ejpmr, 2019,6(1), 78-83

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

STEREOTACTIC BODY RADIOTHERAPY (SBRT) AND OLIGOMETASTATIC BLADDER CANCER: ABOUT A CASE AND REVIEW OF THE LITERATURE

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Article Received on 05/11/2018 **Article Revised on 25/11/2018** **Article Accepted on 15/12/2018**

ABSTRACT

Purpose: The term "oligo-metastasis" could be defined as a transition state between localized and widespread systemic cancer. In the uro-oncology field, very few cases of oligo-metastases of bladder cancer have been described, probably because of the high metastatic potential of muscle invasive bladder cancer. In fact, bladder cancer remains an important cause of morbidity and mortality, the latter being predominantly related to metastasis. Herein we report a case of an oligometastatic bladder cancer treated by SBRT and we review the literature on the treatment of this disease.

Methods: We describe a case of pulmonary and lymph-node metastases of a high grade bladder cancer, which relapsed after surgical resection and chemotherapy.

Results: After the patient was treated with SBRT at his 3 metastatic lesions, and dispite a transient episode of grade 2 dyspnea, he was clinically in good condition without any evidence of disease on PET-CT scan after 22 months.

Conclusion: SBRT is an efficient metastasis-directed treatment, and may be an alternative to chemotherapy or surgery. However, our case highlights that SBRT although easily feasible is not without any risk and should be use with caution, especially outside recognize indications and clinical trials.

KEYWORDS: SBRT, oligometastasis, bladder cancer.

INTRODUCTION

The term "oligo-metastasis" could be defined as a transition state between localized and widespread systemic cancer. It is a potentially curable disease with aggressive treatment in selected patients. In the uro-oncology field, very few cases have been described about oligo-metastases of bladder cancer, probably because of the high metastatic potential of muscle invasive bladder cancer. Currently, several questions remain unanswered, concerning the diagnostic and therapeutic management of this disease. Of course, surgery occupies a prominent place in care, but it is only for a very small proportion of patients. In addition, SBRT is increasingly used in common practice in many cancer sites, and could therefore find its place in this indication; but for that it should surely randomized studies that will validate this technique.

We present a case of distant pulmonary and lymph-node metastases of high grade bladder cancer treated by SBRT and we discuss the management of this disease in relation to data from literature.

Case description

We describe the case of a 44-year-old healthy non-smoking patient diagnosed in January 2013 with a T1 Grade 3 urothelial carcinoma treated by a full cycle of bacille Calmette-Guérin (BCG) instillations following transurethral resection (TUR) to obtain a complete remission. He relapsed at the beginning of 2014 as a T2 G3 and underwent radical cysto-prostatectomy (ypT0N0). In 2015, he developped a single pulmonary metastasis in the median lobe of the right lung treated by 6 cycles of chemotherapy (cisplatin/gemcitabine) followed by a lobectomy. The pathologic results were consistent with urothelial carcinoma and negative surgical margins. He relapsed a second time mid 2016 under form of a superior right lung nodule and a right mediastinal lymphnode. Twenty cycles of weekly paclitaxel led to a stable disease at the cost of a grade I-II neuropathy. PET-CT scan at the end of 2016 showed 3 lesions: at the level of right lung hilum, the right chest wall and a supra-clavicular left lymph-node (Fig.1).

