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Locally advanced cervical cancer in renal transplant patients: A dilemma between control and toxicity

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ABSTRACT

PURPOSE: Treatment of locally advanced cervical cancer in patients with a renal graft requires precautions. The graft is usually in a pelvic position, close to the clinical target volume (CTV). Preserving the graft while ensuring local control is a challenge we have faced in two occasions. We report our experience.

METHODS AND MATERIALS: We report the cases of 2 patients treated at our institution with a modified workup and therapeutic approach compared with our standard approach. The clinical and technical aspects of both treatments were systematically reviewed and contrasted with reports previously cited in the literature.

RESULTS: The first patient received external beam conformal radiotherapy (total dose: 30 Gy in the pelvis) followed by two sessions of MRI-guided brachytherapy (2 × 15 Gy to 90% of the intermediate risk CTV). The second one received pelvic intensity-modulated radiation therapy (total dose: 45 Gy) followed by MRI-guided brachytherapy delivering 15 Gy to 90% of the intermediate risk CTV. Both patients had a complete response and were still in remission more than 2 years after treatment while retaining their graft. No severe late toxicity was reported.

CONCLUSIONS: External beam radiotherapy followed by brachytherapy is feasible in locally advanced cervical cancer, despite the presence of a kidney graft near the targets. Image-guided adaptive brachytherapy allowed an accurate evaluation of the dose distribution, reaching the recommended treatment thresholds with optimal protection of the graft.

Keywords: Image-guided brachytherapy; Cervical cancer; Kidney; Graft; Radiotherapy

Introduction

It is commonly assumed that immunosuppression greatly increases the risk of cancer in kidney grafted patients. This relationship is strong for nonmelanoma skin cancers, lymphoma, or Kaposi sarcomas when compared with the general population (approximately 20-fold). Cervical cancer is thought to be five times more common in kidney grafted patients than in the healthy population (1). However, the mechanism of this susceptibility is not fully understood. Immunosuppression itself is probably an important factor, promoting infection by human papilloma viruses and decreasing vigilance of mitotic checkpoints, but there might also be direct interactions between oncogenic processes and drugs. Thus, the promoter of E6 and E7, the major human papilloma virus oncogenic proteins, includes a glucocorticoid receptor–responsive element and rapamycin, used in recent immunosuppressive protocols, which might disturb the phosoinositide 3-kinase/phosphatase and TENsin homolog/mammalian target of rapamycin pathway (2). This underlines the need for a close surveillance to observe a possible increase in the cancer rate.

Concomitant chemoradiation followed by brachytherapy is currently the standard of care treatment for locally advanced diseases, which leads to major therapeutic challenges in kidney transplanted patients (3). To begin with, the graft is usually implanted in the iliac position, next to the external beam radiotherapy (EBRT) lymph node clinical

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target volume (CTV). Moreover, this position is close enough to the cervix so that the doses delivered with brachytherapy are significant, and should also be considered (Fig. 1). Second, graft tolerance to radiotherapy and its potential variability between cases are unknown. Finally, concomitant chemotherapy can aggravate immunosuppression, and weekly cisplatin, which is the most widely used regimen, is nephrotoxic. The treatment of these patients aims to preserve the functionality of the graft and at the same time ensure control of the cancer, especially because IIB lesions have a rather good prognosis when treated with modern radiation techniques. In the past years, we have faced this situation twice and have proposed two different solutions, which have provided good results.

Methods and materials

Patients

Two patients with histologically proven cervical carcinoma were selected for this study. Their data were retrospectively analyzed. Both were referred from nephrology department. A complete workup associating pelvic MRI and positron emission tomography (PET)/CT was performed in both the cases. Staging was defined according to the International Federation of Gynecology and Obstetrics (FIGO) classification based on clinical examination. Treatment strategy was defined by the tumor board.

