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Review Article

# The role of adjuvant radiotherapy after surgery for upper and lower urinary tract urothelial carcinoma: A systematic review

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**Abstract**

**Objectives:** The role of adjuvant radiotherapy (ART) in patients with bladder cancer (BCa) and upper tract urothelial carcinoma (UTUC) is controversial. We systematically evaluated the oncologic efficacy of ART and its associated toxicity in patients treated with surgery and ART for BCa and UTUC.

**Materials and method:** We performed a literature search on December 2018 using MEDLINE, Web of Science, Cochrane databases and Scopus according to the Preferred Reporting Items for Systematic Review and Meta-analysis statement. Fourteen BCa studies and 14 UTUC studies were included in this systematic review. The data were too scarce and heterogeneous for meta-analytical analysis.

**Results:** The quality and quantity of the data on ART in BCa and UTUC patients are limited. The combination of ART and chemotherapy appears to be beneficial in patients with locally advanced BCa or UTUC. The early and late adverse effects of ART are decreasing reflecting the progress in radiation technology.

**Conclusions:** According to the currently available literature, there is no clear benefit of ART after radical surgery in BCa and UTUC. Future efforts should focus on evaluating multimodal approach using ART with chemotherapy. Until that time comes, ART should be used carefully in patients with BCa and UTUC on a case-by-case basis. 

*Keywords:* Adjuvant radiotherapy; Bladder cancer; Upper tract urothelial carcinoma; Recurrence

## 1. Introduction

Urothelial carcinoma (UC) is the fourth most commonly diagnosed tumors and arises anywhere from the urothelial lining of the urinary tract. UC can be broadly divided into urethral, bladder, and upper tract urothelial carcinoma (UTUC) [1−3]. Bladder cancer (BCa) accounts for 90% to

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95% of UC, UTUC accounts for 5% to 10%, and urethral cancer is a rare entity [4,5]. The standard treatment for muscle invasive BCa and high-risk UTUC is radical surgery; radical cystectomy (RC) and radical nephroureterectomy (RNU). However, approximately 40% and 30% of patients treated with either RC or RNU experience loco-regional recurrence, respectively [6−8], an event that is almost unanimously associated with the patients' demise [9,10]. One possible avenue to lower the loco-regional recurrence rate is the administration of adjuvant treatment in selected patients such as radiotherapy (e.g., based on pT, pN, margin status, and extent of lymphadenectomy) [4,11].

One randomized controlled trial (RCT) demonstrated a beneficial effect of adjuvant radiotherapy (ART) in patients with locally advanced BCa resulting in a significant improvement of recurrence-free survival (RFS) (i.e., 49% for ART vs. 25% for RC only) [12]. However, the authors reported that 10% to 36% of patients experienced intestinal obstruction requiring surgical intervention within 2 years. Novel radiotherapy techniques such as 3D conformal radiotherapy (3DCRT) or intensity-modulated radiotherapy have been shown to minimize the risk for radiation-induced adverse effects for pelvic tumors while maintaining efficacy [13]. Lewis et al. [14] recently reported that ART improved overall survival (OS) in patients with advanced BCa with positive surgical margins after NAC and RC (20.3 vs. 13.1 months, $P$= 0.03). Similarly, Chen et al. [15] reported an OS benefit in patients with pathological T3-4 UTUC who had ART after RNU (29.9 vs. 11.4 months, $P = 0.006$). While these data seem promising, several other studies demonstrated a lack of efficacy for ART with or without AC. Since there are no high-quality data on the risk, benefits or alternatives to ART after radical treatment for BCa and UTUC, we conducted a systematic review of the literature to assess the efficacy of ART after RC or RNU for BCa or UTUC, respectively.

## 2. Material and methods

The protocol has been registered in the International Prospective Register of Systematic Reviews database (PROSPERO: CRD 42019124573).

### 2.1. Literature search

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. A completed PRISMA 2009 checklist is shown in the Supplementary Table 1 to describe the methodology of our study. We searched the electronic databases (MEDLINE, Web of Science, Cochrane Library and Scopus) on December 10th 2018 for studies reporting ART after radical surgical treatment for BCa or UTUC. We used the following string terms: (*urothelial carcinoma* OR *bladder cancer* OR *Upper tract urothelial carcinoma*) AND (*adjuvant* OR *salvage* OR *consolidative*) AND (*radiotherapy* OR *radiation therapy* OR *XRT*).

### 2.2. Inclusion/exclusion criteria

Articles were considered relevant if they included BCa or UTUC patients treated with radical surgery (i.e., RC or RNU) followed ART. We excluded review articles, editorials, case reports, commentaries, meeting abstracts and articles not published in English language. If more than one report of the similar patient cohort population existed, we selected the most recent one. Additional relevant articles were selected from authors' bibliographies.

### 2.3. Data extraction

Two reviewers independently extracted and summarized the following data from the included studies: first author's name, publication year, number of patients, study design, chemotherapy (neoadjuvant (NAC) and adjuvant (AC)), disease stage, follow-up duration, amount of radiotherapy, tumor histology, oncologic outcomes (RFS, local-recurrence-free survival (LRFS), metastasis-free survival (MFS), OS and cancer-specific survival (CSS)) and adverse effects. The definition of local recurrence was any recurrence in the tumor bed or regional lymph nodes or in the radiation field. Any disagreement was discussed and resolved by a third investigator.

### 2.4. Risk of bias

The risk of bias was evaluated according to The Risk of bias in nonrandomized studies of interventions. This tool is based on 7 domains that included bias due to confounding, participant selection, classification of interventions, deviations from intended intervention, missing data, measurement of outcomes, and selection of the reported result (Supplementary Table 2).

## 3. Results

### 3.1. Quantity of evidence identified and characteristics of included studies

A total of 4,320 articles were identified by the initial search (Fig. 1). After removal of duplicates, 3,451 remained for screening of titles and abstracts. We excluded 3,357 articles based on our inclusion and/or exclusion criteria. Then, we assessed the full texts of the remaining selection leaving 14 studies reporting on BCa and other 14 studies on UTUC for the qualitative analysis.

### 3.2. Studies investigating the effect of ART in BCa patients treated with RC

Three RCTs comprising 456 patients and 11 retrospective studies comprising 7,571 patients were included in this systematic review. Characteristics of the studies including BCa are shown in Table 1 [8,12,14,16−26].