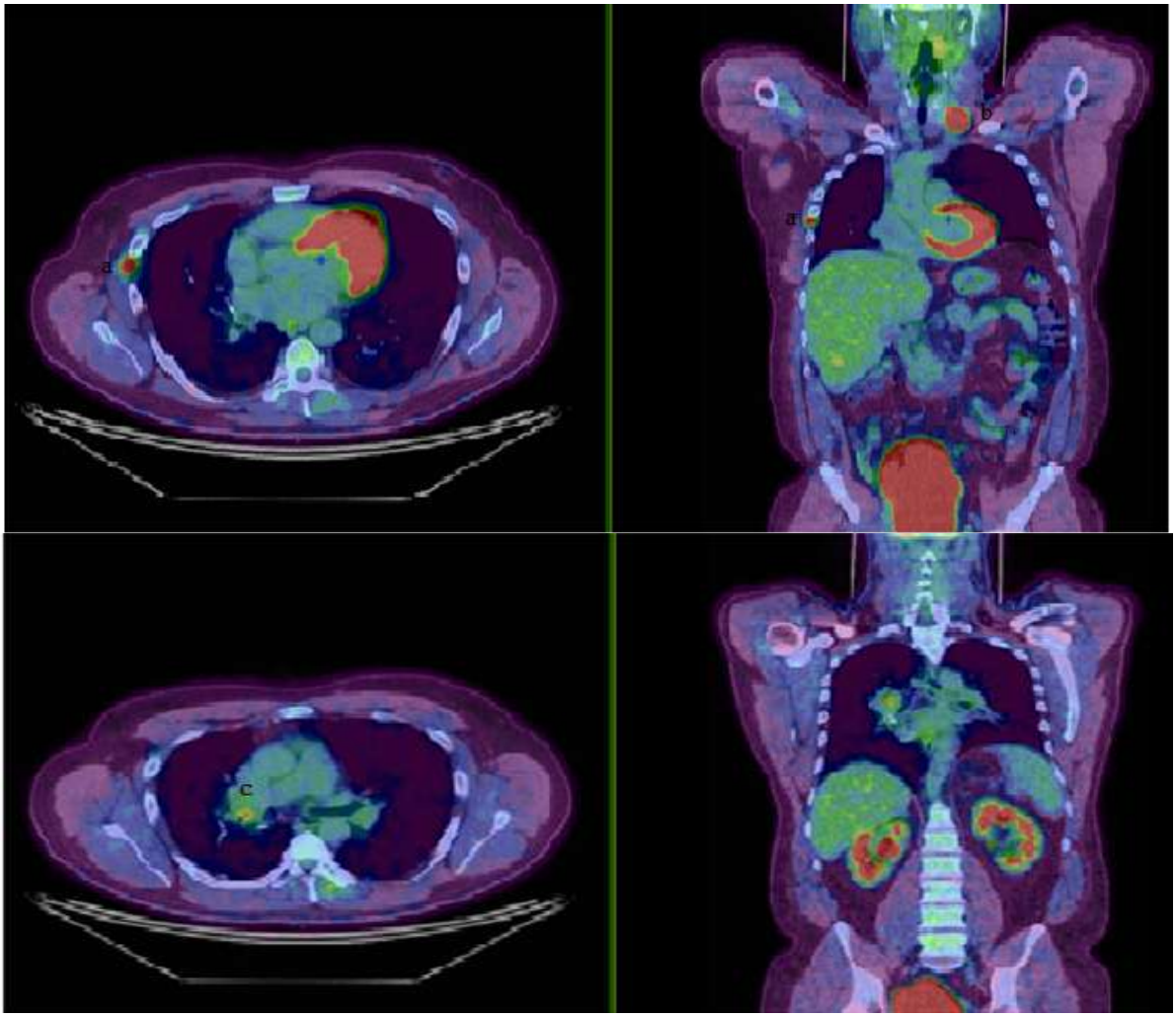
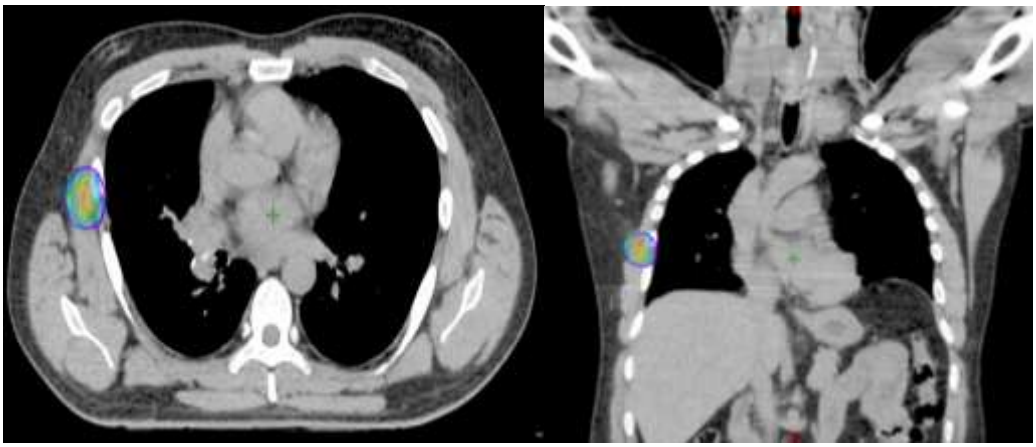


Figure 1: PET-CT scan showing an intercostal right hypermetabolic nodule (a), a large left supra-clavicular hypermetabolic lymph node (b), a discreet right hilar pulmonary hypermetabolism (c).

