







## Systematic Review

# Metastasis-Directed Radiation Therapy with Consolidative Intent for Oligometastatic Urothelial Carcinoma: A Systematic Review and Meta-Analysis

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**Simple Summary:** Patients with oligometastatic urothelial carcinoma represent a challenging subset of subjects to manage. Herein we summarized evidence about the role of metastasis-directed radiation therapy in this clinical setting. Available preliminary evidence supports the role of metastasis-directed radiation therapy as a safe and efficacious option as it has the potential to facilitate local disease control and overall survival. However, in the absence of data from high-quality trials, definitive recommendations cannot be provided, and patients should be counseled on an individual basis.

**Abstract:** The management of patients with oligometastatic urothelial carcinoma (UC) represents an evolving field in uro-oncology, and the role of metastasis-directed therapies, including metastasectomy and metastasis-directed radiation therapy (MDRT), is gaining increasing attention. Herein, we summarize available evidence about the role of MDRT with consolidative intent in oligometastatic UC patients. A systematic review was performed in December 2021. Six studies involving 158 patients were identified. Most patients ( $n = 120$ , 90.2%) had a history of bladder cancer and the most frequent sites of metastases were lymph nodes ( $n = 61$ , 52.1%) followed by the lungs ( $n = 34$ , 29%). Overall, 144 metastases were treated with MDRT. Median follow-up ranged from 17.2 to 25 months. Local control rates ranged from 57% to 100%. Median Overall Survival (OS) ranged from 14.9 to 51.0 months and median progression-free survival ranged from 2.9 to 10.1 months. Rates of OS at one and two years ranged from 78.9% to 96% and from 26% to 63%, respectively. Treatment-related toxicity was recorded in few patients and in most cases a low-grade toxicity was evident. MDRT with consolidative intent represents a potential treatment option for selected patients with oligometastatic UC.

**Keywords:** bladder cancer; upper urinary transitional cell carcinoma; urothelial carcinoma; oligometastatic disease; radiotherapy

## 1. Introduction

Urothelial carcinoma (UC) represents the fourth and twelfth most common malignancy in men and women, respectively, with the bladder being the usual site of occurrence [1–5]. Despite radical therapies, a significant percentage of patients diagnosed with UC develop metastases during follow-up. In detail, metastatic disease is detected in about 50% of patients with bladder cancer undergoing radical cystectomy and most of these patients experience distant recurrence [1–3,6]. Moreover, 10 to 15% of patients are already metastatic at diagnosis [2]. Before the development of effective chemotherapy, patients with metastatic UC had a median survival rarely exceeding three to six months [1–3]. Although the treatment landscape of metastatic UC has been revolutionized in recent years with the advent of immune checkpoint inhibitors, available therapeutic options remain limited, and overall response rates remain suboptimal [1]. Metastatic UC patients represent a heterogeneous group of subjects. In 1995, Hellmann and Weichselbaum [7] hypothesized the existence of an intermediate clinical entity in the sequence of events leading to the progressive acquisition of metastatic ability from localized to metastatic disease: oligometastatic disease (OMD). OMD patients show distant relapse only in a limited number of regions and OMD is becoming more frequently identified thanks to the introduction of highly sensitive diagnostic modalities [8]. Although significant heterogeneity exists in the current OMD definitions in the literature, a recent ESTRO-ASTRO consensus document defined OMD as one to five metastatic lesions, a controlled primary tumor being optional, but where all metastatic sites must be safely treatable [9]. In recent years, the concept of OMD has been extended to UC patients, too [10]. Oligometastatic UC represents a rapidly evolving issue and the management of these patients in everyday clinical practice remains challenging due to the absence of clear recommendations from available guidelines. Metastasis-directed therapies (MDTs), such as metastasectomy and radiotherapy, have been used in the treatment of oligometastatic malignancies such as colorectal cancer with long-term benefits. The use of MDT has gained interest and popularity in the field of uro-oncology for the treatment of oligometastatic renal cell carcinoma and prostate cancer. Several reports, including both upper urinary tract transitional cell carcinoma and bladder cancer patients, support the hypothesis that resection of metastatic lesions could be safe and oncologically beneficial in selected patients with adequate life expectancy [3,11]. More recently, metastasis-directed radiation therapy (MDRT) with consolidative intent has emerged as a potential alternative to metastasectomy in UC patients with OMD. The aim of the present systematic review is to summarize available evidence about the role of metastasis-directed radiation therapy (MDRT) with consolidative intent in patients with oligometastatic UC.

## 2. Materials and Methods

The present analysis was conducted and reported according to the general guidelines recommended by the Primary Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [12]. This protocol was registered in PROSPERO (CRD42021292657).

### 2.1. Literature Search

The search was performed in the Medline (US National Library of Medicine, Bethesda, MD, USA), Scopus (Elsevier, Amsterdam, The Netherlands), and Web of Science Core Collection (Thomson Reuters, Toronto, ON, Canada) databases up to January 2022. The following terms were combined to capture relevant publications: “oligometastatic” AND (“metastasis directed radiation therapy” OR “consolidative radiotherapy”) AND (“bladder cancer” OR “upper urinary tract transitional cell carcinoma” OR “urethra carcinoma” OR “urothelial carcinoma”). Reference lists in relevant articles and reviews were also screened for additional studies. Conference abstracts were also considered.

### 2.2. Selection Criteria, Data Collection, and Statistical Analysis

Two authors (N.L. and G.C.) reviewed the records separately and individually to select relevant publications, with any discrepancies resolved by a third author (L.N.). To

