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*Review*

# Radiotherapy in Metastatic Urothelial Carcinoma: Rationale and Clinical Applications

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**Abstract.** *Urothelial carcinoma is the most common type of bladder cancer including upper urinary tract urothelial cell carcinoma (renal pelvis and ureters) and urethral carcinoma. It exhibits high mortality and morbidity rates and is usually diagnosed at a late, incurable stage, carrying a poor prognosis. Local symptoms in patients with metastatic urothelial carcinoma (mUC) have an adverse impact on quality of life (QoL) and are associated with frequent hospitalizations. Herein, we review the role of palliative radiotherapy in mUC as the means to ameliorate a wide range of symptoms, seeking optimum patient stratification, even though the latter should be balanced against any acute or late toxicity that may arise. For this, links to the molecular biology of mUC are explored and QoL assessments are presented. To maximize patient benefit from radiotherapy, we conclude that multi-modal datasets need to be re-visited to better inform multi-center studies where policy makers, health professionals, researchers, and patient groups meet. Radiotherapy either as a monotherapy or alongside systemic therapy may serve as an added value.*

Urothelial carcinoma (UC) is considered as the most common tumor type that arises from the urinary tract and may present either as bladder carcinoma (BC), upper urinary tract urothelial cell carcinoma (UTUC), or urethral carcinoma (1). BC has been reported as the 10th most common cancer worldwide in 2020 and the 6th most common tumor type in the USA, occurring mainly in older people, with a median age at diagnosis of 73 years (2-4). In developed countries, UTUC shows a lower incidence than that of BC and the ratio of the UC incidence in the renal pelvis, ureter, and bladder is approximately 3: 1: 51 (5, 6). About 25% of patients with UC present with metastatic disease. The 5-year survival for this group of patients is only 7.7% (SEER statistics; 2, 3, 7, 8).

Systemic therapy remains the cornerstone in the management of patients with mUC. Prior to the development of effective chemotherapy, median survival for mUC patients rarely exceeded 3 to 6 months (9). In the last few years, a revolution was witnessed in this field, with platinum-based chemotherapy, therapy with checkpoint inhibitors, and more recently immunotherapy, all giving promising results (10). Although the role of radiotherapy is limited in the management of mUC patients in the context of improving survival, its addition to our therapeutic toolbox offers considerable symptomatic relief especially in patients with hematuria and bone metastases (11, 12).

Our aim was to feature the role of radiotherapy (RT) in mUC, emphasizing the new RT techniques available and offer guidelines on how to apply this treatment modality in different clinical scenarios. To this end, the underlying molecular enigmas and quality of life (QoL) endpoints cannot be overlooked. To maximize patient benefit from RT, either as a monotherapy or alongside systemic therapy, we conclude that multi modal datasets need to be re-visited to better inform multicenter studies where policy makers, health professionals, researchers, and patient groups meet.

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## Radiobiology and Molecular Biology of mUC

To dissect and delineate the molecular basis of mUC to conclude on best RT practices is not a trivial task. Discussing, herein, the whys and hows of mUC, we cannot but start from the long-standing approach that similar principles can be applied to the management of UTUC and BC (13, 14). Indeed, UTUC and BC share a similar morphology as well as cytogenetic changes, despite some controversy regarding their molecular basis (15-17).

The Cancer Genome Atlas (TCGA) highlighted the mutation landscape in muscle invasive urothelial carcinoma (MIUC) (18) suggesting gene expression signatures for tumour subtyping (luminal vs. basal types) and/or efficacy to cisplatin-based chemotherapy (19). In 2015, Sfakianos *et al*. (20) identified similar somatic mutations in UTUC and BC, but at different frequencies. To this end, a comprehensive genomic characterization of UTUC *via* whole exome sequencing, RNA sequencing, and protein analysis, after their correlation with relevant clinical variables, TCGA, and publicly available data revealed that UTUC somatic mutations occur at differing frequencies from BC suggesting four unique molecular and clinical subtypes (21-24). A more recent study by Kamoun *et al*. suggested six muscle invasive bladder cancer (MIBC) subtypes (a consensus MIBC molecular classification), characterized by distinct genomic alterations as well as pathological and clinical characteristics: basal/squamous, luminal non-specified, luminal papillary, luminal unstable, neuroendocrine-like (NE-like), and stroma-rich (25). Today, comprehensive molecular profiling of UC has been limited to localized MIBC (24) and NMIBC (26), although more than two major groups cannot be excluded (27-29).

