Bladder Cancer

Adjuvant Radiotherapy After Radical Cystectomy for Patients with High-risk Muscle-invasive Bladder Cancer: Results of a Multicentric Phase II Trial

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Abstract

Background: High-risk muscle-invasive bladder cancer (MIBC) has a poor prognosis. Old trials showed that external beam radiotherapy (EBRT) after radical cystectomy (RC) decreases the incidence of local recurrences but induces severe toxicity.

Objective: To evaluate the toxicity and local control rate after adjuvant EBRT after RC delivered with volumetric arc radiotherapy.

Design, setting, and participants: This is a multicentric phase 2 trial. From August 2014 till October 2020, we treated 72 high-risk MIBC patients with adjuvant EBRT after RC. High-risk MIBC is defined as \( \geq T3 \) MIBC ± lymphovascular invasion, fewer than ten lymph nodes removed, pathological positive lymph nodes, or positive surgical margins.

Intervention: Patients received 50 Gy in 25 fractions with intensity-modulated radiotherapy to the pelvic lymph nodes ± cystectomy bed.

Outcome measurements and statistical analysis: The primary outcome is acute toxicity. We report on local relapse-free rate (LRFR), clinical relapse-free survival (CRFS), overall survival (OS), and bladder cancer–specific survival (BCSS).

Results and limitations: The median follow-up is 18 mo. Forty-two patients (61%) developed acute grade 2 gastrointestinal (GI) toxicity. Four patients (6%) had acute grade 3 GI toxicity. One patient had grade 5 diarrhea and vomiting due to obstruction at 1 mo. Two-year probabilities of developing grade \( \geq 3 \) and \( \geq 2 \) GI toxicity were 17% and 76%, respectively. Urinary toxicity, assessed in 17 patients with a neobladder, was acceptable with acute grade 2 and 3 urinary toxicity reported in 53% (\( N = 9 \)) and 18% (\( N = 3 \)) of the patients, respectively. The 2-yr LRFR is 83% ± 5% and the 2-yr CRFS rate is 43% with a
1. Introduction

Most patients with nonmetastatic (M0) muscle-invasive bladder cancer (MIBC) are treated with radical cystectomy (RC) and extended pelvic lymph node dissection (ePLND). Cisplatin-based neoadjuvant chemotherapy improves survival and is standard of care for patients with M0 MIBC [1]. The long-term prognosis of MIBC patients remains limited with 5-yr overall survival (OS) rates ranging from 50% [2] to 65% [3]. Five-year bladder cancer–specific survival (BCSS) is 48% for pT3 and 31% for pT4 MIBC, while 5-yr OS drops to 22% [4,5]. Adjuvant chemotherapy (AC) could improve the outcome of MIBC patients, but it remains unclear which patient benefits most from it [6,7]. The first results of the IMvigor010 trial did not show an advantage in disease-free survival (DFS) for adjuvant atezolizumab [8]. In contrast, improved DFS was reported for nivolumab [9].

Ultimately up to 30% of ≥pT3 patients develop a pelvic recurrence [4,10], which is associated with a poor prognosis [4]. Moreover, pelvic recurrences are often debilitating with pain, lymphedema, and venous thrombosis. It has been shown that adjuvant external beam radiotherapy (EBRT) results in a 20% increase in 5-yr DFS [11,12]. However, most patients included in these trials had squamous carcinoma of the bladder, which makes it difficult to extrapolate these results to a current patient cohort in Europe or the USA.

Moreover, excessive toxicity with old radiotherapy techniques hampered enthusiasm to implement adjuvant EBRT after RC in daily practice [13]. Modern image-guided and intensity-modulated radiation therapy allows sparing of critical organs at risk, resulting in an improved toxicity profile for most pelvic indications.

Recently, AC plus EBRT for patients with locally advanced MIBC has been proved to be well tolerated and associated with significant improvement in local relapse-free survival and marginal improvement in DFS compared with chemotherapy alone [14].

We present the results of our phase 2 trial in which the place of adjuvant EBRT after RC for high-risk MIBC patients is explored.