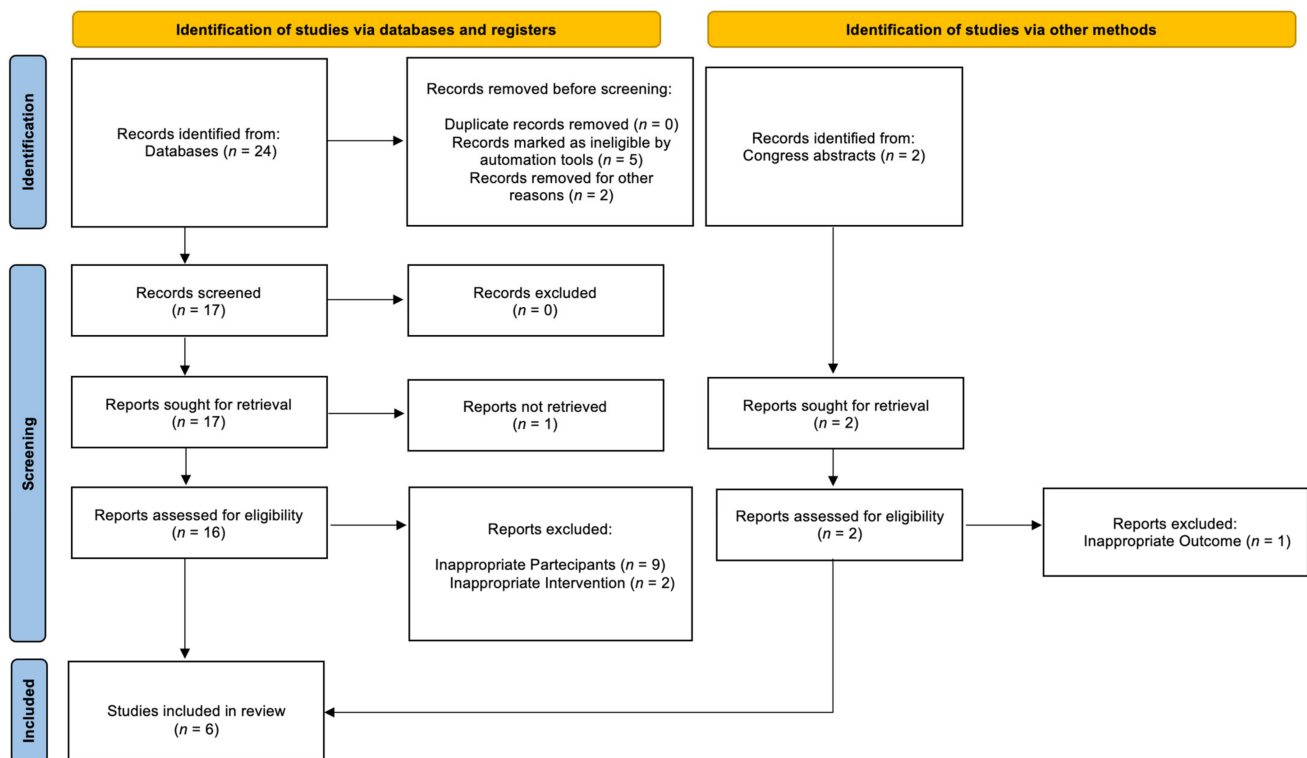
assess eligibility for the systematic review, PICOS (participants, intervention, comparisons, outcomes, and study type) criteria were used [13]. PICOS criteria were set as follows: Participants—patients with oligometastatic UC; Intervention—MDRT with consolidative intent; Comparator—none; Outcome—response rate according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria, Overall Response Rate (ORR), Local Control Rate (LCR), Overall Survival (OS), 1-year OS, 2-year OS, Progression-Free Survival (PFS), 1-year PFS, 2-year PFS, 3-year PFS, toxicity; Study types—conference abstracts, case reports, case series, retrospective and prospective studies. The following data were extracted from eligible studies: first author, year of publication, study design, sample size, patient age, patient gender, primary tumor site and stage, treatment for primary tumor, definition of OMD, OMD classification (synchronous, metachronous, oligoproggressive), performance status (PS), site, number and size of metastases, time to metastasis, MDRT type, overall number of treated lesions, number of lesions treated per patient, metastatic sites treated, metastases not treated, delivered radiation dose, dose fractionation, contemporary systemic treatments, previous systemic treatments, follow-up duration, response rate according to RECIST criteria, ORR, LCR, OS, 1-year OS percentage, 2-year OS percentage, PFS, 1-year PFS, 2-year PFS, 3-year PFS, and MDRT-related toxicity. The quality of included studies was assessed using the Jadad Score or the Methodological Index for Non-Randomized Studies (MINORS) for randomized and non-randomized studies, respectively [14,15]. Ethical approval and patient consent were not required for the present study. The meta-analysis was performed using ProMeta 3 software (Version 2.1) when two or more studies reported the same outcome under the same definition. The effect size (ES) was estimated using the event rate reported with a 95% confidence interval (CI). Heterogeneity among studies was evaluated using  $I^2$  statistics. A  $p$ -value  $< 0.05$  was considered statistically significant. To calculate the pooled effect, a fixed effect model was applied. Egger's linear regression test and Begg and Mazumdar's rank correlation test were also used to evaluate the publication bias of studies included in the meta-analysis.

### 3. Results

The search strategy generated a total of 26 results. The screening of the titles and abstracts determined 18 papers eligible for inclusion. Further assessment of eligibility, based on full-text study of the papers, led to the exclusion of 12 papers. Finally, 6 studies (1 conference abstract and 5 full papers) involving 158 patients were included in the final analysis (Figure 1) [16–21].

#### 3.1. Patient Demographics and Tumor Characteristics

Overall, 6 retrospective studies were identified involving a total of 158 patients. Study characteristics, patient demographics, and tumor features are summarized in Table 1. Most of the patients included were male ( $n = 90$ , 56.9%), with a median age ranging from 63 to 71 years. The most frequent primary tumor site was the bladder ( $n = 120$ , 90.2%). Radical surgery of the primary tumor was performed in 40 patients (39.6%). The median time to metastasis was 15.6 months (range: 0–121.8) and the most common sites of metastases were lymph nodes ( $n = 61$ , 52.1%) followed by the lungs ( $n = 34$ , 29.0%). The type of OMD according to time of occurrence was reported in four studies. Most patients (59.0% to 100%) had metachronous oligometastatic disease (Table 1). The size of metastases was reported by only two authors [17,18]. In the study by Leonetti et al., the diameter of metastases ranged from 10 to 55 mm [17]. In the study by Augugliaro et al. [18], mean metastatic volume ranged from 3 to 88.7 cm<sup>3</sup>.



**Figure 1.** Flow diagram of the systematic review.

### 3.2. MDRT Protocols

MDRT details are summarized in Table 2. A total of 144 lesions were treated. Details about irradiated sites were provided by three studies. The most common irradiated sites were lymph nodes ( $n = 44$ ). In two studies, MDRT was performed to treat all metastatic sites. MDRT was performed through Volumetric Modulated Arc Therapy (VMAT) in 67 patients (59.8%) and through CyberKnife (Accuracy Inc., Sunnyvale, CA, USA) in 15 patients (2.39%). The median delivered radiation dose ranged from 25 to 55 Gy. Dose fractionation was only reported by Augugliaro et al. (median: 5; range: 3–10) and by Franzese et al. (range: 1–10) [18,20]. Overall, 75 patients (47.4%) received systemic therapy before MDRT, while 36 patients (22.7%) received systemic therapy during MDRT. The median duration of follow up was 37.73 months (range: 3–91).

### 3.3. MDRT Outcomes

The outcomes of MDRT are reported in Table 3. Local control was assessed through RECIST criteria in 56 patients (35.4%). CR, PR, and SD were observed in 14 (25.0%), 12 (21.4%), and 15 (26.7%) patients, respectively. PD was observed in 5 patients (8.9%). ORR and LCR were observed in a percentage of patients ranging from 38% to 57% and from 57% to 100%, respectively. Median OS was reported in 4 studies and ranged from 12.3 to 54.0 months. Rates of OS at 1- and 2-year follow-ups ranged from 78.9% to 96.0% and from 26.0% to 63.0%, respectively. A single study reported 3-year OS rates (43.3%). Median PFS was reported in 4 studies and was 20.8 months (range: 1.4–5.5). PFS rates at 1- and 2-year follow-ups ranged from 47.9% to 71.0% and from 19.0% to 38.1%, respectively. Pooled data from studies reporting ORR, 2-year PFS, and OS are reported in Figures 2–4. Bias evaluation is reported in Figures 5–7. Toxicity was evaluated in five studies. Grade 1 acute and late toxicities were reported in six and two patients, respectively. Grade  $\geq 2$  toxicity was reported in six patients.

