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Bladder Cancer

Adjuvant Radiotherapy After Radical Cystectomy for Muscle-invasive Bladder Cancer: A Phase 2 Trial—Results of Secondary Endpoints

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Abstract

Background and objective: Patients with muscle-invasive bladder cancer (MIBC) who develop a recurrence after radical cystectomy (RC) have poor outcomes. This study aims to evaluate the safety and efficacy of adjuvant radiotherapy (ART) in mitigating pelvic recurrences in high-risk MIBC patients. We report on survival outcomes, health-related quality of life (HRQoL), and hematological toxicity for these patients.

Methods: A multicentric phase 2 trial was conducted from August 2014 to October 2020, in which 72 high-risk MIBC patients received ART after RC. High risk was defined by the presence of one or more of the following criteria: pT3 stage and lymphovascular invasion, pT4 stage, fewer than ten lymph nodes removed, positive lymph nodes, and positive surgical margins. Using intensity-modulated radiotherapy, patients with pelvic lymph nodes ± cystectomy bed (in case of a positive surgical margin) received 50 Gy in 25 fractions. Outcomes were local relapse-free rate (LRFR), clinical relapse-free survival (CRFS), overall survival (OS) (Kaplan-Meier statistics), HRQoL (European Organisation for Research and Treatment of Cancer QLQ-C30/QLQ-BLM30 surveys), and hematological toxicity (Common Terminology Criteria for Adverse Events grading).

Key findings and limitations: The median follow-up of patients without a recurrence was 39 mo. At 2 and 5 yr, LRFRs were 81% (95% confidence interval [CI] 71–91%) and 79% (95% CI 68–89%), CRFS rates were 32% (95% CI 21–42%) and 20% (95% CI 11–30%), and OS rates were 48% (95% CI 36–59%) and 34% (95% CI 22–45%), respectively. At the end of ART, several symptoms worsened, most returning to baseline within the first few months. Diarrhea showed the greatest deterioration, recovering to baseline score only

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partially. Hematological toxicity of incidence grade ≥2 included lymphopenia (75%), neutropenia (2%), thrombopenia (2%), and anemia (17%). Limitations include the single-arm design and the limited availability of blood samples and surveys.
Conclusions and clinical Implications: ART after RC is well tolerated and leads to a favorable local control rate, supporting its use in clinical practice.

ADVANCING PRACTICE

What does this study add?
This study adds to the evidence that adjuvant radiotherapy for patients with muscle-invasive bladder cancer is well tolerated, with only a limited and temporary impact on health-related quality of life. It supports the treatment's efficacy by showing a favorable local control rate in a population at a high risk of local relapse. Additionally, the observed high incidence of lymphopenia warrants further investigation, as its clinical significance remains unclear.

Clinical Relevance
Treatment options for patients with a high risk of pelvic recurrence following radical cystectomy for non-metastatic muscle-invasive bladder cancer (MIBC) are limited. The present study reports secondary outcomes of a phase 2 trial investigating the role of adjuvant radiotherapy in patients after radical cystectomy for MIBC. The authors report 5-year local relapse-free rate of 79% and overall survival rates of 34%. Health-related quality of life showed a deterioration at the end of ART, but mostly returned to baseline by month 1. Overall, these data suggest that ART may be a treatment option for patients with high risk of local failure following radical cystectomy for MIBC in reducing the risk of pelvic recurrence. Associate Editor: Malte Rieken, M.D.

Patient Summary
In this report, we evaluated the safety and efficacy of radiotherapy after bladder removal surgery in patients with muscle-invasive bladder cancer who had a high risk of disease relapse. We found that radiotherapy caused only a temporary and limited decrease in patients' quality of life. Over 80% of patients had pelvic disease control, but many still experienced distant cancer spread. Our findings support that postoperative radiotherapy is safe and helps prevent pelvic cancer recurrence.

1. Introduction

Patients with nonmetastatic muscle-invasive bladder cancer (MIBC) who undergo radical cystectomy (RC) and exhibit high-risk pathological features have a poor prognosis. Up to 30% of patients with tumors of pathological (p) stage ≥pT3 experience a pelvic recurrence, which is rarely salvageable and often associated with debilitating sequels [1,2]. In addition, pelvic failures occur frequently before the development of distant metastases, suggesting that some distant sites may originate from locally recurrent disease [2,3]. To improve the outcome of these patients, several treatment strategies were investigated.

