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Brachytherapy Combined with Neoadjuvant Chemotherapy in Locally Advanced Bladder Cancer: A Single-Center Retrospective Study

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ABSTRACT

A retrospective review was undertaken to assess the feasibility, safety, and therapeutic efficacy of brachytherapy in the management of locally advanced bladder cancer. Clinical records were examined for 86 individuals diagnosed with locally advanced bladder cancer who received care in the Department of Urology Surgery at Shanxi Provincial Cancer Hospital from January 2015 through June 2019. Depending on the treatment modality administered, subjects were assigned to either a study arm (n = 45) or a control arm (n = 41). The study arm underwent brachytherapy involving intraoperative placement of radioactive particles alongside neoadjuvant chemotherapy (NAC), while the control arm was given NAC only. Radical cystectomy (RC) with pelvic lymph node dissection was performed in both arms. Subsequent postoperative pathological assessment verified that subjects across both arms bore urothelial carcinoma staged at pT3–pT4. The predefined endpoints included 3-year rates of locoregional recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), disease-free survival (DFS), overall survival (OS), and therapy-emergent adverse events. An evaluation of the safety and effectiveness of interstitial radioactive particle insertion for locally advanced bladder cancer was conducted. Follow-up ranged from 9 to 42 months. The study arm achieved a substantially higher 3-year LRFS (88.9%) relative to the control arm (60.9%) (P = .003). Three-year DMFS did not differ meaningfully between the study arm (71.1%) and the control arm (73.2%) (P = .945). No significant statistical distinction was observed for 3-year DFS or OS when comparing the two arms (DFS: study arm 64.4% versus control arm 51.2%, P = .073; OS: study arm 66.7% versus control arm 58.5%, P = .180). Within the study arm, particle displacement at the local site was observed in three subjects between the 1-week and 1-month postoperative time points, yet no consequent complications occurred. Blood-related toxicities (anemia, leukocytopenia, and thrombocytopenia), hepatic and renal impairment, vomiting, diarrhea, and generalized weakness constituted the principal adverse events, all of which subsided upon symptomatic management. The frequency of major adverse events did not differ significantly between the two arms. When measured against NAC monotherapy, the combination of brachytherapy with NAC confers a notable extension in LRFS among individuals with locally advanced urothelial bladder carcinoma who have undergone RC plus pelvic lymph node dissection. This operative strategy enhances LRFS, enables the formulation of more individualized therapeutic regimens, and improves overall treatment outcomes. Moreover, the approach is both safe and efficacious, yielding only a limited spectrum of adverse effects.

Keywords: Bladder cancer, Brachytherapy, Radiotherapy, Radioactive particles

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Introduction

Urothelial carcinoma (UC) is one of the most frequently encountered malignancies in urology, encompassing both upper tract urothelial carcinoma (UTUC) and urothelial bladder carcinoma (UBC). UC occurs at a high rate, with UBC accounting for the vast majority of diagnoses [1]. On a worldwide scale, bladder cancer sits at the 9th spot in cancer incidence among all malignancies; examining by sex places it 7th for men and below the 10th rank for

women. In terms of mortality rankings, bladder cancer occupies the 13th position among all malignant diseases [2]. Stratifying by disease progression, primary bladder cancers fall into non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer categories. For more than a decade, the established therapeutic benchmark for MIBC has been cisplatin-based neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC) and pelvic lymph node dissection, an approach that improves patient survival and reduces both local recurrence and distant spread [3-5]. Fresh investigations have brought to light evolving therapeutic patterns in muscle-invasive bladder cancer, exemplified by data from Germany spanning 2006 to 2019, which mirror advancements and shifts in real-world clinical practice [6]. That said, pelvic surgical bed recurrence emerges in roughly 30% of cases with locally advanced (T3-T4) UBC [7-11]. What is more, this form of local re-emergence correlates with diminished cancer-specific survival [3, 12], underscoring the poor outcomes associated with salvage interventions [9, 11-13], with median survival extending to only about 9 months [9, 14]. Findings from clinical trials indicate that NAC reduces the likelihood of locoregional recurrence [15], improves disease-free survival (DFS) [16, 17], and, by extension, may contribute to extended longevity.

When compared with standard radiotherapy, brachytherapy—via interstitial implantation of radioactive particles—delivers well-defined treatment effects with a contained side-effect burden in solid tumor contexts and has therefore seen broad adoption. To this point, scant published data address the use of brachytherapy specifically for UBC. Consequently, the current work conducted a retrospective review of clinical records from 86 patients with locally advanced (stage T3-T4) UBC who received either brachytherapy combined with NAC or NAC alone. An appraisal was likewise conducted into the effectiveness and safety profile of the brachytherapy plus NAC protocol. This piece of research belongs to a broader series of investigations focused on interstitial radioactive particle implantation as a treatment approach for UC [18].

