Clinical Case Report

Medicine®

OPEN

Short-term recurrence and distant metastasis following robotic-assisted radical hysterectomy with pelvic lymphadenectomy and chemoradiotherapy for a stage IB1 cervical adenocarcinoma

A case report and literature review

Jinfei Tong, MB[a,b], Hailan Yu, MB[a,b], Jianqiong Li, MM[a,b], Jiena Zhou, MB[c], Xudong Ma, MB[a,b], Jianhua Yang, MD, PhD[a,b,*]

Abstract

Rationale: Postoperative concurrent chemoradiotherapy (CCRT) is considered the standard treatment for patients with early stage cervical cancer with positive pelvic nodes, yet many patients with high-risk factors treated with CCRT still suffered from distant metastasis.

Patient concerns: A 48-year-old woman presented with abnormal vaginal bleeding for 5 months. Thin prep liquid-based cytology test revealed low-grade squamous intraepithelial lesion and the human papillomavirus test (type 58) was positive. Magnetic resonance imaging showed a mass measuring 17 × 15 mm, located predominantly in the posterior lip of uterine cervix. Colposcopy biopsy reported adenocarcinoma of the cervix.

Diagnosis: Cervical adenocarcinoma stage IB1.

Interventions: A robotic-assisted radical hysterectomy with pelvic lymphadenectomy was performed followed by postoperative CCRT.

Outcomes: Distant metastasis was occurred shortly after postoperative CCRT and the patient died 9 months from initial diagnosis.

Lessons: In cases of new nodule in bones, lower abdominal distension and bloating occurring shortly after CCRT in early stage cervical adenocarcinoma, clinicians should bear in mind that recurrence should be considered. Development of more effective treatment to improve the survival outcomes of patients with postoperative metastasis is needed.

Abbreviations: CA = carbohydrate antigen, CCRT = concurrent chemoradiotherapy, HPV = human papillomavirus, MRI = magnetic resonance imaging, NCCN = National Comprehensive Cancer Network.

Keywords: cervical adenocarcinoma, chemoradiotherapy, distant metastasis, robotic-assisted radical hysterectomy

Editor: N/A.

IRB of Sir Run Run Shaw Hospital verified that this case report was exempt.

Informed written consent was obtained from the patient family for publication of this case report and accompanying images.

This study was funded by the Medical and Health Research Project of Zhejiang Province (2018RC008).

The authors have no conflicts of interest to disclose.

[a] Assisted Reproduction Unit, Department of Obstetrics and Gynecology, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, [b] Key Laboratory of Reproductive Dysfunction Management of Zhejiang Province, Hangzhou, [c] Zhibu Town Health Center, Zhuji, Zhejiang Province, China.

[*] Correspondence: Jianhua Yang, Assisted Reproduction Unit, Department of Obstetrics and Gynecology, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Key Laboratory of Reproductive Dysfunction Management of Zhejiang Province, No 3 East Qing Chun Road, Hangzhou 310016, China (e-mail: yjh2006@zju.edu.cn).

Copyright © 2019 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

Medicine (2019) 98:17(e15387)

Received: 12 December 2018 / Received in final form: 24 March 2019 / Accepted: 2 April 2019

http://dx.doi.org/10.1097/MD.0000000000015387

1. Introduction

As the most common malignancy tumor in gynecology, cervical cancer represents the 4th most commonly diagnosed cancer and the leading cause of cancer death in females worldwide, with an estimated 570,000 new cancer cases and 311,000 cancer deaths among females in 2018.[1] Lymph node metastasis is the most important independent risk factor for poor survival outcomes, and distant metastasis is the major problem. According to the National Comprehensive Cancer Network (NCCN) and the European Society of Gynaecological Oncology guidelines, either laparotomy or laparoscopy is an acceptable radical hysterectomy approach in patients with early stage cervical cancer.[2] Guidelines from NCCN also indicate that use of concurrent chemoradiotherapy (CCRT) is recommended as postoperative adjuvant therapy for node-positive early stage cervical cancer. And many studies have confirmed that CCRT can enhance antitumor immunity, even produce antimetastatic effect, to improve overall survival in patients with cervical cancer.[3–6] However, several clinical trials indicated that CCRT showed similar survival outcomes compared with chemotherapy.[7,8] Moreover, several retrospective studies found that radiotherapy following hysterectomy could effectively improve local control, yet distant metastasis was the predominant mode of failure.[8–10] They

demonstrated that radiotherapy can promote tumor progression and induce distant metastasis though the mechanism remains ambiguous and complex. Here, we described an early stage cervical adenocarcinoma metastasis shortly after radical hysterectomy and postoperative CCRT and proposed that radiotherapy may promote tumor survival and metastasis in our case. The patient has provided informed consent for publication of the case.