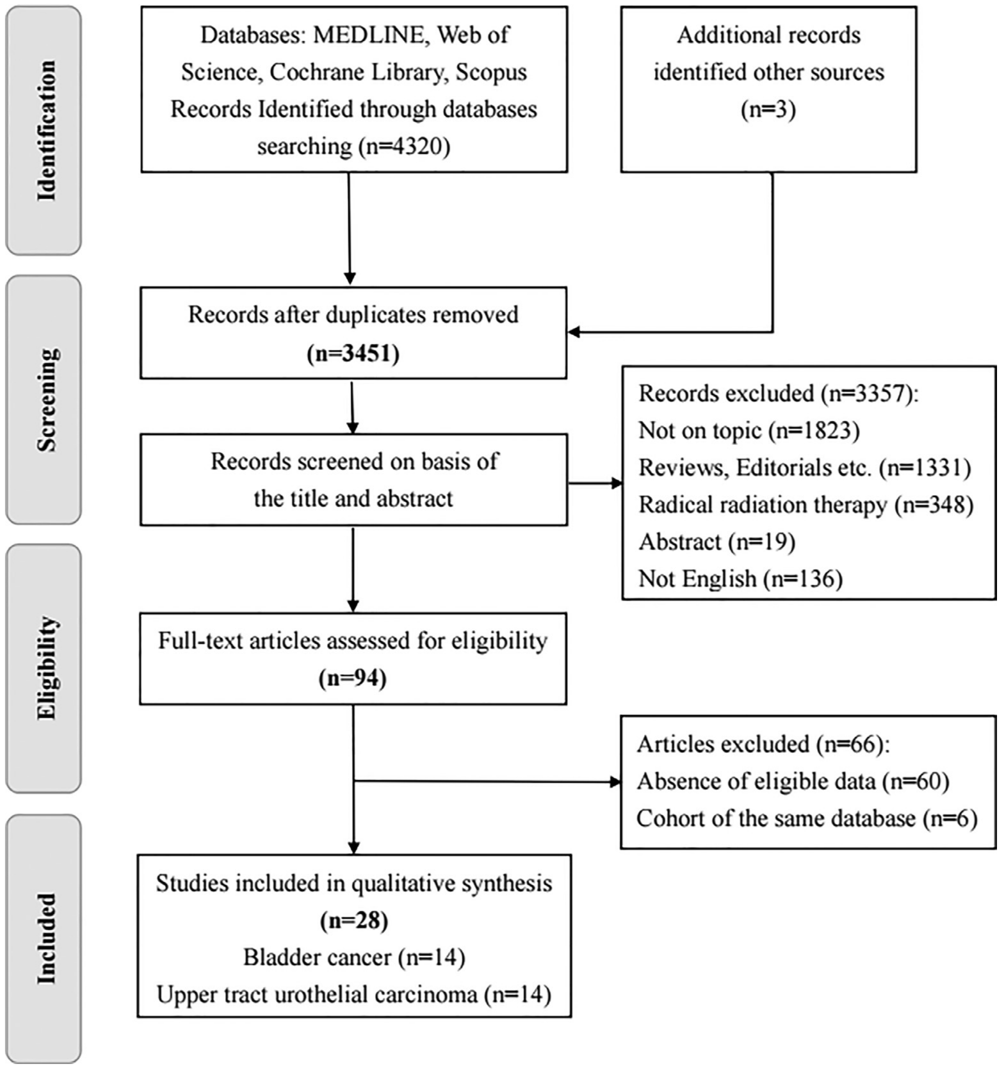


Fig. 1. PRISMA flow-chart of the systematic review.

### *3.1.1. Disease recurrence in BCa patients treated with ART*

Eight, five, and three studies reported the association of ART with RFS, LRFS, and MFS, respectively (Table 2). Four studies [12,19,21,22] reported survival advantage for ART, 3 studies [16,17,23] found no significant difference, while one study [8] found a detrimental effect of ART on RFS. Four studies [12,17,19,22] demonstrated a better LRFS for ART, while one study [16] found no such association. Regarding MFS, all 3 studies [17,19,22] found no association of ART with MFS.

In a RCT, Zaghloul et al. [12] reported 5-year crude RFS rate of 49% during median follow-up of 69 months for patients who received ART compared to 25% for those who underwent RC only ($P < 0.001$). The authors reported a 5-year crude LRFS rate of 87% for patients who received ART compared to 50% for those who underwent RC only ($P < 0.001$). In a more recent RCT, the same investigators [17] reported a 2-year RFS rate of 68% in patients treated with AC and ART compared to 56% for those treated with AC only (HR 0.53, $P = 0.07$). The 2-year LRFS rate was 96% for those who benefited from AC+ART compared to 69% for those who had AC only (HR 0.08, $P < 0.01$). However, they found no association of ART with MFS; 2-year MFS rate was 73% for patients treated with AC and ART compared to 79% for those who had AC only. El-Monim et al. [16], in a RCT, investigated the difference between ART and neoadjuvant radiotherapy. They found no difference in RFS (3-year RFS 34.1% vs. 47.4%, $P = 0.9$) and LRFS (3-year LRFS 80.6% vs. 89.3%, $P = 0.4$). One of the limitations of these 3 studies is that ART was not standardized and these studies were conducted in Egypt where squamous cell carcinoma is more common than urothelial carcinoma. Zaghloul et al. [17] reported in a subgroup analysis comprising urothelial carcinoma only that 2-year LRFS rate was significantly better for patients who received AC and ART compared to those who received AC only (100% vs. 67%, $P < 0.01$).

Bayoumi et al. [22] investigated the effect of ART in 170 patients with locally advanced nonmetastatic BCa and

Table 1
Characteristics of studies reporting the outcomes of patients with bladder cancer who underwent adjuvant radiotherapy after surgery

| Study year | N total ART | Study population | Study design | Total Gy (Median) Gy/F | Technique | Chemo *n* (%) total ART | R+ *n* (%) total ART | Histology *n* (%) total ART | Median follow (Months) |
|---|---|---|---|---|---|---|---|---|---|
| **Randomized controlled trials** | | | | | | | | | |
| Zaghloul 1992 | 236 | pT2b-4 N0-+ without gross residual tumor | RC alone vs. RC + ART(MDF) vs. RC + ART(CF) | 37.5 or 50 | - | - | - | UC 42 (17.8) Squamous 144 (61.0) | 69 (MDF) 49 (CF) |
| | 153 | | | 1.25 Gy/F (MDF) 2 Gy/F (CF) | | | | UC 30 (19.6) Squamous 101 (66.0) | |
| El-Monim 2013 | 100 | pT2-4 N0-+ M0 | NART+RC vs. RC+ART | 50 | 2D | - | - | UC 51 (51.0) Squamous 46 (46.0) | 37 |
| | 50 | | | 2 Gy/F | | | | UC 24 (48.0) Squamous 24 (48.0) | |
| Zaghloul 2018 | 120 | At least one risk factors (≥pT3b, grade3, pN+) | RC+AC+ART vs. RC +AC | 45 | 3DCRT | AC 120 (100)* | 0 | UC 64 (53.3) Squamous 56 (46.7) | 24 |
| | 75 | | | 1.5 Gy/F | | | | UC 41 (54.6) Squamous 34 (45.3) | |
| **Retrospective studies** | | | | | | | | | |
| Reisinger 1992 | 78 | pT0-4 N0-+ M0 | ART vs. Ctl | 45 | - | - | - | - | 52 |
| | 40 | | | 1.8 Gy/F | | | | | |
| Shariat 2006 | 888 | pT1-4 N0-+ M0 | ART vs. Ctl | - | - | NAC 43 (4.8) AC 232 (26.1) | - | UC 888 (100) | 39 |
| | 40 | | | - | | - | | | |
| Zaghloul 2007 | 216 | pT1-4 N0-+ MX | RC+ART vs. RC only | 50 | - | 0 | - | Adeno 216 (100) | 47 |
| | 82 | | | 2 Gy/F | | | | | |
| Svatek 2010 | 3947 | pT0-4 N0-+ MX | ART vs. Ctl | - | - | NAC 0 AC 926 (23.8) | 233 (6.0) | - | 32 |
| | - | | | - | | - | | | |
| Raheem 2011 | 71 | pT2a-3 N0-3 M0 | RC+ART vs. RC only | 50 | - | 0 | - | Squamous 71 (100) | 16 |
| | 38 | | | 2 Gy/F | | | | | |
| Bayoumi 2014 | 170 | pT3−4 N0-1 M0 | ART vs. Ctl | 49 | 3DCRT | - | 30 (17.6) | UC 104 (61.2) Squamous 53 (31.2) | 47 |
| | 92 | | | 2 Gy/F | | | 30 (32.6) | UC 60 (65.2) Squamous 32 (34.8) | |
| Evers 2014 | 148 | pT0-4 N0-+ | ART vs. Ctl | - | - | NAC 16 (10.8) AC 40 (27.0) | - | - | 46.8 |
| | 18 | | | - | | - | | | |
| Zhang 2015 | 124 | pT1-4 N0-3 M0-1 | ART vs. Ctl | - | - | NAC 0 AC 42 (33.9) | - | UC 124 (100) | - |
| | 12 | | | - | | - | | | |
| Pouessel 2016 | 226 | pT0-4 N0-3 MX | RC+AC+ART vs. RC +AC | 45 | 3DCRT | AC 226 (100) | 31 (13.7) | UC 216 (95.8) Others 10 (4.2) | 50.4 |
| | 13 | | | - | | | - | - | |