A limited number of publications offer some insight in the radiobiological characteristics of BC cells, especially the in vitro response of these cells to ionizing radiation (30, 31). A study worth mentioning is by Hinata *et al*., who examined radiation-induced apoptosis in five human BC cell lines and found that p53-dependent cell apoptosis is induced by ionizing radiation in wt-p53 BC cells but not if p53 mutations were present. Considering that among other genes, the TP53 gene plays a key role in drug resistance and autophagy-induced tumorigenesis, these findings can offer cancer drug developments that modulate autophagy, preventing disease progression and overcoming drug resistance (32, 33). BC is regarded as a rapidly proliferating cancer and data suggest a loss of effective radiotherapy dose following approximately five weeks of treatment because of tumor cell repopulation. This information is essential when we plan novel RT regimens, especially hypofractionated schemes (34-36). Regarding the radiobiological aspects of the effects of ionizing radiation on the bladder epithelium, the superficial bladder cells have a life span of several months and accelerated proliferation following irradiation begins after months. Thus, retreatment (reirradiation) of the bladder is not indicated since the organ is not able to recover from the late functional damage (late effects) caused by radiotherapy (37). Figure 1 summarizes what we know and what we hope for to translate molecular information into clinically relevant knowledge.

## The Role of Radiotherapy in mUC

Usually, the symptomatology of mUC consists of skeletal pain, ureter obstruction, hematuria, and oedema of lower extremities and has significant effects on performance status and therefore on the QoL. In addition to that, these patients are likely to be elderly with comorbidities, making the decision to treat or not with radiotherapy challenging. Therefore, any decision for palliative radiotherapy must be individualized and based on the biological age after performing a Comprehensive Geriatric Assessment, rather than the chronological age (38).

## Radiotherapy for Bone Metastases

Even though bones are one of the most common metastatic sites in cancer patients, in mUC patients, exclusive bone metastases develop rarely with an incidence not exceeding 8%. A study published in 2020, among 5,767 patients with mUC reported that up to 30% of patients with BC harbor bone metastases with an increased risk for African American patients (39-42).

The development of skeletal disease is associated with impaired QoL because of severe complications such as pain, pathological fractures, nerve root or spinal cord or compression, reduced mobility, and hypercalcemia (43). Since the pathophysiology and formation mechanism of bone metastases is rather complex, involving several events at the primary site as well as the metastatic sites, a multidisciplinary approach is needed to manage metastatic skeletal disease, including treatment modalities such as surgery, chemotherapy, RT, bisphosphonates, and radioisotopes (44-46).

Most data on the palliative use of RT come from its use in the treatment of painful bone metastases. Regarding mUC, although there is evidence of the benefit of palliative RT for the control of urinary symptoms such as hematuria, there is little evidence for the use of RT for pain relief.

Froehner *et al*.'s review of the treatment of bone metastases in patients with urologic malignancies concluded that single- or multiple- fractions RT may effectively control skeletal pain (47). Regarding patients with mUC to the bones, data from a small, randomized trial support the use of palliative RT and zoledronic acid, for reducing the risk of developing bone-related complications and improving overall survival (48).

