

## Small cell carcinoma of the urinary bladder successfully managed with palliative radiotherapy and immunotherapy.

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### Abstract

**Background:** Small cell carcinoma of the bladder (SCCB) is a rare, poorly differentiated neuroendocrine epithelial tumour linked with a more assertive behaviour and poorer outcome than bladder transitional cell carcinoma (TCC). It is mostly diagnosed at last stage and generally believed to have a high metastatic potential.

**Case report:** A 74 -year-old non-smoker man was having multiples episodes of gross hematuria for three months. The cystoscopic examination revealed a large mass over left lateral and anterior wall. Biopsy was taken and its evaluation revealed tumor to be small cell carcinoma. Patient had no recurrence till last follow up at two years. He died following last follow up due to cancer unrelated cause. The main aim is to describe the complete response without recurrence for two years (till cancer unrelated death) achieved in T4b stage large urinary bladder cancer using palliative radiation, 20 gy radiation (2 gy each) and TLR-2 agonist CADI-05.

**Conclusion:** Probably the first case report describing successful bladder preserving approach using low dose (sub lethal) radiotherapy with active immunotherapy in management of T4b stage SCCB.

**Keywords:** Small cell bladder cancer, Bladder preserving approach, Palliative radiotherapy, Immunotherapy, Stage T4b bladder cancer, CADI-05, Muscle invasive bladder cancer.

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### Introduction

Small cell carcinoma (SCC) represents approximately 20% of lung cancer [1]. The extra pulmonary SCC is relatively rare [2]. It has been described in esophagus, stomach, pancreas, gallbladder, uterine cervix, kidney, urinary bladder, and prostate [3,4]. SCC of urinary bladder (SCCB) has a morphology similar to SCC of the lung [2]. The primary SSCB is seen in less than 1% of bladder cancer [4-9], mostly in patients with a history of heavy smoking [10]. Unlike transitional cell carcinoma of bladder, SSCB is highly aggressive and is rare to find lower stage disease at initial diagnosis [4,9,10]. SCCB is known for rapid progression, early metastases, and poorer prognosis compared to transitional cell of bladder [7-10].

The National Comprehensive Cancer Network's guidelines 2018 (NCCN) recommends neo-adjuvant chemotherapy followed by cystectomy or radiotherapy for any patient with small-cell component histology with localized disease regardless of stage [12]. There is no specific recommendation provided for management of T4b stage bladder cancer with small cell component histology [SCCB] in NCCN.

For stage T4b disease in general, systemic therapy (chemotherapy) or concurrent chemo radiotherapy is recommended by NCCN [11,12]. EAU 2016 guidelines recommend radical cystectomy as a palliative treatment for stage T4b disease [11]. Radical surgery has the greatest morbidity and should be considered only if there are no other options [13]. Radiation therapy can be used to control hemorrhage and pain [13].

An analysis of 960 SCCB patients in the National Cancer Data Base revealed that median overall survival (OS) was 8.3 months [8].

The case report describes complete response without recurrence for two years (till cancer unrelated death) achieved in T4b stage large urinary bladder cancer using palliative radiation, 20 gy radiation (2 gy each) and TLR-2 agonist CADI-05 [14-16]. Achieving complete response in absence of surgery for T4b stage SCCB is not a known possibility. In the light of our case report, we also discuss potential mechanism of action on based on systematic literature review.

### Case Report

A 74 -year-old non-smoker man was having multiples episodes of gross hematuria for three months. He had no other symptoms like pain, burning micturition, weight loss or night sweats. He had no risk factors including previous radiation therapy, occupational risk factors or hereditary factors. In addition, no other pre-existing conditions were known.