**Table 1.** Study characteristics and clinico-pathological features of the patients enrolled.

| Author             | MINORS | Sample Size<br>(n) | Age at MDRT,<br>Years, Median<br>(Range) | M: F  | Primary Tumor                      |  |                        | OMD Criteria   | Time to MTX,<br>Mo,<br>Median (Range) | OMD<br>Classification<br>(n, %)               | PS  | MTX Site (n)  |
|--------------------|--------|--------------------|--|-------|------------------------------------|--|------------------------|--|---------------------------------------|---|---|---|
|                    |        |                    |  |       | Site (n)                           | Stage (n)  | Treatment<br>Type (n)  |  |                                       |   |   |   |
| Leonetti [17]      | 10     | 7                  | 67<br>(47–79)                            | 6:1   | B (5)<br>P or Ur (2)               | pT3N3cM0 (1)<br>pT2N3cM1 (1)<br>pT2N0cM0 (1)<br>pT1cN0M0 (1)<br>pT3N1cM0 (1)<br>pT2cN0M0 (1)<br>pT3cN0M0 (1) | Radical<br>surgery (7) | ≤3 MTX and<br>no liver MTX   | 12.9<br>(0–33.6)                      | SO (1, 14.2)<br>MO (6, 85.7)                  | n.a.  | Ln (14)   |
| Augugliaro<br>[18] | 9      | 13                 | 68<br>(50–80)                            | n.a.  | B (13)                             | n.a.   | RC (12)                | ≤5 MTX   | 23.0<br>(8–105)                       | MO (13, 100)                                  | 90 (80–90) *  | Ln (18)<br>Lung (1)<br>Pelvic<br>recurrence (1)<br>Pelvic bone (1)        |
| Abe [16]           | 8      | 25                 | 64<br>(45–79)                            | 18:7  | n.a.                               | n.a.   | n.a.                   | MTX in a<br>single organ<br>with a small<br>number of<br>MTX                     | n.a.                                  | n.a.  | ECOG 0 (21)<br>ECOG 1 (3)<br>ECOG 2 (0)<br>ECOG 3 (0)<br>n.a. (1) | n.a.  |
| Aboudaram<br>[21]  | -      | 31                 | n.a.                                     | n.a.  | B (31)                             | n.a.   | n.a.                   | ≤5 residual<br>MTX and no<br>disease<br>progression<br>following<br>chemotherapy | n.a.                                  | n.a.  | n.a.  | n.a.  |
| Franzese<br>[20]   | 10     | 61                 | 71<br>(48.2–86.2)                        | 51:10 | B (50)<br>P (7)<br>Ur (3)<br>U (1) | n.a.   | Local control<br>(61)  | ≤5 MTX and<br>maximum<br>diameter ≤5<br>cm                                       | 14.5<br>(0–121.8)                     | SO (3, 4.9)<br>MO (36, 59.0)<br>OP (22, 36.0) | n.a.  | Lung (33)<br>Ln (29)<br>Liver (7)<br>Bone (5)<br>Adrenal (4)<br>Other (4) |
| Miranda [19]       | 8      | 21                 | 63<br>(n.a.)                             | 15:6  | B (21)                             | T2 (n.a.)<br>T3 (n.a.)   | RC (21)                | ≤4 MTX   | 12.1<br>(6.8–36) #                    | SO (3) #<br>MO (49) #                         | ECOG 0–1 (17)<br>ECOG 2–5 (4)                                     | n.a.  |

B: Bladder; ECOG: Eastern Cooperative Oncology Group; Ln: Lymph nodes; MO: Metachronous oligometastatic; n.a.: not available; P: Pelvis; PS: Performance Status; RC: Radical Cystectomy; Ur: Ureter; U: Urethra; \*: Karnofsky Performance Status, median (range); #: values calculated for the overall study population.

Table 2. MDRT details.

| Author          | MDRT Technique (N)               | Overall Number of Treated Lesions (n) | Treated Lesions per Patient n (%)            | Sites Treated Site (n)   | Sites Not Treated, n (%) | Delivered Dose, Gy, Median (Range) | Systemic Therapy before MDRT Type (n) | Systemic Therapy during MDRT Type (n)                     | Fu, Mo, Median (Range) |
|-----------------|----------------------------------|---------------------------------------|--|--|--------------------------|------------------------------------|---------------------------------------|---|------------------------|
| Leonetti [17]   | SBRT (14)                        | 14                                    | 1 lesion: 2 (28.5)<br>>1 lesions: 5 (71.4)   | All sites  | 0                        | 32 (25–40)                         | n.a. (2)                              | n.a. (1)  | n.a.                   |
| Augugliaro [18] | IMRT (n.a.)<br>CyberKnife (n.a.) | 21                                    | 1 lesion: 8 (61.5)<br>>1 lesions: 5 (38.4)   | All sites  | 0                        | 25 (20–36)                         | GC (7)                                | n.a.  | 25 (3–43)              |
| Abe [16]        | n.a.                             | 27                                    | 1 lesion: 20 (80.0)<br>>1 lesions: 5 (20.0)  | Ln (12)<br>Lung (1)<br>Bone (5)<br>Liver (5)<br>Local recurrence (4)<br>Bladder (3)<br>Other sites (1) | 4 (16.0)                 | 55 (30–69)                         | (n.a.) (6)                            | n.a. (5)  | n.a.                   |
| Aboudaram [21]  | n.a.                             | n.a.                                  | n.a.   | n.a.   | a.a.                     | >50                                | 31 (100)                              | n.a.  | 71 (n.a.)              |
| Franzese [20]   | Cyberknife (15)<br>VMAT (67)     | 82                                    | 1 lesion: 37 (60.7)<br>>1 lesions: 24 (39.2) | n.a.   | 24 (39.3)                | 45 (18–70)                         | n.a. (29)                             | GC or carboplatin +<br>gemcitabine, or<br>vinflunine (14) | 17.2 (3–91)            |
| Miranda [19]    | SBRT (16)<br>Non-SBRT (5)        | n.a.                                  | 1 lesion: 9 (43)<br>>1 lesions: 12 (57.0)    | n.a.   | 0                        | n.a.                               | n.a.                                  | n.a. (16)   | n.a.                   |

Fu: Follow-up; GC: Gemcitabine + Cisplatin; IMRT: Intensity-Modulated Radiation Therapy; MDRT: Metastasis-Directed Radio Therapy; n.a.: not available; SBRT: Stereotaxic Body Radiation Therapy; VMAT: Volumetric Modulated Arc Therapy.

Table 3. MDRT outcomes.

| Author             | Response Rate **<br>Type, n (%)   | ORR (%) | LCR (%) | OS, Mo,<br>Median (95%<br>CI) | 1-Year OS<br>(%) | 2-Year OS<br>(%) | 3-Year OS<br>(%) | PFS, Mo,<br>Median (95%<br>CI) | 1-Year PFS<br>(%) | 2-Year PFS<br>(%) | Systemic<br>Therapy after<br>MDRT<br>Type (n) | Prognostic<br>Variables   | Toxicity<br>Grade (n)                            |
|--------------------|---|---------|---------|-------------------------------|------------------|------------------|------------------|--------------------------------|-------------------|-------------------|---|---|--|
| Leonetti [17]      | PR, 6 (43.0)<br>SD, 8 (57.0)  | 43.0    | 100     | 14.9<br>(12.3–17.5)           | n.a.             | n.a.             | n.a.             | 2.9 (2.6–3.1)                  | n.a.              | n.a.              | n.a.  | Higher dose<br>of SBRT<br>associated<br>with higher<br>lesion<br>progression-<br>free<br>interval   | 0  |
| Augugliaro<br>[18] | CR, 11 (52.0)<br>PR, 1 (5.0)<br>SD, 0 (0)<br>LPE, 8 (38.0)<br>NE, 1 (5.0)     | 57.0    | 57.0    | n.a.                          | n.a.             | 26.0             | n.a.             | 5.8 (n.a.)                     | n.a.              | n.a.              | GC (1)  | n.a.  | Grade 1<br>(Acute) (1)                           |
| Abe [16]           | n.a.  | n.a.    | n.a.    | 29.0 (17–54)                  | n.a.             | n.a.             | 43.3             | n.a.                           | n.a.              | n.a.              | n.a.  | n.a.  | n.a.   |
| Aboudaram<br>[21]  | n.a.  | n.a.    | n.a.    | n.a.                          | 96.0             | 63.0             | n.a.             | n.a.                           | 71.0              | 29.0              | n.a.  | n.a.  | Grade ≥ 3 (0)                                    |
| Franzese [20]      | n.a.  | n.a.    | 88.9    | 25.6 (n.a.)                   | 78.9             | 50.7             | n.a.             | 10.1 (n.a.)                    | 47.9              | 38.1              | n.a.  | Lines of<br>systemic<br>therapy<br>before SBRT<br>associated<br>with inferior<br>local control.<br>Higher<br>number of<br>metastases<br>associated<br>with inferior<br>PFS<br>Total<br>delivered<br>dose<br>associated<br>with OS | Grade 1<br>(Acute) (5)<br>Grade 1<br>(Late) (2)  |
| Miranda [19]       | CR, 3 (14.0)<br>PR, 5 (24.0)<br>SD, 7 (34.0)<br>PD, 5 (24.0)<br>n.a., 1 (4.8) | 38.0    | 72.0    | 51.0 (n.a.)                   | n.a.             | 60.0             | n.a.             | 8.2 (1.4–5.5)                  | n.a.              | 19.0              | n.a.  | Concurrent<br>systemic<br>therapy<br>during<br>MDRT<br>associated<br>with<br>improved OS  | CTCAE<br>Grade ≥ 2 (5)<br>CTCAE<br>Grade ≥ 3 (1) |

