Editorial Commentary

Will chemoradiation-based bladder-sparing therapy become a standard of care for muscle-invasive bladder cancer?

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Huddart *et al.* prospectively investigated changes of health-related quality of life (HRQoL) during and after bladder-sparing therapy (BST) with chemoradiotherapy (CRT) or radiotherapy (RT) alone among participants of BC2001, the largest randomized trial of BST for muscle-invasive bladder cancer (MIBC) (1), which had found superior loco-regional controls of CRT with fluorouracil plus mitomycin C over those of RT alone (2). This study demonstrated that although declined at the end of treatment, HRQoL recovered to baseline at 6 months and remained similar to baseline subsequently until 5 years (1). There was no significant difference in HRQoL between the CRT and RT group at any time point. They concluded that there is no evidence of impairment of HRQoL resulting from the addition of chemotherapy among MIBC patients treated with RT (1).

The reference standard of care for MIBC is radical cystectomy (RC) with urinary diversion. In current clinical guidelines (3,4), CRT-based BST is an alternative to RC for carefully selected MIBC patients who desire bladder preservation (elective cases) and for those medically unfit for RC (imperative cases). Although the pioneer centers of CRT-based BST reported excellent long-term outcomes in elective MIBC patients comparable to those of RC (5,6), CRT-based BST is currently not a standard of care because of the lack of randomized trials comparing CRT-based BST versus RC. The unfortunate closure of the SPARE trial, which launched in the UK in 2007, made clear the difficulty of carrying out such randomized trials; many participants of the trial declined to randomization because they preferred the BST arm (7).

How can we raise the evidence level of BST for MIBC? The best way next to randomized trials would be meta-analysis and systematic review of accumulating high-quality data of non-randomized prospective studies comparing oncological outcomes of CRT-based BST versus RC. It is also important to prospectively evaluate HRQoL between the two treatment modalities. Despite a retrospective study focusing on oncological outcomes, one of such studies is a report from the Princess Margaret Cancer Center, Canada (8). In this cancer center, all MIBC patients were evaluated for treatment decision making by a multidisciplinary team composed of expert urologic oncologists, radiation oncologists, medical oncologists, and pathologists. This study demonstrated comparable overall survivals (around 60% at 5 years) between patients undergoing CRT-based BST versus RC after propensity matching for well-known prognostic factors such as clinical stage, performance status, and comorbidity index (8). Excellent results of post-treatment HRQoL demonstrated by Huddart *et al.* (1) would also promote advancement of CRT-based BST for MIBC.

The advent of immuno-oncology agents (IOAs) such as pembrolizumab has improved prognosis of advanced bladder cancer patients. Combinatory use of IOAs is expected to make a great progress in BST for MIBC. First, indication of elective CRT-based BST for MIBC may be expanded. To date, MIBC patients with metastatic diseases are not indicated for elective CRT-based BST. A subset of metastatic MIBC patients treated with IOA may need curative treatment for the primary site when the disease persists or progresses at the primary site while remaining regressed at metastatic sites on IOA. In such

conditions, CRT may be conceptually preferable to RC as a curative modality because RT can exert the abscopal effect, whereby RT at one site may lead to regression of non-irradiated diseases at distant sites (9). In fact, prognostic contribution of the abscopal effect with combinatory use of IOA has recently been reported; the Pembro-RT study, where metastatic non-small cell lung cancer patients were randomized to pembrolizumab either alone or after RT to a single lesion, demonstrated significantly better progression-free and overall survival for the RT plus pembrolizumab arm in patients with the programmed death-ligand 1-negative tumors (10). Second, IOAs can boost the therapeutic effects of CRT. IOAs would enhance anti-cancer immune responses which are involved in cancer cell killing by RT (11). In addition, IOAs are considered to boost the abscopal effect (9) as observed in the Pembro-RT study (10). Currently, several clinical trials are ongoing to investigate the roles of IOAs in combination with CRT-based BST for non-metastatic MIBC. Their results are awaited.

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Footnote

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