Neoadjuvant cisplatin-based chemotherapy improves overall survival (OS) but has no impact on mitigating local failure [2,4]. Trials investigating the role of adjuvant immunotherapy have shown mixed results regarding improvements in survival outcomes. In these trials, the impact of adjuvant immunotherapy on the prevention of local failure was not distinctly measured as an outcome [5–7].

In the past, adjuvant radiotherapy (ART) has been proved to be an effective strategy for preventing pelvic recurrences, albeit at the cost of a high burden of toxicity [8]. More recently, Egyptian and Belgian phase 2 trials, utilizing more conformal radiation techniques, have reported high local control rates with acceptable toxicity [9–11]. This report presents updated locoregional and survival outcomes, health-related quality of life (HRQoL), and hematological toxicity from the Belgian phase 2 trial.

2. Patients and methods

This multicenter phase 2 study is approved by the Ethics Committee of Ghent University Hospital (EC2014/0630) and is registered on clinicaltrials.gov (NCT02397434). Comprehensive details regarding the study design, treatment protocols, sample size calculation, endpoints, and screening/inclusion have been reported previously [11,12].

2.1. Participants

Between August 2014 and October 2020, 72 patients with high-risk MIBC were treated with ART after RC. High-risk MIBC was defined by the presence of one or more of the following characteristics: pT3 stage with lymphovascular invasion, pT4 stage, fewer than ten lymph nodes removed, positive lymph nodes, and a positive surgical margin. Patients

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eligible for cisplatin-based chemotherapy were offered neoadjuvant treatment. No further adjuvant therapies, such as chemotherapy or immunotherapy, were administered unless disease progression occurred. Since October 2016, an 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) computed tomography (CT) scan was used routinely within 4–10 wk after RC to exclude distant metastases.

2.2. Intervention

A median dose of 50 Gy was prescribed to the pelvic lymph nodes and, in case of a positive surgical margin, to the bladder bed. This was delivered in 25 fractions over 5 d/wk using volumetric modulated arc therapy (VMAT). Radiotherapy started within 6–12 wk following RC. The elective pelvic lymph node area included the nodes along the common, internal, and external iliac arteries; the obturator fossa; and the presacral nodes. Suspicious lymph nodes identified on 18F-FDG-PET-CT were delineated separately and received a simultaneous integrated boost up to 70 Gy (isoeffective dose of 74 Gy in 2 Gy fractions, calculated with an α/β ratio of 10). More extensive details regarding the radiotherapy protocol have been reported previously [11,12].

2.3. Follow-up

Follow-up included CT imaging (thorax/abdomen/pelvis) every 3–6 mo in the 1st year after ART, then every 6 mo for up to 5 yr or until disease progression. Patient-reported HRQoL and hematological toxicity were evaluated prior to, at the end of, and at 1 mo after ART, then 3 monthly during the 1st year and 6 monthly up to 2 yr. HRQoL was evaluated using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life questionnaire (QLQ-C30) [13] and Quality of Life Core Questionnaire – Bladder Cancer Muscle Invasive (QLQ-BLM30) [14]. Hematological toxicity was assessed via complete blood counts, including red blood cells (RBCs), white blood cell (WBCs) (including differential count), platelet (PLT) count, and hemoglobin levels. Toxicity grading followed the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [15]. Assessment of hematological toxicity was limited to patients who completed the full ART course, and had both the baseline and at least one blood analysis after ART available. Hematological data collected after the start of subsequent oncological therapy (ie, in case of relapse) were excluded from the analysis.

2.4. Statistical analysis

The Kaplan-Meier estimator was used to assess the 2- and 5-yr survival outcomes, including the local relapse-free rate (LRFR), that is, the time from ART without any evidence of a pelvic recurrence; clinical relapse-free survival (CRFS), that is, the time from ART without a disease recurrence or death from any cause; and OS, that is, the time from ART until death from any cause. Changes in HRQoL and blood count values were evaluated over time using a linear mixed model with a compound symmetry covariance structure, comparing post-ART values with baseline (pre-ART) values, with time as a fixed factor. To assess the impact of neoadjuvant chemotherapy on the longitudinal pattern in blood count values, an interaction term between neoadjuvant chemotherapy status and time was included in this model. Statistical analyses were performed using SPSS, version 29.0 (SPSS Inc., Chicago, IL, USA). The level of significance was set at (two sided) $p \leq 0.05$.