CSS: Cancer-Specific Survival; CR: Complete Response; GC: Gemcitabine + Cisplatin; LCR: Local Control Rate; LPD: Local Progression Disease; MDRT: Metastasis-Directed Radiation Therapy; NE: not evaluable; n.a.: not available; OS: Overall Survival; ORR: Overall Response Rate; PD: Progressive Disease; PFS: Progression-Free Survival; PR: Partial Response; SCTCAE: Common Terminology Criteria for Adverse Events; SD: Stable Disease; \*\*: According to RECIST (Response Evaluation Criteria in Solid Tumors) criteria.

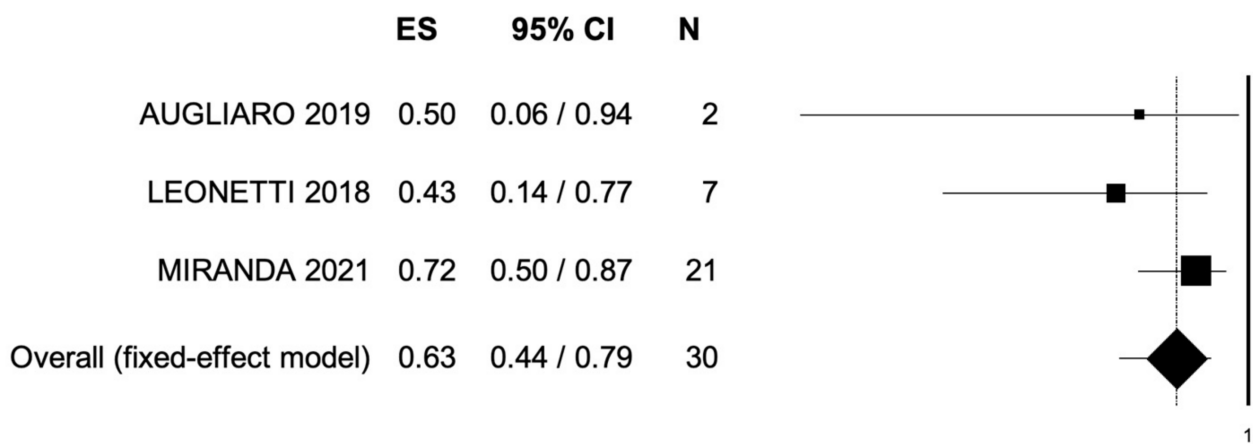


Figure 2. Forest plot showing the event rate for Overall Response Rate. ES, effect size; CI, confidence interval. ( $I^2 = 0.00, p = 0.368.$ )

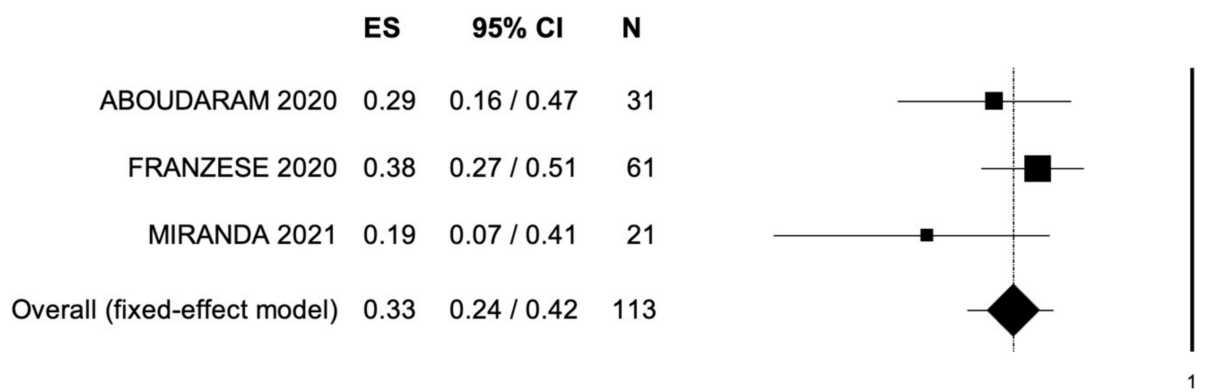


Figure 3. Forest plot showing the event rate for 2-year progression-free survival. ES, effect size; CI, confidence interval. ( $I^2 = 25.39, p = 0.262.$ )