In 2018, a retrospective, multicenter study by Necchi *et al*., reported on the treatment received by 128 patients with

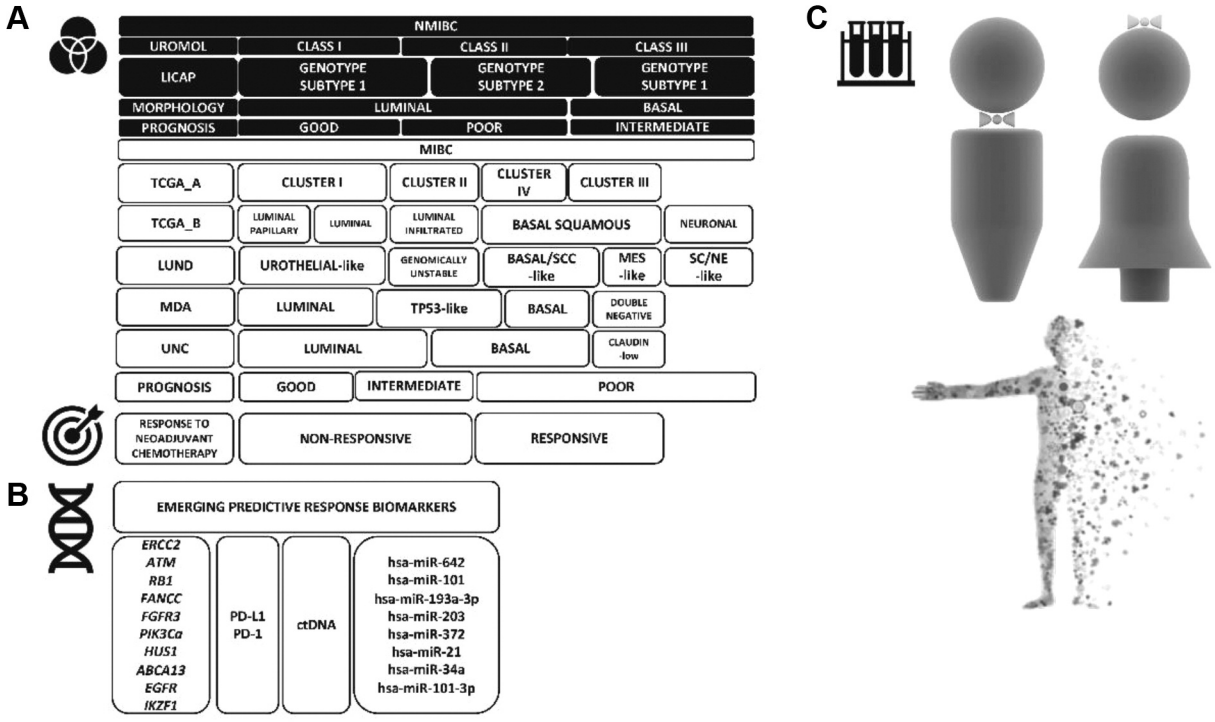


Figure 1. *Current status and future calls for urothelial and metastatic urothelial cancer. A) Schematic representation of non-muscle invasive bladder cancer (NMIBC) and muscle invasive bladder cancer (MIBC) molecular classification; B) Candidate response biomarkers; C) Multi-omics approaches may re-word UC and mUC management. LICAP: Leeds Institute of Cancer and Pathology; TCGA_A: TCGA (2014); TCGA_B: TCGA (2017); LUND: Lund University; MDA: MD Anderson Cancer Center; UNC: University of North Carolina; MES: mesenchymal; SCC: squamous cell carcinoma; SC/NE: small cell/neuroendocrine; ABCA13: ATP binding cassette subfamily A member 13; EGFR: epidermal growth factor receptor; ERCC2: excision repair cross complementing 2; FGFR3: fibroblast growth factor receptor 3; HUS1: HUS1 checkpoint clamp component; IKZF1: IKAROS family zinc finger 1; PIK3CA: phosphatidylinositol-4: 5-bisphosphate 3-kinase: catalytic subunit a; PD-L1: programmed cell death-ligand 1; PD-1: programmed cell death protein 1.*

exclusive bone metastases from UC and concluded that these patients are less likely to receive systemic therapy compared to those with other metastatic sites. Among the 55 patients who did not receive any systemic therapy in the study group, 24 received palliative RT on metastatic bone lesions, but data on the regimen used or response to radiotherapy are not included in the paper (40). Lessons learned from the management of cancer patients with bone metastases, can apply equally to the group of mUC patients with skeletal disease.