3. Results

Patient characteristics are summarized in Table 1. The median follow-up times for patients without a disease recurrence and those still alive were 39 mo (interquartile range [IQR] 19–60 mo) and 60 mo (IQR 40–60 mo), respectively.

Table 1 – Patient characteristics

	Patients, *n* (%) *N* = 72
Age (yr), median (IQR)	70 (61–75)
Gender (male)	54 (75)
Tumor histology	
Urothelial	61 (85)
Squamous cell carcinoma	8 (11)
Other	3 (4)
Pathological tumor stage	
≤pT2	15 (21)
pT3	35 (49)
pT4	22 (31)
Positive pathological nodes [a]	47 (67)
Fewer than 10 lymph nodes removed [a]	17 (24)
Positive surgical margin	14 (19)
Prior neoadjuvant chemotherapy	31 (43)
Type of urinary tract diversion	
Ileal conduit	55 (76)
Neobladder	17 (23)
PET-CT prior to radiotherapy	46 (64)

CT = computed tomography; IQR = interquartile range; PET = positron emission tomography.
[a] Data on pathological nodal status are missing for two patients, and the number of lymph nodes removed is missing for one patient.

3.1. Survival outcome

Thirteen patients developed a local recurrence. Twelve of these recurrences occurred within the 1st year after ART. The 2- and 5-yr LRFRs were 81% (95% confidence interval [CI] 71–91%) and 79% (95% CI 68–89%), respectively (Fig. 1). Details regarding the local pattern of failure were published previously [16]. A total of 43 patients developed distant metastases, ten of whom were diagnosed with local and distant failure simultaneously. CRFS rates at 2- and 5-yr were 32% (95% CI 21–42%) and 20% (95% CI 11–30%), respectively (Fig. 2), and the median CRFS time was 9 mo (95% CI 4–14 mo). The 2- and 5-yr OS rates were 48% (95% CI 36–59%) and 34% (95% CI 22–45%), respectively (Fig. 3), and the median OS time was 23 mo (95% CI 12–34 mo). Details regarding the site of disease relapse and subsequent postrelapse oncological treatments are reported in Supplementary Fig. 1 and Supplementary Table 1.

3.2. Health-related quality of life

Detailed results (estimated means with 95% CIs) of all evaluated HRQoL domains and survey response rates are presented in Supplementary Table 2.

Global health status and all functioning scores declined (ie, deterioration) at the end of ART, but all returned to baseline by month 1, except cognitive functioning, which returned to baseline by month 3. Improvement of global health status and functioning scores continued thereafter. In addition, several symptom scores increased (ie, deterioration) at the end of ART, with diarrhea showing the largest increase. Although improved at month 1, the diarrhea score

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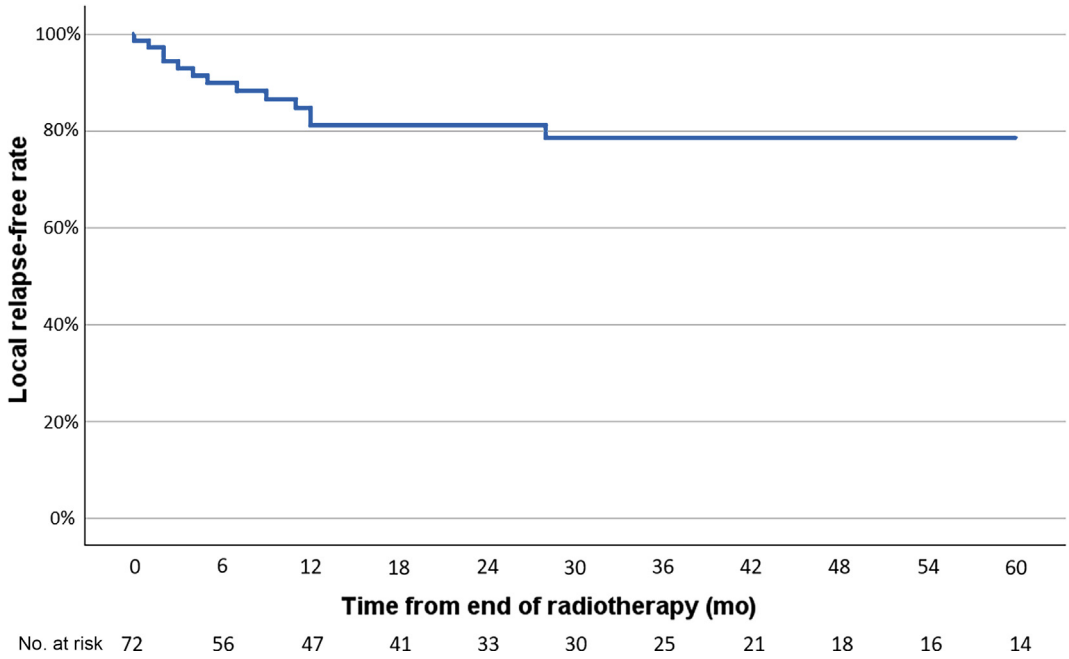