Materials and Methods

Clinical data

Enrolled in this analysis were 86 patients bearing locally advanced (stage T3-T4) UBC, staged per the TNM classification criteria (8th edition) established by the Union for International Cancer Control (UICC), all of whom received management within the Department of Urology Surgery, Shanxi Provincial Cancer Hospital, across the interval from January 2015 to June 2019. Assignment to either of two arms hinged upon the therapeutic modality administered: a study arm receiving brachytherapy combined with NAC, and a control arm treated exclusively with NAC. Authorization to perform brachytherapy for solid malignancies (including UC) has been held by Shanxi Provincial Cancer Hospital since 2001. The institutional Ethics Committee sanctioned the study, which conformed to the Standards of Technical Management for Treatment by Radioactive Particle Implantation (2017 edition) (GUOWEIBANYIFA [2017]). Participants in each arm completed 4 preoperative chemotherapy cycles according to the gemcitabine plus cisplatin (GC) protocol. The final composition of the study arm included 45 participants—30 (66.7%) male and 15 (33.3%) female—with a median age of 62.7 years (range, 46–75 years), and pelvic local lymph node metastasis documented in 9 (20.0%) cases. The control arm included 41 participants, of whom 27 (65.9%) were male, and 14 (34.1%) were female, with a median age of 64.1 years (47–75 years); local pelvic lymph node metastases were present in 8 (19.5%) of these individuals. Baseline clinical parameters proved statistically comparable between the two arms (all $P > .05$) **(Table 1).**

Table 1. Comparison of clinical data between the two groups.

Clinical characteristics	P	χ^2	Study group (n = 45)	Control group (n = 41)
Age (years)	0.992	0		
≤ 60			23 (51.11)	21 (51.22)
> 60			22 (48.89)	20 (48.78)
Tumor diameter (cm)	0.321	0.985		
< 4			10 (22.22)	13 (31.71)
≥ 4			35 (77.78)	28 (68.29)
Pathology	0.758	0.095		
High-grade			35 (77.78)	33 (80.49)
Low-grade			10 (22.22)	8 (19.51)

TNM	0.454	0.561		
T3			36 (80)	30 (73.17)
T4			9 (20)	11 (26.83)
Lymph node metastasis	0.955	0.003		
N0			36 (80)	33 (80.49)
N1-N2			9 (20)	8 (19.51)

Entry into the study required: (1) clinical staging designated as ≥ cT3 or N1-N2; (2) an ECOG performance status score within the 0–1 range; (3) confirmation of no distant metastatic spread before NAC initiation; (4) completion of RC coupled with pelvic lymph node dissection; (5) written informed consent duly provided. Grounds for exclusion comprised: (1) surgical pathology findings indicating a stage below pT3; (2) non-completion of the prescribed preoperative NAC regimen.

Radical cystectomy (RC) plus pelvic lymph node dissection was carried out on participants from both arms. The surgical objective was the excision of no fewer than 10–12 lymph nodes to permit precise pathological staging. Nonetheless, the substantial share of advanced-stage presentations, the technical challenges posed by the surgery, and the prioritization of patient well-being and postoperative quality of life meant that, on average, only 4 lymph nodes were specifically targeted, the largest measuring up to 12 cm.

Preoperative preparations

The sealed radioactive iodine [125I] source (designated herein as particles) comprised a silver bar core enclosed within imported, high-purity titanium capsules. Dimensions of the silver core were: diameter 0.5 mm, length 4.5 mm, and thickness 0.55 mm. The nuclide iodine [125I] decays with a half-life of 59.43 days, has a half-value layer thickness of 0.025 mmPb, and gives off γ-rays at a starting dose rate of 7 cGy/h, sufficient for penetration across tissue depths of 1.7 cm. Radioactive activity per single particle fell between 0.1 and 6.0 mCi. Manufacture of the particles employed in the present work was undertaken by Seeds Biological Pharmacy (Tianjin) Ltd.

