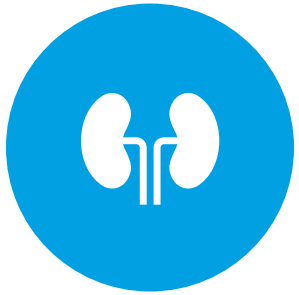
Immunotherapy Combined with Radiotherapy in Urological Malignancy

Dr Saurabha Kumar,
Consultant Radiation Oncology,
Mazumdar Shaw Medical Center,
Narayana Health City,
Bangalore

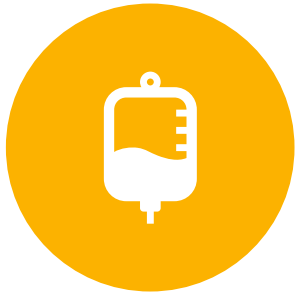
Narayana Health

Introduction



Trimodality therapy is as effective as surgery in carefully selected MIBC, T2-T4a non metastatic disease.

Atezolizumab and Pembrolizumab are also approved as first line treatment in patients who are cisplatin-ineligible PD-L1 (≥ 5%)



Since 2016, five immune checkpoint inhibitors have been approved by the FDA as second-line agents in the treatment of metastatic MIBC

Only about 20% of patients will respond to ICIs, although the majority of responders have a durable response.

Rationale

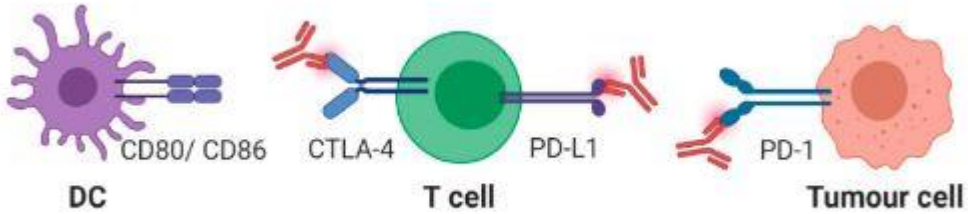


Table 1 The effects of radiotherapy on the immune system

Immune-stimulating effects of radiotherapy	Immune-suppressing effects of radiotherapy
Induces immunogenic cell death: Release of tumor antigens and DAMPs (calreticulin, HSP70, HMGB1) Increased MHCI expression and APCs maturation Increased CD8+T-cell infiltration and tumor cell death	Radiation-induced lymphopenia (RIL): Preferential depletion of CD4+T cells and B cells after RT
Increases: Pro-inflammatory cytokines: interferon gamma, tumor necrosis factor-α, type I interferons Cos-stimulatory molecules Adhesion molecules	Effects on infiltrating immune cells: ↑ CD4+T-reg cells ↑ MDSCs
Activates the innate immune system: Upregulation of NKG2D type II NK-cell activation	Effects on immune cell surface markers: ↑ PDL1 expression ↑ CTLA4 expression on T-reg cells
Abscopal effect: ↑ tumor antigens → ↑APCs → ↑ pro-inflammatory cytokines → ↑ CD8+T cells	

Radiotherapy and immune system

- Immunogenic cell death and modulation of the tumour microenvironment.
- Priming of T Cell in the TME and lymph nodes.
- Radiation Induced Abscopal effect Well documented in metastatic RCC, Melanoma and HCC
- Formenti et al. showed an objective abscopal response in 9/34 patients (27%) with solid metastatic cancers that received GM-CSF and irradiation to one metastatic lesion.
- In a randomized phase 1 trial, Sundahl et al. compared Pembrolizumab with sequential versus concomitant stereotactic body radiotherapy (SBRT) to the largest metastatic lesion in MIBC patients. There was a 44% ORR in non-irradiated metastatic sites when SBRT was given concomitantly vs. 0% when given sequentially.
- Radioresistant tumor cells can still be recognized and destroyed by retargeting of T cells

Narayana Health

Radiation induced Lymphopenia

- RIL is characterized by acute preferential depletion of CD4 + T-cells and B-cells
- In a retrospective study of 167 patients treated with Nivolumab or Pembrolizumab, baseline and 3-month lymphopenia were associated with shorter PFS.
- Rudra et al. compared standard RTOG fields with more limited fields in patients with glioblastoma undergoing concurrent temozolomide and RT, and found that the standard field had a greater decline in total lymphocyte counts at 3 mo.
- In pancreatic cancer, a series compared patients undergoing SBRT to smaller target volumes with patients undergoing concurrent chemoradiotherapy to larger target volumes and found a lower incidence of radiation-induced lymphopenia in the SBRT group, albeit the concurrent chemotherapy may have been a confounder in this study.