Patients with metastatic lesions in weight bearing bones are treated with prophylactic or reactive surgery followed by postoperative RT (49). Fractures of axial skeleton causing vertebrae instability, are treated with interventional or operative means followed by RT if indicated (50). Bone metastases leading to spinal cord and cauda equina compression pose an emergency and require prompt multidisciplinary care (51).

Patients presenting with bone metastases and receiving RT alone, are typically managed by using hypofractionated schedules such as 20 Gy in 5 fractions or 30 Gy in 10 fractions and patients with limited life expectancy may be managed with a single fraction of 8 Gy (52, 53).

Currently, there is great interest in oligometastatic osseous disease, with single and multiple fraction stereotactic body radiotherapy (SBRT) schedules being investigated as the promise of cure. Patients fitting the oligometastatic phenotype should be preferably treated within clinical trials, as evidence confirming or refuting the curative promise is still developing. In a recent study, fractionated external beam radiotherapy (20 Gy in five daily fractions) was compared to SBRT (24 Gy in two daily fractions). After a median follow up of 6.7 months, complete pain response rates were significantly improved in the stereotactic group. At 3 months, 40 (35%) of 114 patients in the SBRT, and 16 (14%) of 115 patients in the conventional external beam radiotherapy group had a complete response for pain (risk ratio 1.33, 95%CI=1.14-1.55; $p$=0.0002). The authors concluded that SBRT is superior to multifractionated radiotherapy for the improvement of the complete response rate for pain (54). Promising results were also published in a

retrospective trial involving patients with oligoprogressive and oligorecurrent UC (55).

SBRT therapy can be thought of as an alternative strategy to metastasectomy for controlling mUC oligometastatic sites, especially lung metastases. Considering poor prognosis, co-administration of SBRT with immunotherapy and targeted therapy should be explored for their synergistic effect. Franzese *et al*. investigated the role of SBRT to manage oligometastatic UC. Data for 61 patients and 82 lesions were analyzed. The primary tumor was in the bladder (82%), followed by kidney pelvis (11.5%). The lung was the most common treated metastatic site (40.2%), and the median follow-up was 17.2 months. Rates of local control at 1 and 2 years were 92% and 88.9%, respectively. Overall progression-free survival at 1 and 2 years was 47.9% and 38.1%, respectively. The number of metastases was a predictive factor, and the median overall survival was 25.6 months. No grade 2 adverse events were reported. The authors concluded that from these preliminary data, SBRT is considered as a safe and effective treatment in mUC, but prospective randomized trials are required to better evaluate the benefit on delaying the onset of new systemic therapies (56).

A special issue emerging often in the clinical praxis, is the role of radiotherapy as a consolidation treatment in patients with mUC. Two recent studies offer some insight to this issue. Shah *et al*. reported in 2017 on 22 patients out from a total of 2,597 metastatic BC patients, who received consolidative RT after being partial responders to chemotherapy. All studied patients had undergone cystectomy or nephrourectomy. They found that the progression-free survival was 19 months after radiation. OS was 49 months (after 6 years, 36% of patients were disease-free). The authors claimed that these data are consistent with surgical consolidation outcomes, which show similar 5-year OS rates (57-59).