2. Case summary

A 48-year-old woman was referred to our hospital on April 21, 2017, with abnormal vaginal bleeding for 5 months. Four months ago, she went to the community hospital, thin prep liquid-based cytology test revealed low-grade squamous intraepithelial lesion and human papillomavirus (HPV) test showed HPV58(+). Her medical history was otherwise unremarkable. Regarding the family history, one of her sisters died of gastric cancer. The patient reported 5 pregnancies (1 live birth and 4 abortions). Physical examination revealed cervical erosion, a remarkable thicken in the posterior lip of uterine cervix, an enlarged uterus without tenderness. Laboratory data revealed the patient's squamous cell carcinoma antigen was negative (0.70 IU/mL), yet her carbohydrate antigen (CA) 125 level was evaluated at 95.36 IU/mL (normal, <35 IU/mL), and CA19-9 level was 108.10 IU/mL (normal, <37 IU/mL). Magnetic resonance imaging (MRI) showed a mass measuring 17 × 15 mm, located predominantly in the posterior lip of uterine cervix, as well as abdominally enlarged iliac lymph nodes, of which the larger one was about 9 mm (Fig. 1). Colposcopy biopsy was performed, reported adenocarcinoma of the cervix at positions 1, 4, 8, and 10 o'clock, diagnosed with cervical adenocarcinoma with an International Federation of Gynecology and Obstetrics stage of IB1.

On April 24, 2017, the patient underwent robotic-assisted radical hysterectomy with bilateral adnexectomy, pelvic lymph node dissection, adhesion release, and abdominal drainage were performed. During the surgery, parts of the greater omentum were found densely adhered to the right pelvic wall, no obvious effusion in the pelvic cavity. Macroscopic examination of the excised specimens showed a tumor measuring 30 × 35 mm in cervical lower lip with hemorrhagic necrosis, invading the deep stromal layer. The specimens were removed by the vaginal route. The patient was discharged postoperative day 6 after an uneventful recovery.

Histopathologic examination revealed uterine cervical adenocarcinoma (moderate to poor differentiated adenocarcinoma) (Fig. 2), measuring 25 × 19 mm with 5-mm invasion of the uterine wall. While there were 2 more metastatic lymph nodes on 47 lymph nodes sampled, no invasion of the parametrium was observed and the surgical margins were free of disease. Metastases were present in the left obturator and right external iliac lymph nodes, giving the tumor-node metastasis classification of pT1BN1M0.

On immunohistochemical analysis, CK-low and CK7 were positive, CEA-R, CK-high, p40, p63, and CK20 were focally positive, whereas p53 and p16 were negative. Ki-67 was 20% positive.

Postoperatively the patient was treated with pelvic intensity-modulated radiotherapy (45 Gy given in 25 fractions) for 35 days to high-risk pelvic region with concurrent intravenous chemotherapy consisting of 130 mg nedaplatin at 3-week intervals for 2 cycles from June 2017 to July 2018. Because of severe

