

Efficacy of Combined Pembrolizumab and Pelvic Radiotherapy for Bladder Cancer With Rectal Metastases

CHIKA NAGAHISA¹, JUNPEI IIZUKA¹, YUKI KOBARI¹, RYO MINODA¹, HIRONORI FUKUDA¹, KAZUHIKO YOSHIDA¹, HISASHI OKUDA², HIDEKI ISHIDA¹, YOJI NAGASHIMA³ and TOSHIO TAKAGI¹

¹Department of Urology, Tokyo Women's Medical University, Tokyo, Japan;

²Department of Urology, Shiseikai Daini Hospital, Tokyo, Japan;

³Department of Surgical Pathology, Tokyo Women's Medical University, Tokyo, Japan

Abstract. *Background/Aim:* Rectal metastases from urothelial carcinoma (UC) are extremely rare with poor prognosis when treated with gemcitabine and cisplatin (GC) chemotherapy, radiation therapy, and total pelvic exenteration. Long-term survival has not been observed in patients treated with GC chemotherapy, radiation therapy, or total pelvic resection. However, there have been no reports on the efficacy of pembrolizumab therapy for this specific condition. *Herein, we describe a case of rectal metastasis from UC, treated with combined pembrolizumab and pelvic radiotherapy. Case Report:* A 67-year-old male patient with an invasive bladder tumour underwent robot-assisted radical cystectomy and ileal conduit diversion followed by neoadjuvant GC chemotherapy. The pathological findings showed high-grade UC, pT4a, with a negative surgical margin. He presented with an impacted ileus due to severe rectal stenosis on postoperative day 35 and underwent a colostomy. Pathologically, rectal biopsy confirmed rectal metastasis; thus, the patient was started on pembrolizumab 200 mg every 3 weeks and pelvic radiotherapy with a total dose of 45 Gy. The rectal metastases remained well controlled with stable disease status, and no adverse events were observed 10 months after the initiation of combined pembrolizumab and pelvic radiotherapy. *Conclusion:* Pembrolizumab combined with

radiation therapy may be an alternative treatment for rectal metastases from UC.

Bladder tumours commonly metastasize to the regional lymph nodes, liver, lung, and bone. Although these may involve the distal gastrointestinal tract, they are most commonly caused by direct invasion; hence, non-contiguous metastases are rare (1). Rectal metastases from urothelial carcinoma (UC) are extremely rare and have a poor prognosis (2). Several reports have described bladder cancer with rectal metastases treated with gemcitabine-cisplatin (GC) chemotherapy, radiation therapy, and total pelvic exenteration. However, long-term survival was not observed in these cases (3-5).

The Keynote045 trial confirmed the effectiveness of pembrolizumab as a second-line therapy for metastatic or advanced UC (6). However, there have been no reports of pembrolizumab use for rectal metastases from bladder cancer. Herein, we report a case of bladder cancer with rectal metastases successfully managed with combined pembrolizumab and pelvic radiotherapy after radical cystectomy.

Case Report

A 67-year-old man presented with gross haematuria and was admitted to a nearby hospital. Ultrasonography and magnetic resonance imaging revealed a bladder tumour. He underwent transurethral resection of the bladder tumour, and pathological findings showed UC, pT2, G3>G2 high-grade. After two cycles of neoadjuvant GC chemotherapy, the patient was referred to our institute for radical surgery, where he subsequently underwent robot-assisted radical cystectomy with bilateral pelvic lymph node dissection and ileal conduit diversion. Histopathological examination confirmed UC, pT4a, negative surgical margins, and no lymph node metastases. The patient was discharged on postoperative day (POD) 15 without any complications. However, on POD 35, he was readmitted to our hospital emergently due to ileus

Correspondence to: Junpei Iizuka, MD, Ph.D., Department of Urology, Tokyo Women's Medical University 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan. Tel: +81 333538111, Fax: +81 333560293, e-mail: jizuka@twmu.ac.jp

Key Words: Urothelial carcinoma, rectal metastasis, pembrolizumab, radiation therapy.



This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY-NC-ND) 4.0 international license (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).