CT imaging of the head, chest, and abdomen was utilized to rule out distant metastatic deposits. Pelvic magnetic resonance imaging (MRI), along with other imaging evaluations, was used to assess invasion of the perivesical adipose tissue, enlargement of pelvic lymph nodes, and clinical stage assignment. Individuals with T3-T4 clinical stage received 3 NAC cycles before the brachytherapy preparation phase. Three-dimensional (3D) stereoscopic imaging techniques enabled reconstruction of the bladder neoplasm and any suspected metastatic pelvic lymph node deposits, thereby capturing pertinent tumor characteristics, including anatomic location, size, configuration, and spatial relationships with adjacent visceral structures. During the surgical procedure, RC with pelvic lymph node dissection was executed, after which the zone immediately surrounding the bladder tumor and pelvic lymph nodes was demarcated as the tumor bed—conceptualized as the region of possible residual disease, or a sub-volume of the original tumor—and designated as the radiotherapy target. The matched peripheral dose, corresponding to the tumor's peripheral dose, was adopted as the prescribed target dose. The radiation dose was 70–75 Gy for UC and 50–60 Gy for lymph node metastases; the targeting dose was approximately one-fifth to one-quarter of the standard tumor radiotherapy dose. Consequently, the prescribed radiation dose for the bladder tumor bed equaled 14–18 Gy, and for the lymph node metastasis bed, 10–15 Gy. Particles with a radioactive activity of 0.5 mCi were selected for therapeutic deployment. An inter-particle spacing of 1 cm was maintained in the layout, yielding an equivalent radioactivity of 4285 cGy midway between two particles at 0.5 cm; the target volume received a minimum of four to six implanted particles. Radiation doses tolerated by normal tissues far exceed those used in tumor radiotherapy.

Surgical methods

RC in combination with pelvic lymph node dissection was performed on both arms. Readiness measures for both groups covered standard preoperative protocols alongside particle implantation planning. Intraoperatively, particle implantation needles were guided into the tumor bed using ultrasonographic visualization or direct visualization, maintaining a spacing of 0.5–1.0 cm between neighboring needles and restricting the vertical puncture depth to < 1.0 cm; a single particle was then deployed at each puncture locus. When the implant gun exceeded 2.0 cm in dimension, two particles were sequentially placed in a backward-loading configuration with a 1 cm vertical gap. Utmost caution was exercised throughout particle insertion to steer clear of great vessels.

Hemostasis was secured, and particles were affixed using localized compression applied immediately after implantation. A proprietary biogel (biological glue) particle-chain suturing approach, conceived in-house, was applied to the tumor bed overlying tissues adjacent to vasculature, neural structures, and the local pelvic sidewall; this construct was subsequently covered by nearby adipose and connective tissues and sutured firmly to immobilize the particles. Fabrication of the in-house biogel particle chain proceeded as follows: upon institution of intraoperative radiation safeguards, a single particle was inserted perpendicularly through the implant gun, after which four to six additional particles were deposited in sequence at 1 cm intervals onto a gelatin sponge carrier. Biogel was coated across the sponge's outer aspect, which was thereafter enveloped in a hemostatic gauze wrap and secured with sutures for fixation.

Preoperative NAC

A cystoscopic examination was performed before NAC commencement, and tissue sampling with histopathological confirmation established the diagnosis of UC. The neoadjuvant protocol employing GC was then rolled out as outlined here: gemcitabine, infused intravenously at 100 mg/m² on days 1 and 8, in combination with cisplatin, delivered intravenously at 70 mg/m² on day 2. Each cycle corresponded to a 3-week block, and each participant underwent 4 complete cycles. Operative scheduling occurred within a 3–4-week window post-NAC wrap-up. Investigations comprising blood routine, urine routine, hepatic parameters, renal parameters, and electrocardiography (ECG) were arranged on the day before chemotherapy dosing and on days 1, 8, and 14 after administration. Any arising complications or detrimental effects were identified and addressed promptly.

Follow-up

For individuals in the study arm, plain computed tomography (CT) of the regions targeted by particle placement was performed between days 3 and 5 after surgery to confirm particle counts and screen for migration. Toxicity surveillance extended throughout chemotherapy delivery and persisted for a fortnight beyond its conclusion. Issues related to the implantation procedure were assessed at 1 week to 1 month and again 3 months after the operation. Both arms were subject to repeat testing—covering blood and urine routines, blood biochemistry, ECG, chest radiography, and abdominal color ultrasound—while thoracic plus abdominal CT was obtained on an as-needed clinical basis.

Efficacy and adverse event assessment

The primary outcome measure selected for this investigation was 3-year locoregional recurrence-free survival (LRFS). Fallback endpoints comprised 3-year distant metastasis-free survival (DMFS), disease-free survival (DFS), and overall survival (OS). The safety metric was represented by the incidence of adverse events observed in the short- and long-term.