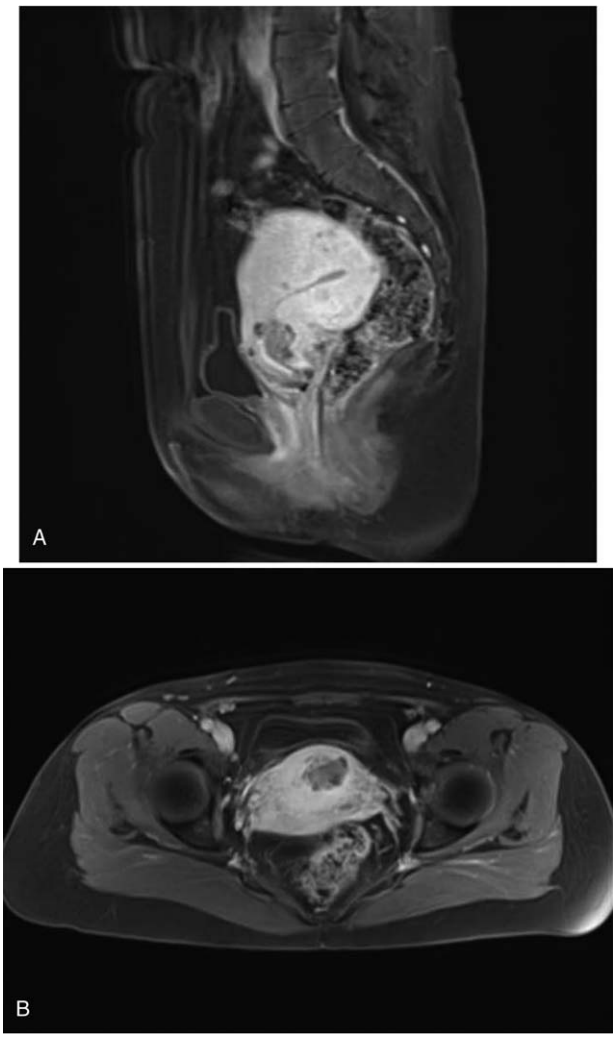

Figure 1. (A) Sagittal view of pelvic magnetic resonance imaging (MRI). MRI shows a mass measuring 17 × 15 mm in the posterior lip of uterine cervix. (B) Cross-sectional view of pelvic MRI. Magnetic resonance imaging shows a mass measuring 17 × 15 mm in the posterior lip of uterine cervix.

myelosuppression, the dose of nedaplatin was decreased to 110 mg the 2nd cycle. Postoperatively, CA 125 was 42.47 IU/mL; and it normalized (21.01 IU/mL) after CCRT. However, on July 8, 2017, MRI found a new nodule in the left pubic symphysis, indicating the bone metastasis.

Three months following surgery and 1 month and a half following completion of chemoradiotherapy, the patient noted the gradual onset of lower abdominal distension and bloating; and she also complained of short of breath sometimes. Physical examination was notable for distended abdomen and fluid wave test was positive. Computed tomography scan showed moderate to large ascites in abdomen and pelvis, indicative of peritoneal metastasis. Tumor marker CA 125 was also increased (1039.00 IU/mL) on September 14, 2017. Cytologic examination of ascetic fluid confirmed the presence of malignant cells. Immunohistochemical strain of ascetic fluid cells: calretinin: (−), WT-1: (−), CD68/KP-1: (−), CK7: (+), EA: (local +), EMA: (+), P40: (a little +), P16: (−), PAX-8: (+), ER/control: (−).

Three cycles of chemotherapy with paclitaxel intravenous and cisplatin intraperitoneal injection were administered from

