**Commentary**
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# Modern Management and Future Directions for Trimodality Therapy for Bladder Cancer

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## Description

In contemporary oncology, organ preservation combined with multimodal therapy is utilised to treat a variety of cancers, including head and neck, breast, anal, and prostate cancers. Trimodality therapy (TMT) delivers equivalent oncologic outcomes while retaining the native bladder in more than 70% of patients, despite the fact that radical cystectomy is the most often utilised treatment for muscle invasive bladder cancer (MIBC) [1]. The role of radiation treatment in bladder preservation and adjuvant radiation therapy (ART) after radical cystectomy are both covered in this paper. The most extensive transurethral resection of the bladder tumour (TURBT) is followed by concomitant chemotherapy and external beam radiation (EBRT). Most TMT patients experience a clinical complete response (cCR) (70–80%), avoiding the need for a salvage radical cystectomy and providing long-term survival rates that are comparable to those of modern radical cystectomy series. Giacalone discovered that 88% of patients with modern-day treatment had cCR, 75% had bladder intact disease-specific survival (DSS), and 84% had 5-year overall survival (OS). Similar outcomes were reported by a group in Madrid with long-term follow-up of prospectively enrolled patients. With a 10-year bladder preservation rate of 79%, the 10-year cancer-specific mortality and OS rates were, respectively, 76.3 and 43.2%. For bladder preservation, patients with tiny tumours, complete TURBT, no hydronephrosis, and a functional bladder work well. Numerous MIBC patients also have age-related comorbidities, which exclude them from receiving chemotherapy or surgery [2]. These conditions include renal function impairment, cardiovascular illness, and respiratory disease. On the other hand, according to a propensity score analysis of the National Cancer Database (NCDB), combining chemotherapy to radiation therapy was beneficial for OS in patients over the age of 80 (56 versus 42% at 2 years, P 0.001). Additionally, one propensity analysis of individuals enrolled in the programme discovered that TMT has comparable results (DSS 61.2 versus 68.6% at 5 years) and tolerability in patients over 75 compared with younger patients. Different chemosensitization protocols are suggested by two recently finished phase II studies. In individuals who were not candidates for radical cystectomy, Radiation Therapy Oncology Group (RTOG) 0524 was a multiinstitutional phase I/II trial of daily radiation therapy with weekly paclitaxel, with the addition of trastuzumab for those with Her2/Neu overexpression [3]. The cCR was 61.5% in Her2/Neu-positive patients and 62.5% in Her2/Neu-negative patients at 12 weeks following the end of radiation therapy. Although there was no information on survival, acute toxicity was comparable to earlier RTOG experiments. The findings of RTOG 0712, a phase II trial comparing fluorouracil (5-FU) and cisplatin with twice-day radiation to gemcitabine and daily radiation, have just been published. At three years, the rates of distant metastasis-free survival with 5-FU/cisplatin and gemcitabine were comparable (78 versus 84%, respectively, P=0.73), as well as the rates of complete response (88 versus 78%, respectively). At three years, the combined bladder intact and distant metastasis-free survival was 67 against 72%, and there was no difference in grade 3 or higher toxicity (64 versus 55%, P=0.45) [3].

The TMT standard, developed by RTOG 9506 and RTOG 0233, uses twice-daily radiation as opposed to the most recent RTOG trials. Patients who experienced a complete or almost complete response following TMT showed excellent long-term disease control and bladder preservation, according to a pooled analysis of these trials. Although the effectiveness and toxicity shown in the daily radiation arms of RTOG 0524 and RTOG 0712 were positive, various chemotherapeutic regimens prevent a direct comparison of the effect of radiation fractionation. However, daily radiation is more practical for patients and more compatible with standard therapeutic routines. There are no RCTs that contrast patients who receive TMT with those who undergo radical cystectomy. The most accurate information contrasting TMT with radical cystectomy comes from retrospective investigations, a systematic review, and metaanalysis in the absence of finished RCTs. In a recent retrospective analysis, propensity scores were utilised to compare 56 patients who got complete TMT (maximal TURBT, EBRT with concurrent chemotherapy) at the Princess Margaret Hospital with patients who underwent radical cystectomy. The NCDB has been used in several investigations to compare radical cystectomy with TMT. TMT is not clearly coded, though, thus researchers must make an effort to deduce which patients received TMT. In one retrospective NCDB analysis, Cahn et al. found that radical cystectomy had a better OS than TMT; however they used a broad definition of TMT. Any radiation therapy combined with the use of chemotherapy within three months of radiation therapy. This may incorrectly include people who get radiation treatment and experience a recurrence that necessitates chemotherapy within three months. Patients who get subtherapeutic radiation doses may also be included. Additionally, the authors did not account for individuals being advanced from a clinical stage to a pathologic stage [4].