External beam radiation therapy

Both patients were treated with pelvic EBRT. Treatment planning was based on a CT scan. Axial slices were acquired (3 mm thick) with an intravenous iodine injection to enhance the cervix, as well as the lymph nodes, and facilitate the contouring. Organs at risk (OARs; a pelvic CTV encompassing the cervix, the whole uterus, the parametria, and the proximal third of the vagina) and lymph nodes CTV (external and internal iliac area, as well as ilio-obturator, presacral, and common iliac) were delineated on an IsoGray platform (DOSIsoft, SA, Cachan, France). A planning target volume was generated applying a three-dimensional (3D) margin of 7 mm around the lymph nodes CTV and 10 mm around the pelvic CTV. The leaves were automatically placed to ensure a perfect coverage of the planning target volume. The EBRT was delivered using high-energy photons (18 or 20 MeV), with standard fractionation: 1.8 Gy per fraction, one fraction per day, and five fractions per week.

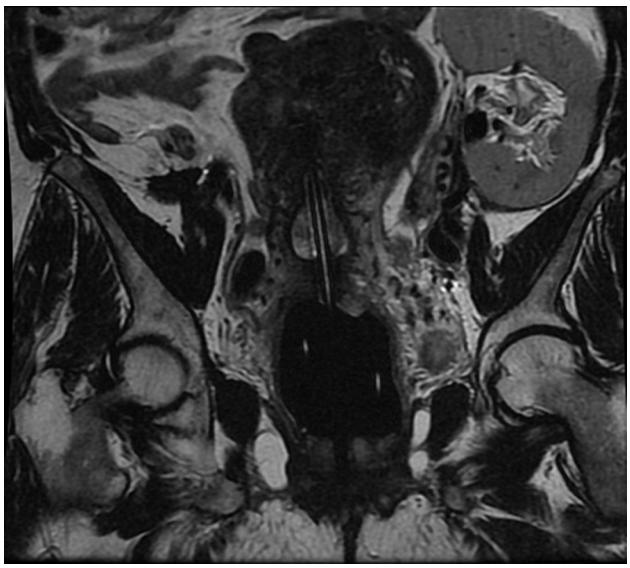

Fig. 1. The T2-weighted MRI of the brachytherapy implant, frontal slice, illustrating the proximity of the graft to the uterus (Case 1).

Brachytherapy

The EBRT was followed by MRI-guided uterovaginal brachytherapy, after completion of the whole EBRT course. Implants were performed under general anesthesia in an operation room. A personalized vaginal mold was used in both patients, which requires performing a vaginal impression before brachytherapy (4). The technique used was strictly intracavitary. Patients were treated with pulsed-dose rate, empty bladder, both at the time of the acquisition of images and during treatment. The pulses were repeated hourly without night interruptions.

Dosimetry

After implantation, patients were transferred to the radiology department for a pelvic MRI. A 1.5-T machine was used. Dummy sources were inserted into the three tubes of the applicator to locate the tip end position of the sources with accuracy and facilitate the applicator reconstruction. Sequence fast spin echo T2-weighted axial, coronal, and sagittal images were acquired without contrast enhancement, with a thickness of 3 mm without gap and a matrix size of 256 × 224. The images were then transferred onto OncentraGyn (Nucletron Medical Systems, an Elekta company, Stockholm, Sweden) for delineation of intermediate risk (IR) and high risk CTV and OAR (rectum, sigmoid, bladder, and graft). Point A, International Commission on Radiation Units and Measurements, rectum and bladder points were added. The active lengths were determined based on the target volumes and clinical examination. Starting from a standard loading pattern, an optimization was done manually with Plato (Nucletron), with the aim to reach the recommendations of the Groupe Européen de Curiethérapie–European Society for Radiation Oncology (GEC-ESTRO) (5, 6). The planning aim was to deliver at least 60 Gy to 90% of the IR-CTV and a minimum of 85 Gy to 90% of the high-risk CTV in 2-Gy equivalent doses (EqD2), adding brachytherapy and EBRT doses. The dose constraints applied to OAR for dosimetry were 75 Gy to the maximal 2 cm^3 (D_2 cm^3) of the rectum and 85 Gy to the maximal 2 cm^3 of the bladder (EqD2). By analogy with the rectum, at the limit applied to the sigmoid