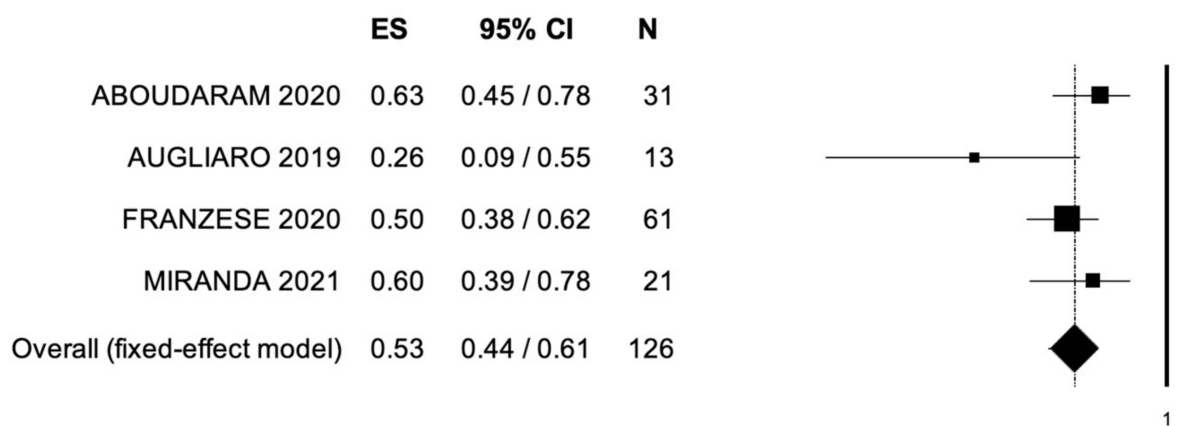
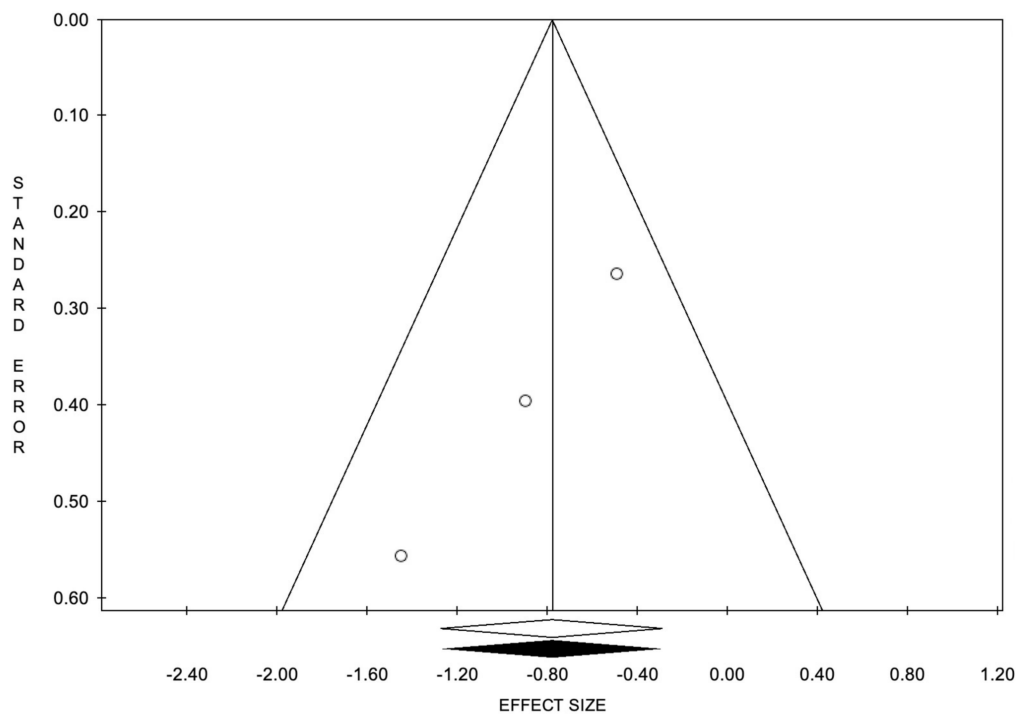
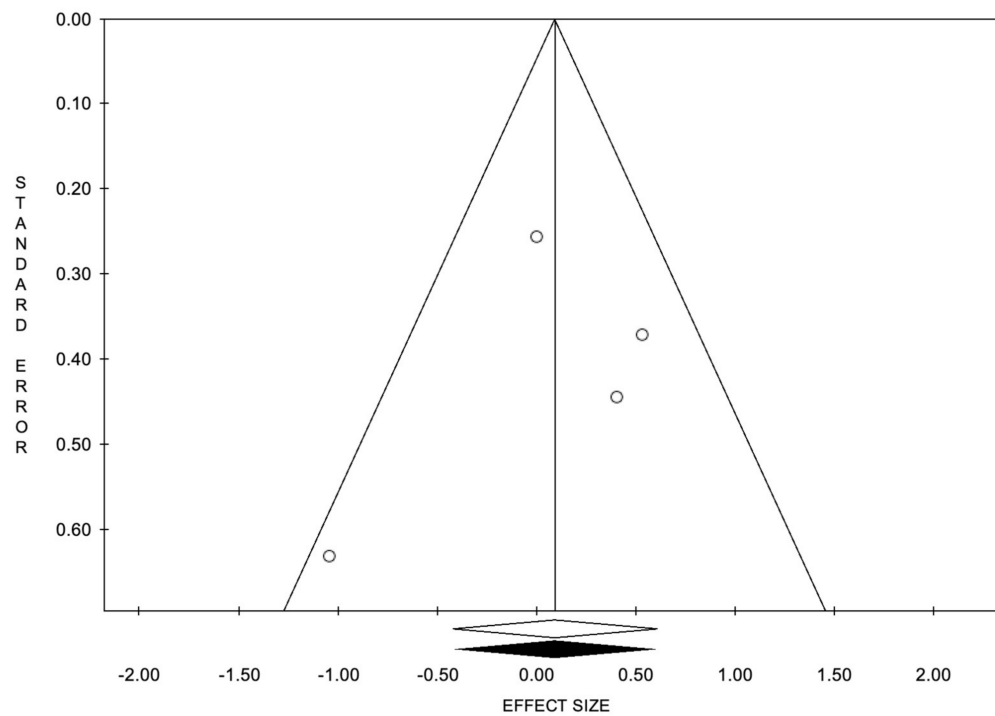


Figure 4. Forest plot showing the event rate for 2-year overall survival. ES, effect size; CI, confidence interval. ( $I^2 = 42.91, p = 0.154.$ )

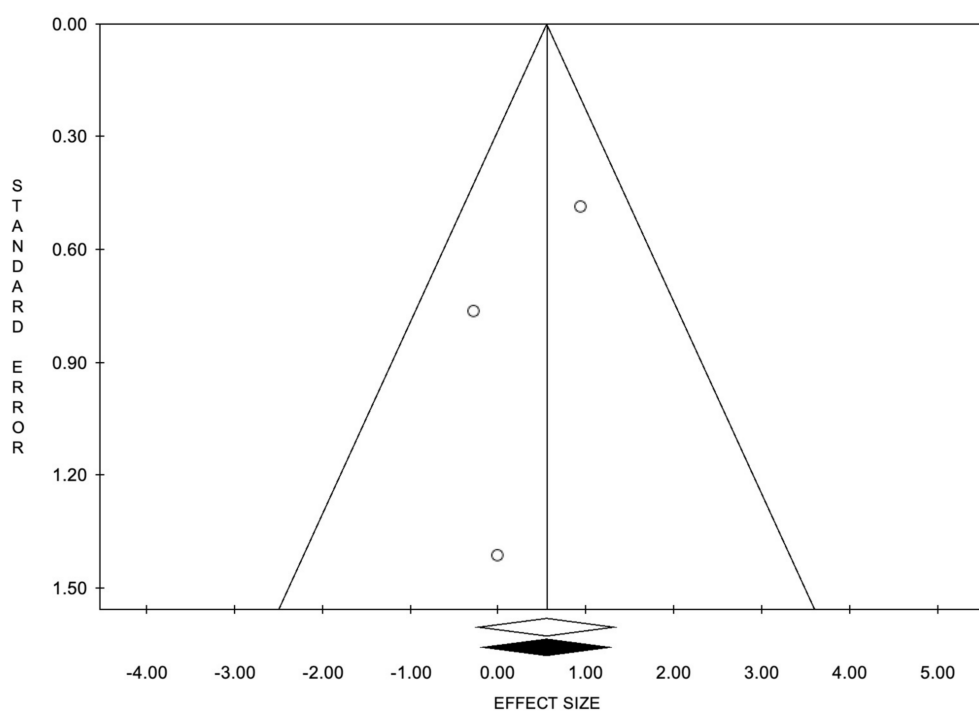




**Figure 5.** Funnel plots of the meta-analysis evaluating the event rate for 2-year progression-free survival. Egger's linear regression ( $t = -28.93, p = 0.022$ ) and Begg and Mazumdar's rank correlation test ( $z = -1.57, p = 0.117$ ).