Practical considerations of combining RT with Immunotherapy: Sequencing /Dose Fractionation

- Pre-clinical studies have shown that dose per fraction greater than 6–8 Gy are required to produce an effective immunogenic response.
- A multi-fractionated regimen was superior to single dose regimens in decreasing tumor growth at non-irradiated sites.
- In bladder cancer mouse models, ICIs were more effective when combined with a 10 Gyx2 or 6.25 Gyx2 RT regimens than with a 10 Gyx1 regimen.
- Optimal sequencing of immunotherapy and RT, the optimal immunotherapy agent and its duration, and the role of chemotherapy need to be elucidated.
- Additionally, details regarding the RT, such as the optimal dose/fractionation, target volume, and site to irradiate are not known.

- Dovedi et al. found that 10 Gy directed to tumors in mice with colon cancer induced tumor cell PD-L1 expression, which peaked at 72 h and declined significantly in the 1st week. In this study, concurrent administration of anti- PD-L1 antibody, rather than after RT, led to improved survival.
- A similar increase in PD-L1 expression after RT was seen in an in vivo study of mice injected with murine bladder cancer, with improved survival with anti-PD-L1 antibody delivered concurrently.
- Young et al. compared the efficacy of anti-OX40 and anti-CTLA4 with 20Gy in a single fraction in a CT26 murine colorectal cancer model in mice. The investigators found that survival with RT and anti-OX40 was best if immunotherapy was delivered 1 d after RT, while survival with RT and anti-CTLA4 was best if immunotherapy was delivered 7 d prior to the start of RT.

Narayana Health

RT volume and sites of disease

- Whether pelvic elective nodal irradiation (ENI) could directly or indirectly affect the immune response.
- ENI also adversely affected survival when combined with ICIs.
- Other studies have shown a strong correlation between the RT volume and RT-induced lymphopenia.
- Which metastatic site to irradiate if several are present. Most reported cases of the abscopal effect involved RT to visceral metastases. Visceral sites may be more immunogenic than osseous sites.
- In the phase I trial by Tang et al. combining ipilimumab with SBRT for metastatic cancers, irradiation to the liver led to a greater immunologic response than treatment to lung tumors.

- Irradiating multiple sites of disease reduces tumor burden while also increasing the likelihood of exposure and priming to the desired tumor-associated antigens. This would circumvent the inhibitory effects of the TME within each individual tissue bed, thus increasing the probability of activation of the anti-tumor immune process
- Inconsistency between the gene mutation of the primary lesion and the metastasis might cause the antigen released by radiotherapy of a single lesion not suitable for other lesions, which makes it unable to entirely exert the immune effect induced by radiotherapy.
- Lemons et al. reported on patients treated in an institutional trial of pembrolizumab and SBRT for metastatic disease, and found that large tumors that underwent partial irradiation had similar local control to smaller tumors that were entirely encompassed by SBRT doses

NCT03317158	NMIBC	To establish the safety of durvalumab monotherapy and durvalumab in combination with BCG and EBRT in NMIBC patients	Phase I/II	Durvalumab alone, durvalumab + EBRT, or durvalumab + BCG	Hoosier Cancer Research Network
NCT02662062	MIBC	To assess the safety and feasibility of combining pembrolizumab with chemoradiotherapy for patients with MIBC	Phase II	RT + cisplatin + pembrolizumab	Australian and New Zealand Urogenital and Prostate Cancer Trials Group
NCT03171025	MIBC	To evaluate the rate of failure free survival at 2 years after start of chemoradiation with adjuvant nivolumab in adult subjects who undergo chemoradiation for localized bladder cancer	Phase II	Chemoradiation followed by nivolumab	University of Utah
NCT03419130	MIBC	How well radiation therapy and pembrolizumab work in treating patients with urothelial bladder cancer that is restricted to the site of origin, without evidence of spread	Phase II	Pembrolizumab + (conventional RT or hypofractionated RT)	University of California

Trial	Condition	Aims	Phase	Intervention	Institution/Group
NCT01436968	Intermediate-high risk localized PCa	The purpose of this study is to evaluate the effectiveness of ProstAtak immunotherapy in combination with RT for patients with intermediate-high risk localized PCa	Phase III	RT + valacyclovir ± AdV-tK	Advantagene, Inc. d. b.a. Candel Therapeutics
NCT02107430	High risk localized PCa	To determine whether DCVAC/PCa added after radical primary prostatectomy can improve PSA progression times within 5 years for patients with high risk localized PCa	Phase II	RT ± dendritic cells (DCVAC/PCa)	Sotio a.s. (Czech Republic)
NCT01807065	mCRPC	To study how well giving sipuleucel-T with or without RT works in treating patients with mCRPC	Phase II	RT followed by sipuleucel-T	City of Hope Medical Center
NCT01818986	mCRPC	Sipuleucel-T and SABR for patients with mCRPC	Phase II	SABR + sipuleucel-T	University of Texas Southwestern Medical Center
NCT01303705	Metastatic PCa	To examine a novel combination of anti-OX40 to induce proliferation of memory and effector T-cells in conjunction with cyclophosphamide (CTX) and radiation to induce tumour antigen release with the overall goal of promoting an immune response against prostate cancer	Phase I/II	RT + cyclophosphamide + anti-OX40	Providence Portland Medical Center