Fig. 1 – Local relapse-free rate.

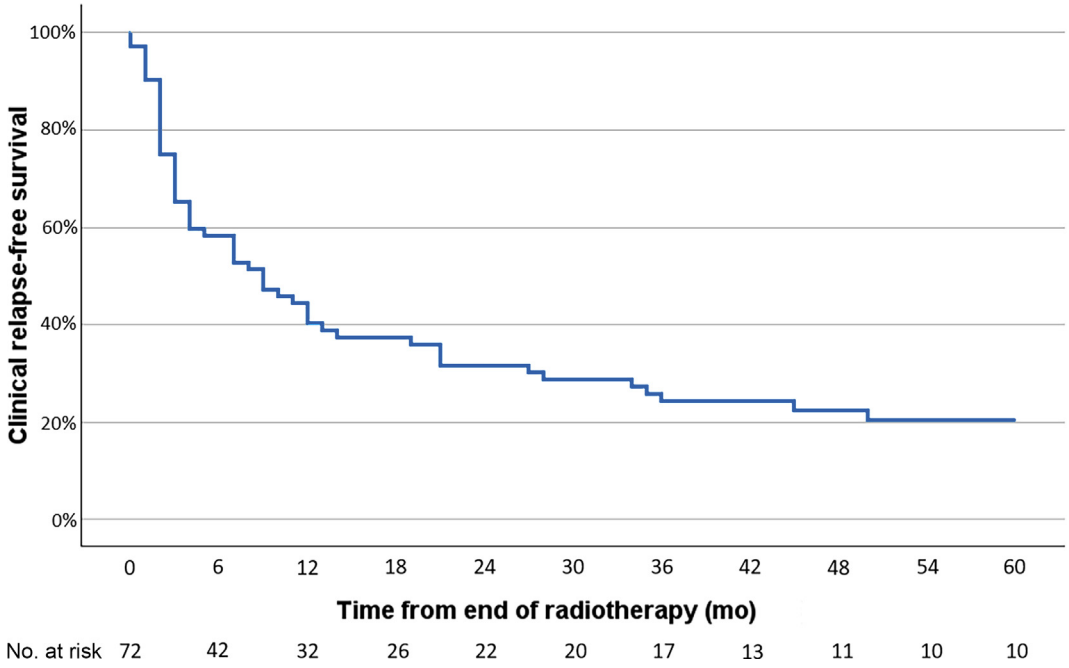

Fig. 2 – Clinical relapse-free survival.

remained above the baseline level during further follow-ups. Increased scores of fatigue, nausea/vomiting, and appetite loss returned to baseline by month 1. The pain score was increased from the end of ART until month 9, and at month 18. The symptom scores of abdominal bloating/flatulence, urostomy problems, body image, catheter use, and sexual functioning increased at the end of ART and fluctuated around their baseline scores during subsequent follow-ups.

3.3. Hematological toxicity

Hematological toxicity observed after ART is reported in Table 2. Longitudinal follow-up of the RBC count, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and PLT count is shown in Supplementary Figs. 2A–D.