The multidisciplinary oncologic concertation referred the patient to our department for irradiation of the remaining lesions. With stereotactic body radiotherapy (SBRT), we gave 50 Gy in 10 fractions to the right pulmonary hilum, 50 Gy in 10 fractions to the left supra clavicular lymph-node and 30 Gy in 3 fractions to the right thoracic wall (Fig.2). Planning was achieved using image fusion between dosimetry CT-scan and PET-CT.



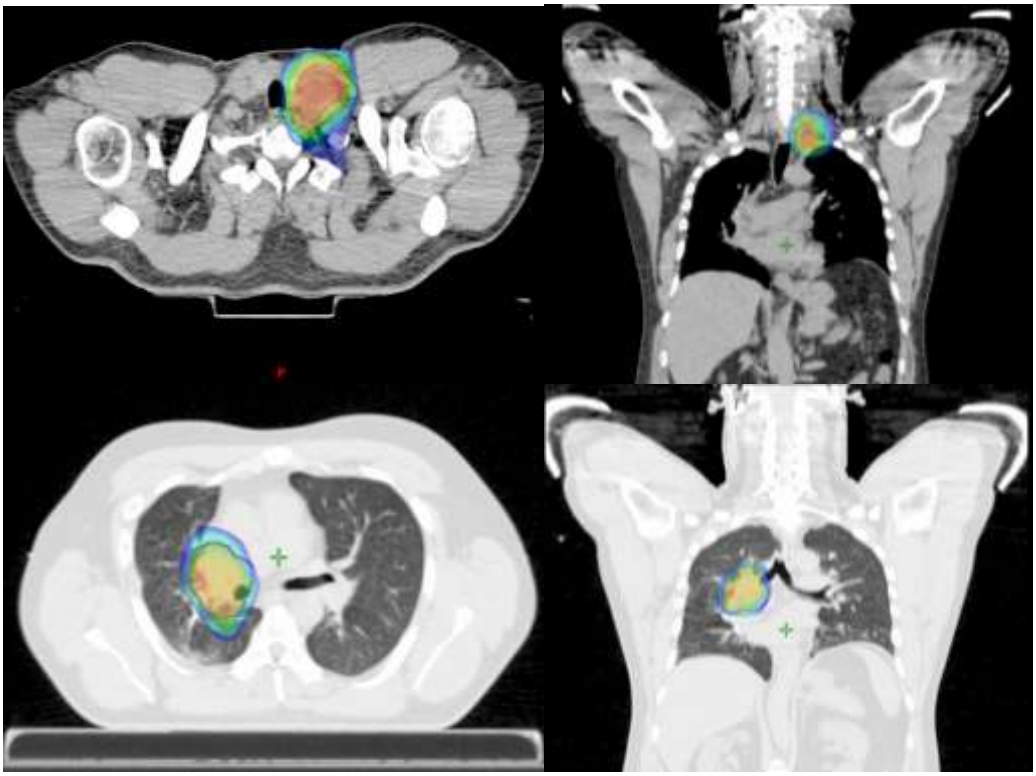


Figure 2: Stereotactic body radiotherapy (SBRT) of the 3 metastatic sites.

Two and a half months after SBRT, the PET-CT scan showed complete metabolic response (CMR)(Fig.3).