NCT02232230	mCRPC	To assess the effect of RT to augment antitumor responses from immune therapy with Provenge	Phase II	RT + sipuleucel-T	21st Century Oncology
NCT03477864	Locally advanced prostate cancer	To study the side effects of anti-PD-1 monoclonal antibody REGN2810 and/or ipilimumab when given together with SBRT before surgery in treating participants with progressive advanced or oligometastatic PCa	Phase I	SBRT + anti-PD-1 ± ipilimumab before radical prostatectomy	Sidney Kimmel Cancer Center at Thomas Jefferson University
NCT03007732	Hormone-naïve oligometastatic PCa	SBRT and pembrolizumab with or without intratumoral SD-101 in patients with newly diagnosed hormone-naïve oligometastatic PCa	Phase II	SBRT + ADT + pembrolizumab ± TLR9 agonist (SD-101)	Lawrence Fong, University of California
NCT01833208	mCRPC	Impact of radiation therapy on the immunogenicity of sipuleucel-T	Pilot study	RT + sipuleucel-T	Roswell Park Cancer Institute
NCT02463799	mCRPC	To study the effect of radium-223 when added to sipuleucel-T for treating castrate-resistant prostate cancer that has spread to the bone	Phase II	Radium-223 + sipuleucel-T	Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

NCT02781506	Metastatic ccRCC	To increase the RR of treatment with Nivolumab by the concurrent administration of SABR	Phase II	SABR + nivolumab	University of Texas, Southwestern
NCT01884961	Metastatic RCC or melanoma	Radiotherapy as an immunological booster in patients with metastatic melanoma or renal cell carcinoma treated with high-dose IL-2	Phase II	RT boost + high-dose IL-2	Istituto Scientifico Romagnolo (Italy)
NCT02855203	Metastatic ccRCC	To examine the safety, efficacy and biological effects of combining pembrolizumab (MK-3475) an antibody targeted against anti-(PD-1), with SABR for oligometastatic RCC	Phase I/II	SABR + pembrolizumab	Peter MacCallum Cancer Centre (Australia)
NCT03050060	Metastatic RCC, melanoma, or NSCLC	To study how well image guided hypofractionated radiation therapy works with nelfinavir mesylate, pembrolizumab, nivolumab, and atezolizumab in treating patients with metastatic RCC, melanoma, or NSCLC	Phase II	IGRT + nelfinavir + (pembrolizumab or nivolumab or atezolizumab)	University of Washington

irAE

- Grade ≥ 3 irAEs ranging from 7–31% across studies.
- It is important to note that the toxicity of combined ICIs and RT could be enhanced when chemotherapy is used in the context of TMT.

Study	Study characteristics	Intervention	Safety outcomes	Type of toxicities including those that were not DLT (*n*)
NCT02560636 (PLUMMB trial)	Phase I trial involving 5 patients in first cohort with locally advanced or metastatic MIBC (T2–T4, N0–3, M0–1)	Pembrolizumab 2 weeks before weekly hypofractionated RT (24 Gy/6 vs 24 Gy/4 vs 30 Gy/5 fractions)	2/5 patients met the predefined definition of dose-limiting toxicity Trial was stopped and RT doses reduced	G4 bowel perforation[a] (1) G3 non-infective cystitis (1) G3 urinary tract/bladder infection (2) G3 hematuria (1) G3 urinary pain (1) G3 fatigue (1) G2 urinary urgency, incontinence (1) G2 pain (1) G2 anemia (1)
NCT03620435	Phase I trial TMT in first cohort of 8 patients with T2–T4a N0M0 MIBC	Concurrent atezolizumab with gemcitabine and hypofractionated RT (50 Gy/20 fractions) after TURBT (TMT)	Study stopped after 50% of patients experienced grade 3 GI toxicities despite atezolizumab dose reduction. No grade 4 toxicity	G3 colitis (3) G3 proctitis (1) G3 lymphopenia (1) G3 neutropenia (1)

Conclusion

- *There are promising scientific rationales for combining immunotherapy and RT to lead to both local and systemic durable responses in genitourinary malignancies, which have been corroborated by a growing body of both preclinical and clinical evidence.*
- *The combination of immunotherapy and RT presents novel opportunities for treatment strategies in which radiation is no longer limited to local control when used as a backbone for systemic immunotherapy.*

THANK YOU