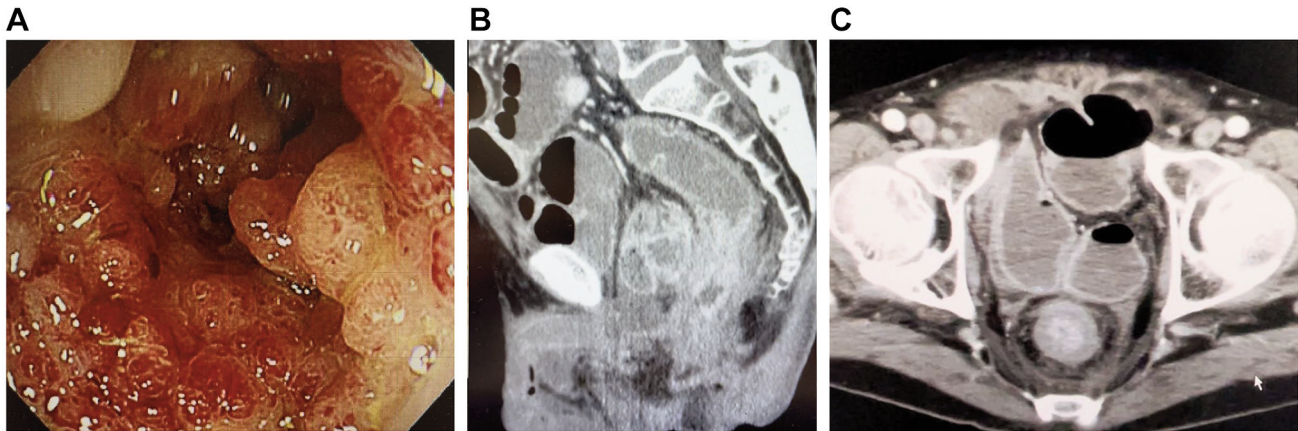


Figure 1. Colonoscopy and computed tomography findings prior to pembrolizumab treatment. Colonoscopy showing a granular prominence a few centimetres from the anal verge and a stenosis (A). Sagittal (B) and transverse (C) computed tomography showing circumferential thickening of the rectal wall.

with severe constipation and anal pain. Digital rectal examination revealed severe stenosis. Tumour markers, including carcinoembryonic antigen and carbohydrate antigen 19-9, were within the normal ranges. The colonoscope could not pass through the rectum (Figure 1A), and a computed tomography (CT) scan confirmed extensive thickening of the surrounding tissue (Figure 1B and C). Subsequently, transverse colostomy was performed on POD 39, and pathological findings on rectal biopsy revealed UC. Immunohistochemically, the tumour cells stained positive for GATA3 with high molecular weight cytokeratins (HMW-CK) and negative for CDX2, which is not a typical pattern of primary rectal cancer. Based on these results, a diagnosis of rectal metastasis from bladder cancer was made.

Retrospective examination of the CT scan performed after neoadjuvant GC therapy revealed that slight rectal wall thickening could already be seen, which was considered to be disease progression during neoadjuvant GC therapy; thus, we selected pembrolizumab as second-line therapy.

The patient was started on pembrolizumab 200 mg every 3 weeks and pelvic radiotherapy with a total dose of 45 Gy. After four courses of pembrolizumab, the anal pain resolved, and the CT scan showed no exacerbation of rectal metastases, suggesting stable disease (SD). The rectal metastases remained controlled on SD status, and no adverse events were observed 10 months after the initiation of pembrolizumab therapy.

Discussion

It is common for invasive bladder cancer to metastasize to the regional lymph nodes, liver, lung, and bone, with further invasion to the muscular layer or the bladder surface. However, it is extremely rare for bladder cancer to progress to the rectum

(1, 2). There are three hypotheses to explain the mechanism underlying the metastasis of bladder tumours to the rectum. First, it could be due to a previous iatrogenic exposure-caused deposition. Second, the direct invasion may be caused by penetration of the bladder wall *via* Denonvilliers' fascia to the rectum. Lastly, metastasis could spread *via* the lateral pedicles of the bladder to the posterior rectal wall, subsequently resulting in wall infiltration (2). In the present case, the pathological diagnosis was negative for surgical margins, but the vascular invasion was positive; hence, we hypothesized that the tumour may have metastasized or disseminated.