2. Patients and methods

This multicentric study has been approved by the Ethics Committee (EC2014/0630) and registered on clinicaltrials.gov (NCT02397434). Six centers participated (Supplementary Fig. 1).

The study started in August 2014, and the last patient was included in October 2020. The study design, treatment details, sample size calculation, and endpoints have previously been reported in detail [15].

2.1. Participants

Eligible patients had M0-MIBC (both urothelial carcinoma and variant histology of urothelial carcinoma were allowed), were treated with RC and ePLND, and had one or more of the following characteristics:

1. Stage pT3-MIBC with lymphovascular invasion on pathological examination
2. Stage pT4-MIBC
3. Fewer than ten lymph nodes removed
4. Presence of pathological positive lymph nodes
5. Positive surgical margins

Patients were offered neoadjuvant chemotherapy if they were eligible for cisplatin-based chemotherapy. F-18-labeled fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) computed tomography (CT) was recommended but not obligatory within 4–10 wk after RC to rule out distant metastases. No additional adjuvant therapies were administered except at the time of progression.

2.2. Intervention

All patients received pelvic EBRT to the lymph nodes located along the common, internal, and external iliac artery; obturator fossa; and presacral nodes. A clinical target volume (CTV_Lnn) and a planning target volume (PTV_Lnn) were created using an isotropic expansion of 5 mm and of 12 mm around the delineated lymph node areas, respectively. The bladder bed was included in the radiation field in case of positive surgical margins. Pre-RC imaging as well as information obtained from the surgical report and anatomopathological evaluation were used to delineate the bladder bed.

A median dose of 50 Gy, delivered in 25 fractions, five times a week, was prescribed to the PTV_Lnn ± bladder bed. Suspicious lymph nodes on 18F-FDG-PET-CT were delineated separately and received a simultaneous integrated boost (SIB) up to 70 Gy (corresponding to a normalized isoeffective dose of 74 Gy in 2 Gy fractions calculated with an α/β of 10).

An overview of the planning objectives is presented in Supplementary Table 1. An example of a dose distribution is presented in Supplementary Figure 2. All plans were delivered with intensity-modulated arc therapy using 6–18 MV photons and multileaf collimation. Patient positioning during treatment was controlled by daily cone beam CT.

2.3. Outcome measures

The primary endpoint is acute toxicity defined as toxicity occurring during or within 3 mo following adjuvant EBRT, and scored by the Acute Radiation Therapy Oncology Group (RTOG) small and large intestine tox-
Urinary toxicity was scored in patients with a neobladder according to the acute RTOG [16] and CTC v4.0 [17] toxicity scoring systems.

Secondary endpoints are late toxicity, local control rate (defined as absence of recurrence within the pelvis evaluated on pelvic CT scans performed at predefined time points), local relapse-free rate (LRFR, defined as survival without evidence of local recurrence), clinical relapse-free survival (CRFS, defined as survival without evidence of disease recurrence [neither of local recurrence, recurrence in lymph nodes, or distant metastasis]), BCSS, and OS.

Quality of life was assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 supplemented with QLQ-BLM30 prior to, at the end, and 1 mo after adjuvant EBRT, then 3-monthly during the 1st year and 6-monthly up to 2 yr.

Fig. 1 – Probability of developing (A) grade ≥3 and (B) grade ≥2 gastrointestinal toxicity.

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2.4. Follow-up

Patients were followed weekly during EBRT, 1 mo after EBRT, 3-monthly thereafter during the 1st year, 6-monthly thereafter up to a period of 5 yr, and yearly thereafter or until progression.

2.5. Statistical analysis

Based on previous experience with EBRT, a maximum severe toxicity rate of 25% was deemed acceptable [11–13]. With inclusion of 76 patients, there is a probability to obtain a Wilson score of 95% confidence interval (CI) for a single proportion, with a half width of maximum 10% for the proportion of the patients who develop severe toxicity (ie, grade ≥3 toxicity requiring hospitalization and/or surgical reintervention) after adjuvant EBRT, assuming a true proportion in the population of 25%.

Kaplan-Meier statistics are applied to calculate the 2-yr survival outcomes from the date of end of radiotherapy till the event or death, as well as the overall probability of developing grade ≥2 and ≥3 gastrointestinal (GI) toxicity. Statistical analyses were performed in SPSS version 27.0 software (Chicago, IL, USA).