LRFS captured the time elapsed between treatment finalization and the reappearance of disease within the pelvic cavity (encompassing internal/external iliac nodal stations, obturator nodes, anterior sacral nodes, the cystectomy bed, and the lateral pelvic sidewall) occurring within 30 days from the very first documentation of distant spread. DMFS was taken to signify the stretch from therapy completion until the emergence of metastatic deposits outside the pelvic confines (including lymphatic stations beyond the true pelvis and visceral sites). DFS corresponded to the duration from the end of therapy until documentation of pelvic tumor relapse, distant metastatic involvement, or fatality driven by tumor advancement. OS captured the time to treatment completion and patient death. Grading of untoward events followed the World Health Organization (WHO) classification framework. Adverse events post-therapy encompassed those arising from the onset of chemotherapy through 2 weeks post-cycle conclusion, from the first week after surgery through 1 month post-implantation, and across the 3 months after treatment. Comparative analyses were conducted between the two arms for LRFS, DMFS, DFS, OS, and the frequencies of both short- and long-duration toxicities. Chemotherapy-emergent toxicities were assessed according to the WHO criteria for chemotherapy adverse events (1997 edition).

Statistical analysis

Statistical computations were performed in SPSS 26.0. Quantitative descriptors relied on median (range), with qualitative descriptors using frequency (%). Continuous variables, depicted as median (range), were contrasted by means of the Mann–Whitney U test. Categorical variables, shown as frequency (%), were evaluated through the chi-square test. The Kaplan–Meier technique generated estimates of LRFS, DMFS, DFS, and OS, and

between-group differences were assessed using the log-rank test. Multivariate Cox regression was used to identify independent predictors of LRFS, DFS, DMFS, and OS. Results achieving P-values below .05 were deemed statistically significant.

Results and Discussion

In the study arm, the number of particles inserted ranged from roughly 30 to 48, with a mean of 36. T3-stage disease affected 36 individuals within the study arm and 30 within the control arm, whereas T4-stage disease was present in 9 and 11 individuals, respectively. Moreover, pelvic nodal metastatic involvement was documented in 9 study-arm patients and 8 control-arm patients. The pooled median follow-up interval across both arms was 32.5 months (range: 9 to 42 months). Evaluations for 3-year LRFS, DMFS, DFS, and OS following surgery were performed in each cohort. A figure of 88.9% (40/45) for 3-year LRFS was attained in the study arm versus 60.9% (25/41) in the control arm; this between-group divergence reached the threshold for statistical significance (hazard ratio (HR) 0.210, 95% confidence interval (CI): 0.08–0.58, P = .003). The 3-year DMFS rates were 71.1% (32/45) in the study arm and 73.2% (30/41) in the control arm, with no significant difference (HR 0.97, 95% CI: 0.43–2.20, P = .945). Three-year DFS was recorded at 64.4% (29/45) among study-arm subjects and 51.2% (21/41) among controls, again without reaching statistical separation (HR 0.54, 95% CI: 0.27–1.06, P = .073). For 3-year OS, the study arm registered 66.7% (30/45) while the control arm registered 58.5% (24/41), a discrepancy that likewise fell short of significance (HR 0.61, 95% CI: 0.30–1.25, P = .180). The Kaplan–Meier survival trajectories for each arm are illustrated in **Figure 1.**

