EJGO European Journal of Gynaecological Oncology

Uterine cervical cancer after liver transplantation: a case report

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Summary

Concomitant external beam radiotherapy and chemotherapy followed by brachytherapy has been the primary treatment option for locally advanced cervical cancer. A patient with International Federation of Gynecology and Obstetrics (FIGO) Stage IIIB cervical cancer diagnosed after liver transplantation, who was not the candidate of chemotherapy due to her impaired liver and renal function, was treated with radiotherapy alone including three-dimensional conformal radiotherapy (3D-CRT) and brachytherapy. The diagnosis, treatment, and prognosis were reviewed in detail. No tumor progression or metastatic lesions and no severe complications were observed at 33-month follow-up.

Key words: Liver transplantation; Uterine cervical cancer; Three-dimensional conformal radiotherapy; Brachytherapy.

Introduction

The survival time after liver transplantation has been significantly prolonged, mainly due to the use of immunosuppressive agents. However, *de novo* malignancy is a serious complication after liver transplantation, and has been increasingly reported in recent years [1]. The incidence rate of a *de novo* neoplasm increases from 13% to 26% after liver transplantation, and is about two- to four-fold higher than age-matched healthy controls [2]. The most common *de novo* malignancies are skin cancer [3], post-transplantation lympho-proliferative disorder [4], the head and neck tumor [5], Kaposi's sarcoma [6], and non-Hodgkin's lymphoma [7]. The incidence of cervical cancer after liver transplantation is rare and less well-characterized. The authors herein reported their first case of squamous cell cervical cancer after liver transplantation.

Case Report

A 53-year-old woman presented with frequent urination for 20 days and irregular vaginal bleeding for two days. She was diagnosed with chronic hepatitis B in 1980. The patient suffered from loss of appetite, abdominal distension, jaundice, and deteriorating liver function. Eventually, massive ascites and peripheral edema appeared. These symptoms did not respond to conservative therapy, including diuretic treatment, and hepatic encephalopathy occurred repeatedly. Finally, the patient underwent living-donor orthotopic liver transplantation in September, 2004. Immunosuppression consisted of tacrolimus and low-dose steroids. Histopathological examination of the explanted liver revealed typical cirrhosis. The patient was discharged on postoperative day 62 without significant complications, and treated with long-term lamivudine (100 mg qd), tacrolimus (three mg bid) and immunoglobulin (400 IU/month).

Seven years after liver transplantation, she was found to have an irregular menstrual cycle and abnormal vaginal bleeding in 2011. The patient denied fever, chills, weight loss, or systemic symptoms. Gynecological examination revealed a cauliflower-like neoplasm of the cervix (about six cm in diameter), invading the upper one-third of the vagina. The tumor extended to the left pelvic wall and almost reached the right pelvic wall (Figure 1). The rectal mucosa was smooth with no palpable mass or bleeding. The serum squamous cell carcinoma antigen (SCC) level was 7.1 ng/ml (normal: 0~1.5 ng/ml). Cervical biopsy showed moderately differentiated squamous cell carcinoma of the cervix (Figure 2). Enlarged groin lymph nodes were identified using B-mode ultrasound (12×5 mm and 8×6 mm, respectively), which were compatible with inflammatory disease. No other distant lesions or metastases were recognized by computer tomography (CT) (Figure 3A). The patient was staged as cervical squamous cell carcinoma IIIB, using the International Federation of Gynecology and Obstetrics Classification (FIGO, 2009).

The patient was administered three-dimensional conformal radiotherapy (3D-CRT) using an accelerator, with ten MV X-ray for the pelvic field. The clinical target volume (CTV) was defined as an area of potential microscopic disease including the gross tumor, entire uterus, bilateral parametrium, paravaginal tissues, and the upper two-thirds of the vagina, and also pelvic bilateral common iliac lymph nodes, external iliac lymph nodes, internal iliac lymph nodes, and obturator lymph nodes. The lymph node groups were contoured according to the recommendations of Small *et al.* [8]. The planning target volume (PTV) was expanded with a one-cm margin based on the CTV. The prescription dose of PTV was 3,600 cGy/20F for whole pelvis. Then the plan was changed to administer a middle shield pelvic field irradiation dose of 900 cGy/5F (Figure 4). A boost was administered to the left parametrium of 5,220 cGy. The brachytherapy dose of point A was 2,900 cGy, using intracavitary irradiation with high dose rate ^{192}Ir. During treatment, abnormal liver and kidney function were observed. Alanine aminotransferase (ALT, 116U/L), creatinine (93.9 μmol/L), and