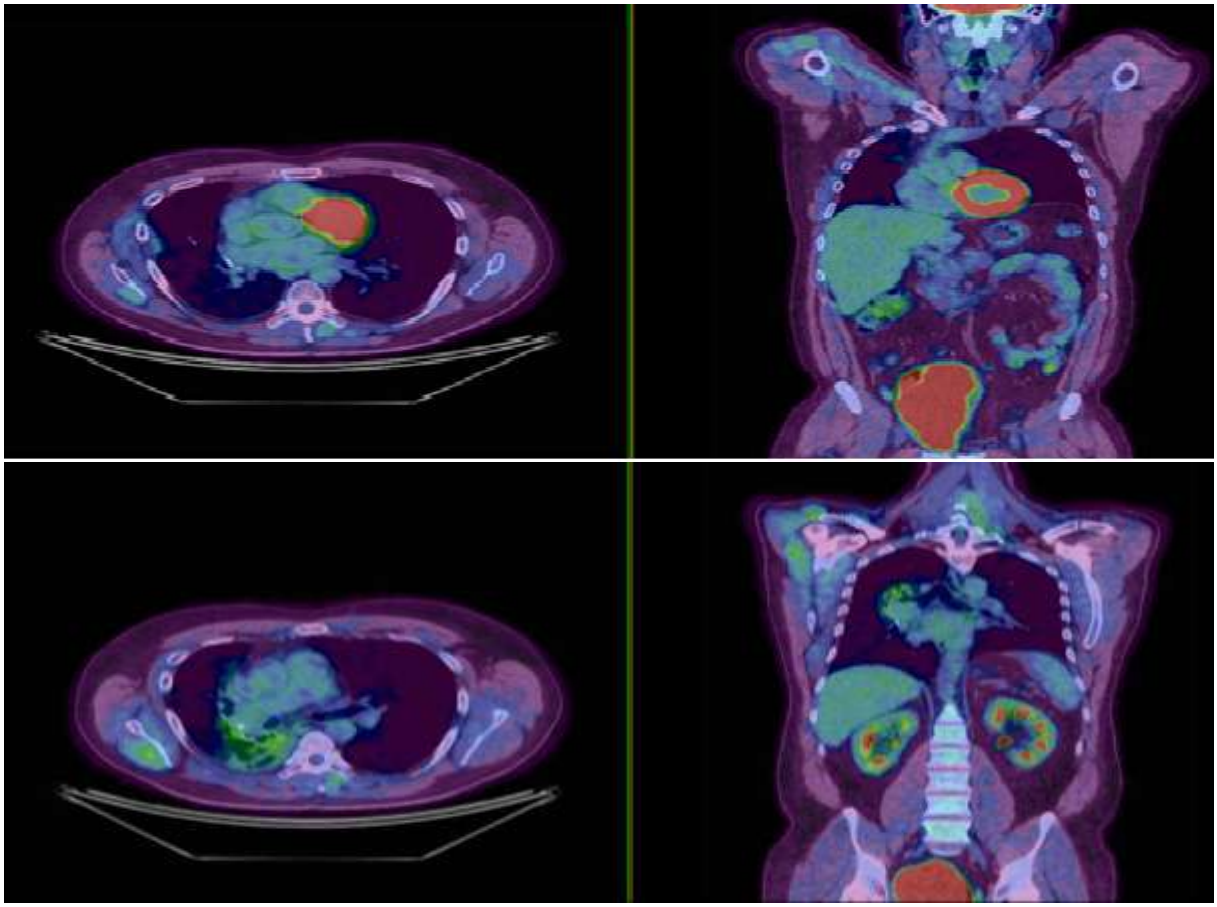


Figure 3: Follow-up PET-CT scan, two and a half months after SBRT showing complete metabolic response (CMR) on the 3 metastatic sites.

However, the patient developped a grade 2 dyspnea. A thoracic CT scan showed a pneumonitis of the right inferior lobe, probably radio-induced, treated by antibiotics and corticoids. A PET-CT scan at five months confirmed the CMR and showed a resolution of the pneumonitis (Fig.4).