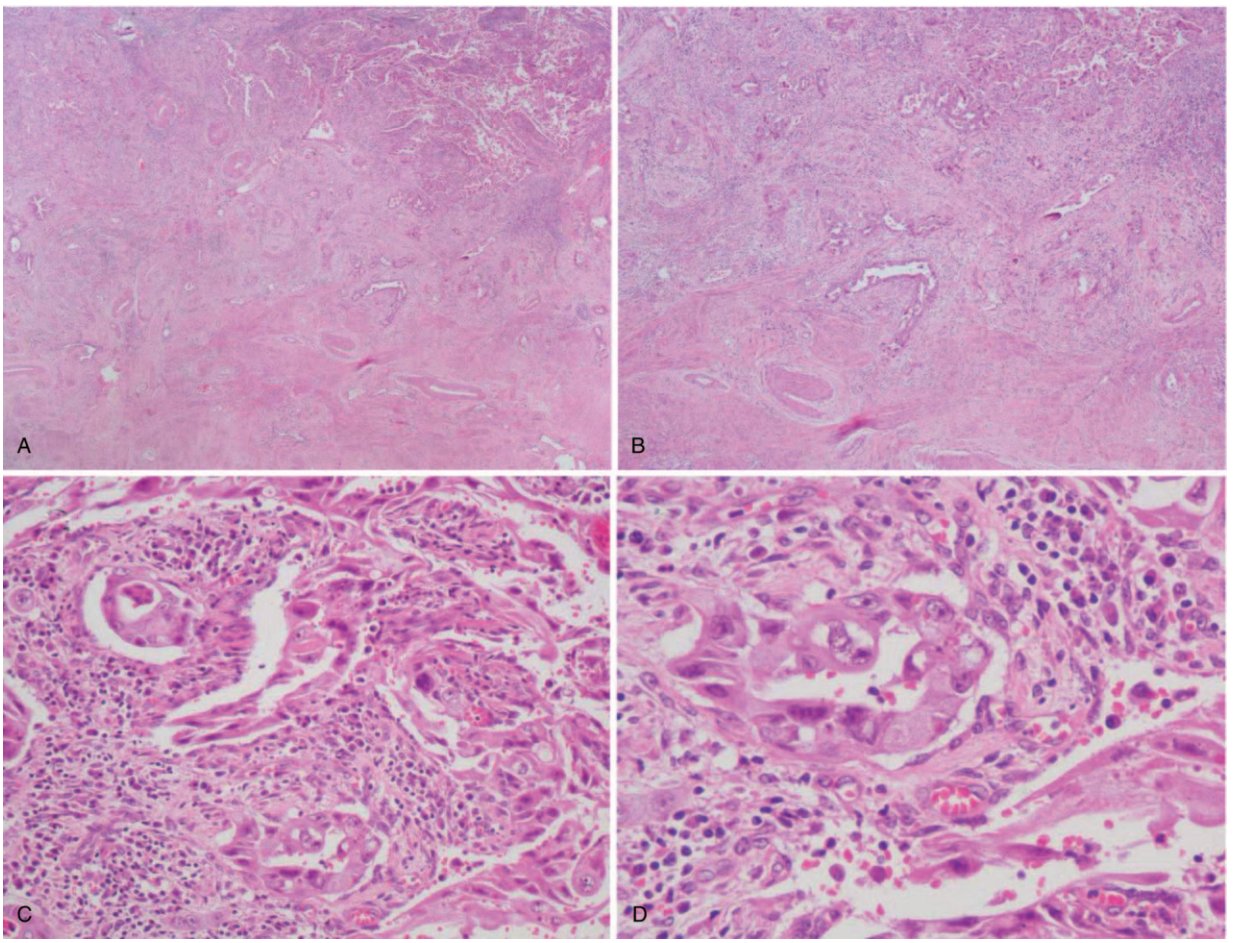

Figure 2. (A) Microscopic photograph of cervical adenocarcinoma. The cervical adenocarcinoma invaded the stroma (20×). (B) Microscopic photograph of cervical adenocarcinoma. The cervical adenocarcinoma invaded the stroma (40×). (C) Microscopic photograph of cervical adenocarcinoma. The atypical neoplastic glands with enlarged nuclei in the neoplastic epithelium (200×). (D) Microscopic photograph of cervical adenocarcinoma. The atypical neoplastic glands with enlarged nuclei in the neoplastic epithelium (400×).

September 2017 to November 2017. On November 16, 2017, the patient noted left lower-extremity edema. Results of left Doppler ultrasonography showed blood flowed slowly with thrombosis. A right abdominal wall mass was found, and CA 125 level was elevated (2021.00 IU/mL). A staging positron emission tomography/computed tomography scan showed multiple hypermetabolic lymph nodes in the hilar region and pancreatic, a nodular lesion with FDG uptake in the right adrenal gland, multiple bone mineral changes in the body with increased metabolism, indicative of metastasis to the liver and pancreatic lymph node, right adrenal gland, and bones. The patient died in January 2018 with distant metastasis.