(*continued on next page*)

Table 1 (*Continued*)

| Study year | N total ART | Study population | Study design | Total Gy (Median) Gy/F | Technique | Chemo *n* (%) total ART | R+ *n* (%) total ART | Histology *n* (%) total ART | Median follow (Months) |
|---|---|---|---|---|---|---|---|---|---|
| Orre 2017 | 57 | pT1-4 pN0-3 M0 | RC+ART (+chemotherapy) | 45<br>1.8-2 Gy/F | 3DCRT or IMRT | NAC 7 (12.3)<br>AC 14 (24.6) | 15 (26.3) | UC 57 (100) | 40.4 |
| Lewis 2018 | 1646 | pT3/4 N0-3 M0 | NAC+RC+ART vs. NAC+RC | - | - | NAC 1646 (100)<br>AC 0 | 144 (15.4) | - | 19.5 |
| | 59 | | | - | | | 30 (50.9) | | |

AC = adjuvant chemotherapy; ART = adjuvant radiotherapy; CF = conventional fractionation; Ctl = control; F = fraction; MDF = multiple daily fractionation; NAC = neoadjuvant chemotherapy; R+ = positive surgical margin; RC = radical cystectomy; UC = urothelial carcinoma.

* All regimen is gemcitabine and cisplatin.

compared it with RC only. They found a significant RFS improvement in patients treated with ART (5-year RFS 65% vs. 40%, $P = 0.04$ and crude LRFS 67% vs. 45%, $P < 0.01$). The authors did not detect any association with MFS (crude MFS 61% vs. 62% $P = 0.08$) during a median follow-up of 47 months.

#### *3.1.2. Survival outcomes in BCa patients treated with ART*

Seven and three studies reported the association of ART with OS and CSS, respectively (Table 2) [8,14,16,17,20,22−25]. Five studies [16,17,22−24] found no significant difference, while 2 studies [14,25] reported an OS benefit of ART. One study [23] found no significant difference, and 2 studies [8,20] reported a detrimental effect of ART in term of CSS.

Most studies were consistent showing no OS benefit of ART. Lewis et al. [14] also demonstrated that there was no difference in median OS between patients treated with NAC and ART and patients treated with NAC only (17.7 vs. 23.4 months, $P = 0.09$). In a subgroup analysis, however, they found an improvement in median OS for patients with positive surgical margins treated with NAC and ART (20.3 vs. 13.1 months, $P = 0.03$). On multivariable analysis, they also found that ART was independently associated with OS (HR 0.474, $P = 0.005$). Interestingly, 2 retrospective studies found that ART had an inverse relation with CSS. Shariat et al. [8] found a detrimental effect of ART on CSS, but as the authors stated their results should be interpreted with caution when assessing the effect of ART, since patients with adverse clinicopathological features (i.e., with positive soft tissue surgical margins) were selected for ART. The authors concluded that the benefit of ART can only be assessed in RCT settings. In a recent RCT, Zaghloul et al. [17] reported that 2-year OS rate was 71% for patients treated with AC and ART compared to 60% for those who had AC only (HR 0.61, $P = 0.11$). This study showed that ART and AC was more likely to be associated with better OS without statistical significance even when they excluded the patients with positive soft tissue surgical margins.

### *3.2. Studies investigating the effect of ART in UTUC patients treated with RNU*

Fourteen retrospective studies comprising 6,047 patients were included in this systematic review. Characteristics of the studies including UTUC are shown in Table 3 [15,27−39]. One study [32] reported on concurrent chemoradiotherapy (CCRT) and one study [33] investigated the difference between ART and salvage radiotherapy (SRT).

#### *3.2.1. Disease recurrence in UTUC patients treated with ART*

The associations of ART with RFS, LRFS, and MFS were reported in 3 [34,35,38], 5 [27,30,31,35,38] and 5 studies [27,30,34,35,38], respectively (Table 4). One study

Table 2
Oncologic outcomes in patients with bladder cancer who underwent adjuvant radiotherapy after surgery

| Study year | RFS | LRFS | MFS | OS | CSS | Other findings |
|---|---|---|---|---|---|---|
| Zaughloul 1992 | 5-yr crude RFS 49% vs. 25% ($P < 0.001$) | 5-yr crude LRFS 87% vs. 50% ($P < 0.001$) | - | - | - | |
| El-Monim 2013 | 3-yr RFS 34.1% vs. 47.4% ($P = 0.9$) | 3-yr LRFS 80.6% vs. 89.3% ($P = 0.4$) | - | 3-yr OS 51.8 vs. 53.4% ($P = 0.7$) | - | |
| Zaughloul 2018 | 2-yr RFS 68% vs. 56%<br>HR 0.53, $P = 0.07$ | 2-yr LRFS 96% vs. 69%<br>HR 0.08, $P < 0.01$ | 2-yr MFS 73% vs. 79% | 2-yr OS 71% vs. 60%<br>HR 0.61, $P = 0.11$ | - | (only UC) 2-yr LRFS 100% vs. 67% ($P < 0.01$) |
| Shariat 2006 | HR 3.30, $P < 0.001$ | - | - | - | HR 2.70, $P < 0.001$ | Extravesical disease (80% vs. 41%, $P < 0.001$)<br>LVI (66% vs. 35%, $P < 0.001$)<br>LN involvement (40% vs. 22%, $P = 0.016$) |
| Zaughloul 2007 | HR 1.243, $P < 0.001$<br>5-yr RFS<br>low risk<br>80% vs. 63% $P = 0.5$<br>intermediate risk<br>74% vs. 28%<br>$P = 0.0004$<br>high risk<br>42% vs. 11%<br>$P = 0.0002$ | 5-yr LRFS<br>low risk<br>100% vs. 69% $P = 0.01$<br>intermediate risk<br>100% vs. 45%<br>$P = 0.0005$<br>high risk<br>87% vs. 35% $P = 0.001$, | 5-yr MFS<br>low risk<br>89% vs. 100%<br>intermediate risk 77% vs. 68%<br>high risk<br>56% vs. 68% | - | - | - |
| Svatek 2010 | - | - | - | - | HR 1.81, $P = 0.003$ | - |
| Raheem 2011 | 3-yr RFS 48% vs. 29% ($P = 0.03$)<br>OR 0.19, $P = 0.02$ | - | - | - | - | - |
| Bayoumi 2014 | 5-yr RFS 65% vs. 40% ($P = 0.04$) | Crude LRFS 67% vs. 45% ($P < 0.001$) | Crude MFS 61% vs. 62% ($P = 0.08$) | 5-yr OS 52% vs. 38% ($P = 0.3$) | - | - |
| Evers 2014 | HR 2.13, $P = 0.085$ | - | - | HR 0.22, $P = 0.056$ | HR 0.21, $P = 0.064$ | - |
| Zhang 2015 | - | - | - | HR 0.530, $P = 0.207$ | - | - |
| Pouessel 2016 | - | - | - | HR 0.26, $P = 0.03$ | - | - |
| Orre 2017 | - | 3-yr LRFS 45% | 3-yr MFS 37% | 3-yr OS 49% | - | - |
| Lewis 2018 | - | - | - | 17.7 vs. 23.4 mo<br>(R+) 20.3 vs. 13.1 mo<br>(R+) HR 0.474, $P = 0.005$ | - | (pN2-3) 16.6 vs. 15.1 mo, $P = 0.2$<br>(pT4) 18.5 vs. 16.7 mo, $P = 0.6$ |

CSS = cancer-specific survival; HR = hazard ratio; LRFS = local-recurrence-free survival; MFS = metastasis-free survival; mo = months; OS = overall survival; R+ = positive surgical margin; RFS = recurrence-free survival; UC = urothelial carcinoma.