Revised manuscript accepted for publication February 17, 2016

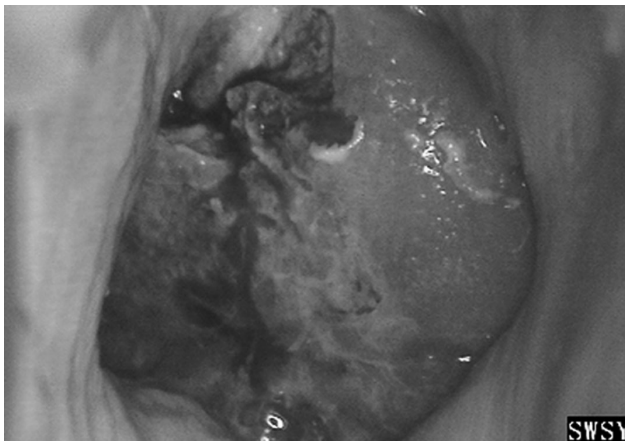

Figure 1. — Cervical biopsy reveals a cauliflower-like neoplasm of approximately 6.0 cm in diameter in the cervix. The tumor extends to the left pelvic wall and almost reaches the right pelvic wall.

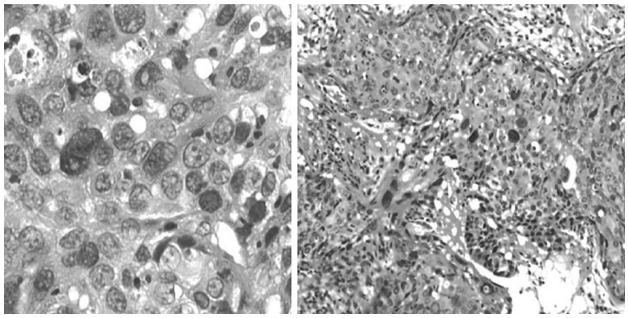

Figure 2. — The tumor cells form moderately-differentiated squamous cell carcinoma of the cervix. Hematoxylin-Eosin staining (left: ×100, right: ×400).

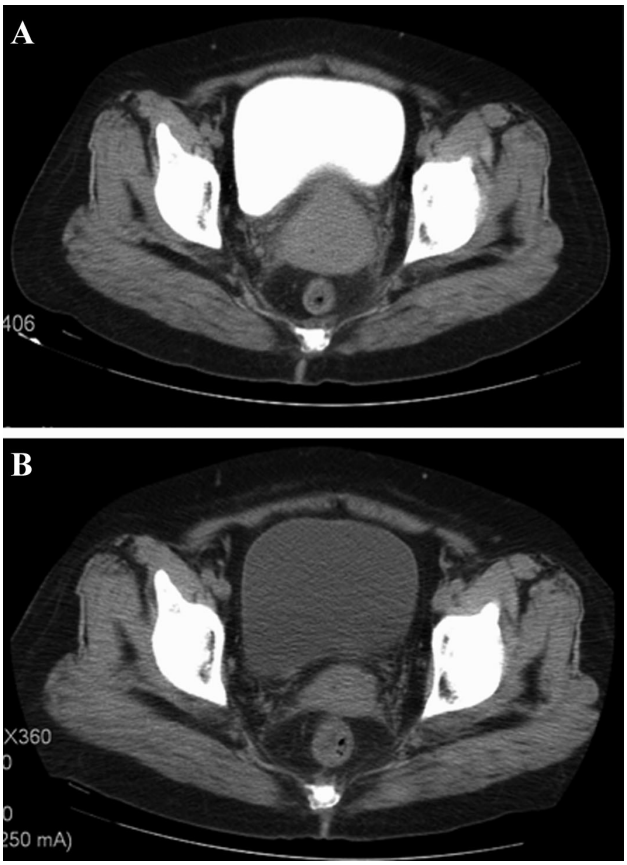

Figure 3. — A) CT before radiotherapy shows obvious space-occupying lesions and significant thickening of the cervix with inhomogeneous enhanced. No other distant metastases are revealed in uterus, bladder, rectum, and rectouterine depression. B) Post-irradiation CT reveals no obvious space-occupying lesions, no significant thickening of the cervix, and no enlarged pelvic lymph nodes.

uric acid (452 μmol/L) levels were all elevated. Bone marrow suppression was found with leukopenia (2.5×10^9/L) and neutropenia (1.4×10^9/L). These findings prevented concurrent chemotherapy. The patient received radiation therapy and the serum level of SCC decreased to 3.0 ng/ml. The last follow-up level of SCC was 1.5 ng/ml. Post-irradiation CT (Figure 3B) revealed no obvious space-occupying lesions, no significant thickening of the cervix, and no enlarged pelvic lymph nodes.