3. Results

From August 2014 till October 2020, 92 patients were screened, of whom 66 had PET-CT after RC and prior to adjuvant EBRT. Finally, 72 patients were included in the trial (Supplementary Fig. 1). Nineteen patients had metastatic disease on PET-CT, and one patient died because of disease progression before the start of adjuvant EBRT. These patients were excluded from this per-protocol analysis.

Patient characteristics are summarized in Table 1. The median follow-up of all patients was 18 mo (range 1–72 mo). The median time between surgery and start of EBRT was 59 d (range 21–176 d). Of the patients, 53% received no neoadjuvant cisplatin-based chemotherapy (Table 1). Nine patients (13%) had suspicious lymph nodes on PET-CT and received a SIB. One patient stopped adjuvant EBRT early after 15 fractions due to disease progression under EBRT.

3.1. Adverse events

Forty-four patients (61%) developed acute grade 2 GI toxicity. Four patients (6%) had acute grade 3 GI toxicity. One patient developed grade 5 diarrhea and vomiting due to obstruction 1 mo after radiotherapy. The most frequently reported acute grade ≥2 GI toxicities were diarrhea, abdominal cramps, and frequency (Table 2). Late toxicity was assessed in 51 patients. The incidence of late grade 2 GI toxicity was 35% (N = 18 patients). Four patients (8%) developed late grade 3 GI toxicity.

Overall, nine and 52 patients experienced acute and/OR late grade ≥2 and ≥3 GI toxicity, resulting in 2-yr probabilities of developing grade ≥3 and ≥2 GI toxicity of 17% and 76%, respectively (Fig. 1A and 1B).

Acute grade 2 and 3 urinary toxicity, evaluated in 17 patients with a neobladder, is reported in 53% (N = 9) and 18% (N = 3) of the patients, respectively (Table 2). Late urinary toxicity was evaluated in 11 patients with late grade 2 and 3 urinary toxicity present in 45% (N = 5) and 18% (N = 2) of the patients, respectively.

3.2. Efficacy

Eleven patients (15%) developed a locoregional recurrence resulting in a 2-yr LRFR of 83% ± 5% (Fig. 2). In total, 38 patients (53%) developed distant metastases of whom ten patients were simultaneously diagnosed with local and dis-
The median OS time is 30 mo (95% CI: 10–51 mo). The estimated median BCSS time was not yet reached. Two patients with metastatic MIBC requested euthanasia at 1 and 24 mo after the end of EBRT.

### 4. Discussion

High-risk MIBC patients have a ≥30% risk of developing a pelvic recurrence [4,10].

Older trials showed that adjuvant EBRT decreases this risk, but it is associated with severe toxicity [11–13]. The aim of our study was to re-evaluate toxicity after adjuvant EBRT when delivered with modern radiotherapy techniques. By combining highly conformal EBRT and daily image guidance, we observed an acceptable incidence of severe (grade ≥3) toxicity, despite delivering a relatively high dose to the entire pelvis. Moreover, as 6% of patients developed acute grade ≥3 GI toxicity, we remained far below our predefined threshold of >25%. One patient died after hospitalization for symptoms of vomiting and diarrhea caused by obstruction and simultaneous diagnosis of a urinary infection 1 mo after the end of EBRT and 77 d after RC. As ileus and urinary tract infection after RC are observed in 17% and 14% of the patients, respectively, with a reported 90-d mortality rate of 4.7% [18], it is questionable whether this event must be attributed to adjuvant EBRT.

We observed a high (61%) but transient incidence of acute grade 2 GI toxicity. In the study of Zaghloul et al [14], the authors reported consistently higher rates of acute grade 2 nausea, diarrhea, and abdominal cramps, but comparison is difficult because of both the combination with chemotherapy and the use of a standard three-beam setup. Urinary toxicity was evaluated in 17 patients with a neobladder. We found that the incidence of severe urinary toxicity remained low. This confirms that adjuvant EBRT for MIBC is feasible, even for patients with a neobladder [19].