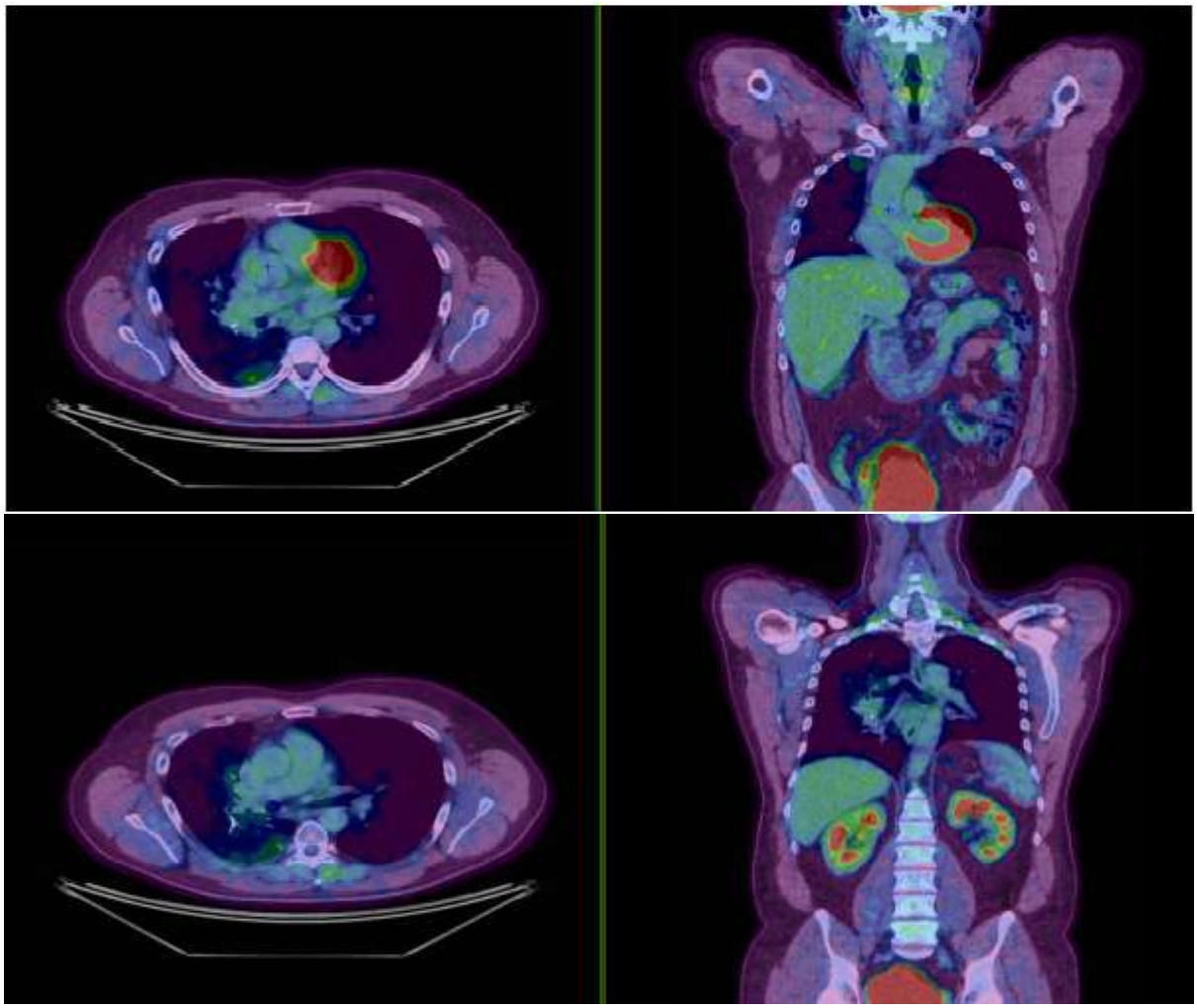


Figure 4: Follow-up PET-CT scan, five months after SBRT confirming complete metabolic response (CMR) on the 3 metastatic sites.

At 22 months after SBRT, there were no signs of relapse nor of respiratory symptoms.

DISCUSSION

The oligo-metastatic state is a widely described concept in current oncology developments. It could be defined as a transition state between localized and true systemic disease.[1] Metastasis-directed treatment has been used in non-small-cell lung cancer and colorectal cancer, with some improvement in outcome of patients.[1] In the uro-oncology field, it has been described in clear cell renal carcinoma and, especially these last few years, in prostate cancer with a clear advantage in delaying systemic treatment.[1] SBRT is a safe and efficient metastasis-directed treatment, less invasive than surgery. However, only few articles have been published about oligo-metastases of bladder cancer. This is probably a consequence of the high metastatic potential of invasive urothelial bladder tumors which therefore requires aggressive systemic treatment. Cisplatin-containing combination therapy is also the mainstay of metastatic bladder cancer treatment. However, up to 70% of patients will experience rapid tumor progression after early good response to chemotherapy. FDG-PET / CT, in addition to CT-scan and MRI, seem to be a necessary tool in early detection of local and distant recurrences. Some small studies have shown good outcome for patients who underwent ***surgical resections*** of these metastases, especially in patients with limited metastases who have responded well to neoadjuvant chemotherapy.[2-5] *Lehmann et al.* reported a progression free survival (PFS) of 15 months after resection, but the vast majority of these patients had either neoadjuvant or adjuvant chemotherapy.[2] The overall 5-year survival rate after metastasectomy was 28%. *Abe et al.* showed a better survival of 81 months in a subgroup of their cohort for patients who underwent resection of solitary lymph node or bone metastasis (compared to 19 months for other subgroups).[3] *Matsugama et al.* reported a 5-year overall survival (OS) rate of 50% in 32 patients with