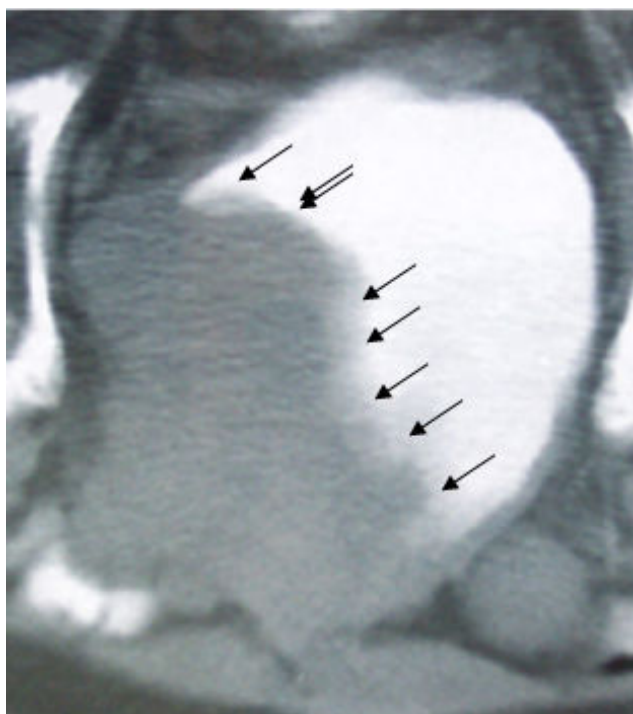
The performance status (PS) was equal to 1. Ultrasound evaluation revealed a mass in bladder. Ultrasound evaluation of abdomen did not reveal any abnormality. Contrast enhanced computed tomography (CT) scan of the pelvis showed a bladder mass at left wall and anterior wall measuring 8.9 × 7.6 cm with extra vesicle extension to left rectus abdominal muscle without enlargement of the pelvic lymph nodes (Figure 1).

The cystoscopic examination revealed a large mass over left lateral and anterior wall. Biopsy was taken and its evaluation revealed tumor to be small cell carcinoma.

The patient received 10 sittings of radiation (2 gy each) as a palliative therapy. After five sittings of radiotherapy, immunotherapy was added. Immunotherapy comprised of CADI-05 (Potent TLR 2 agonist) and was administered intradermally over deltoid. The first dose of 0.2 ml was administered over both detours. Subsequently 0.1 ml was administered every two weeks.

Hematuria disappeared following first administration of CADI-05 and prior to second administration of CADI-05. Ultrasound repeated six weeks later failed to reveal mass lesion. Bladder wall thickness of 9 mm was the only finding. Contrast enhanced CT scan suggested remission of mass to the great extent (Figure 2). Subsequent contrast enhanced CT scans did not reveal any mass lesion (Figure 3).

Patient had no recurrence till last follow up at two years. He died following last follow up due to cancer unrelated cause.



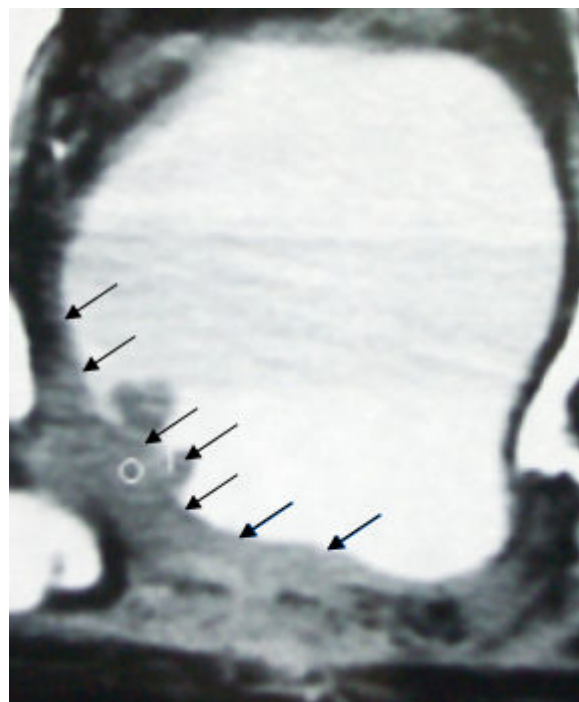
**Figure 1. Pre-treatment:** Contrast enhanced CT-scan demonstrating tumor bladder mass measuring  $8.9 \times 7.6$  cm with extra vesical extension to left rectus abdominis muscle

## Discussion

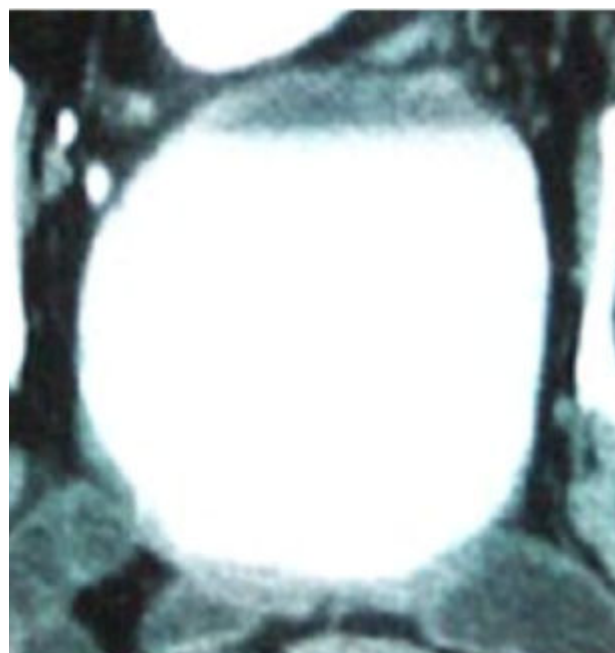
There is a synergy between radiotherapy and immunotherapy [17-23]. Combination therapy while improving outcome also generates strong protective response to provide resistance to recurrence [24]. Synergy does not need tumor to be immunogenic and is also seen in absence of antigen sharing between tumor and immunotherapy [24,25].