Besides adjuvant EBRT, other adjuvant therapies to improve survival have been studied.

Several trials evaluated the place of AC. The EORTC 30994 trial was closed prematurely and failed to show a significant OS benefit for immediate versus deferred chemotherapy [20]. Nomograms were developed to guide decisions on AC [21]. A retrospective study, stratifying patients based on the nomogram of Bandini et al [21] suggests that AC increases the relapse-free survival of patients with a 1-yr recurrence probability of >0.4 [22]. Despite a lack of clear benefit from randomized trials in favor of AC, the use of cisplatin-based combination chemotherapy is strongly recommended in international guidelines for high-risk MIBC patients if no neoadjuvant chemotherapy was administered. In our trial, 53% of the patients did not receive neoadjuvant chemotherapy, representing real-life clinical practice.

The place of AC in high-risk MIBC patients who received neoadjuvant chemotherapy is even less clear. A recent meta-analysis, solely based on the data of five retrospective trials, suggests that AC has an impact on OS for patients with pT3–pT4 disease, but this may not apply for N+ patients [23].

Two phase 3 trials evaluated adjuvant immunotherapy in patients with high-risk MIBC. The IMvigor010 trial showed no improvement in DFS with atezolizumab and failed to meet the primary endpoint [8]. Local pelvic recurrences were reported in 22% and 28% of the patients treated with or without atezolizumab, respectively [8]. In contrast, adjuvant nivolumab is associated with a significant improvement in DFS. The incidence of noninvasive local recurrences was low both in the experimental and in the observational arm (10% and 14%, respectively). Of importance, 18% of the patients developed grade 3–4 toxicity [9]. Recently, the Food and Drug Administration approved

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**Table 1 – Patient characteristics**

<table>
<thead>
<tr>
<th>Reason for not giving neoadjuvant chemotherapy</th>
<th>Number of patients (N = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal impairment</td>
<td>6 (16)</td>
</tr>
<tr>
<td>Non-MIBC prior to RC</td>
<td>9 (24)</td>
</tr>
<tr>
<td>Variant histology</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Age</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Nephrectomy in the past</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Chemotherapy in the past for other primary tumor</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Cor decompensation</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Patient refusal</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>9 (24)</td>
</tr>
</tbody>
</table>

**Type of urinary tract diversion**

| Ileal conduit                          | 55 (76) |
| Neobladder                              | 17 (23) |

**Definitive pathological stage**

| pT1 ≤2N1                                 | 14 (19) |
| pT2 ≤2Nx                                 | 2 (3)   |
| pT3N0                                    | 16 (22) |
| pT3N1                                    | 19 (27) |
| pT4N0                                    | 8 (11)  |
| pT4N1                                    | 13 (18) |

MIBC = muscle-invasive bladder cancer; RC = radical cystectomy; SCC = squamous cell carcinoma.
nivolumab as adjuvant therapy for patients with high-risk urothelial carcinoma.

We observed local recurrences in 15% of our patients, resulting in a 2-yr LRFR of 83%. This is lower than the reported 2-yr LRFR of 96% for combined radiochemotherapy by Zaghoul et al [14]. In the comparative arm (chemotherapy only), 2-yr LRFR was only 69% [14]. Similarly, for AC, locoregional relapses were observed in 29% of patients [20]. In 23 patients (16%), a locoregional relapse was the first site of progression [20]. The combination of