3. Discussion

The radical hysterectomy and pelvic lymph node dissection is 1 component of standard surgical management for early stage cervical cancer. And CCRT is recommended as postoperative adjuvant therapy for node-positive early stage cervical cancer by NCCN guidelines. However, distant metastasis will still occur following radical hysterectomy and adjuvant CCRT. Previous studies have identified tumor features such as tumor size, clinical stage, histologic subtypes, parametrial involvement, pelvic lymph node metastasis, lymphovascular space invasion, and depth of stromal invasion as adverse prognostic traits in early stage cervical cancer.[11,12] The high-risk factor of this patient was remarkable for node-positive low-intermediate differentiated cervical adenocarcinoma. The bone is the third most common site of distant metastasis after the lungs and liver. A study by Nartthanarung and Thanapprapasr[13] showed that the incidence of bone metastasis cervical cancer was 1.1%. They found that the median intervals from cervical cancer diagnoses to diagnoses of bone metastasis were 14 months (95% confidence interval [CI], 9.14–18.86) and the median survivals after diagnosis of bone metastasis were 4 months (95% CI, 0.76–7.24) in patients received radical hysterectomy with CCRT. The study reported that primary treatment with CCRT or radiotherapy showed no difference in survival benefits among patients with bone metastasis. In our case, the patient developed bone metastasis rapidly after the end of CCRT. Although the survival from diagnoses of bone metastasis was 6 months treated with chemotherapy after relapse.

To the best of our knowledge, this is the 1st reported case of early stage cervical adenocarcinoma following radical hysterectomy with pelvic lymph node dissection and adjuvant CCRT recurrence and distant metastasis in such a short time. We cannot

deny the possibility of laparoscopic surgery leading to abdominal dissemination and distant metastasis. Additionally, we cannot confirm whether the distant metastasis was related to radiotherapy.

Minimally invasive radical hysterectomy was reported to be associated with poor survival outcomes than open abdominal surgery in patients with early stage cervical cancer by Ramirez et al.[14] The prospective, randomized trial found that minimally invasive radical hysterectomy was associated with a higher rate of recurrence and a lower rate of disease-free survival (4.5-year rate, 86.0% vs 96.5%) than open surgery in patients with early stage cervical cancer. The potential reason is that the routine use of a uterine manipulator might increase the propensity for tumor spillage. Besides previous studies suggested that the insufflation gas (CO_2) would have an influence on tumor-cell growth or spread.[15,16]

Radiotherapy remains one of the keystone treatments in cervical cancer and proved its benefits in improving overall survival in many clinical studies. However, radio-resistance remains a major clinical challenge in cervical cancer therapy[17,18] and some patients treated with radiotherapy present local recurrence or distant metastasis.[8–10] Weichselbaum et al[19] investigated the relative roles of both intrinsic tumor radiosensitivity and the immune system, named radiation-induced tumor equilibrium. They demonstrated that radio-resistant tumor cells could remain stable to radiotherapy, nevertheless, large dose of radiation each day would damage the normal tissues and host immune system, leading to tumor regrowth. Current studies indicate that radiotherapy can either promote tumor-cell death, or support tumor-cell survival via multiple mechanisms.[19] A study by Vargo et al[10] showed that extended field intensity modulated radiation therapy was well tolerated and resulted in low regional recurrence in node-positive cervical cancer. However, distant metastasis is the predominant mode of failure. The mechanisms how radiotherapy enhances metastasis is still unknown. One hypothesis[20] is that the beneficial local effects of radiotherapy are counteracted by its systemic proinvasive and prometastatic effect and therefore does not lead to an increased overall survival. Another hypothesis[21] is that radiotherapy could change the local microenvironment, facilitating tumor cells to migrate and invade.

4. Conclusion

In conclusion, this was a rare case of early stage cervical cancer which received radical hysterectomy with CCRT and was found to have bone metastasis shortly after the treatment. In cases of new nodule in bones and lower abdominal distension and bloating occurring shortly after CCRT in early stage cervical adenocarcinoma, clinicians should bear in mind that recurrence should be considered. In addition, enhancing innate and adaptive immunity by combining chemoradiotherapy and immunotherapy may be a crucial strategy to improve patient survival. Furthermore, more clinical trials might be needed to confirm the security of laparoscopy in high-risk early stage cervical cancer.

Author contributions

Data curation: Hailan Yu, Jiena Zhou, Xudong Ma.
Writing – original draft: Jinfei Tong.
Writing – review & editing: Jianqiong Li, Jianhua Yang.