Underlying mechanism of synergy is due to complex effect of radiotherapy on tumor cells, tumor microenvironment and vessels [17,23,26,27]. Effect on tumor cells make them more

sensitive for cytotoxic T cell responses, due to an increased expression of immunogenic surface molecules like adhesion molecules (ICAM-1), death receptors (Fas/CD95), classical stimulatory molecules (MHC I), costimulatory molecule (CD80), mannose 6phosphate receptor etc. [17,18,25,28-32].



**Figure 2.** Marked reduction in tumor size 6 weeks after initiation of radiotherapy



**Figure-3.** Absence of Tumor following treatment.

As concerns the tumor microenvironment, RT triggers the timely restricted release of many pro-inflammatory molecules such as chemokines, cytokines, and immune-activating danger signals (DAMPs) as well as exosomes [18]. This effect is seen even with sub lethal radiation [32-34]. Up regulation of surface

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proteins leads to sensitization of tumor cells killing by immune cells [17,25,28,33,34] mainly CTL [18].

Radiation also induces tumor specific cytotoxic T lymphocytes (CTL) [17,18]. Radiation facilitates infiltration of immune cells into tumor [23,26,27,35,36] by up regulation of chemokines CXCL9, CXCL10, and CXCL16 [37]. Tumor infiltration by T cells is also facilitated by up regulation of vascular cellular adhesion molecule 1 (VCAM-1) on tumor endothelium [37]. Radiation-induced up-regulation of surface proteins on surviving tumor cells improves their recognition and killing by T cells [37]. Radiation also induces immunosuppression. It promotes accumulation of regulatory T cells (Treg) and protumorigenic M2 macrophages [37].

CADI-05 is a potent Toll like Receptor-2 (TLR-2) agonist [15,16] which induces a potent Th1 type of cell mediated immune response even in presence of tumor [38, 39]. Immune response generated is adaptive in nature and its cytotoxic activity is mediated by CD8<sup>+</sup> cells secreting IFN gamma [39]. Following intradermal or subcutaneous administration of CADI-05, there is a significant increase in tumor infiltrating cells which includes IFN-gamma secreting CD4 cells, CD8 cells, NK cells, NKT cells, dendritic cells and macrophages [38]. CADI-05 also reduces tumor induced cell mediated immunosuppression by reducing the number of Treg, CTLA-4 and PD-1 expressing lymphocytes and M2 macrophages [38-41]. CADI-05 administration also reduces production of immunosuppressive cytokines like IL-6, IL-10, and TGF-beta [39-41].

The administration of CADI-05 to small-size tumor-bearing animals results in delayed tumor progression with improved survival but has no effect on larger tumor [38,40]. CADI-05 is found to be synergistic with chemotherapy, radiotherapy and monoclonal antibodies targeting immune check point [36,38].

CADI-05 along with chemotherapy is found useful in management of non-small cell lung cancer [15,40]. It improves response rate, progression free survival and overall survival in those completing four cycles of chemotherapy. CADI-05 with radiotherapy is found useful in management of muscle invasive bladder cancer also [42,43].

It achieves complete response which is durable. As a monotherapy CADI-05 is found useful in management of advanced melanoma [44]. It is approved in India for use with chemotherapy in management of advanced non-small cell lung cancer.

The possible mechanism based on current knowledge seems to be synergy between sensitizing effect of radiation for immune mechanism mediated killing and Th1 type of cell mediated immune response generated by CADI-05. Both activates immune cells and potentates their infiltration in tumor. Both work mainly through IFN-gamma secreting CD8<sup>+</sup> T cells. CADI-05 also reduces Trig and known to convert M2 macrophage to M1 type.

This is probably the first case report describing successful bladder preserving approach using low dose (sub lethal)

radiotherapy with active immunotherapy in management of T4b stage SCCB.

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