Table 3
Characteristics of studies reporting the outcomes of patients with upper urinary tract urothelial carcinoma who underwent adjuvant radiotherapy after surgery

| Study year | N total ART | Study population | Study design | Total Gy (Median) Gy/F | Technique | Chemotherapy *n* (%) total ART | R+ *n* (%) Total ART | Follow (Months) |
|---|---|---|---|---|---|---|---|---|
| Cozad 1995 | 67<br>10 | pT1-3 N0-1 M0 | ART vs. Ctl | 48 (37−56)<br>- | - | AC 2 (3.0)<br>0 | 6 (9.0)<br>3 (30.0) | - |
| Catton 1996 | 101<br>86 | pT1-4 N0-1 M0 | ART vs. Ctl | 35 (20−60)<br>1−2 Gy/F | - | 0 | - | 111.6 |
| MaulardDurdux 1996 | 26 | pT2-3 N0-1 M0 | ART only | 45 | - | NAC 1 (3.8) | | 45 |
| Hall 1998 | 74<br>28 (15 stageⅢ) | pT3-4 N0-1 M0-1 | ART vs. Ctl | 39.8 (10−60)<br>- | - | AC 10 (13.5)<br>AC 3 (10.7) | - | 21 |
| Ozsahin 1999 | 126<br>45 | pTa-4 N0-3 M0 | ART vs. Ctl | 50 (20−66)<br>2 Gy/F | - | AC 12 (10%)<br>- | 33 (26.2)<br>15 (33.3) | 39 |
| Czito 2004 | 31<br>22 | pT1-4 N0-2 M0 | ART vs. CCRT | 46.9 (34−63)<br>1.5−2 Gy/F | - | CCRT 9 (29.0)<br>0 | 10 (31.3)<br>6 (27.3) | 31.2 |
| Chen 2011 | 133<br>67 | pT1-4 N0-1 M0 | ART+AC vs. AC | 50 (36−30)<br>2 Gy/F | - | 133 (100) Intravesical (MMC or Epi) | 25 (17.5)<br>12 (18.0) | 26.6 |
| Vassilakopoulou 2011 | 140<br>9 | pT3-4 N0-1 M0-1 | ART+AC vs. AC | -<br>- | - | AC 140 (100) | 104 (16.6)<br>- | 22.5 |
| Fan 2012 | 40<br>20 | pT3-4 N0-+ M0 | ART (+AC) vs. SRT (+AC) | 50<br>1.8−2 Gy/F | 3DCRT or IMRT | AC 34 (85.0)<br>AC 16 (80.0) | -<br>3 (15.0) | 20 |
| Jwa 2014 | 127<br>36 | pT3-4 N0-3 M0 | ART vs. Ctl | 46 (45−60)<br>2 Gy/F | 3DCRT | AC 47 (37.0)<br>AC 21 (58.3) | 20 (15.7)<br>12 (33.3) | 38.3 |
| Sakano 2015 | 502<br>48 | pT1-4 N0-+ M0 | ART vs. Ctl | -<br>- | - | AC 164 (32.7)<br>- | - | 41.4 |
| Hahn 2016 | 2572<br>113 | pT1-4 N0-+ M0 | ART vs. Ctl | -<br>- | - | - | - | - |
| Huang 2016 | 198<br>40 | pT3 N0 M0 | ART vs. Ctl | 50.4 (23.4−64.8)<br>1.8−2 Gy/F | 3DCRT or IMRT | -<br>AC 21 (52.5) | 9 (4.5)<br>4 (10.0) | 29.1 |
| Ding 2017 | 1910 (154 without surgery)<br>146 (25 radiation only) | pT1-4 N0-3 M0-1 | ART vs. Ctl | -<br>- | - | - | - | - |

AC = adjuvant chemotherapy; ART = adjuvant radiotherapy; CCRT = concurrent chemoradiotherapy; Ctl = control; Epi = epirubicin; F = fraction; MMC: mitomycin C; NAC = neoadjuvant chemotherapy; R + = positive surgical margin.

Table 4
Oncologic outcomes in patients with upper tract urothelial carcinoma who underwent adjuvant radiotherapy after surgery

| Study year | RFS | LRFS | MFS | OS | CSS | Other findings |
|---|---|---|---|---|---|---|
| Cozad 1995 | - | 5-yr crude LRFS 90% vs. 76% | No improve | No improve ($P = 0.07$) | - | |
| MaulardDurdux 1996 | 5-yr RFS 30% | - | - | 5-yr OS 49% | - | |
| Hall 1998 | - | Crude local recurrence 20% vs. 6% | No improve | 7 vs. 9 mo | (stageⅢ) 5-yr CSS 45% vs. 40% | |
| Ozsahin 1999 | - | 5-yr LRFS 33% vs. 38% ($P = 0.92$) | - | 5-yr OS 21% vs. 33% ($P = 0.04$) HR 0.74, $P = 0.15$ | - | |
| Czito 2004 | - | 5-yr local recurrence 45% vs. 22% ($P = 0.57$) | 5-yr MFS 38% vs. 67% ($P = 0.21$) | 5-yr OS 27% vs. 67% ($P = 0.01$) | 5-yr CSS 41% vs. 76% ($P = 0.06$) | (stageⅢ/Ⅳ) 5-yr OS 21% vs. 65% ($P = 0.01$) 5-yr CSS 34% vs. 76% ($P = 0.03$) |
| Chen 2011 | - | - | - | 5-yr OS 49.6% vs. 44.7% ($P = 0.198$) | - | (pT3/4) 29.9 vs. 11.4 mo ($P = 0.006$) |
| Vassilakopoulou 2011 | (Univariable) No association | - | HR0.60, $P = 0.04$ | - | (Univariable) No association | |
| Fan 2012 | - | - | - | 3-yr OS 45% vs. 16% 29 vs. 15 mo ($P = 0.03$) | - | 3-yr PFS 41% vs. 12% |
| Jwa 2014 | 3-yr RFS 49% vs. 33% ($P = 0.05$) HR 0.44, $P < 0.01$ | 3-yr LRFS 89% vs. 61% ($P = 0.01$) HR 0.21, $P < 0.01$ | 3-yr MFS 60% vs. 57% ($P = 0.59$) HR 1.02, $P = 0.95$ | 3-yr OS 66% vs. 62% ($P = 0.78$) HR 0.98, $P = 0.96$ | - | |
| Sakano 2015 | - | - | - | - | HR 0.90, $P = 0.73$ | |
| Hahn 2016 | - | - | - | 5-yr OS 24% vs. 44% ($P < 0.05$) HR 0.88, $P = 0.30$ | - | |
| Huang 2016 | 2-yr RFS 66.3% vs. 61.2% ($P = 0.742$) HR 0.71, $P = 0.371$ | 2-yr LRFS 86.2% vs. 86.9% ($P = 0.996$) | 2-yr MFS 74.4% vs. 67.4% ($P = 0.423$) | 2-yr OS 73% vs. 72% ($P = 0.979$) HR 0.59, $P = 0.158$ | 2-yr CSS 75.3% vs. 73.2% ($P = 0.844$) HR 0.60, $P = 0.213$ | |
| Ding 2017 | - | - | - | 5-yr OS 15.6% vs. 47.2% HR 1.463, $P < 0.001$ | 5-yr CSS 22.7% vs. 60.3% HR 1.521, $P < 0.001$ | (stageⅢ/Ⅳ) 5-yr OS 13.9% vs. 25.8% 5-yr CSS 20.2% vs. 34.7% ($P < 0.001$) |