The second study by Abe *et al*. from Japan reports on 97 patients out of 228 with mUC who underwent RT (mainly to metastatic sites). Overall, there was no significant difference in survival, when patients with and without RT were considered, but when analyzing the patients undergoing consolidative RT separately, the 25 patients who received a dose higher than 50 Gy had significantly longer survival than the 72 patients receiving a dose below 50 Gy, with a 3-year overall survival of 43.3%. Of the evaluated cohort, 22 underwent metastasectomy for disease consolidation, and there was no overlapping case between the metastasectomy cohort and the cohort receiving consolidative RT. RT for disease consolidation reported a marginal value, while metastasectomy remained significant, after controlling for four independent prognostic factors (sex, performance status, hemoglobin level, and number of organs with metastasis) (60).

The conclusion that we can draw from this limited literature is that there is no consensus on the optimal management of patients with residual disease following chemotherapy in mUC and that consolidative RT after chemotherapy may lead to the control of long-term disease. Nevertheless, the treatment decision must be individualized as randomized control trials are lacking.

## Radiotherapy for Brain Metastases

Brain metastases in mUC patients are extremely rare (61). An increased incidence is associated with prior chemotherapy in patients with mUC (62, 63). Yet, their management remains the most common indication of stereotactic radiotherapy (SRT) (64-66) (Table I).

For the management of brain metastases, two main scientific questions are raised: firstly, does whole brain radiotherapy (WBRT) eradicate occult micrometastases? A strategy of initial neurosurgery or SRT with a limited number of brain metastases, accompanied by close surveillance and salvage therapy, if needed later, is widely supported. The second question is whether there is an upper limit of lesions above which SRT is not appropriate and WBRT should be employed. Numerous reports indicate that prognosis of a patient upon SRT treatment is predominantly driven by performance status and other factors and not the number of lesions. Data suggest that the number of brain metastases is not predictive of overall survival or distant brain failure.

Most patients with multiple lesions undergo a typical course of whole-brain radiotherapy (WBRT), consisting of 10 to 20 fractions, delivering a total midline dose to the brain of 30 and 40 Gy, respectively. As mentioned earlier, because radiosensitivity of BC cells is relatively low, metastases from BC may be treated better with hypofractionated RT. The main late side effect of radiotherapy to the brain is impairment of the cognitive status of the patients. Decline in cognitive function was more frequently seen with WBRT than with SRT, most studies showing no difference in overall survival between the treatment groups (67).

The treatment of solitary brain metastases represents a challenge for the radiotherapist. The standard treatment is either SRT or combination surgery and postoperative RT. The assessment by a neurosurgeon is mandatory. If the excision of the lesion is contraindicated, then, a SRT or WBRT technique should be applied after performing an MRI of the brain. Usually, the total dose and the fractionation scheme, depends on the anatomical localization and size of the lesion (67, 68).

## Inferior Vena Cava Obstruction (IVCS)

Malignant IVCS has been described in patients with several tumors including adrenal carcinomas, renal carcinomas, pancreatic carcinomas, pheochromocytomas, ovarian carcinomas, hepatocellular carcinomas, cervical carcinomas, gastric cancer, prostatic cancer, retroperitoneal sarcomas, primary lymphomas, and metastatic malignant disease

Table I. *Selected publications on metastatic urothelial carcinoma – brain metastases and radiotherapy*

| Author | Treatment | Outcome |
|---|---|---|
| Rosenstein et al., 1993 (64) | Retrospective study<br>19 patients<br>Surgical excision +/– radiotherapy | Survival: Surgery and radiotherapy 19 months *vs*. radiotherapy 6 months/<br>In patients with solitary site and good performance surgery and postoperative radiotherapy is indicated |
| Rades et al., 2010 (65) | Retrospective study<br>33 patients<br>WBRT 20 Gy *vs*. 30 or 40 Gy | OS at 6 months: 40% for 20 Gy, 24% for 30 or 40 Gy/Improved OS in patients with less than 4 metastatic sites and lack of extracranial metastases<br>Local Control (LC): 83% for 20 Gy, 27% for 30 or 40 Gy/Improved LC if KPS>70<br>Short course WBRT is indicated |
| Fokas et al., 2010 (66) | Retrospective study<br>62 patients<br>WBRT +/– Stereo *vs*.<br>Surgery + WBRT | OS and LC: No significant differences/Stereo offers excellent LC rates/Improved OS in patients without extracranial metastases |

involving the pelvic and retroperitoneal lymph nodes. IVCS is a complex condition and therefore, an interdisciplinary team approach is needed for the best management.

