

Place and Complications of Concomitant Chemotherapy for Invasive Bladder Cancer

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Abstract

Original Research Article

Although radical cystectomy remains the standard treatment for muscle-invasive bladder cancer, concurrent chemoradiotherapy offers a curative option to patients medically unfit for radical surgery and an alternative conservative treatment for selected patients who are potential candidates for cystectomy. Pelvic irradiation techniques in the various pelvic cancers such as bladder cancer are most often accompanied by toxicity over the course and the long term, despite new advances in radiotherapy such as IMRT and VMAT. Which were still able to reduce the rate of acute and late toxicities after treatment? A good knowledge of these complications makes it possible to: detect them, treat them or better, prevent them for a better quality of life. Survival rates are poor for muscle-invasive bladder cancer, with around 45% of patients surviving for 5 years regardless of the type of treatment.

Keywords: bladder cancer, chemoradiotherapy, cystectomy, brachytherapy.

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INTRODUCTION

Radiation treatment techniques for pelvic malignancy vary including whole pelvis, low pelvis, organ-only, 3D conformal radiation therapy (3D-CRT), intensity-modulated RT (IMRT), or brachytherapy. Selection of these specific techniques may be based on disease factors, the choice to use concurrent systemic therapy, and a variety of patient factors including comorbidities and performance status. Several grading schemes exist for RT toxicity, including the toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer Cox JD [1] and the Common Terminology Criteria for Adverse Events [2]. US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. 2010. USA: National Institutes of Health, National Cancer Institute, which are useful when following patients in clinic and comparing outcomes [3].

There is, however, a need to assess the quality of bladder conservation and other late effects of concurrent chemoradiotherapy. Retrospective studies have reported excellent functional results [3], but the quality of life (QoL) after concurrent radiotherapy and chemotherapy has only been assessed prospectively in

one Phase I trial of concurrent gemcitabine and total bladder irradiation [4].

PATIENTS AND METHODS

The retrospective analysis focused on 45 patients - Hematology and Oncology Center, University Teaching Hospital, Marrakesh, Morocco - with stage II and III bladder tumors treated with concurrent radiotherapy, cisplatin, and 5-fluorouracil between 2013 and 2020. The preferred technique was three-dimensional conformal radiotherapy at an average dose of 65.5 Gy. Acute and late toxicity factors were assessed with a median follow-up of 40 months. Eligibility criteria were as follows: nonmetastatic, biopsy-proven, normal serum creatinine level, age >18 years, World Health Organization performance status score 0–2, and Normal heart function on transthoracic ultrasound.

Before treatment, referring urologists had to specify whether patients were eligible for radical cystectomy. Staging procedures included cystoscopy with TUR as complete as possible, chest radiography, radionuclide bone scan, and computed tomographic scan or magnetic resonance imaging of the abdomen and pelvis. Two patients did not receive treatment after

TUR and were excluded. Forty three patients were evaluated.

Treatment

Pelvic irradiation using a four-field box technique was given to a dose of 45 Gy in 25 fractions over 5 weeks. For patients who were potentially candidates for radical cystectomy, a cystoscopy with TUR of the initial tumor site was performed 15 days after the end of radiation. In cases of persistent tumor, radical surgery was recommended. In the absence of residual tumor, as for patients not suitable for surgery, a radiation boost to the bladder volume followed, using a four-field technique for 18 Gy in 10 fractions. Concomitant 4-day continuous infusion of cisplatin at a dose of 20 mg/ m²/day and 5-fluorouracil 600 mg/m²/day was administered on Weeks 1, 4, and 7 of radiotherapy.

QoL assessment and follow-up:

Quality of life was assessed in two ways. A self-assessment questionnaire using the European Organization for Research and Treatment of Cancer (EORTC) [6] QLQ-C30 questionnaire [7] was administered, which incorporates eight specific questions on urinary function and other symptoms. Bladder function was evaluated by five complementary questions to the QLQ-C30. Quality of life evaluations were performed before the beginning of treatment, 6 and 12 months later, and then once per year.

Local control was evaluated by cystoscopy and TUR 6–8 weeks after completion of therapy. Follow-up cystoscopy and thoracic and abdominal computed tomography were carried out every 6 months during the first 2 years and annually thereafter.