CSS = cancer-specific survival; HR = hazard ratio; LRFS = local-recurrence-free survival; MFS = metastasis-free survival; mo = months; OS = overall survival; PFS = progression-free survival; R+ = positive surgical margin; RFS = recurrence-free survival.

reported a benefit of ART in term of RFS, LRFS, and MFS, respectively [34,35]. Jwa et al. [35] found that ART was independently associated with better RFS and LRFS compared to RNU only; 3-year RFS rates were 49% vs. 33% (HR 0.44, $P < 0.01$) and 3-year LRFS rates were 89% vs. 61% (HR 0.21, $P < 0.01$). However, they failed to find an association between ART and MFS; 3-year MFS rates were 60% vs. 57% (HR 1.02, $P = 0.95$).

Huang et al. [38] found no association of ART with RFS, LRFS, or MFS compared to RNU only in patients with pathological T3N0M0 UTUC. The authors reported 2-year RFS rates of 66.3% vs. 61.2% (HR 0.71, $P = 0.37$), 2-year LRFS rates of 86.2% vs. 86.9% ($P = 1.00$) and 2-year MFS rates of 74.4% vs. 67.4% ($P = 0.42$).

Some studies reported an association between ART and survival outcomes in patients with pathological T3-4 UTUC [15,30,35,38]. Two studies [30,38] did not show survival advantage for ART in term of local recurrence in patients with advanced UTUC. Conversely, Jwa et al. [35] found that ART was associated with an improvement in LRFS and Chen et al. [15] found a benefit to ART in OS. However, the authors of these studies concluded the beneficial effect of ART must be interpreted with caution as the studies were retrospective in design and comprised only a small number of patients with a relatively short follow-up period.

### 3.2.2. *Survival outcomes in UTUC patients treated with ART*

Eight and five studies reported an association between ART and OS and CSS, respectively (Table 4) [15,27,30,31,34−39]. In terms of OS, one study [15] reported an advantage of ART, 6 studies [27,30,31,35,37,38] found no significant difference, and one study [39] reported a detrimental effect of ART. Four studies [30,34,36,38] found no association, while one study [39] found a detrimental effect of ART on CSS.

Chen et al. [15] found that 5-year OS rate was 49.6% for patients treated with AC and ART compared to 44.7% for those treated with AC only ($P = 0.2$). In a subgroup analysis, an OS benefit was observed in patients with pathological T3-4 treated with AC and ART (29.9 vs. 11.4 months, $P = 0.006$). Owing to the rarity of UTUC, RCTs in locally advanced tumors are unlikely to be performed. Therefore, in a population-based study, Ding et al. [39] found that 5-year OS rate was 15.6% for patients treated with ART compared to 47.2% for those without ART (HR 1.46, $P < 0.001$). The authors also found 5-year OS rate was 13.9% for patients treated with ART compared to 25.8% for those without ART in patients with stageⅢ/Ⅳ UTUC. They showed that 5-year CSS rate was 22.7% for patients treated with ART compared to 60.3% for those without ART (HR 1.52, $P < 0.01$); 5-year CSS rate was 20.2% for patients treated with ART compared to 34.7% for those without ART in patients with stageⅢ/Ⅳ UTUC. However, their study included 154 patients without surgery and 25 patients with radiation therapy only. Meanwhile, in another population-based study, Hahn et al. [37] showed that ART was not associated with OS after adjusting for the effects of standard covariates (HR 0.68, $P = 0.85$).

### 3.3. *Adverse effect*

With the advancement in radiotherapy techniques using 3DCRT and intensity-modulated radiotherapy, the maximal radiation dose to the tumor can be delivered while limiting the dose to the adjacent tissues to a minimum. These techniques could minimize both early as well as late adverse effects.

Three RCTs and four retrospective studies reported on the adverse effects of ART in BCa patients [12,16−19, 21,22,26] (Table 5). Zaghloul et al. [12] found that a late ileal obstruction rate varied from 10% to 36% during a median follow-up of 69 months. The same group reported that a late ileal obstruction rate was 2.7% during a median follow-up of 24 months using 3DCRT [17]. El-Monim et al. [16] compared neoadjuvant with adjuvant radiotherapy in a RCT, and reported no late ileal obstruction in patients treated with neoadjuvant vs. 4.5% after ART. Reisinger et al. [18] found as high as 37% of patients experienced late obstruction after ART. Recently, Bayoumi et al. [22] reported late obstruction rate after ART of 8% using 3DCRT during a median follow-up of 47 months.

Four retrospective studies reported on the adverse effects of ART in UTUC patients [15,28,35,38]. Chen et al. [15] reported 3.0% grade III gastrointestinal adverse events and 3.0% grade III neutropenia in 67 patients treated with RNU and ART without AC. Jwa et al. [35] reported that 11 (31%) patients treated with ART had severe neutropenia including 10 (27.8%) with grade III and one (2.8%) with grade IV; all received systemic chemotherapy which may have caused or exacerbated these adverse events.

## 4. Discussion

Urothelial carcinoma has a high morbidity and mortality rate. The loco-regional recurrence rate after RC is generally estimated to be 10% to 20% and can occur up to 30% to 50% [40,41]. Local disease control seems to correlate with favorable long-term oncologic outcomes [42]. In a systematic review, Bruins et al. [43] reported that extended lymphadenectomy had a superior oncologic outcome compared to standard lymphadenectomy. In UTUC, template-based lymphadenectomy appear to improve CSS and reduces the risk of local recurrence in patients with advanced tumor stage [44]. The rationale behind using ART is reducing loco-regional recurrence potentially halting distant disease progression and delaying metastasis thereby improving OS.

### 4.1. *Bladder cancer*

In this systematic review of the literature, some studies found that ART improved survival outcomes as well as

Table 5
Studies reporting adverse effect regarding adjuvant radiotherapy and control arm in patients with bladder cancer and upper tract urothelial carcinoma