urothelial cancer who underwent pulmonary metastasectomy.[6] Furthermore, they showed that solitary metastases less than 3cm were associated with improved outcomes compared with patients with larger metastases. *Han et al* reviewed 16 patients with urothelial carcinoma who underwent resection of their pulmonary lesion. Five-year OS and disease-free survival (DFS) were 65.3% and 37.5%, respectively.[7] Among these patients, 12 had a single pulmonary nodule and 11 had a nodule less than 3cm. *Otto et al.* performed metastasectomy in 70 patients resistant to MVAC (methotrexate, vinblastine, doxorubicin and cisplatin).[5] He observed a better quality of life (QoL) among symptomatic patients. Asymptomatic patients did worse in term of QoL while no gain in OS or PFS was observed.

The role of metastasectomy in oligometastatic bladder cancer has not yet been clearly defined. However, based on the literature data, it seems that it remains an excellent indication provided that patients are carefully selected.

What about other local treatments, especially ***radiotherapy****?*

In recent years, radiotherapy has made enormous progress, particularly with the advent of SBRT, which delivers high doses per fraction in the most precise way.

It is therefore tempting for the radiation-oncologist to tackle oligometastatic disease with this new technique.

Milano et al. published in 2012 a study in which they reported in 121 oligometastatic patients treated with SBRT, a 2-year OS and freedom for distant metastases (FFDM) of 50% and 35% respectively, with a toxicity of less than 1%.[8]

Likewise, *Wong et al.* reported a 2- and 5- year OS of 57% and 32% respectively, in 61 patients with oligometastases treated by SBRT. Only 3.3% of these patients experienced acute grade ≥ 3 toxicity.[9]

More Recently, ASTRO 2018 was an opportunity for *Sutera et al.* to report on the initial outcome of their study assessing the role of stereotactic ablative radiotherapy (SABR) for oligometastatic cancer.[10]

This international multi-center phase II prospective trial on 147 patients with five or fewer oligometastases from any primary site treated two-hundred and eighteen lesions including 114 pulmonary metastases. The patient population of this study was extremely heterogeneous including a variety of primary tumours and a variety in number and location of metastases. After a median follow up of 41.3 months, the median OS was 42.3 months with a 1- and 5-year OS of 84% and 43%, respectively. The five-year local progression free survival (LPFS) and distant progression free survival (DPFS) are 74% and 17%, respectively. Following SABR, 2% of patients experienced acute grade ≥ 3 toxicity and late grade ≥ 3 toxicity was 1.4%. Moreover, they identified the primary tumor site to be significantly associated with both OS and DMFS for the five most common malignancies (lung cancer, colorectal adenocarcinoma, head and neck cancer, breast carcinoma, prostate carcinoma). In general, this study has demonstrated the feasibility and safety of SBRT with excellent local control and overall survival for patients with oligometastatic cancer.

Comparing oligometastatic bladder cancer and oligometastatic states of other malignancies is difficult, considering the high metastatic potential of muscle invasive bladder cancer, hence the need for future randomized phase III trials.

Immunotherapy, in the light of various preclinical and clinical studies, has been shown to be effective in different solids tumors. Therapies blocking the PD-1/PD-L1 pathway seem to give good results in patients with metastatic urothelial cancer, with an overall response rate of 15-26%.[11-15]

However, there are a significant number of patients who do not respond to this expensive treatment.[16,17]

Radiotherapy has demonstrated its ability to create a highly immunogenic micro-environment within the tumor, resulting in increased PD-L1 expression and antitumor CD8 + T lymphocyte infiltration.[18,19]

This effect is particularly observed when radiotherapy is delivered at a certain high dose per fraction, which is possible with the SBRT.

Thus, the combination of these two therapeutic modalities could generate a synergistic effect, making it possible to obtain better therapeutic responses on a larger part of patients.[20]

This motivated the group of Piet Ost (*Sundahl et al.*) to conduct a phase I / II study aiming to evaluate the safety and the efficacy of a combination treatment (pembrolizumab and SBRT) in metastatic urothelial carcinoma.[21] The results of this study could lead to a new therapeutic approach improving the prognosis of these patients.