The linear mixed model showed that the interaction between time and neoadjuvant chemotherapy status was not significant for any of the evaluated blood count values

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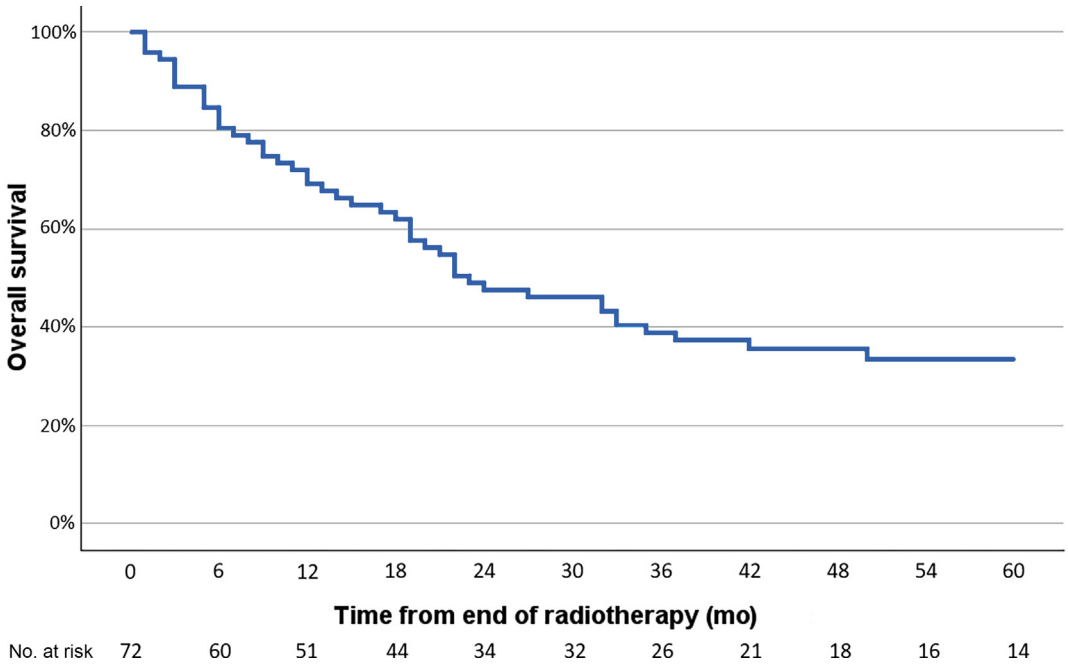

Fig. 3 – Overall survival.

Table 2 – Hematological toxicity after adjuvant radiotherapy (0–24 mo)

	Common Terminology Criteria for Adverse Events version 5		
	Grade 2	Grade 3	Grade 4
Leukopenia	WBC <3.0–2.0 × 10^9/l	WBC <2.0–1.0 × 10^9/l	WBC <1.0 × 10^9/l
(*N* = 61)	6 (10%)	0	0
Lymphopenia	ALC <0.8–0.5 × 10^9/l	ALC <0.5–0.2 × 10^9/l	ALC <0.2 × 10^9/l
(*N* = 58)	20 (34%)	30 (52%)	5 (9%)
Neutropenia	ANC <1.5–1.0 × 10^9/l	ANC <1.0–0.5 × 10^9/l	ANC <0.5 × 10^9/l
(*N* = 58)	1 (2%)	0	0
Thrombopenia	PLT <75–50 × 10^9/l	PLT <50–25 × 10^9/l	PLT <25 × 10^9/l
(*N* = 60)	0	1 (2%)	0
Anemia	Hb <10–8 g/dl	Hb <8 g/dl	Life threatening
(*N* = 43)	5 (12%)	2 (5%)	0

ALC = absolute lymphocyte count; ANC = absolute neutrophil count; Hb = hemoglobin; PLT = platelet count; WBC = white blood cell count.

(ie, RBC count [p = 0.12], ALC [p = 0.8], ANC [p = 0.16], and PLT count [p = 1]). Thus, over time, blood count value patterns did not differ significantly between patients who received neoadjuvant chemotherapy and those who did not.

4. Discussion

The updated survival results confirm the previously reported favorable locoregional control [11], with a 5-yr rate of 79%. This compares favorably with the historical data, where 5-yr local failure rates after RC were 28% and 32% for patients with ≥pT3 disease [1,2]. Notably, our study had a higher proportion of patients with pathologically involved lymph nodes (65% vs 30% and 20%) [1,2] and nearly double the proportion with pT4 disease (31% vs 16%) [1].