In the last decades, percutaneous interventional techniques have fundamentally amended therapeutic options in this group of symptomatic patients, leaving the application of RT if the obstruction is caused by enlarged paraaortic lymph nodes. The "classic" technique consists of parallel opposed fields encompassing all the gross tumour area as it is defined by CT, MRI, and PET-CT. The dose described can be either 37.5 Gy in 15 fractions or 40 Gy in 20 fractions, depending on the patients' general condition. Side effects include nausea, vomiting, anorexia, diarrhoea, and myelosuppression (69, 70).

## Tumour Recurrence in the Pelvis

BC invading adjacent organs (mainly the rectum) or spread to the pelvic lymph nodes can be treated by chemotherapy followed by consolidation chemo-radiotherapy with curative intent, if there is response or a need for symptom palliation, such as pain or rectal bleeding (71).

## Radiotherapy Combined With Novel Anticancer Agents

Since 2016, a novel treatment modality has emerged for patients with UC: checkpoint inhibition therapy (CPI). Soon after, these new agents have been widely implemented as first- and second-line therapy of mUC. Limited data are available on the effectiveness of these treatment options in such patients. A recent publication in muBC patients who showed disease progression following immune checkpoint inhibition, supports the use of the antibody-drug-conjugate enfortumab vedotin (72). Several studies of novel combinations of immune checkpoint inhibitors with other agents are ongoing; thus, we anticipate a continuous and rapid evolution of the treatment landscape of metastatic bladder and kidney cancer.

Pre-clinical and clinical data provide support for RT instigating a systemic anti-cancer immune effect. For better outcomes with radiation in localized BC, immunotherapy is administered together with radiation in an ongoing trial with pembrolizumab. By modulating a more permissive tumor microenvironment through the increase of PD-L1 expression on tumor cells and the accumulation and activation of CD8+ T cells, radiotherapy may increase response rates. Pembrolizumab use in muscle mUC is also investigated in combination with RT in an ongoing phase I trial to assess their effectiveness, tolerability, and safety. Furthermore, patients with metastatic disease will also be recruited. Pembrolizumab will continue after the conclusion of RT for a year or until disease progression (73-81).

Sundhal *et al*. published data from a phase I/II trial in 20 patients with mUC. This relatively small-sized trial explored the anti-tumor activity and toxicity of the SBRT (total dose 24 Gy in 3 fractions every other day) combined with anti-PD1 treatment (Pemprozilumab 200 mg i.v. every 3 weeks), also empowering candidate drug response or resistance biomarkers identification (82). In a more recent analysis, Daro-Faye *et al*. concluded that RT has the potential to synergize with immunotherapy to improve oncological outcomes in patients with localized or metastatic BC (83).

Three trials involving patients with mUC receiving immunotherapy and RT were identified from the ClinicalTrials.gov database (84). More results from clinical trials are eagerly awaited, measuring effectively and accurately treatment responses, and improving outcomes in muBC and broaden treatment options for this group of patients.