CONCLUSION

Systemic treatment remains the standard of care in patient with (oligo)metastatic urothelial carcinoma, the literature for metastasis-directed treatment being poor. Outside a study protocol, metastasis-directed treatment and SBRT could be considered for patients with good performance status and solitary/limited lung or lymph-node metastasis. Patients intolerant or resistant to chemotherapy may be candidates as well although there still is no formal evidence of any improvement in PFS or OS. Our case highlights that SBRT although easily

feasible is not without any risk toxicity and should be used with caution, especially outside recognized indications and clinical trials.

REFERENCES

1. Mertens L.S. and Horenblas S. Bladder cancer: Oligometastases and imaging. Nat Rev Urol. 2017.
2. Lehmann, J., Suttman H., Albers P., et al. Surgery for metastatic urothelial carcinoma with curative intent: the German experience (AUO AB 30/05). Eur. Urol., 2009; 55: 1293–1299.
3. Abe, T., Ryuji M., Nobuo S. Outcome of metastasectomy for urothelial carcinoma: a multi-institutional retrospective study in Japan. J. Urol., 2014; 191: 932–936.
4. Siefker-Radtke, A. O., Walsh G.L., Pisters L.L., et al. Is there a role for surgery in the management of metastatic urothelial cancer? The M. D. Anderson experience. J. Urol., 2004; 171: 145–148.
5. Otto T., Krege S., Suhr J., et al. Impact of surgical resection of bladder cancer metastases refractory to systemic therapy on performance score: a phase II trial. Urology, 2001; 57(1): 55-90.
6. Matsugama H., Yoshino I., Ito H., et al. Is there a role for pulmonary metastasectomy with a curative intent in patients with metastatic urinary transitional cell carcinoma? The Annals of Thoracic Surgery, 2011; 92(2): 449-53.
7. Han W.S., Kim K., Park J.S. Result of surgical resection for pulmonary metastasis for urothelial carcinoma. The Korean Journal of Thoracic and Cardiovascular Surgery, 2012; 45(4): 242-5.
8. Milano M.T., Katz A.W., Zhang H., et al. Oligometastases treated with stereotactic body radiotherapy: long-term follow-up of prospective study. International journal of radiation oncology, biology, physics, 2012; 83: 878-86.
9. Wong A.C., Watson S.P., Pitroda S.P., et al. Clinical and molecular markers of long-term survival after oligometastasis-directed stereotactic body radiotherapy (SBRT). Cancer, 2016; 122: 2242-50.
10. Sutera P., Clump D.A., Kalash R., et al. Initial Results of a Multicenter Phase II Trial of Stereotactic Ablative Radiation Therapy for Oligometastatic Cancer. Int J Radiat Oncol Biol Phys. Pii: S0360-3016 (18)33573-9.
11. Kim J.W., Tomita Y., Trepel J., et al. Emerging immunotherapies for bladder cancer. Curr Opin Oncol., 2015; 27: 191–200.
12. Powles T., Eder J.P., Fine G.D., et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature, 2014; 515: 558–62.
13. Balar A.V., Galsky M.D., Rosenberg J.E., et al. Atezolizumabas first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet., 2017; 389: 67–76.
14. Rosenberg J.E., Hoffman-Censits J., Powles T., et al. Atezolizumabin patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet., 2016; 387: 1909–20.
15. Bellmunt J., de Wit R., Vaughn D.J., et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med., 2017; 376: 1015–26.
16. Sharma P., Retz M., Siefker-Radtke A.O., et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. Lancet Oncol., 2017; 18: 312–22.
17. Powderly J.D., Koeppen H., Hodi F.S., et al. Biomarkers and associations with the clinical activity of PD-L1 blockade in a MPDL3280A study. In: ASCO annual meeting proceedings, 2013; 3001.
18. Deng L., Liang H., Burnette B., et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. J Clin Investig., 2014; 124: 687–95.
19. Teng F., Mu D., Meng X., et al. Tumor infiltrating lymphocytes (TILs) before and after neoadjuvant chemoradiotherapy and its clinical utility for rectal cancer. Am J Cancer Res., 2015; 5: 2064–74.
20. Twyman-Saint Victor C., Rech A.J., Maity A., et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature, 2015; 520: 373–7.
21. Sundahl N., De Wolf K., Rottey S., et al. A phase I/II trial of fixed-dose stereotactic body radiotherapy with sequential or concurrent pembrolizumab in metastatic urothelial carcinoma: evaluation of safety and clinical and immunologic response. J Transl Med, 2017; 15: 150.
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