Several Egyptian trials investigated the role of ART. A randomized trial comparing pre- and postoperative radiotherapy reported a 3-yr locoregional control rate of 81% in the postoperative group [17]. A phase 2 trial by Zaghloul et al [9], which randomized patients between adjuvant radiochemotherapy and adjuvant chemotherapy, reported 2-yr local control rates of 96% and 69%, respectively. In both trials, approximately half of the patients had squamous cell carcinoma, whereas 85% of our patients had urothelial carcinoma. In a recently published randomized trial by Zaghloul et al [10], ART (without sandwich chemotherapy) improved 3-yr locoregional recurrence-free survival rate to 81% compared with 71% for RC alone in high-risk urothelial MIBC patients, although OS was not significantly better. Moreover, the Egyptian trials had lower rates of pathologically involved lymph nodes and pT4 disease (20–47% and 4–19%, respectively) than our cohort (65% and 31%, respectively) [8–10]. Additionally, both trials by Zaghloul et al [9,10] excluded patients with a positive surgical margin, a group with a reported local failure rate as high as 68% [2]. Interestingly, after ART with cystectomy bed inclusion, pelvic failure was observed in only three out 14 patients with a positive surgical margin. Also, pattern of failure analyses

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showed that patients with a negative surgical margin remain at risk of recurrence at the cystectomy bed region [16,18]. Therefore, ART contouring guidelines were updated to recommend the inclusion of the cystectomy bed region for all patients, regardless of margin status. Recent ART trials aligned with this recommendation [10,19]. Despite a high local control rate and postoperative 18F-FDG-PET-CT screening (64% of patients) to exclude distant metastases, 43 of 72 study patients still developed distant metastases. Of these metastatic patients, 28 had postoperative PET-CT screening. In contrast, the ART trial by Zaghloul et al [10] reported a lower, but still high, incidence of 27%. This difference may be due to the higher rates of pT4 disease and pathologically involved lymph nodes in our cohort. The high rate of distant metastases highlights the need for therapies targeting systemic disease. Current guidelines recommend adjuvant chemotherapy in high-risk MIBC patients who did not receive neoadjuvant chemotherapy [20,21]. The European Association of Urology (EAU) guidelines further suggest that for patients who are candidates for ART and did not receive neoadjuvant chemotherapy, it may be reasonable to sandwich ART between cycles of adjuvant chemotherapy [21].

Adjuvant immunotherapy in high-risk MIBC patients is investigated in several phase 3 trials, with mixed results. The IMvigor010 trial found no improvement in disease-free survival (DFS) with adjuvant atezolizumab, while the CheckMate274 and AMBASSADOR trials showed improved DFS with nivolumab and pembrolizumab, respectively [5,6]. Only the AMBASSADOR trial included patients with a positive surgical margin. None of our study patients received adjuvant immunotherapy, as it was not considered standard of care at the time of the study. Recently published results of a phase 3 trial investigating neoadjuvant chemotherapy with or without perioperative durvalumab in patients with MIBC demonstrated improved event-free survival and OS with the addition of perioperative durvalumab. The specific impact on the prevention of pelvic recurrences was not reported [7]. The authors believe that in high-risk MIBC patients, ART and systemic therapies (chemo- and/or immunotherapy) can complement each other by reducing local and distant disease relapse, respectively. Further research should refine the treatment algorithm for high-risk MIBC patients, in which a combination of ART and adjuvant systemic therapies should be considered (ie, sequential or concurrent), potentially using biomarkers for guidance.

We previously reported acute and late genitourinary and gastrointestinal toxicity data, demonstrating that ART using more conformal radiotherapy techniques, such as VMAT, is safe [11]. Furthermore, recent randomized ART trials report only an increase in acute grade 2 gastrointestinal toxicity, with similar rates of late gastrointestinal and genitourinary side effects between the ART and cystectomy-only arms [10,19]. The patient-reported HRQoL results of this trial further confirm that ART is well tolerated. As expected, at the end of ART, there is temporary deterioration of several symptoms, most returning to the baseline level within the first few months and improving thereafter. It is reassuring that the expected recuperation of HRQoL is observed several months after RC despite using ART [22]. Diarrhea, the symptom showing the most pronounced deterioration at the end of ART, remains elevated during subsequent follow-ups despite initial rapid improvement, indicating that this symptom could be more persistent for some patients.