| Study year | GI toxicity *n* (%) | Nausea *n* (%) | Diarrhea *n* (%) | Tenesmus *n* (%) | Acute skin reaction *n* (%) | Late ileal obstruction *n* (%) | Others |
|---|---|---|---|---|---|---|---|
| **BCa (Randomized controlled studies)** | | | | | | | |
| Zaughloul 1992 | | (MDF) G1 (8)<br>G2 (15) G3 (5)<br>(CF) G1 (11)<br>G2 (12) G3 (3) | (MDF) G1 (33)<br>G2 (12) G3 (19)<br>(CF) G1 (24)<br>G2 (24) G3 (19) | (MDF)<br>G1 (51) G2 (3)<br>(CF)<br>G1 (56) G2 (1) | (MDF)<br>G1 (56) G2 (1)<br>(CF)<br>G1 (53) | (MDF)<br>G3 (10)<br>(CF)<br>G3 (36) | |
| El-Monim 2013 | G1-2 25 (56) vs. 5 (10)<br>G3 2 (4.5) vs. 1 (2) | | | | | G3 2(4.5) vs. 0 | G3 0 vs. 2 (4.3) |
| Zaughloul 2018 | | G2<br>46 (61.3) vs. 11 (24.4)<br>G3<br>28 (37.3) vs. 25 (55.6)<br>G4<br>1 (1.3) vs. 0 | G2<br>44 (58.7) vs. 6 (13.3)<br>G3<br>15 (20.0) vs. 9 (20.0)<br>G4<br>1 (1.3) vs. 0 | G2 15 (20.0)<br>G3 6 (8.0)<br>G4 4 (5.3) | | G3<br>2 (2.7) vs. 1 (2.2) | Liver disorder<br>G2 2 (2.7) vs. 2 (4.4)<br>Renal disorder<br>G2 2 (2.7) vs. 9 (20.0)<br>G3 4 (5.3) vs. 0<br>Anemia<br>G2 28 (37.3) vs. 16 (35.6)<br>G3 20 (26.6) vs. 4 (8.9)<br>G4 3 (4.0) vs. 0<br>Neutropenia<br>G2 9 (12.0) vs. 9 (20.0)<br>G3 1 (1.3) vs. 4 (8.9)<br>Thrombocytopenia<br>G2 1 (1.3) vs. 0 G3 2 (2.7) vs. 0 |
| **BCa (Retrospective studies)** | | | | | | | |
| Reisinger 1992 | | - | - | - | - | G3 3 (7.5) vs. 1 (2.6)<br>G4 9 (22.5) vs. 2 (5.3)<br>G5 3 (7.5) vs. 0 | GU toxicity<br>4 (10) vs. 5 (13) |
| Zaughloul 2007 | | | | | | G3 9 (11) vs. 10 (7.5)<br>G5 1 (1.2) vs. 1 (0.7) | Renal disorder<br>8 (10) vs. 10 (7.5) |
| Raheem 2011 | | | G1 11 (29)<br>G2 10 (26) | | | 0 | |
| Bayoumi 2014 | | | G3 17 (19) | | | G3 7 (8) | |
| Orre 2017 | G1-2 52 (91.2)<br>G3-4 2 (3.5)<br>G5 1 (1.8) | | | | | | GU toxicity<br>G1-2 52 (91.2) G3-4 2 (3.5)<br>Renal disorder<br>G1-2 53 (93) G3-4 2 (3.5)<br>Neutropenia<br>G1-2 54 (94.7) G3-4 1 (1.8) |
| **UTUC (Retrospective studies)** | | | | | | | |
| Catton 1996 | G3<br>2 (2.3) | - | - | | - | - | - |
| Chen 2011 | - | G1 34 (50.7)<br>G2 2 (3)<br>G3 2 (3) | G1 18 (26.9)<br>G2 4 (6.0) | - | - | - | Neutropenia GU toxicity<br>G1 23 (34.3) G1 35 (52.2)<br>G2 10 (14.9) G2 4 (6)<br>G3 2 (3.0) G3 2 (3) |

(*continued on next page*)

local disease control. However, all studies failed to observe a role of ART in lowering the rate of distant metastasis.

The National Comprehensive Cancer Network Guidelines recommend considering ART after RC in patients with ≥pathological T3, positive lymph nodes or high-grade BCa [45]. Zaghloul et al. showed that ART and AC were more likely to be associated with OS benefit in the patients with at least one risk factor (pathological T3b, grade3, or positive lymph nodes) and negative surgical margin. The authors, additionally, observed that ART and AC was independently associated with LRFS benefit even in patients with urothelial carcinoma subtype. The rationale for the combination of radiotherapy and chemotherapy is to achieve local control and theoretically a synergistic effect [46]. Baumann et al. [47] demonstrated that future efforts might investigate the role of ART in combination with chemotherapy. Solanki et al. [48] demonstrated that the combination of radiation therapy and immunotherapy presents novel opportunities for treatment strategies in which radiation is no longer limited to local control when used as a backbone for immunotherapy. Several clinical trials (NCT02316548, NCT02951325, NCT02397434, NCT03718741, NCT03333356, NCT01954173) on ART in BCa patients are recently recruiting patients around the world. Moreover, future efforts should focus on the efficacy and safety of ART combined with chemotherapy and/or immunotherapy in a personalized treatment strategy.

### 4.2. Upper tract urothelial carcinoma

In this systematic review of the literature, all studies except for 2 studies [15,35] did not observe a survival advantage of ART in patients with UTUC treated with RNU. It is still unclear whether immediate adjuvant or salvage therapy (i.e., SRT) at the time of relapse is the most effective treatment strategy. Fan et al. [33] investigated the differential impact of ART and SRT in advanced UTUC. The 3-year OS rates was 45% for patients treated with ART compared to 16% for those treated with SRT ($P = 0.03$). The optimal perioperative therapy including ART and chemotherapy remains controversial in patients with UTUC. Nevertheless, AC is the most widely used perioperative treatment in patients with UTUC. Leow et al. [49] reported a potential benefit of AC in patients with UTUC in term of OS and CSS. Some studies reported the benefit of CCRT in UTUC patients after RNU [32,34]. Czito et al. [32] found 5-year OS rate was 27% for patients treated with ART compared to 67% for those treated with CCRT ($P = 0.01$). In a subgroup of patients with stageIII/IV, the 5-year OS rates were 21% vs. 65% ($P = 0.01$). Conversely, in a network meta-analysis, Yang et al. [50] found that ART and CCRT had no OS or RFS benefit. In this systematic review, we found that ART combined with chemotherapy had a beneficial effect on oncologic outcomes in patients with UTUC. Currently and up to the best of our knowledge, there are no ongoing clinical trials on the impact of ART in UTUC

Table 5 (*Continued*)

| Study year | GI toxicity *n* (%) | Nausea *n* (%) | Diarrhea *n* (%) | Tenesmus *n* (%) | Acute skin reaction *n* (%) | Late ileal obstruction *n* (%) | Others |
|---|---|---|---|---|---|---|---|
| Jwa 2014 | G1 16 (44.4)<br>G2 14 (38.9) | - | - | - | - | - | Neutropenia GU toxicity<br>G3 10 (27.8) G1 3 (8.3)<br>G4 1 (2.8) G2 5 (13.9) |
| Huang 2016 | - | - | - | - | - | - | Overall AE<br>G1-2 31 (77.5)<br>G3 3 (7.5) |

ART = adjuvant radiotherapy; BCa = bladder cancer; CF = conventional fractionation; G = grade; GI = gastrointestinal; GU = genitourinary; MDF = multiple daily fractionation; UTUC = upper tract urothelial carcinoma.

patients. These results could suggest important clinical implications of ART combined with chemotherapy or immunotherapy and patients selection most likely to benefit from ART.

### 4.3. Limitations

This systematic review suffers from several limitations. Because of inclusion of retrospective studies, these results are not devoid of bias, notably selection bias. The selected studies were heterogeneous regarding their design, comparators, adjustment for the effect of relevant prognostic factors and endpoints. In general, sample sizes were relatively small with short follow-up. RCTs were also affected by regional bias (e.g., Egypt) where the most common type of histology is different from that in developed countries. Another limitation is that radiation was performed by various techniques across different studies over a long period, which might influence survival outcomes and undermine safety.

## 5. Conclusions

According to the currently available literature, there is no clear evidence of survival advantage of ART after radical surgery in patients with BCa and UTUC. Nevertheless, patient selection is the key step in identifying candidates most likely to benefit from ART. The results of ongoing RCTs regarding ART are awaited. Until then, ART should be used in BCa and UTUC with a case-by-case basis. Future efforts should focus on ART combined with chemotherapy in a personalized treatment strategy.