### Table 2 – Acute and late gastrointestinal and urinary toxicity

<table>
<thead>
<tr>
<th>Gastrointestinal toxicity</th>
<th>Acute (N = 72)</th>
<th>Late (N = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19 (26)</td>
<td>34 (47)</td>
</tr>
<tr>
<td>Incontinence</td>
<td>11 (15)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Urgency</td>
<td>18 (25)</td>
<td>7 (10)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (11)</td>
<td>7 (10)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>2 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal cramps</td>
<td>14 (19)</td>
<td>16 (22)</td>
</tr>
<tr>
<td>Bloating</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>2 (3)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Inflammation</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Obstruction</td>
<td>0</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Perforation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anal pain</td>
<td>3 (4)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Frequency</td>
<td>11 (15)</td>
<td>12 (17)</td>
</tr>
<tr>
<td>RBPA</td>
<td>2 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Mucus loss</td>
<td>6 (8)</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genitourinary toxicity</th>
<th>Acute (N = 17)</th>
<th>Late (N = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Hematuria</td>
<td>0</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Frequency</td>
<td>2 (12)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Incontinence</td>
<td>7 (41)</td>
<td>5 (29)</td>
</tr>
<tr>
<td>Urgency</td>
<td>5 (29)</td>
<td>0</td>
</tr>
<tr>
<td>Nocturia</td>
<td>4 (24)</td>
<td>5 (29)</td>
</tr>
<tr>
<td>Stricture</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

N = number of patients; RBPA = red blood loss per annum.

* One patient had acute grade 5 diarrhea and vomiting.
chemotherapy and radiotherapy undoubtedly withholds advantages, which needs to be explored further.

Our preliminary survival analysis, with 2-yr BCSS of 62% and 2-yr OS of 52%, must be interpreted cautiously and taking into consideration the high percentage of patients with clinically N+ disease at diagnosis (32%) and pN+ disease (65%), and still 13% of patients having suspicious lymph nodes on PET-CT. Node-positive disease is associated with poor prognosis [24]. Moreover, the patients included in our trial were significantly older than in other trials [8,14,20].

Patients for adjuvant therapies are solely selected based on tumor characteristics [20], and it remains unclear which patient benefits most from one treatment or another. Ideally, “proper” patient selection should include radiological and biological predictors for local, locoregional, and distant failure, the latter benefitting most from systemic therapies, and should take into consideration the toxicity profile of each therapy.

Only few studies evaluated the role of 18F-FDG-PET-CT in the staging of patients with MIBC, but specificity and negative predictive values mount to >90%, rendering it an interesting tool in the (re)staging of MIBC patients [25].

Since October 2016, we routinely implemented 18F-FDG-PET-CT prior to the start of adjuvant EBRT.

Nine patients had suspicious pelvic lymph nodes on 18F-FDG-PET-CT. Of them, six patients developed clinical progression and only four were alive at the time of evaluation, of whom three died due to MIBC. This confirms the poor prognosis of patients with early recurrence. Nevertheless, the median OS of these patients was 72 mo (30–114 mo), which compares favorably with the 1-yr OS of 17% [26] and median OS of 18 mo [27] after recurrence reported in the literature.

The shortcomings of the trial are the nonrandomized study design and short follow-up. The number of patients included in our trial is comparable with the sample size of the patients treated with radiochemotherapy in the study of Zaghloul et al [14].

5. Conclusions

With contradictory evidence on improved outcome with adjuvant immunotherapy and acknowledging that there is no significant difference in outcome when treating patients with adjuvant or deferred chemotherapy, adjuvant EBRT can be considered. This is supported by the results of a randomized phase 2 trial that proved adjuvant radiochemotherapy to be safe and effective for poor prognosis MIBC patients. Our results add to the evidence that adjuvant EBRT can be administered safely. Further enrollment in phase III randomized controlled trials remains mandatory to confirm the place of adjuvant radio(chemo)therapy for high-risk bladder cancer patients to improve the outcome of these patients.

Author contributions: Valérie Fonteyne had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Fonteyne.

Acquisition of data: Fonteyne, Ost, Dirix, De Meerleer, Decaestecker, Van Praet, Noé, Liefhoooghe, Junius, Berghen, Albersen, De Maeseneer.

Analysis and interpretation of data: Fonteyne.

Drafting of the manuscript: Fonteyne.

Critical revision of the manuscript for important intellectual content: Dirix, Van Praet, Berghen, Albersen, Junius, Liefhoooghe, Noé, De Meerleer, Ost, Villeirs, Verbeke, De Maeseneer, Verghote, Elhaseen, De Man, Decaestecker.

Statistical analysis: Fonteyne

Obtaining funding: Fonteyne.

Administrative, technical, or material support: Elhaseen, Verghote, Villeirs, De Man, Verbeke.

Supervision: Verbeke.

Other: None.

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Appendix A. Supplementary data

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References


