that failure to diagnose will lead to failure in customizing treatment in regards to the patient's anatomy. Successful management of cervical carcinoma among women with Müllerian duct anomalies will be facilitated by detection of such coexistences, and then, with the optimization of the available resources to customize the best possible plan for the individual patient.

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