A concern with modulated radiotherapy is the increased spread out of dose to the normal tissue, such as the bone marrow, which is known to be susceptible to both acute and chronic radiation toxicity [23]. Since the pelvic region contains over half of the body's proliferating bone marrow [24], the following planning objectives were set to reduce bone marrow suppression: V18.9 Gy $\leq$50% and D90 $\leq$7.5 Gy. These bone marrow constraints were applied in daily practice for gynecological tumors at one of the participating centers (ie, Ghent University Hospital) at the time of study design and were therefore adopted in the current trial. While only a few patients experienced grade $\geq$2 leukopenia, neutropenia, thrombocytopenia, or anemia, there was a high incidence of grade 2 and 3 lymphopenia (Table 2). Lymphocyte counts showed slight recovery but did not return to baseline levels even 2 yr after radiotherapy (Supplementary Fig. 2D). The lasting impact on the lymphocyte counts has also been reported after pelvic nodal irradiation for prostate cancer [25]. While the clinical significance of reduced lymphocyte counts remains uncertain, a retrospective study identified lower lymphocyte counts as an independent prognostic factor associated with worse outcomes in metastatic urothelial cancer patients undergoing immunotherapy [26]. Given that high-risk MIBC patients often progress to metastatic disease and may require immunotherapy, this is important to consider. Our unpublished data yielded reassuring results. We identified ten patients in our study with lymphopenia (grade 1: N = 5; grade 2: N = 5) before starting subsequent immunotherapy due to disease recurrence. Six of these patients responded to immunotherapy, including four with grade 2 lymphopenia, who achieved a complete response.

There are several limitations to acknowledge. The main limitation of this study is its single-arm design. Although this is a prospective trial requesting blood sampling on fixed time points, adherence to the protocol was difficult. Frequent exclusion of blood samples due to postrelapse therapies further reduced the number of patients available for the evaluation of hematological toxicity. Additionally, only 80% of the patients completed baseline HRQoL questionnaires, and this number dropped with longer follow-up. In addition to death, possible reasons of dropout are disease relapse and clinical deterioration, leading to missing of informative data. Since these reasons of dropout are likely associated with lower HRQoL, absence of data from these patients may lead to an overestimation of HRQoL recovery following ART. However, most scales show rapid improvement within the 1st month after ART. During this phase, the survival rate remains high and the response rate decline is relatively limited.

Despite these limitations, our study further underlines the feasibility and potential of ART in reducing locoregional failures in high-risk MIBC. Currently, the role of ART is being evaluated by two randomized trials, the GETUG-AFU30

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(NCT03333356) and BART (NCT02951325) trial [27], which are expected to provide more evidence regarding the efficacy and role of ART in routine clinical practice. In the meantime, guidelines of the EAU and National Comprehensive Cancer Network state that ART can be considered in selected high-risk patients [20,21].

5. Conclusions

The mature survival data corroborate the previously reported high local control rate in this high-risk MIBC population, supporting the value of ART in preventing local relapses and endorsing current guideline recommendations to consider ART in selected MIBC patients. Patient-reported HRQoL confirms that, by using more conformal radiation techniques, ART can be used safely after RC. The observed high incidence of grade 2 and 3 lymphopenia warrants further investigation to determine its clinical significance.

***Author contributions*:** Flor Verghote 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: Verghote, Rammant, Dirix, Van Praet, Berghen, Junius, Liefhooghe, Noé, Ost, Decaestecker, Villeirs, Decruyenaere, De Man, Verbeke, De Maeseneer, Fonteyne.
Analysis and interpretation of data: Verghote, Rammant, Fonteyne.
Drafting of the manuscript: Verghote.
Critical revision of the manuscript for important intellectual content: Rammant, Dirix, Van Praet, Berghen, Junius, Liefhooghe, Noé, Ost, Decaestecker, Villeirs, Decruyenaere, De Man, Verbeke, De Maeseneer, Fonteyne.
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Appendix A. Supplementary material

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