## Declaration of conflict of interest

The authors declare that they have no conflict of interest.

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## Supplementary materials

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## References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7–30. https://doi.org/10.3322/caac.21442.

[2] Green DA, Rink M, Xylinas E, Matin SF, Stenzl A, Roupret M, et al. Urothelial carcinoma of the bladder and the upper tract: disparate twins. J Urol 2013;189:1214–21. https://doi.org/10.1016/j.juro.2012.05.079.

[3] Isbarn H, Jeldres C, Shariat SF, Liberman D, Sun M, Lughezzani G, et al. Location of the primary tumor is not an independent predictor of cancer specific mortality in patients with upper urinary tract urothelial carcinoma. J Urol 2009;182:2177–81. https://doi.org/10.1016/j.juro.2009.07.035.

[4] Alfred Witjes J, Lebret T, Comperat EM, Cowan NC, De Santis M, Bruins HM, et al. Updated 2016 EAU guidelines on muscle-invasive and metastatic bladder cancer. Eur Urol 2017;71:462–75. https://doi.org/10.1016/j.eururo.2016.06.020.

[5] Roupret M, Babjuk M, Comperat E, Zigeuner R, Sylvester RJ, Burger M, et al. European Association of Urology Guidelines on Upper Urinary Tract Urothelial Cell Carcinoma: 2015 Update. Eur Urol 2015;68:868–79. https://doi.org/10.1016/j.eururo.2015.06.044.

[6] Boorjian SA, Tollefson MK, Cheville JC, Costello BA, Thapa P, Frank I. Detection of asymptomatic recurrence during routine oncological followup after radical cystectomy is associated with improved patient survival. J Urol 2011;186:1796–802. https://doi.org/10.1016/j.juro.2011.07.005.

[7] Margulis V, Shariat SF, Matin SF, Kamat AM, Zigeuner R, Kikuchi E, et al. Outcomes of radical nephroureterectomy: a series from the upper tract urothelial carcinoma collaboration. Cancer 2009;115:1224–33. https://doi.org/10.1002/cncr.24135.

[8] Shariat SF, Karakiewicz PI, Palapattu GS, Lotan Y, Rogers CG, Amiel GE, et al. Outcomes of radical cystectomy for transitional cell carcinoma of the bladder: a contemporary series from the Bladder Cancer Research Consortium. J Urol 2006;176:2414–22. https://doi.org/10.1016/j.juro.2006.08.004:discussion 22.

[9] Rink M, Lee DJ, Kent M, Xylinas E, Fritsche HM, Babjuk M, et al. Predictors of cancer-specific mortality after disease recurrence following radical cystectomy. BJU Int 2013;111:E30–6. https://doi.org/10.1111/j.1464-410X.2012.11433.x.

[10] Rink M, Sjoberg D, Comploj E, Margulis V, Xylinas E, Lee RK, et al. Risk of cancer-specific mortality following recurrence after radical nephroureterectomy. Ann Surg Oncol 2012;19:4337–44. https://doi.org/10.1245/s10434-012-2499-8.

[11] Sargos P, Baumann BC, Eapen L, Christodouleas J, Bahl A, Murthy V, et al. Risk factors for loco-regional recurrence after radical cystectomy of muscle-invasive bladder cancer: a systematic-review and framework for adjuvant radiotherapy. Cancer Treatment Rev 2018;70:88–97. https://doi.org/10.1016/j.ctrv.2018.07.011.

[12] Zaghloul MS, Awwad HK, Akoush HH, Omar S, Soliman O, el Attar I. Postoperative radiotherapy of carcinoma in bilharzial bladder: improved disease free survival through improving local control. Int J Radiat Oncol Biol Phys 1992;23:511–7.

[13] Lawrie TA, Green JT, Beresford M, Wedlake L, Burden S, Davidson SE, et al. Interventions to reduce acute and late adverse gastrointestinal effects of pelvic radiotherapy for primary pelvic cancers. Cochrane Database Syst Rev 2018;1:Cd012529. https://doi.org/10.1002/14651858.CD012529.pub2.

[14] Lewis GD, Haque W, Verma V, Butler EB, Teh BS. The role of adjuvant radiation therapy in locally advanced bladder cancer. Bladder Cancer 2018;4:205–13. https://doi.org/10.3233/blc-180163.

[15] Chen B, Zeng ZC, Wang GM, Zhang L, Lin ZM, Sun LA, et al. Radiotherapy may improve overall survival of patients with T3/T4 transitional cell carcinoma of the renal pelvis or ureter and delay bladder tumour relapse. BMC Cancer 2011;11:297. https://doi.org/10.1186/1471-2407-11-297.

[16] El-Monim HA, El-Baradie MM, Younis A, Ragab Y, Labib A, El-Attar I. A prospective randomized trial for postoperative vs. preoperative adjuvant radiotherapy for muscle-invasive bladder cancer. Urol Oncol 2013;31:359–65. https://doi.org/10.1016/j.urolonc.2011.01.008.

[17] Zaghloul MS, Christodouleas JP, Smith A, Abdallah A, William H, Khaled HM, et al. Adjuvant sandwich chemotherapy plus radiotherapy vs adjuvant chemotherapy alone for locally advanced bladder cancer after radical cystectomy: a randomized phase 2 trial. JAMA Surg 2018;153:e174591. https://doi.org/10.1001/jamasurg.2017.4591.

[18] Reisinger SA, Mohiuddin M, Mulholland SG. Combined preoperative and postoperative adjuvant radiation-therapy for bladder-cancer - a 10

year experience. Int J Radiat Oncol Biol Phys 1992;24:463–8. https://doi.org/10.1016/0360-3016(92)91060-z.

[19] Zaghloul MS, El Baradie M, Nouh, Abdel-Fatah S, Taher A, Shalaan M. Prognostic index for primary adenocarcinoma of the urinary bladder. Gulf J Oncol 2007:47–54. PMID: 20084724.

[20] Svatek RS, Shariat SF, Lasky RE, Skinner EC, Novara G, Lerner SP, et al. The effectiveness of off-protocol adjuvant chemotherapy for patients with urothelial carcinoma of the urinary bladder. Clin Cancer Res 2010;16:4461–7. https://doi.org/10.1158/1078-0432.Ccr-10-0457.

[21] Raheem AMA, Hameed DA, ElGanainy EO, Mosad E, Abdelwanis ME, Kamel NA, et al. Can Bcl-XL expression predict the radio sensitivity of Bilharzial-related squamous bladder carcinoma? A prospective comparative study. BMC Cancer 2011:11. https://doi.org/10.1186/1471-2407-11-16.

[22] Bayoumi Y, Heikal T, Darweish H. Survival benefit of adjuvant radiotherapy in stage III and IV bladder cancer: results of 170 patients. Cancer Manage Res 2014;6:459–65. https://doi.org/10.2147/cmar.S69055.

[23] Evers PD, Logan JE, Sills V, Chin AI. Karnofsky performance status predicts overall survival, cancer-specific survival, and progression-free survival following radical cystectomy for urothelial carcinoma. World J Urol 2014;32:385–91. https://doi.org/10.1007/s00345-013-1110-7.

[24] Zhang GM, Zhu Y, Luo L, Wan FN, Zhu YP, Sun LJ, et al. Preoperative lymphocyte-monocyte and platelet-lymphocyte ratios as predictors of overall survival in patients with bladder cancer undergoing radical cystectomy. Tumor Biol 2015;36:8537–43. https://doi.org/10.1007/s13277-015-3613-x.