We summarized several case reports of bladder cancer with rectal metastasis (Table 1) (2-5, 7-12). From 2002 to 2021, 12 cases of UC metastasis to the rectum, including the present case, have been reported. The mean time to rectal metastasis after initial therapy was 15.7 months (range=1-48 months) for 11 cases and unknown for one case. One patient was treated with total pelvic exenteration; colostomy was performed in 8 cases, radiotherapy in 4 cases, and chemotherapy was performed in 6 cases, which included GC, M-VAC (methotrexate, vinblastine, doxorubicin, and cisplatin), and unclear regimens. Only one case, treated with a colostomy, chemotherapy, and radiotherapy, had a long survival time after treatment (12). None of the patients was treated with pembrolizumab. To the best of our knowledge, our case is the first report of bladder cancer with rectal metastases treated with pembrolizumab and pelvic radiotherapy that was well controlled with SD status.

The use of Pembrolizumab as a second-line treatment can allow significantly improved overall survival in patients with locally advanced or metastatic UC as compared to standard-of-care chemotherapy, as shown in the Keynote 045 trial (6). However, the effectiveness of pembrolizumab for rectal metastasis from UC has not yet been discussed. We

Table I. Previous case reports of bladder cancer with rectal metastases.

Case/ Author	Age (years)	Sex	TNM*	Treatment provided prior to rectal metastasis	Time (in months) to metastasis after prior treatment	Treatment after rectal metastases	Outcome
1. Hong, 2002 (7)	63	M	Unknown	RC, M-VAC	10	Radiation therapy	Alive (4 M)
2, 3. Yusuf, 2005 (4)	54 73	M M	Unknown Unknown	RC RC	24 24	Chemotherapy Total pelvic exenteration	Unclear Unclear
4. Kobayashi, 2006 (8)	76	M	Unknown	TUR-Bt	1	Colostomy	Death (5 M)
5. Ito, 2008 (9)	74	M	Unknown	RC	11	Colostomy M-VAC, GC Radiation	Death (6 M)
6. Ying-Yue, 2010 (3)	83	M	Unknown	None	Unclear	Chemotherapy	Unclear
7. Katayama, 2010 (10)	64	M	T3N0M0	RC	16	Colostomy	Death (18 M)
8. Asfour, 2014 (11)	55	M	Unknown	TURBT GC, RC	15	Colostomy	Alive
9. Ma, 2015 (12)	65	M	T3N0M0	RC, GC	23	Colostomy Chemotherapy Radiation	Alive (4 Y)
10. Ii, 2021 (5)	72	M	TaN0M0	TURBT	48	Colostomy GC	Alive (10 M)
11. Liu, 2021 (2)	65	M	TisN0M0	TURBT BCG	Unclear	Colostomy	Unclear
12. Present Case	67	M	T2N0M0	TUR-Bt GC, RC	1	Colostomy Pembrolizumab Radiotherapy	Alive (10 M) SD

*TNM at initial diagnosis of urothelial carcinoma. BCG: Bacille de Calmette et Guérin; GC: gemcitabine and cisplatin; M: male; MVAC: methotrexate, vinblastine, doxorubicin, and cisplatin; RC: radical cystectomy; SD: stable disease; TUR-Bt: transurethral resection of bladder tumour.

estimated the effectiveness of pembrolizumab combined with radiotherapy for rectal metastasis of bladder cancer from two perspectives. First, the rectal metastasis was radiographically well controlled as SD status on enhanced CT. Although the average survival time after rectal metastasis is reported to be approximately 5 months (10), in the present case, the SD status has been controlled for 10 months using pembrolizumab. Second, the patient's anal pain remarkably improved. Before treatment, anal pain was approximately 7/10 on the Numerical Rating Scale (NRS) even with tramadol hydrochloride and acetaminophen; however, after treatment, the NRS score was reduced to 2/10 without the use of analgesics. Vassiliou *et al.* concluded that RT has the potential to synergize with immunotherapy to improve oncological outcomes in patients with localized or metastatic bladder cancer, and Palliative RT in the form of external beam irradiation in combination with chemotherapy, targeted therapies and, more recently, immunotherapy, offers palliation and relief from symptoms (13).

The results of this case suggest that pembrolizumab combined with radiation therapy for patients with rectal

metastasis from UC can help to effectively manage the disease. It is necessary to study multiple cases of rectal metastasis of bladder cancer treated with pembrolizumab combined with radiation therapy.

Conclusion

We report a case of rectal metastasis from UC treated with pembrolizumab combined with radiation therapy. Although further verification is needed, pembrolizumab could be an effective treatment for rectal metastasis from UC.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

CN wrote the manuscript and provided the table and figure. JI, KY, RM, HF, KY, HO, HI, YN, and TT cared for the patient and administered pembrolizumab in combination with radiation therapy. All Authors have read and approved the final manuscript.