**Figure 6.** Funnel plots of the meta-analysis evaluating the event rate for 2-year overall survival. Egger's linear regression ( $t = -0.47, p = 0.683$ ) and Begg and Mazumdar's rank correlation test ( $z = -0.68, p = 0.497$ ).



**Figure 7.** Funnel plots of the meta-analysis evaluating the event rate for Overall Response Rate. Egger's linear regression ( $t = -0.98$ ,  $p = 0.505$ ) and Begg and Mazumdar's rank correlation test ( $z = -0.52$ ,  $p = 0.602$ ).

#### 4. Discussion

Recently, the overall perspective on metastatic disease has changed dramatically, due to both the availability of novel imaging modalities and the improvement of treatment options. With respect to metastatic UC patients, there have been two major advancements that have significantly modified their prognoses. On the one hand, immune checkpoint inhibitors have emerged as a promising alternative to conventional chemotherapy, with the advantage of improving objective response rates [20–30]. On the other hand, the concept of OMD, firstly introduced by Hellman et al. in 1995 as that of tumor states intermediate between purely localized and widely metastatic disease, has also been extended to UC, and patients with low burden of disease have been considered amenable to local treatment of metastatic disease [7,20]. Metastases represent potential sources of further metastatic spread. Therefore, the rationale behind MDT is that the eradication of a low number of metastases will hamper further metastatic dissemination, thus improving PFS and OS [31]. Typically, MDTs can be achieved by surgical metastasectomy or MDRT. Patient selection and treatment allocation represent a debated and complex topic when dealing with oligometastatic patients. Surgical metastasectomy has been incorporated into National Comprehensive Cancer Network guidelines as an option for selected oligometastatic UC patients with good response to systemic therapy [32]. However, due to the often extensive and difficult nature of the surgery, this procedure can be proposed only for highly selected patients with adequate performance and comorbidity status [32]. Traditionally, radiotherapy has been limited to disease palliation. In recent years, MDRT with consolidative intent has emerged as a more-attractive alternative to metastasectomy in oligometastatic patients thanks to its being less invasive [19]. The SABR-COMET and ORIOLE randomized trials demonstrated improved oncologic outcomes with MDRT in patients with several metastatic cancers [33,34].

Herein, we have summarized for the first-time available evidence about the role of MDRT with consolidative intent in patients with oligometastatic UC. Current evidence mainly derives from retrospective small series mainly involving oligometastatic bladder cancer patients with a history of radical surgery. Baseline patient characteristics deserve

consideration as they reveal the tendency to select metastatic UC patients at good prognosis for treatment with MDRT. Most patients were young, had lymph node metastases, and good PS. These characteristics define a subgroup of patients with good prognoses. Indeed, a Karnofsky PS of  $\leq 80\%$  and presence of visceral metastases have been reported to represent independent prognostic factors of poor survival after treatment with MVAC, and these prognostic factors have also been validated for newer combination chemotherapy regimens [2,35]. Another relevant aspect is the timing of occurrence of OMD. In this context, OMD is commonly classified as synchronous or metachronous (often referred to as oligorecurrent) based on the time interval between primary cancer diagnosis and the development of OMD [9]. Metachronous OMD occurs when metastases are diagnosed 3–6 months from the diagnosis of the primary tumor. Most patients enrolled in the studies summarized in the present review had metachronous disease with a median time between diagnosis of the primary tumor to metastasis ranging from 12.9 to 2 months. The length of the disease-free interval has been reported as having a prognostic impact [9]. In patients with oligometastatic non-small cell lung cancer, metachronous metastases represent a significant predictor for improved OS [36].

Results from the present systematic review show LCRs (tumor volume equal to or less than the tumor volume at the start of radiotherapy) ranging from 72.0% to 100% and ORRs (complete or partial response) ranging from 38% to 57%. In comparison, in their recent systematic review assessing the outcomes of radiotherapy in oligometastatic prostate cancer patients, Rogowsky et al. reported LCRs ranging between 76 and 100% at 2 years [37].

Although response to therapy is commonly performed through computerized tomography, improvements in response evaluation are considered necessary and the use of radionuclides may represent a valid alternative [38].

Median OS ranges from 14.9 to 51.0 months with a median PFS ranging from 2.9 to 8.2 months. Of note, Muilwijk et al. found a median OS of 98.2 months in their subset of 22 oligometastatic UC patients undergoing metastasectomy [1]. In comparison, Rogowsky et al. reported PFS values ranging from 38 to 100% at 1 year and from 22–83% at 2 years and a median PFS ranging from 7 to 63 months [37]. Predictors of MDRT efficacy have been investigated only in a few cases. In the study by Miranda et al., the exploratory analysis of factors influencing OS among patients treated with MDRT with consolidative intent showed improved OS in patients treated with concurrent systemic therapy during MDRT (51 vs. 12 months,  $p = 0.01$ ) and no difference with respect to ECOG performance status, number of metastatic sites, radiation modality, and radiologic response in the target lesion [19]. Interestingly, the majority (67%) of patients in the study by Miranda et al. received concurrent treatment with immuno-oncology agents. In this context, preliminary evidence suggests the existence of a potential synergistic effect deriving from the combination of immuno-oncology agents and MDRT [35]. Recent evidence suggests that the tumor immune microenvironment can be stimulated by radiation. Indeed, radiation can lead to the activation of adaptive and innate immune response, with activation of cytotoxic T cells following the release of tumor antigens caused by cell death [39]. Other prognostic variables associated with better outcomes include higher dose of SBRT, lower number of metastases, and lower number of lines of systemic therapy before SBRT. Of note, the available evidence demonstrates that MDR carries minimal morbidity, with only a minority of patients experiencing toxicity. Although this finding is in line with published studies on MDRT, data are still poor and suboptimal and further studies are needed to confirm long-term safety [33,34]. Evidence synthesized in the present review indicates the limitations of the current literature regarding the role of MDRT in oligometastatic UC patients and provides a basis for further investigations. Major limits of the available studies include retrospective, single-institution, and often uncontrolled designs, small sample sizes, and short follow-up periods. Moreover, series are heterogeneous in terms of patient characteristics, definitions of oligometastatic states, treatment protocols, and outcomes assessed. Finally, MDRT has been carried out at different time-points along the natural history of the disease and details about the type of chemotherapy performed before, during, or after MDRT are

often unavailable. Future research efforts should include rigorous definitions of diagnostic modalities and criteria for the definition of OMD in UC patients. Despite promising preliminary results, the role of fluorodeoxyglucose-positron emission tomography-computed tomography deserves further investigation [31,40]. Molecular biomarkers such as miRNAs and exosomes that have been reported to be involved in the regulation of the metastatic cascade and in the switch from oligometastatic to polymetastatic states may represent potential alternatives [41]. Moreover, predictors of response to MDRT should be carefully investigated to adequately select patients as candidates for this treatment strategy. In this context, a phase II, multicenter, randomized open-label, and comparative study designed to evaluate whether local consolidative radiotherapy plus standard of care can improve OS as compared to standard of care in patients with limited metastatic urothelial bladder cancer and without progression following the initial phase of first-line systemic therapy is ongoing (ClinicalTrials.gov Identifier: NCT04428554).

## 5. Conclusions

In conclusion, available evidence supports the role of MDRT as a safe and efficacious option in treating selected oligometastatic UC patients. It has the potential to facilitate local disease control and overall survival. Nonetheless, in the absence of data from randomized controlled trials, patients should be evaluated on an individual basis and the decision to perform MDRT with consolidative intent should be made in a joint decision-making process with the patient.