The authors also analyzed the HPV infection using flow-through hybridization and gene chip technology provided by a HPV GenoArray Test Kit. The chip containing 32 type-specific probes consist of 18 high-risk HPV groups (16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, and 68), five low-risk HPV groups (6, 11, 42, 43, and 44) and more susceptible CP8304 subtype in Chinese. HPV types 16 and 58 were identified in the cervicovaginal smear. However, both of the two types had turned to negative after radiation therapy.

To assess the short- and long-term outcomes, the authors recorded the clinical and follow-up results, any complaints or subjective were obtained from the patient. During the 33-month follow-up, the patient was clinically examined at regular intervals, and no complications or recurrence were recorded during this period.

Discussion

Liver transplantation is the final treatment for acute liver failure, end-stage liver disease, and several primary hepatic malignancies. Improved survival rates achieved in these patients are due to the substantial improvements in surgical techniques and immunosuppressive therapy [9]. However, development of *de novo* malignancies after organ transplantation has become at serious complication affecting long-term survival. Its occurrence rate has reported to be increasing annually. A two- to four-fold increase in the incidence of cancer has been reported in transplant patients, compared with age-matched controls [2, 10, 11].

Cervical cancer is the third most common malignancy in the general population worldwide, but occurs rarely following liver transplantation. Tanaka *et al*. first reported a 50-year-old patient with a uterine malignancy after liver transplantation in 2005 [12]. Nagarsheth *et al*. reported a 67-year-old woman with monomorphic B-cell post-transplantation lympho-proliferative disorder in the endocervix

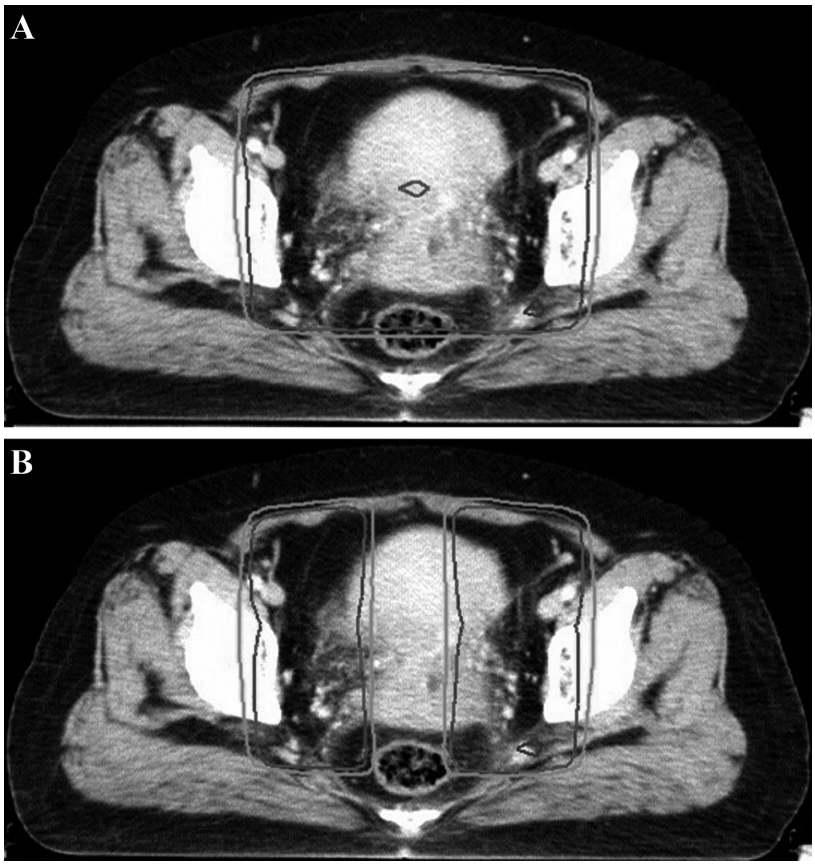

Figure 4. — CT imaging of the patient, high-risk clinical target volume (HR-CTV) and organs at risk (bladder and rectum). The 100%- and 95%-isodose lines are shown in red and green colors, respectively. A) Dose of CTV in the first plan (3,600 cGy/20F), B) Total dose of CTV (4,500 cGy/25F).