[25] Pouessel D, Bastuji-Garin S, Houédé N, Vordos D, Loriot Y, Chevreau C, et al. Adjuvant chemotherapy after radical cystectomy for urothelial bladder cancer: outcome and prognostic factors for survival in a french multicenter, contemporary cohort. Clin Genitourin Cancer 2017;15:e45–52. https://doi.org/10.1016/j.clgc.2016.07.012.

[26] Orre M, Latorzeff I, Flechon A, Roubaud G, Brouste V, Gaston R, et al. Adjuvant radiotherapy after radical cystectomy for muscle-invasive bladder cancer: a retrospective multicenter study. PloS One 2017;12:e0174978. https://doi.org/10.1371/journal.pone.0174978.

[27] Cozad SC, Smalley SR, Austenfeld M, Noble M, Jennings S, Raymond R. Transitional cell carcinoma of the renal pelvis or ureter: patterns of failure. Urology 1995;46:796–800. https://doi.org/10.1016/s0090-4295(99)80346-x.

[28] Catton CN, Warde P, Gospodarowicz MK, Panzarella T, Catton P, McLean M, et al. Transitional cell carcinoma of the renal pelvis and ureter: outcome and patterns of relapse in patients treated with postoperative radiation. Urol Oncol 1996;2:171–6. https://doi.org/10.1016/S1078-1439(96)00095-6.

[29] MaulardDurdux C, Dufour B, Hennequin C, Chretien Y, Vignes B, Droz D, et al. Postoperative radiation therapy in 26 patients with invasive transitional cell carcinoma of the upper urinary tract: no impact on survival? J Urol 1996;155:115–7. https://doi.org/10.1016/s0022-5347(01)66563-7.

[30] Hall MC, Womack JS, Roehrborn CG, Carmody T, Sagalowsky AI. Advanced transitional cell carcinoma of the upper urinary tract: patterns of failure, survival and impact of postoperative adjuvant radiotherapy. J Urol 1998;160:703–6.

[31] Ozsahin M, Zouhair A, Villa S, Storme G, Chauvet B, Taussky D, et al. Prognostic factors in urothelial renal pelvis and ureter tumours: a multicentre Rare Cancer Network study. Eur J Cancer 1999;35:738–43.

[32] Czito B, Zietman A, Kaufman D, Skowronski U, Shipley W. Adjuvant radiotherapy with and without concurrent chemotherapy for locally advanced transitional cell carcinoma of the renal pelvis and ureter. J Urol 2004;172:1271–5.

[33] Fan KH, Chen YC, Leung WM, Chuang CK, Pang ST, Hong JH. Adjuvant and salvage radiotherapy for urothelial cell carcinoma of the upper urinary tract: experience in a single institution. Chang Gung Med J 2012;35:247–54.

[34] Vassilakopoulou M, Rouge TD, Colin P, Ouzzane A, Khayat D, Dimopoulos MA, et al. Outcomes after adjuvant chemotherapy in the treatment of high-risk urothelial carcinoma of the upper urinary tract (UUT-UC). Cancer 2011;117:5500–8. https://doi.org/10.1002/cncr.26172.

[35] Jwa E, Kim YS, Ahn H, Kim CS, Lee JL, Kim SO, et al. Adjuvant radiotherapy for stage III/IV urothelial carcinoma of the upper tract. Anticancer Res 2014;34:333–8.

[36] Sakano S, Matsuyama H, Kamiryo Y, Hayashida S, Yamamoto N, Kaneda Y, et al. Impact of variant histology on disease aggressiveness and outcome after nephroureterectomy in Japanese patients with upper tract urothelial carcinoma. Int J Clin Oncol 2015;20:362–8. https://doi.org/10.1007/s10147-014-0721-3.

[37] Hahn AW, Giri S, Pathak R, Bhatt VR, Martin MG. Effect of adjuvant radiotherapy on survival in patients with locoregional urothelial malignancies of the upper urinary tract. Anticancer Res 2016;36:4051–5.

[38] Huang YC, Chang YH, Chiu KH, Shindel AW, Lai CH. Adjuvant radiotherapy for locally advanced upper tract urothelial carcinoma. Sci Rep 2016;6:38175. https://doi.org/10.1038/srep38175.

[39] Ding T, Zheng Z, Xu R, Zhou C. Prognostic factors and outcomes of primary transitional cell carcinoma of the ureter: a population-based study. Oncotarget 2017;8:65983–96. https://doi.org/10.18632/oncotarget.19623.

[40] Christodouleas JP, Baumann BC, He JW, Hwang WT, Tucker KN, Bekelman JE, et al. Optimizing bladder cancer locoregional failure risk stratification after radical cystectomy using SWOG 8710. Cancer 2014;120:1272–80. https://doi.org/10.1002/cncr.28544.

[41] Griffiths G, Hall R, Sylvester R, Raghavan D, Parmar MK. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. J Clin Oncol 2011; 29:2171–7. https://doi.org/10.1200/jco.2010.32.3139.

[42] Kluth LA, Black PC, Bochner BH, Catto J, Lerner SP, Stenzl A, et al. Prognostic and prediction tools in bladder cancer: a comprehensive review of the literature. Eur Urol 2015;68:238–53. https://doi.org/10.1016/j.eururo.2015.01.032.

[43] Bruins HM, Veskimae E, Hernandez V, Imamura M, Neuberger MM, Dahm P, et al. The impact of the extent of lymphadenectomy on oncologic outcomes in patients undergoing radical cystectomy for bladder cancer: a systematic review. Eur Urol 2014;66:1065–77. https://doi.org/10.1016/j.eururo.2014.05.031.

[44] Dominguez-Escrig JL, Peyronnet B, Seisen T, Bruins HM, Yuan CY, Babjuk M, et al. Potential benefit of lymph node dissection during radical nephroureterectomy for upper tract urothelial carcinoma: a systematic review by the European Association of Urology Guidelines Panel on Non-muscle-invasive Bladder Cancer. Eur Urol Focus 2017. https://doi.org/10.1016/j.euf.2017.09.015.

[45] National Comprehensive Cancer Network (NCCN)Clinical practice guidelines in oncology. NCCN Guidelines: bladder cancer Version 2: 2017; 2017.doi.

[46] James ND, Hussain SA, Hall E, Jenkins P, Tremlett J, Rawlings C, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. N Engl J Med 2012;366:1477–88. https://doi.org/10.1056/NEJMoa1106106.

[47] Baumann BC, Sargos P, Eapen LJ, Efstathiou JA, Choudhury A, Bahl A, et al. The rationale for post-operative radiation in localized bladder cancer. Bladder Cancer 2017;3:19–30. https://doi.org/10.3233/blc-160081.

[48] Solanki AA, Bossi A, Efstathiou JA, Lock D, Mondini M, Ramapriyan R, et al. Combining immunotherapy with radiotherapy for the treatment of genitourinary malignancies. Eur Urol Oncol 2019;2:79–87. https://doi.org/10.1016/j.euo.2018.09.013.

[49] Leow JJ, Martin-Doyle W, Fay AP, Choueiri TK, Chang SL, Bellmunt J. A systematic review and meta-analysis of adjuvant and neoadjuvant chemotherapy for upper tract urothelial carcinoma. Eur Urol 2014;66:529–41. https://doi.org/10.1016/j.eururo.2014.03.003.

[50] Yang X, Li P, Deng XH, Dong HQ, Cheng YD, Zhang XL, et al. Perioperative treatments for resected upper tract urothelial carcinoma: a network meta-analysis. Oncotarget 2017;8:3568–80. https://doi.org/10.18632/oncotarget.12239.