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## References

1. Muilwijk, T.; Akand, M.; Van der Aa, F.; Dumez, H.; De Meerleer, G.; Van Raemdonck, D.; De Leyn, P.; Van Poppel, H.; Albersen, M.; Joniau, S. Metastasectomy of oligometastatic urothelial cancer: A single-center experience. *Transl. Androl. Urol.* **2020**, *9*, 1296–1305. [[CrossRef](#)] [[PubMed](#)]
2. Witjes, J.A.; Bruins, H.M.; Cathomas, R.; Comp erat, E.M.; Cowan, N.C.; Gakis, G.; Hern andez, V.; Linares Espin os, E.; Lorch, A.; Neuzillet, Y.; et al. European Association of Urology Guidelines on Muscle-invasive and Metastatic Bladder Cancer: Summary of the 2020 Guidelines. *Eur. Urol.* **2021**, *79*, 82–104. [[CrossRef](#)] [[PubMed](#)]
3. Lemke, E.; Sahasrabudhe, D.; Guancial, E.; Bylow, K.; Johnson, S.; Messing, E.; Kilari, D. The Role of Metastasectomy in Urothelial Carcinoma: Where are We in 2020? *Clin. Genitourin. Cancer* **2020**, *18*, e478–e483. [[CrossRef](#)] [[PubMed](#)]
4. Tarantino, G.; Crocetto, F.; Di Vito, C.; Creta, M.; Martino, R.; Pandolfo, S.D.; Pesce, S.; Napolitano, L.; Capone, D.; Imbimbo, C. Association of NAFLD and Insulin Resistance with Non Metastatic Bladder Cancer Patients: A Cross-Sectional Retrospective Study. *J. Clin. Med.* **2021**, *10*, 346. [[CrossRef](#)] [[PubMed](#)]
5. Coll a Ruvolo, C.; Nocera, L.; Stolzenbach, L.F.; Wenzel, M.; Califano, G.; Tian, Z.; Verze, P.; Shariat, S.F.; Saad, F.; Briganti, A.; et al. Tumor Size Predicts Muscle-invasive and non-organ-confined Disease in Upper Tract Urothelial Carcinoma at Radical Nephroureterectomy. *Eur. Urol. Focus* **2021**, in press. [[CrossRef](#)]
6. Creta, M.; Fusco, F.; La Rocca, R.; Capece, M.; Celentano, G.; Imbimbo, C.; Imperatore, V.; Russo, L.; Mangiapia, F.; Mirone, V.; et al. Short- and Long-Term Evaluation of Renal Function after Radical Cystectomy and Cutaneous Ureterostomy in High-Risk Patients. *J. Clin. Med.* **2020**, *9*, 2191. [[CrossRef](#)]
7. Hellman, S.; Weichselbaum, R.R. Oligometastases. *J. Clin. Oncol.* **1995**, *13*, 8–10. [[CrossRef](#)]

8. Matsushita, H.; Jingu, K.; Umezawa, R.; Yamamoto, T.; Ishikawa, Y.; Takahashi, N.; Katagiri, Y.; Kadoya, N. Stereotactic Radiotherapy for Oligometastases in Lymph Nodes—A Review. *Technol. Cancer Res. Treat.* **2018**, *17*, 1533033818803597. [[CrossRef](#)]
9. Lievens, Y.; Guckenberger, M.; Gomez, D.; Hoyer, M.; Iyengar, P.; Kindts, I.; Méndez Romero, A.; Nevens, D.; Palma, D.; Park, C.; et al. Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document. *Radiother. Oncol.* **2020**, *148*, 157–166. [[CrossRef](#)]
10. Ogihara, K.; Kikuchi, E.; Watanabe, K.; Kufukihara, R.; Yanai, Y.; Takamatsu, K.; Matsumoto, K.; Hara, S.; Oyama, M.; Monma, T.; et al. Can urologists introduce the concept of “oligometastasis” for metastatic bladder cancer after total cystectomy? *Oncotarget* **2017**, *8*, 111819–111835. [[CrossRef](#)]
11. Faltas, B.M.; Gennarelli, R.L.; Elkin, E.; Nguyen, D.P.; Hu, J.; Tagawa, S.T. Metastasectomy in older adults with urothelial carcinoma: Population-based analysis of use and outcomes. *Urol. Oncol.* **2018**, *36*, e11–e19. [[CrossRef](#)] [[PubMed](#)]
12. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* **2021**, *372*, n71. [[CrossRef](#)] [[PubMed](#)]
13. Schardt, C.; Adams, M.B.; Owens, T.; Keitz, S.; Fontelo, P. Utilization of the PICO framework to improve searching PubMed for clinical questions. *BMC Med. Inform. Decis. Mak.* **2007**, *7*, 16. [[CrossRef](#)] [[PubMed](#)]
14. Jadad, A.R. *Randomised Controlled Trials*; BMJ Publishing Group: London, UK, 1998.
15. Slim, K.; Nini, E.; Forestier, D.; Kwiatkowski, F.; Panis, Y.; Chipponi, J. Methodological index for non-randomized studies (minors): Development and validation of a new instrument. *Anz. J. Surg.* **2003**, *73*, 712–716. [[CrossRef](#)] [[PubMed](#)]
16. Abe, T.; Minami, K.; Harabayashi, T.; Sazawa, A.; Chiba, H.; Kikuchi, H.; Miyata, H.; Frumido, J.; Matsumoto, R.; Osawa, T.; et al. Prognostic impact of local radiotherapy on metastatic urothelial carcinoma patients receiving systemic chemotherapy. *Jpn. J. Clin. Oncol.* **2020**, *50*, 206–213, Erratum in *Jpn. J. Clin. Oncol.* **2020**, *50*, 727. [[CrossRef](#)]
17. Leonetti, A.; D’Abbiero, N.; Baldari, G.; Andreani, S.; Ruffini, L.; Viansone, A.A.; Buti, S. Radiotherapy for the treatment of distant nodes metastases from oligometastatic urothelial cancer: A retrospective case series. *Int. J. Urol.* **2018**, *25*, 879–886. [[CrossRef](#)]
18. Augugliaro, M.; Marvaso, G.; Ciardo, D.; Zerini, D.; Riva, G.; Rondi, E.; Vigorito, S.; Comi, S.; De Cobelli, O.; Orecchia, R.; et al. Recurrent oligometastatic transitional cell bladder carcinoma: Is there room for radiotherapy? *Neoplasma* **2019**, *66*, 160–165. [[CrossRef](#)]
19. Miranda, A.F.; Howard, J.M.; McLaughlin, M.; Meng, X.; Clinton, T.; Şanlı, Ö.; Garant, A.; Bagrodia, A.; Margulis, V.; Lotan, Y.; et al. Metastasis-directed radiation therapy after radical cystectomy for bladder cancer. *Urol. Oncol.* **2021**, *39*, e1–e790. [[CrossRef](#)]
20. Franzese, C.; Francolini, G.; Nicosia, L.; Alongi, F.; Livi, L.; Scorsetti, M. Stereotactic Body Radiation Therapy in the Management of Oligometastatic and Oligoprogressive Bladder Cancer and Other Urothelial Malignancies. *Clin. Oncol.* **2021**, *33*, 50–56. [[CrossRef](#)]
21. Aboudaram, A.; Chaltiel, L.; Graff, P.; Pouessel, D.; Chevreau, C.; Khalifa, J. Role of consolidative radiotherapy for metastatic urothelial bladder cancer patients without progression and with no more than five residual metastatic lesions following first line systemic therapy: A retrospective analysis. *Int. J. Radiat. Oncol. Biol. Phys.* **2020**, *108*, e871–e872. [[CrossRef](#)]
22. Creta, M.; Mirone, V.; Di Meo, S.; Buonopane, R.; Fusco, F.; Imperatore, V. Endoscopic Spatulation of the Intramural Ureter: A Technique to Prevent Stenosis of the Ureterovesical Junction in Patients Undergoing Resection of the Ureteral Orifice. *J. Endourol.* **2016**, *30*, 913–917. [[CrossRef](#)] [[PubMed](#)]
23. Creta, M.; Celentano, G.; Napolitano, L.; La Rocca, R.; Capece, M.; Califano, G.; Collà Ruvolo, C.; Mangiapia, F.; Morra, S.; Turco, C.; et al. Inhibition of Androgen Signalling Improves the Outcomes of Therapies for Bladder Cancer: Results from a Systematic Review of Preclinical and Clinical Evidence and Meta-Analysis of Clinical Studies. *Diagnostics* **2021**, *11*, 351. [[CrossRef](#)] [[PubMed](#)]
24. Regnier, S.; Califano, G.; Elalouf, V.; Albisinni, S.; Aziz, A.; Di Trapani, E.; Krajewski, W.; Mari, A.; D’Andrea, D.; Pradère, B.; et al. Restaging transurethral resection in ta high-grade nonmuscle invasive bladder cancer: A systematic review. *Curr. Opin. Urol.* **2022**, *32*, 54–60. [[CrossRef](#)] [[PubMed](#)]
25. Francolini, G.; Desideri, I.; Detti, B.; Di Cataldo, V.; Masi, L.; Caramia, G.; Visani, L.; Terziani, F.; Muntoni, C.; Lo Russo, M.; et al. Stereotactic radiotherapy in oligoprogressive and oligorecurrent urothelial cancer patients: A retrospective experience. *Cancer Treat. Res. Commun.* **2019**, *19*, 100124. [[CrossRef](#)]
26. Peyrottes, A.; Ouzaid, I.; Califano, G.; Hermieu, J.F.; Xylinas, E. Neoadjuvant Immunotherapy for Muscle-Invasive Bladder Cancer. *Medicina* **2021**, *57*, 769. [[CrossRef](#)]
27. Califano, G.; Ouzaid, I.; Verze, P.; Stivalet, N.; Hermieu, J.F.; Xylinas, E. New immunotherapy treatments in non-muscle invasive bladder cancer. *Arch. Esp. Urol.* **2020**, *73*, 945–953.
28. Califano, G.; Ouzaid, I.; Verze, P.; Hermieu, J.F.; Mirone, V.; Xylinas, E. Immune checkpoint inhibition in upper tract urothelial carcinoma. *World J. Urol.* **2021**, *39*, 1357–1367. [[CrossRef](#)]
29. Pradère, B.; Califano, G.; Xylinas, E. Perioperative chemotherapy for upper tract urothelial carcinoma: Show me the evidence. *Curr. Opin. Urol.* **2021**, *31*, 66–67. [[CrossRef](#)]
30. Califano, G.; Xylinas, E. Re: Phase II Trial of Neoadjuvant Systemic Chemotherapy Followed by Extirpative Surgery in Patients with High Grade Upper Tract Urothelial Carcinoma. *Eur. Urol.* **2020**, *78*, 113–114. [[CrossRef](#)]
31. Berghen, C.; Joniau, S.; Vulsteke, C.; Albersen, M.; Devos, G.; Rans, K.; Haustermans, K.; De Meerleer, G. Metastasis-directed therapy for oligometastatic urological tumours: Still no second-hand news. *Ecancermedicalscience* **2020**, *14*, 1036. [[CrossRef](#)]