## Health-related Quality of Life Assessment

Patients with mUC are faced with considerable symptom burden resulting from the disease itself, potential recurrences and the complex, invasive treatment protocols with their challenging side effects, leading them to physical impairments and to social and psychological sequalae (85). Yet, the impact of the disease and its treatment on the multiple dimensions of life, including but not confined to physical symptoms, known as health-related QoL, as experienced by patients in the advanced and metastatic context, is reported to be under-researched. It is however, widely recognized that HRQoL assessment should be an important outcome of trials and in clinical practice to monitor safety concerns and signal timely interventions. Researchers assessing HRQoL in patients with BC (typically in the context of MIVBC post-treatment and disease free) have used a variety of tools, which can be broadly classified according to their target patient group, for example diagnosis or treatment modality (86). A summary of these measures is outlined in Table II.

Generic, non-cancer specific measures have been used in BC and allow for comparisons across patient groups and the general population. Goosens-Laan *et al*. (2013) used the World Health Organization Quality of Life questionnaire (WHOQOL-BREF) and the Medical Outcomes Study Short Form 12 survey (SF-12) to compare patients with BC-related hematuria and those with hematuria from other causes (87, 88).

Cancer-specific measures, such as the core quality of life questionnaire (QLQ) of the European Organization for Research and Treatment of Cancer (EORTC) group (EORTC QLQ-C30) and the Functional Assessment of Cancer Therapy – General (FACT-G) can be applied to any cancer type but lack sensitivity to the unique issues associated with BC (89, 90).

These measures are often supplemented with BC specific measures. While the FACT-BL is applicable to all bladder cancer types, the EORTC QLQs are further refined in terms of grade of infiltration with the EORTC QLQ-NMIBC24 designed for non-invasive bladder cancer and the EORTC QLQ-BLM30 for MIBC (91, 92).

The Functional Assessment of Cancer Therapy-Bladder-Cystectomy (FACT-Bl-Cys, (originally FACT – Vanderbilt Cystectomy Index, FACT-VCI) was also developed for MIBC and is treatment-specific. The Bladder Cancer Index (BCI) is designed for all BC types irrespective of tumor infiltration or treatment modality and is a standalone measure (93, 94).

Although there is a portfolio of HRQoL tools designed specifically for BC, some researchers have adapted existing measures, including those developed for a different patient group (for example, prostate cancer) or developed their own bespoke questions to address a particular research objective (95, 96).

In addition, researchers interested in the effects of RT on HRQoL in patients with BC have used tools specifically designed for this purpose, for example, the Late Effects in Normal Tissue – Subjective, Objective, Management and Analytic scale for late effects of radiotherapy (SOMA) (97-99).

There is no measure specifically developed for muBC. Studies involving patients with metastatic disease have used generic cancer and / or BC specific modules or generic (non-cancer specific) palliative assessments to evaluate overall HRQoL and pain (100, 101).

Given the importance placed on HRQoL assessment, it follows that the choice of HRQoL tool should be carefully considered according to the patient group and treatment modality as well as the objective of the assessment, whether this is in the clinical trial setting to evaluate safety profiles to support product labelling claims or in clinical practice to inform treatment decision making. There is no gold standard tool that is likely to capture all relevant and important HRQoL experienced by patients with muBC. To enhance sensitivity, it is recommended that cancer-specific measures are supplemented with disease and treatment specific measures, and in the case of muBC, this could also include measures relevant to the site of metastases such as the EORTC QLQ brain neoplasm (EORTC QLQ-BN20) or the EORTC QLQ for patients with bone metastases (EORTC QLQ-BM22) (102-104).

It is also important to take care not to over-burden patients with too many questions, or questions with overlapping question content or perceived irrelevant. Recently the EORTC Quality of Life Group has advocated the use of a flexible measurement strategy with items selected from the EORTC item library to supplement existing measures which could have potential merit for use with muBC (105).

## Conclusion

The treatment of mUC has changed considerably in recent years. Chemotherapy, targeted therapies, and immunotherapy are now applied almost as standard therapy in the neoadjuvant, adjuvant, and palliative setting. Basic research findings along with the histological and molecular genetic characteristics of BC appear to have an impact on the clinical use of new therapeutic agents. This landscape characterized by rapid changes corresponds to the most exciting era we have seen in mUC.