References

[1] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
[2] Cibula D, Potter R, Planchamp F, et al. The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology guidelines for the management of patients with cervical cancer. Radiother Oncol 2018;127:404–16.
[3] Matsuo K, Shimada M, Aoki Y, et al. Comparison of adjuvant therapy for node-positive clinical stage IB-IIB cervical cancer: systemic chemotherapy versus pelvic irradiation. Int J Cancer 2017;141:1042–51.
[4] Song S, Song C, Kim H, et al. 20 year experience of postoperative radiotherapy in IB-IIA cervical cancer patients with intermediate risk factors: impact of treatment period and concurrent chemotherapy. Gynecol Oncol 2012;124:63–7.
[5] Kim K, Kang S, Chung H, et al. Comparison of chemoradiation with radiation as postoperative adjuvant therapy in cervical cancer patients with intermediate-risk factors. Eur J Surg Oncol 2009;35:192–6.
[6] Kim K, Chie EK, Wu H, et al. Efficacy of paclitaxel and carboplatin as a regimen for postoperative concurrent chemoradiotherapy of high risk uterine cervix cancer. Gynecol Oncol 2006;101:398–402.
[7] Takekuma M, Kasamatsu Y, Kado N, et al. Adjuvant chemotherapy versus concurrent chemoradiotherapy for high-risk cervical cancer after radical hysterectomy and systematic lymphadenectomy. Int J Clin Oncol 2016;21:741–7.
[8] Falcetta F, Medeiros LR, Edelweiss M, et al. Adjuvant platinum-based chemotherapy for early stage cervical cancer. Cochrane Database Syst Rev 2016;11: Cd005342.
[9] Kim H, Rhee W, Choi S, et al. Clinical outcomes of adjuvant radiation therapy and prognostic factors in early stage uterine cervical cancer. Radiat Oncol J 2015;33:126–33.
[10] Vargo J, Kim H, Choi S, et al. Extended field intensity modulated radiation therapy with concomitant boost for lymph node-positive cervical cancer: analysis of regional control and recurrence patterns in the positron emission tomography/computed tomography era. Int J Radiat Oncol Biol Phys 2014;90:1091–8.
[11] Twu N, Ou Y, Liao C, et al. Prognostic factors and adjuvant therapy on survival in early-stage cervical adenocarcinoma/adenosquamous carcinoma after primary radical surgery: a Taiwanese Gynecologic Oncology Group (TGOG) study. Surg Oncol 2016;25:229–35.
[12] Ayhan A, Al R, Baykal C, et al. Prognostic factors in FIGO stage IB cervical cancer without lymph node metastasis and the role of adjuvant radiotherapy after radical hysterectomy. Int J Gynecol Cancer 2004; 14:286–92.
[13] Nartthanarung A, Thanapprapasr D. Comparison of outcomes for patients with cervical cancer who developed bone metastasis after the primary treatment with concurrent chemoradiation versus radiation therapy alone. Int J Gynecol Cancer 2010;20:1386–90.
[14] Ramirez P, Frumovitz M, Pareja R, et al. Minimally invasive versus abdominal radical hysterectomy for cervical cancer. N Engl J Med 2018;379:1895–904.
[15] Kong T, Chang S, Piao X, et al. Patterns of recurrence and survival after abdominal versus laparoscopic/robotic radical hysterectomy in patients with early cervical cancer. J Obstet Gynaecol Res 2016;42:77–86.
[16] Lin F, Pan L, Li L, et al. Effects of a simulated CO2 pneumoperitoneum environment on the proliferation, apoptosis, and metastasis of cervical cancer cells in vitro. Med Sci Monit 2014;20:2497–503.
[17] Recoules-Arche A, Rouzier R, Rey A, et al. Does adenocarcinoma of uterine cervix have a worse prognosis than squamous carcinoma? Gynecol Obstet Fertil 2004;32:116–21.
[18] Nuryadi E, Sasaki Y, Hagiwara Y, et al. Mutational analysis of uterine cervical cancer that survived multiple rounds of radiotherapy. Oncotarget 2018;9:32642–52.
[19] Weichselbaum R, Liang H, Deng L, et al. Radiotherapy and immunotherapy: a beneficial liaison? Nat Rev Clin Oncol 2017; 14:365–79.
[20] Sundahl N, Duprez F, Ost P, et al. Effects of radiation on the metastatic process. Mol Med 2018;24:16.
[21] Barker H, Paget J, Khan A, et al. The tumour microenvironment after radiotherapy: mechanisms of resistance and recurrence. Nat Rev Cancer 2015;15:409–25.