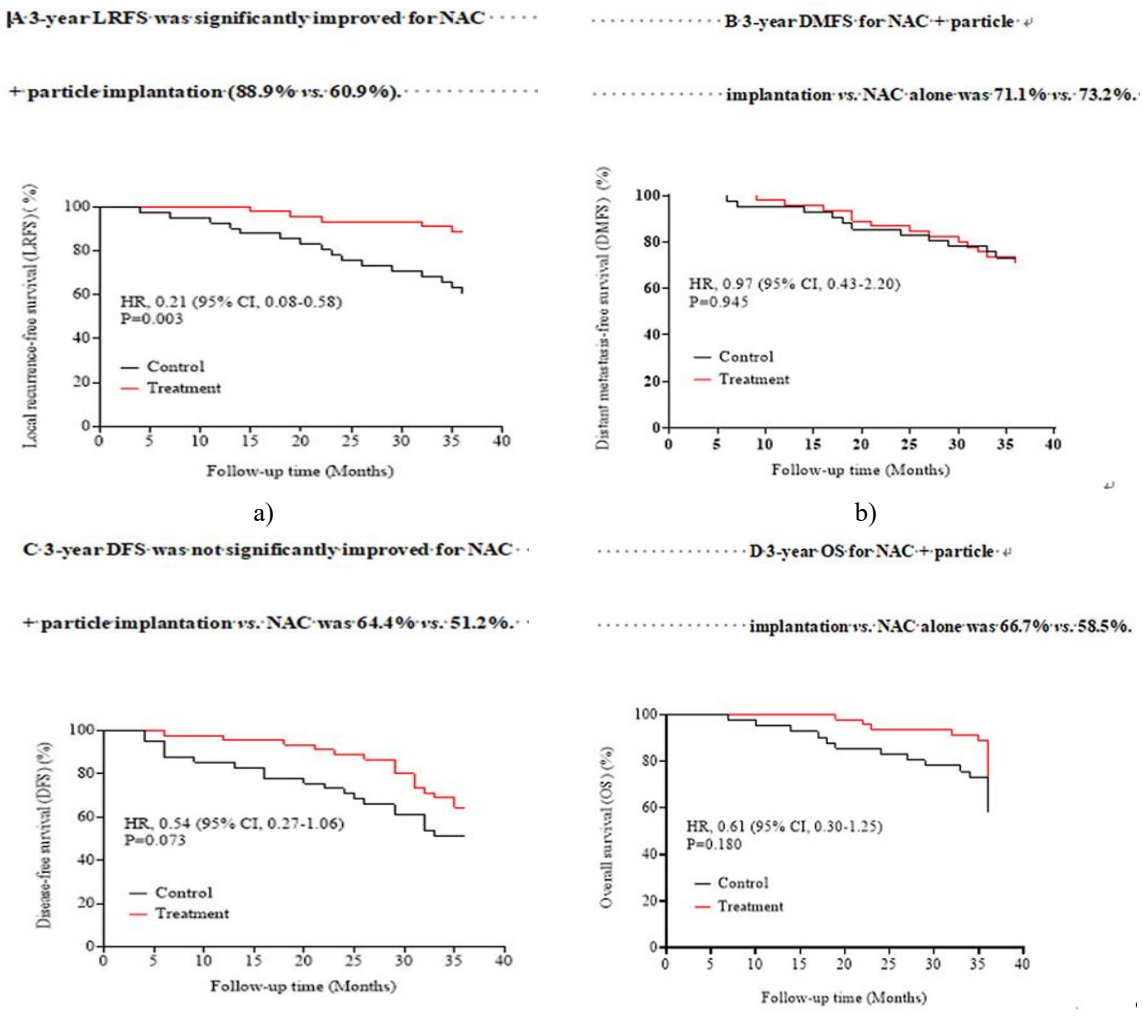

Figure 1. Comparison of Kaplan–Meier survival curves of patients with locally advanced UC in the study group (particle implantation + NAC) vs. the control group (NAC).

Assessment via multivariate regression confirmed that the paired strategy of brachytherapy plus NAC acted as a significant predictor of LRFS (HR: 0.210, 95% CI: 0.08–0.58, P = .003). None of the additional examined factors—age, tumor dimensions, histological classification, pathological staging, or nodal metastatic status—showed predictive capacity for LRFS. Because lymph node metastases are associated with local recurrence, and despite its failure to qualify as a statistically significant covariate, nodal status was retained in the model as a confounder. It could be interpreted as a marginal predictor of LRFS (HR: 2.54, 95% CI: 0.92–7.00, P = .073) **(Table 2).** No variable with meaningful predictive power for DMFS was identified in this cohort through multivariate regression. Three-year DMFS showed no statistically meaningful divergence when the brachytherapy-plus-NAC arm (71.1%; 32/45) was placed alongside the NAC-only arm (73.2%; 30/41) (HR: 0.97, 95% CI: 0.43–2.20, P = .945). The presence of lymph node metastases, however, was a significant independent predictor of DMFS (HR: 2.48, 95% CI: 1.01–6.13, P = .048) **(Table 2).** Multivariate regression did not identify any significant predictors of DFS in these data. Furthermore, the 3-year DFS rates for the brachytherapy-plus-NAC arm (64.4%; 29/45) and the NAC arm (51.2%; 21/41) did not separate in a significant manner (HR: 0.54, 95% CI: 0.27–1.06, P = .073). That said, the dual approach of particle implantation plus NAC, together with lymph node metastases, might be considered marginal predictors of DFS (HR: 2.17, 95% CI: 0.97–4.89, P = .061) **(Table 2).** Multivariate regression revealed no significant predictor of OS. Three-year OS showed no significant divergence between those receiving brachytherapy plus NAC (66.7%; 30/45) and those administered neoadjuvant chemotherapy exclusively (58.5%; 24/41) (HR: 0.61, 95% CI: 0.30–1.25, P = .180); even so, the combination of particle implantation with NAC and the status of lymph node involvement emerged as marginal predictors (HR: 2.25, 95% CI: 0.99–5.1, P = .052) **(Table 2).**

Table 2. Multivariate Cox regression analysis: LRFS, DFS, DMFS, and OS.

