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Dose-volume correlation of cumulative vaginal doses and late toxicity after adjuvant external radiation and brachytherapy for cervical cancer

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ABSTRACT

PURPOSE: To investigate dose-response relationship between vaginal doses and long-term morbidity.

METHODS AND MATERIALS: Patients receiving adjuvant pelvic (chemo) radiation and brachytherapy for cervical cancer from January 2011 to December 2014 were included. Baseline vaginal length was determined clinically and from imaging at BT planning. Dose points were defined along mucosa and at 5 mm depth at 12, 3, 6, and 9 'o' clock positions at every 2 cm from apex to introitus. Cumulative equivalent doses in 2 Gy were calculated. Vaginal stenosis was reported in reference to baseline length according to CTCAE version 3.0. Receiver operator characteristics curve was used to identify dose thresholds for univariate and multivariate analysis.

RESULTS: Overall, 78 women with median age of 49 (32−71) years were included. The median dose at vaginal apex mucosa and 5 mm depth was 118 Gy_3 (78−198) and 81 Gy_3 (70−149) respectively. At median follow-up of 36 (18−60) months, vaginal stenosis ≥25%, and grade ≥ II telangiectasia was observed in 33.3% and 45.7%, respectively. On receiver operator characteristics analysis, apical mucosal dose >142 Gy_3 and recto-vaginal point dose >86 Gy_3 predicted for stenosis on univariate ($p = 0.02$, $p = 0.06$) and multivariate analysis ($p = 0.04$). The probability of stenosis increased from 32% at 70 Gy_3, 38% at 80 Gy_3, and 45% at 90 Gy_3 rectovaginal point dose. No correlation was observed between vaginal doses and telangiectasia and vaginal stenosis and sexual quality of life.

CONCLUSION: Vaginal apex mucosal dose >142 Gy_3 independently predicts for vaginal stenosis.

Keywords: Vaginal morbidity; Cervical cancer; Brachytherapy

Introduction

Postoperative chemo radiation and/or vaginal brachytherapy is associated with reduced local recurrence and prolonged progression-free survival (1−3). Treatment-related late toxicities have significant impact on quality of life (QOL) (4). Although gastrointestinal and genitourinary morbidity has been reported, there is paucity of data on late vaginal morbidity and its impact on sexual QOL. Recently the International study on MRI-guided Brachytherapy study (EMBRACE), reported low incidence of any serious

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vaginal side effects with the use of image-guided brachytherapy. Most common morbidity was vaginal stenosis followed by vaginal dryness (5). A subsequent study by the same group reported dose-response relationship in reference to recto-vaginal dose point (6). Another study from India however reported lack of association between the vaginal doses and toxicity (7). Discordant results could possibly be attributed to difficulty in defining a uniform vaginal reference points during fractionated brachytherapy in the presence of intracavitary applicators and packing. This is even more pronounced in patients who have residual disease at brachytherapy. Therefore, we hypothesized that the dose-volume relationship could possibly be best defined in clinical situations wherein there is no residual disease at brachytherapy and in applications that allow uniform circumferential dose fall off. Vaginal brachytherapy in patients undergoing adjuvant radiation represents one such situation where vaginal length and dose points can be easily defined in reference to the radiation source as there is no residual disease and vaginal packing. This study was therefore designed to investigate dose-volume relationship for vaginal radiation dose and late toxicity and sexual QOL in patients undergoing postoperative radiation and brachytherapy for cervical cancer.