Palliative RT in the form of external beam irradiation remains an important treatment option in this group of patients and in combination with chemotherapy, targeted therapies and more recently immunotherapy, offers palliation and relief from symptoms.

The optimal regimen of palliative RT in mUC causing local symptoms remains a discussion topic. Many patients are too fragile and old for curative RT or have distant metastases and a short survival expectancy. Palliative

Table II. *Generic cancer and BC-specific measures*.

| Measure | Target patient group | Number of questions | Domains | Single items |
|---|---|---|---|---|
| FACT–G | All cancer types | 27 | Physical well-being Social/Family well-being<br>Emotional well-being<br>Functional well-being | None |
| FACT-BI | All bladder cancer types | 39 | FACT-G subscales and<br>Bladder Cancer Subscale (12 questions) | Urinary function<br>Sexual function<br>Bowel function<br>Appetite<br>Ostomy care<br>Body image |
| FACT-Bl-Cys | Muscle-invasive bladder cancer treated with cystectomy | 44 | FACT-G subscales and<br>Bladder/Cystectomy Subscale (17 questions) | None |
| EORTC QLQ-C30 | All cancer types | 30 | Physical functioning<br>Role functioning<br>Emotional functioning<br>Cognitive functioning<br>Social functioning<br>Fatigue<br>Nausea<br>Vomiting<br>Pain | Dyspnea<br>Insomnia<br>Appetite<br>Constipation<br>Diarrhea<br>Finances |
| EORTC QLQ - NMIBC24 | Non-muscle invasive bladder cancer | 24 | Urinary symptoms<br>Malaise<br>Future worries<br>Bloating and flatulence<br>Sexual function<br>Male sexual problems | Intravesical treatment issues<br>Sexual intimacy<br>Risk of contaminating partner<br>Sexual enjoyment<br>Female sexual problems |
| EORTC QLQ-BLM30 | T2-T4 muscle-invasive bladder cancer | 30 | None | Urinary symptoms<br>Sexual function<br>Urostomy issues<br>Catheter use<br>Body image |
| BCI | All bladder cancer types | 36 | Urinary<br>Bowel<br>Sexual | None |

treatment aims to relieve symptoms. Several retrospective studies and clinical trials have shown that hypofractionated RT is effective and safe for these patients.

The current literature supports that:

- Tumor induced urinary symptoms such as hematuria are rapidly and effectively decreased by radiotherapy.
- Hypofractionated palliative RT results in similar symptom improvement as a multifractionated treatment.

In summary, RT achieves rapid and excellent palliation of symptoms in mUC patients. Short hypofractionated treatment regimens are recommended, given the clear absence of benefit for both symptom control and overall survival from prolonged regimes. Shorter treatment schemes are characterized by several socioeconomic advantages in any health-care system. If evidence of superiority of treatment can be provided, with no difference in long-term side-effects or detriment to the patient experience, these protocols should be adopted as standard of care.

- Searching for novel biomarkers. To improve patient stratification selecting for those patients with a low tendency of diffuse metastasis biomarker studies are needed. Such patients really benefit from ablative local approaches.

- Use of more advanced RT techniques, such as stereotactic RT in everyday practice.
- Promote and enhance personalized medicine and better allocation of resources.

## Conflicts of Interest

The Authors declare that they have no competing interests in relation to this study.

## Authors' Contributions

Conceptualization of the work: Dimitrios Kardamakis. Reviewing the literature: Vasileios Vassiliou, Theodora Katsila. Drafting the article: Vasileios Vassiliou, Theodora Katsila, Samantha Sodergren, Dimitrios Kardamakis. Revising the article: Dimitrios Kardamakis, Theodora Katsila, Samanths Sodergren. Figure and table preparation: Theodora Katsila, Samantha Sodergren, Dimitrios Kardamakis. Final approval of the version to be published: All Authors.

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