32. Flaig, T.W.; Spiess, P.E.; Agarwal, N.; Bangs, R.; Boorjian, S.A.; Buyyounouski, M.K.; Chang, S.; Downs, T.M.; Efstathiou, J.A.; Friedlander, T.; et al. Bladder Cancer, Version 3.2020, NCCN Clinical Practice Guidelines in Oncology. *J. Natl. Compr. Cancer Netw.* **2020**, *18*, 329–354. [[CrossRef](#)] [[PubMed](#)]
33. Palma, D.A.; Olson, R.; Harrow, S.; Gaede, S.; Louie, A.V.; Haasbeek, C.; Mulroy, L.; Lock, M.; Rodrigues, G.B.; Yaremko, B.P.; et al. Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers: Long-Term Results of the SABR-COMET Phase II Randomized Trial. *J. Clin. Oncol.* **2020**, *38*, 2830–2838. [[CrossRef](#)] [[PubMed](#)]
34. Phillips, R.; Shi, W.Y.; Deek, M.; Radwan, N.; Lim, S.J.; Antonarakis, E.S.; Rowe, S.P.; Ross, A.E.; Gorin, M.A.; Deville, C.; et al. Outcomes of Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer: The ORIOLE Phase 2 Randomized Clinical Trial. *JAMA Oncol.* **2020**, *6*, 650–659. [[CrossRef](#)]
35. Bajorin, D.F.; Dodd, P.M.; Mazumdar, M.; Fazzari, M.; McCaffrey, J.A.; Scher, H.I.; Herr, H.; Higgins, G.; Boyle, M.G. Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. *J. Clin. Oncol.* **1999**, *17*, 3173–3181. [[CrossRef](#)] [[PubMed](#)]
36. Werner, R.S.; Opitz, I. Patient Selection for Local Aggressive Treatment in Oligometastatic Non-Small Cell Lung Cancer. *Cancers* **2021**, *13*, 6374. [[CrossRef](#)]
37. Rogowski, P.; Trapp, C.; von Bestenbostel, R.; Schmidt-Hegemann, N.S.; Shi, R.; Ilhan, H.; Kretschmer, A.; Stief, C.; Ganswindt, U.; Belka, C.; et al. Outcomes of metastasis-directed therapy of bone oligometastatic prostate cancer. *Radiat. Oncol.* **2021**, *16*, 125. [[CrossRef](#)] [[PubMed](#)]
38. Mertens, L.S.; Horenblas, S. Bladder cancer: Oligometastases and imaging. *Nat. Rev. Urol.* **2017**, *14*, 513–514. [[CrossRef](#)] [[PubMed](#)]
39. Ukleja, J.; Kusaka, E.; Miyamoto, D.T. Immunotherapy Combined With Radiation Therapy for Genitourinary Malignancies. *Front. Oncol.* **2021**, *11*, 663852. [[CrossRef](#)]
40. Sundahl, N.; Vandekerckhove, G.; Decaestecker, K.; Meireson, A.; De Visschere, P.; Fonteyne, V.; De Maeseneer, D.; Reynders, D.; Goetghebeur, E.; Van Dorpe, J.; et al. Randomized Phase 1 Trial of Pembrolizumab with Sequential Versus Concomitant Stereotactic Body Radiotherapy in Metastatic Urothelial Carcinoma. *Eur. Urol.* **2019**, *75*, 707–711. [[CrossRef](#)]
41. Lussier, Y.A.; Xing, H.R.; Salama, J.K.; Khodarev, N.N.; Huang, Y.; Zhang, Q.; Khan, S.A.; Yang, X.; Hasselle, M.D.; Darga, T.E.; et al. MicroRNA expression characterizes oligometastasis(es). *PLoS ONE* **2011**, *6*, e28650. [[CrossRef](#)]