Variable	HR	P
LRFS		
Operation	0.210 (0.08–0.58)	0.003
Age	0.49 (0.19–1.23)	0.127
Tumor diameter	0.61 (0.25–1.49)	0.282
Pathology	1.39 (0.5–3.83)	0.527
TNM	1.09 (0.38–3.12)	0.867
Lymph node metastases	2.54 (0.92–7.00)	0.073
DFS		
Operation	0.54 (0.27–1.06)	0.073
Age	0.67 (0.34–1.31)	0.239
Tumor diameter	0.74 (0.36–1.5)	0.402
Pathology	0.99 (0.43–2.26)	0.972
TNM	1.15 (0.53–2.47)	0.730
Lymph node metastases	2.17 (0.97–4.89)	0.061
DMFS		
Operation	0.97 (0.43–2.20)	0.945
Age	0.73 (0.32–1.65)	0.442
Tumor diameter	0.56 (0.24–1.3)	0.176
Pathology	1.53 (0.61–3.81)	0.363
TNM	1.32 (0.52–3.4)	0.56
Lymph node metastases	2.48 (1.01–6.13)	0.048
OS		
Operation	0.61 (0.30–1.25)	0.180
Age	0.69 (0.34–1.41)	0.309
Tumor diameter	0.63 (0.3–1.32)	0.220
Pathology	1.08 (0.45–2.59)	0.856

TNM	1.28 (0.59–2.81)	0.532
Lymph node metastases	2.25 (0.99–5.1)	0.052

Assessment of adverse events: Within the study arm, migration of particles from their original sites was observed in three cases on imaging studies performed in the window from 1 week to 1 month post-surgery (with local particle shifting defined as discordance between abdominal and pelvic plain CT images captured at 1 day postoperatively versus those taken at 1 week to 1 month following the procedure); notably, no clinical sequelae stemmed from this displacement. There was no evidence of injury to the intestinal tract or vascular structures, and no other implantation-related issues, such as compromised wound closure, were encountered. The rate of adverse events tied specifically to particle placement—especially complaints of a bearing-down sensation—was markedly elevated in the study arm relative to the control arm ($p < .01$), though most such events were mild, falling into the grade 1–2 bracket. Participants in both arms completed the full GC chemotherapy regimen, and toxicities were systematically cataloged. Hematologic derangements (anemia, leukocytopenia, and thrombocytopenia), disturbances in hepatic and renal function, vomiting, diarrhea, and asthenia constituted the chief adverse effects, each of which responded to supportive care measures. A consolidated view of adverse event occurrence in the two arms is offered in **Table 3.**

Table 3. Comparison of adverse events in UC patients between the study and control groups [n (%)].

Adverse event	***P* value**	**Control group (n = 41)**		**Study group (n = 45)**	
		Grade 3-4	**Grade 1-2**	**Grade 3-4**	**Grade 1-2**
Anemia	0.532	5 (12.2)	20 (48.8)	13 (28.9)	24 (53.3)
Leukocytopenia	0.132	3 (7.3)	30 (73.1)	4 (8.8)	35 (77.8)
Thrombocytopenia	0.346	5 (12.2)	30 (73.3)	6 (13.3)	36 (80.0)
Liver dysfunction	0.165	0 (0)	14 (29.3)	0 (0)	11 (24.4)
Renal dysfunction	0.361	0 (0)	12 (29.2)	2 (4.4)	16 (35.5)
Malignant vomit	0.532	14 (34.1)	22 (53.7)	17 (37.8)	28 (62.2)
Diarrhea	0.062	3 (7.3)	8 (19.5)	7 (15.6)	21 (46.7)
Weakness	0.072	1 (2.4)	20 (48.8)	5 (11.1)	31 (68.9)
Bearing down sensation	15 (33.3)	0.002	0 (0)	0 (0)	2 (4.4)

Among UBC patients undergoing RC, the pathological stage exerts the dominant influence on long-term outcomes; individuals presenting with locally advanced disease (T3-T4) face a 5-year OS below 40% [8], and those with lymph node positivity, this figure drops to roughly 30% [4]. The challenge of improving postoperative survival for patients burdened with locally advanced (T3-T4) UBC remains a central theme in clinical inquiry. An established body of evidence confirms that platinum-based multi-agent NAC achieves a high response rate in bladder cancer. The benchmark therapeutic protocol for MIBC in everyday practice marries platinum-based NAC with RC and pelvic lymph node dissection [19-22]. When NAC is added, a survival increment of 5–10% is observed, and the relative risk of mortality decreases by 16%-33% compared with individuals who proceed straight to RC [22-26]. The present series included 86 cases of T3-T4 UBC, all of whom were treated with NAC in conjunction with RC plus pelvic lymph node dissection.