Methods

Patients with early-stage cervical cancer receiving external radiation and vaginal brachytherapy treated between January 2011 and December 2014 within NCT 01279135 (PARCER study) were eligible. A separate institutional scientific review board approval was obtained for the present study, and patients were consented for intravaginal photography in addition to pelvic examination during follow up. All patients had completed treatment and were disease free before inclusion in this study. The details of external radiation planning have been previously reported (8−10). As a significant proportion of patients had simple hysterectomy with or without oophorectomy (rather than type III hysterectomy) therefore after completing external radiation to a dose of 50 Gy/25 fractions/5 weeks and concurrent chemotherapy, all patients received boost brachytherapy to minimize the chances of vaginal relapse. Brachytherapy was performed with vaginal cylinders. The circumference of the cylinder prescribed was determined by maximum distance between the examining fingers and largest diameter that could be comfortably accommodated in the vagina was selected. Brachytherapy planning was performed on Oncentra planning system (version 4.1; Nucletron B.V. Elekta, Stockholm, Sweden), and 12 Gy/2 fractions/7 days was delivered to upper one-third of vaginal length with central vaginal source cylinder (Nucletron B.V. Elekta, Stockholm, Sweden, Vaginal applicator #084.350) with dose prescribed at 5 mm from the surface of the applicator. No dose point optimization was performed.

For the dose-point correlation, vaginal mucosal dose points were described from vaginal apex up to introitus at interval of 2 cm and circumferentially at 12, 3, 6, and 9'o clock positions. Additional points were also described at 5 mm outside distance from vaginal surface at similar intervals (Fig. 1). Doses were derived using the live dose options available on Oncentra planning system Version 4.1. Combined contribution of external radiation and brachytherapy was calculated using $\alpha/\beta = 3$ and 10 using Medical University of Vienna sheet (11). For late toxicity assessment $\alpha/\beta = 3$ was used for all calculations.

Pre-brachytherapy vaginal length was obtained by clinical examination before vaginal brachytherapy and corroborated with cylinder length in brachytherapy planning scans. This length was used as a reference for evaluating vaginal stenosis at follow up. At each follow up, bi-digital, bimanual, and per speculum examination was performed to assess the disease status. A detailed evaluation of vaginal sequelae included assessment of vaginal length and telangiectasia. Vaginal symptoms were scored as per CTCAE version 3.0. The length was measured from vaginal apex to introitus. Telangiectasia mapping was done along the circumference and the length according the 'o' clock position and a grade was attributed as per CTCAE version 3.0 (12). Worst grade during the course of follow up and corresponding maximum and mean dose was used for statistical analysis.

Quality of life (QOL)

Because the patients were a part of ongoing clinical trial, they were administered English or validated vernacular version (Hindi, Marathi) of EORTC QLQ-C30 and Cx 24 (13, 14) at baseline and subsequently at each follow up. For the present study, 13 questions pertaining to sexual

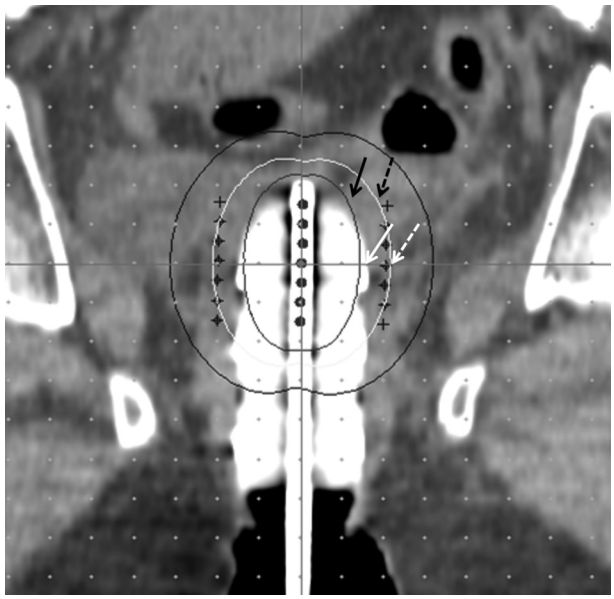

Fig. 1. Coronal section of planning CT cut showing CVS applicator with loading and 100% isodose line (white) at 5 mm from CVS surface. Dose was estimated at cylinder surface and at 5 mm depth at vaginal apex (black solid and dashed arrow) and at 2 cm from vaginal apex (solid white and dashed white arrow). CVS = central vaginal source.