### Modulatory radiotherapy

After radical cystectomy, local-regional recurrence (LRR) is a serious issue for patients with at least pT3 illness since salvage therapy for local-regional failure are seldom effective and can cause distant metastases. We now know that pelvic recurrences in locally advanced bladder cancer are more common than previously believed because to routine and improved surveillance imaging using computed tomography (CT) and MRI, and treatment alone has not been shown to lower the risk of LRR. According to a retrospective research by Reddy et al., the extent of lymph node dissection or perioperative chemotherapy had no bearing on the LRR, which might reach 31% in patients with pathologic T4 and node-positive illness. 34 percent of the patients who had LRR had it without distant metastases. A metaanalysis of randomised controlled trials with or without platinum-based chemotherapy following local therapy (typically radical cystectomy) shows that 26% of patients experienced local recurrence as a first event with or without synchronous distant failure, which is consistent with other studies' findings. ART can enhance local management and possibly stop the progression of distant disease down the road, improving DFS and OS. Despite the fact that ART is most frequently utilised in patients with positive surgical margins or pT4 illness, oncologists have not historically embraced treatment, mostly due to worries about gastrointestinal radiation toxicity [5]. The most reliable information is from Egypt, which Zaghloul first mentioned in 1992. Radial cystectomy for MIBC patients were randomised to observation, ART using 1.25Gy three times per day to a total dose of 37.5Gy, or ART using 2Gy per fraction per day to 50Gy utilising two-dimensional radiation treatment methods. Patients on the ART regimens showed better local control over the

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course of their 5-years (87 and 93 against 50%, P0.0001) and better DFS over the course of their 5-years (49 and 44 versus 25%, P0.0001). This regimen was not frequently used outside of Egypt due to the majority of patients having SCC (67%) and a greater incidence of late radiation enteritis (36%).

By adopting 3-dimensional conformal radiotherapy, improvements in radiation therapy methods can lower late stage 3 or higher gastrointestinal damage below the 7% recorded in the ACRT arm (3DCRT). Radiation oncologists can administer doses of at least 50Gy to clinical target volumes within the pelvis while avoiding administering excessive doses to organs at risk thanks to intensitymodulated radiation treatment (IMRT) and imaging guidance. Rates of severe late gastrointestinal or genitourinary toxicities are incredibly rare, based on pelvic IMRT's success in the treatment of other cancers. In the postoperative environment, IMRT helps prevent bowel and urine diversion. Orthotopic neobladders can tolerate postoperative radiation therapy, despite earlier being thought to be a contraindication to ART, according to a small series using current imaging and treatment methods. In a study comparing the effects of three distinct treatment modalities on rectal and bowel dose, Baumman et al. discovered that IMRT and pencil beam-scanned proton radiation outperformed 3DRT in terms of dosimetry.

### Immunotherapy for future perspective

Combining immunotherapy to TMT and ART is gaining popularity. Intravesical immunotherapy with Bacille Calmette Guerin has long been the preferred treatment for people with high-risk bladder cancer. It induces an inflammatory response that activates the body's innate and adaptive immune systems, leading to an immune response against bladder tumours that is mediated by cytotoxic T cells (CTLs). Similar to this, checkpoint inhibitors stimulate the generation of CTLs by targeting the immunological cascade. Recent clinical trials have shown that checkpoint inhibitors are active in patients with metastatic bladder cancer who have progressed after receiving first-line platinum-based chemotherapy or in those who are cisplatin-intolerant. During a study, it was discovered that the presence of the programmed death ligand 1 (PD-L1) in bladder tumours was linked to decreased rates of local control with TMT and cCR. In contrast to irradiation alone, their in-vivo mouse model showed that PD-L1 inhibition paired with radiation led to enhanced CTL recruitment and subsequent tumour cytolysis [6]. Combining radiotherapy and immunotherapy is thought to increase management of the primary tumour due to radiosensitization and produce immunological memory that could have systemic effects. Studies that evaluate the effectiveness of immunotherapy in the perioperative context or when used in conjunction with radiation therapy are currently being conducted to treat MIBC.

## Conclusion

Radiation therapy has an expanding role in the trimodal care of MIBC. After NAC and radical cystectomy, ART may be crucial in preventing LRR and subsequent distant metastases. ART is more practical with contemporary radiation therapy techniques like IMRT or proton therapy. TMT appears to produce equivalent results with extended eligibility in the elderly and cisplatin-intolerant individuals for those who are unable or unable to undergo radical cystectomy. Future clinical trials that look into the beneficial interactions between radiation and immunotherapy in TMT and ART settings are something we are excited about.

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## Conflict of Interest

None.

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