For those confronting pT3-T4 UBC, the reappearance of disease at the operative site stands as a critical factor eroding treatment success, tightly interwoven with dismal cancer-specific survival [3, 12]. The armamentarium of salvage therapies for this subgroup yields meager results [9, 11-13], with median survival hovering around 9 months [9, 14]. Multiple retrospective surgical analyses have shown [27] that even when postoperative pathological assessment reveals no lymphatic involvement, more extensive lymph node clearance can confer survival benefits. These patterns suggest that pairing preoperative NAC with intraoperative deposition of radioactive sources may sterilize clinically occult micrometastatic disease within lymph nodes, reducing the frequency of both pelvic relapses and distant dissemination, with downstream gains in patient survival. Evidence from ongoing trials indicates that NAC reduces the risk of locoregional failure. Stacked against adjuvant chemotherapy alone, the triple-modality regimen of radical cystectomy and chemoradiotherapy yields a

meaningful improvement in DFS and may extend OS [15-17, 28]. In a contribution by Zaghloul *et al*. [29], adjuvant chemoradiotherapy was dispensed to patients with locally advanced bladder cancer post-RC, and the outcomes juxtaposed with those from a cohort receiving adjuvant chemotherapy exclusively. Their data demonstrated that subjects tolerated the supplementary radiotherapy well and achieved substantial gains in LRFS and prolonged DFS compared with counterparts who received chemotherapy as the sole adjuvant treatment.

The presence of radiosensitive vital structures—the small bowel within the abdominopelvic cavity, representing a prime example—places firm constraints on what can be achieved with routine external beam radiotherapy; deploying high-dose external radiation to bring aggressive recurrent bladder cancer under control is thus generally inadvisable, given the immediacy of such organs to the treatment field [30]. Even where adjuvant local modalities do not move the needle on overall survival, they succeed in averting pelvic locoregional relapse—a morbid scenario that precipitates intractable local pain, swelling of the lower extremities through venous and lymphatic compression, and hydronephrosis owing to ureteric obstruction [14, 31, 32].

Set against standard external beam techniques, brachytherapy through the interstitial placement of radioactive seeds carries distinct strengths: (1) a wider band of eligibility criteria and a more compressed hospital admission span; (2) neoplastic cell populations are bathed in continuous low-dose-rate irradiation over an extended timeframe, a condition that preferentially triggers programmed cell death within tumor elements while largely safeguarding the surrounding normal cellular milieu. These properties endow interstitial seed brachytherapy with well-substantiated therapeutic punch and a tempered side-effect profile in the management of solid-organ malignancies. This combination has propelled its widespread integration into clinical workflows [33, 34]. A breadth of published work has validated the place of brachytherapy within the urothelial carcinoma treatment landscape. To illustrate, research spearheaded by Zaghloul *et al*. [29] highlighted the improved locoregional disease control achieved with brachytherapy in muscle-invasive bladder cancer. In parallel, Cozzarini *et al*. [17] reported improvements in disease-free survival (DFS) when brachytherapy was combined with radical cystectomy (RC) and neoadjuvant chemotherapy (NAC). What these studies collectively underscore is brachytherapy's promise in paring down local recurrence rates and lifting overall survival among people with bladder cancer.

Moving past its deployment in bladder cancer, enthusiasm has been building around the extension of brachytherapy to the arena of upper tract urothelial cancers (UTUC). A sustained program of investigations into interstitial radioactive seed implantation as a treatment avenue for UTUC was carried forward by Xuebing *et al*. [18]. The signals emerging from their work pointed toward a combination of brachytherapy with surgical extirpation and systemic chemotherapy being both well-tolerated and therapeutically active, manifesting as a reduced tally of adverse events and possible dividends in overall survival. Such findings imply that the foundational rationale and tangible benefits of brachytherapy in the bladder cancer context could be applied to the UTUC setting. We accord considerable weight to the call for expanded investigative effort and rigorous clinical trial activity to define the precise efficacy and safety contours of brachytherapy for cancers arising in the upper urinary tract. As discovery within this niche advances, it may furnish a broader repertoire of treatment modalities for the UTUC population, with the attendant prospect of sharpening prognostic outlooks and raising quality-of-life benchmarks.

An additional consideration is that brachytherapy for UTUC offers several advantages over conventional external irradiation. The ability to deliver radiation with anatomical precision directly to the tumor volume keeps collateral injury to neighboring uninvolved tissues to a minimum—an imperative in the spatially confined, structurally intricate corridors of the upper urinary tract. The hallmark of brachytherapy, namely protracted low-dose exposure, efficiently ushers tumor cells into apoptotic pathways while generating a substantially lighter adverse-effect footprint.