and lower uterine segment after liver transplantation [13]. HPV is widely accepted as a causative agent of anogenital cancer. Immunosuppression per se is a known risk factor for HPV oncogenic viral-disease, and immunosuppressive agents and HPV play synergistic roles in carcinogenesis [14, 15]. Several HPV subtypes are classified as high risk, according to their oncogenic potential. HPV type CP8304 has been shown to be the most common susceptible type in Chinese population [16]. Morva *et al*. reported a 42-year-old woman who underwent two liver transplantations and was diagnosed with moderately differentiated grade of micro-invasive adenocarcinoma of the cervix [17]; Kim *et al*. reported a 16-year-old girl with pediatric vulvar squamous cell carcinoma after liver transplantation [18]. Both cases were associated with a high-risk HPV infection. In the present case, HPV subtypes 16 and 58 were identified. Both subtypes were not identified after radiation therapy. The serum level of SCC is related to cervical tumor local progression and metastasis. It can be used as an independent predictive and prognostic factor [19]. In the present patient, the level of SCC decreased to normal after radiotherapy.

The risk of malignancy increases with time after transplantation [5]. In the present patient, the neoplasm was diagnosed seven years after transplantation. The time to tumor occurrence in published cases has varied widely, ranging from eight to 61.7 months in a series of tumors of the upper respiratory tract, gastrointestinal tract, and lung. Aberg *et al*. studied the risk of malignancy after liver transplantation. They found that the risk of cancer was more elevated in the immediate post-transplant period compared to later periods [20].

The prognosis of patients with post-transplant tumors is worse than in the normal population. Systemic treatment options are limited because of the patient's immunocompromised status. Early detection and treatment of malignant diseases is more crucial in transplant patients. Patients with increased risks of malignancy deserve more aggressive investigation and meticulous therapy, because of the considerably higher cancer mortality rate after liver transplantation. There is no standard screening procedure for solid tumors in transplant patients. Transplanted patients with gynecologic symptoms should be carefully evaluated, and endoscopic evaluation should be considered.

There is a wide range of radiotherapy applications for cervical cancer. It can be used for invasive cancer and carcinoma in situ which is unsuitable for surgical resection. The program of routine pelvic external beam radiation therapy followed by brachytherapy has been approved. However, there are organs at risk (OARs) such as rectum,

bladder, small intestine, and bone marrow in the treatment field. In recent years, CT-based 3D-CRT and intensity modulated radiation therapy (IMRT) have greatly improved. 3D-CRT ensures a more uniform dose on tumor target volumes compared with conventional plan for cervical carcinoma, and better protects the OARs, especially bladder, small bowel, and rectum. Chicago radiotherapy centers compared conventional radiotherapy, 3D-CRT and IMRT in ten patients, 3D-CRT and IMRT reduced irradiation of the bladder and rectum by 23% [21]. Several reports have introduced intensity modulated radiation for external irradiation and intracavitary brachytherapy for the treatment of cervical cancer. The ideal dose distribution was obtained for the tumor target, and the incidence of complications was reduced [22]. The relatively high cost of this treatment had limited its application in the present population. The present patient was staged as IIIB using the FIGO classification, and was treated with 3D-CRT followed by brachytherapy. Concurrent chemoradiotherapy as the standard treatment of cervical cancer has replaced radiotherapy alone. A recent meta-analysis showed that concurrent chemoradiotherapy increased absolute five-year survival rate of 6% compared with radiotherapy alone [23]. However, impaired liver function prevented the patient from concurrent chemotherapy. No tumor progression or metastatic lesions, and no severe complications were found during follow-up.

In conclusion, with the increasing size of the liver transplant population, secondary malignancies are becoming a larger health problem. Although the occurrence of different cervical tumors after liver transplantation has been reported, the present authors describe a patient with squamous cell carcinoma in detail. More attention should be given to post-transplant patient chronic immunosuppression. Radiotherapy is feasible for the treatment of a liver transplanted recipient with advanced stage cervical cancer.

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