Acknowledgements

The Authors would like to thank Ms. Nobuko Hata (Department of Urology, Tokyo Women's Medical University) for her secretarial work.

References

- 1 Shinagare AB, Ramaiya NH, Jagannathan JP, Fennessy FM, Taplin ME and Van den Abbeele AD: Metastatic pattern of bladder cancer: correlation with the characteristics of the primary tumor. *AJR Am J Roentgenol* 196(1): 117-122, 2011. PMID: 21178055. DOI: 10.2214/AJR.10.5036
- 2 Liu YH, Pu TW, Yu HW, Kang JC, Yen CH and Chen CY: Invasive urothelial carcinoma of urinary bladder presenting with annular constriction and mimicking proctitis observed by colonoscopy: A case report. *Int J Surg Case Rep* 82: 105785, 2021. PMID: 33865196. DOI: 10.1016/j.ijscr.2021.105785
- 3 Ying-Yue J, Shen SH and Wang JH: Unusual presentation of urothelial carcinoma of the bladder with noncontiguous rectal and diffuse muscular skeletal metastases. *J Urol* 184(3): 1163-1164, 2010. PMID: 20650481. DOI: 10.1016/j.juro.2010.05.067
- 4 Yusuf TE, Levy MJ and Wiersema MJ: EUS features of recurrent transitional cell bladder cancer metastatic to the GI tract. *Gastrointest Endosc* 61(2): 314-316, 2005. PMID: 15729254. DOI: 10.1016/s0016-5107(04)02578-7
- 5 Ii Y, Munakata S, Honjo K, Kawai M, Kawano S, Sugimoto K, Isotani S, Kojima Y, Horie S, Yao T and Sakamoto K: Rectal metastasis from bladder urothelial carcinoma: a case report. *Surg Case Rep* 7(1): 100, 2021. PMID: 33881649. DOI: 10.1186/s40792-021-01186-8
- 6 Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, Vogelzang NJ, Climent MA, Petrylak DP, Choueiri TK, Necchi A, Gerritsen W, Gurney H, Quinn DI, Culine S, Sternberg CN, Mai Y, Poehlein CH, Perini RF, Bajorin DF and KEYNOTE-045 Investigators: Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med* 376(11): 1015-1026, 2017. PMID: 28212060. DOI: 10.1056/NEJMoa1613683
- 7 Hong SP, Park SW, Lee SJ, Chung JP, Song SY, Chung JB, Kang JK and Cho NH: Bile duct wall metastasis from micropapillary variant transitional cell carcinoma of the urinary bladder mimicking primary hilar cholangiocarcinoma. *Gastrointest Endosc* 56(5): 756-760, 2002. PMID: 12397294. DOI: 10.1067/mge.2002.129083
- 8 Kobayashi S, Kato H, Iijima K, Kinebuchi Y, Igawa Y and Nishizawa O: Annular rectal constriction due to infiltration by bladder cancer. *Hinyokika Kyo* 52(7): 569-572, 2006. PMID: 16910593.
- 9 Ito Y, Nishimoto K, Ogata K and Fujioka T: [Annular constriction of the rectum secondary to urothelial carcinoma of the bladder]. *Hinyokika Kyo* 54(8): 553-555, 2008. PMID: 18788446.
- 10 Katayama H, Mituzuka K, Kawasaki Y and Kato S: [Annular rectal constriction caused by infiltrating bladder carcinoma: a case report]. *Hinyokika Kyo* 56(4): 229-231, 2010. PMID: 20448448.
- 11 Asfour R, Stettler G, Pinzon MM, Hayden D, Eberhardt J, Saclarides T and Slogoff M: Recurrent urothelial cell carcinoma presenting with gastrointestinal symptoms. *Am Surg* 80(8): E240-E242, 2014. PMID: 25105381.
- 12 Ma Y, Shilton H and Strauss P: Rectal constriction secondary to metastatic micropapillary adenocarcinoma of the bladder. *ANZ J Surg* 85(12): 984-986, 2015. PMID: 24698081. DOI: 10.1111/ans.12587
- 13 Vassiliou V, Katsila T, Sodergren SC and Kardamakis D: Radiotherapy in metastatic urothelial carcinoma: rationale and clinical applications. *Anticancer Res* 42(8): 3767-3778, 2022. PMID: 35896266. DOI: 10.21873/anticancer.15867

Received December 26, 2022

Revised January 5, 2023

Accepted January 20, 2023