Building on the track record of accomplishment in bladder cancer and the preliminary glimmers of benefit observed in UTUC, a pressing need exists for further investigation and prospective clinical trials to robustly define the efficacy and safety parameters of brachytherapy in upper tract urothelial malignancies. Persistent lines of inquiry along this front could open up supplementary management pathways for individuals confronting UTUC, carrying the potential to better both their long-term disease trajectory and the fabric of their daily lives.

The existing literature on the radiotherapeutic management of locally advanced UC remains limited in scope, and the attendant treatment benefit has yet to be clearly characterized. An earlier publication described the clinical trajectory of 22 patients with locally advanced UC who received seed placement, documenting encouraging therapeutic responses [35]. The cumulative evidence emerging from this line of investigation [18] indicates that supplementing surgery plus chemotherapy with implanted radioactive 125I seeds in the context of locally

advanced (stage T3-T4) UTUC is associated with a comparatively milder toxicity profile than the surgery-plus-chemotherapy pairing on its own; additionally, the modality was judged to be both tolerable and therapeutically impactful, conferring possible advantages in OS.

Given that subclinical locoregional tumor deposits occur more frequently in individuals with locally advanced (T3-T4) UBC [36], LRFS was adopted as the primary outcome measure in the present investigation. The data generated here demonstrate that the incorporation of an intraoperative brachytherapy step—via seed placement—materially bolsters LRFS; the absolute gain in 3-year LRFS amounted to approximately 28 percentage points (88.9% against 60.9%), a differential that proved statistically robust upon comparison of the experimental and control cohorts (HR 0.210, 95% CI: 0.08–0.58, P = .003).

Turning to 3-year DFS, the figures were 64.4% (29/45) in the investigational arm and 51.2% (21/41) in the comparator arm, falling just shy of the conventional boundary for statistical significance. Even so, the addition of intraoperative radioactive seed brachytherapy yielded a situation in which the pronounced benefits documented for 3-year LRFS cascaded into what may be interpreted as a borderline improvement in 3-year DFS (64.4% against 51.2%, P = .073). Regarding 3-year OS, the rates observed were 66.7% (30/45) and 58.5% (24/41) in the study and control arms, respectively; the inter-arm difference similarly did not reach formal significance.

In the present series, surveillance imaging performed within the 1-week to 1-month postoperative window among study-arm participants revealed localized seed drift in 3 cases; notably, no untoward clinical consequences were observed. Equally, there was no evidence of bowel perforation, great vessel injury, defective wound apposition, or any other complication specifically ascribed to the implantation process. Adverse phenomena attributable to the seed placement procedure—among which a sensation of pelvic pressure featured prominently—were encountered at a markedly higher rate in the study arm compared with controls when assessed 3 months following surgery (P < .01); the vast preponderance of these occurrences were mild in nature, classified as grade 1 or 2. The pattern of implantation-related morbidity thus paralleled that already described in prior reports and remained substantially below the toxicity burden customarily linked with conventional external beam radiotherapy [29, 30].

Several caveats bearing on the interpretation of this work must be underscored. The modest enrollment figure and the relatively brief follow-up period constitute the principal shortcomings. It follows that subsequent investigations drawing on larger patient samples and featuring longer surveillance intervals will be indispensable to strengthen the inferential power of this ongoing program of research focused on interstitial radioactive seed therapy. A further consideration arises from the study's retrospective design, which inherently introduces susceptibility to various forms of bias—selection bias and information bias are prominent among them. Studies anchored in retrospective record review depend on documentation amassed for clinical rather than investigational purposes and, as such, may not consistently or completely capture all variables of interest. An additional constraint is the single-institution nature of the dataset, which may limit the extent to which the conclusions can be generalized. Treatment paradigms and the composition of the patient base at our facility may depart from those characterizing other centers, thereby clouding the external validity of the results presented here.

Conclusion

To distill the foregoing, when set against neoadjuvant chemotherapy delivered as the sole modality, the intraoperative embedding of radioactive seeds in conjunction with neoadjuvant chemotherapy for patients diagnosed with locally advanced urothelial bladder carcinoma who proceed to radical cystectomy plus pelvic lymph node dissection yields a notable amplification of locoregional recurrence-free survival and an extension of disease-free survival, translating into tangible survival dividends. Over and above this, the approach can be characterized as both safe and efficacious, its deployment accompanied only by a narrow band of adverse consequences.

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Conflict of Interest: None

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Ethics Statement: The study met the requirements of the Standards of Technical Management for Treatment by Radioactive Particle Implantation (2017 edition) (GUOWEIBANYIFA [2017]). The study was approved by the ethics committee/Institutional Review Board of Shanxi Province Cancer Hospital. All methods were carried out in accordance with relevant guidelines and regulations or the Declaration of Helsinki. Informed consent was obtained from all subjects and their legal guardian(s).

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