RESULTS

Patient and Tumor Characteristics

Median age was 66 years (range, 43–78 years). Thirty seven patients were male, 8 female. Tumor stage, according to the 1992 International Union against Cancer classification, was based on TUR findings. 22% presented with extravesical invasion (T3 or T4a). Most tumors were high grade (94%). Surgical lymphadenectomy was performed for 1 patient, and had iliac node involvement. Among the 48 remaining

patients, 2 had suspicious pelvic lymph nodes on computed tomography or magnetic resonance imaging. Ureteral dilatation was present before TUR for 3 patients (6.7%). A maximal TUR was systematically attempted but was macroscopically complete for only 21 patients (46, 7%).

Toxicity and Therapy

Two severe adverse events were reported during treatment: one iliac artery thrombosis, one transient ischemic attack. Radiotherapy was carried out as planned for 40 patients (90%), at decreased doses or increased duration for 2 patients. Concurrent chemotherapy was performed as planned for 33 patients (73.3%), at decreased doses for 3 patients.

QoL Assessment by Patients

39 patients returned 120 QoL questionnaires, among the 193 expected, leading to a 58% response rate. Evaluation of QoL was limited to patients alive without disease. Mean scores for global QoL as well as for physical, emotional, personal, cognitive, and social functions were slightly improved 6 months after treatment and were maintained over 70% for all patients alive without relapse. Bladder function was evaluated with five specific questions for patients alive without disease at each time interval (Table 1).

Each question was scored from 1 (best score) to 4 (worse). The sum of the scores for these five questions led to a global bladder function score that varied from 5 (best) to 20 (worse).

Questionnaires were not available for 11 patients. The overall bladder function score was below 8 for 35% of patients before treatment (range, 5–16), 43% (range, 5–12), 70% (range, 5–13), 57% (range, 5–15), 67% (range, 5–10), and 29% (range, 6–10), at 6, 12, 18, 24, and 36 months, respectively.

The improvement of bladder function was maintained until 24 months, but 1 patient had presented symptoms of Grade 3 daily frequency of urination. After this date, few patients presented with new Grade 3 symptoms. One (of 7 patients) had frequent pain and 2 (of 8 patients) had urge incontinence.

Table 1: Complementary questions to the EORTC QLQC-30 questionnaire for bladder function and symptoms assessment

Five specific questions for bladder function assessment				
Daytime interval between urination	1: >3 h	2: 2 to 3 h	3: 1 to <2 h	4: <1 h
Night frequency of urination	1: Once or never	2: 2 to 3 times	3: 4 to 5 times	4: >5 times
Pain at urination	1: Never	2: Occasionally	3: Frequently	4: Systematically
Urine leakage	1: Never	2: Occasionally	3: Under circumstances*	4: Daily
Do you wear pads?	1: Never	2: Under circumstances*	3: Every night	4: Night and day
Three specific questions for other symptoms assessment				
Stool frequency	1: 1 or 2 per day	2: 3 or 4 per day	3: >4 per day	
Blood in stool	1: Never	2: Occasionally	3: Frequently	4: Systematically
Sexual life	1: Unchanged	2: Decreased but satisfying	3: Decreased and difficult	4: No more activity
Abbreviation: EORTC = European Organization for Research and Treatment of Cancer.				
* Effort and long expectancy.				

Table 2: Evaluation of bladder function for patients alive without disease with specific items of quality-of-life questionnaire, at different intervals after the beginning of treatment

Parameter	Score			
	1	2	3	4
Daily frequency of urination				
Before treatment	14 (30.4)	21 (45.7)	6 (13)	5 (10.9)
6 mo	6 (42.9)	5 (35.7)	2 (14.3)	1 (7.1)
12 mo	8 (80)	2 (20)	0	0
24 mo	3 (50)	2 (33.3)	1 (16.7)	0
36 mo	2 (28.6)	5 (71.4)	0	0
Nightly frequency of urination				
Before treatment	13 (28.3)	20 (43.5)	10 (21.7)	3 (6.5)
6 mo	7 (50)	4 (28.6)	1 (7.1)	2 (14.3)
12 mo	6 (60)	3 (30)	1 (10)	0
24 mo	5 (83.3)	1 (16.7)	0	0
36 mo	2 (28.6)	4 (57.1)	1 (14.3)	0
Pain at urination				
Before treatment	21 (45.7)	14 (30.4)	3 (6.5)	8 (17.4)
6 mo	5 (35.7)	4 (28.6)	5 (35.7)	0
12 mo	5 (50)	4 (40)	1 (10)	0
24 mo	5 (83.3)	1 (16.7)	0	0
36 mo	3 (42.9)	3 (42.9)	1 (14.2)	0
Urine leakage				
Before treatment	32 (69.6)	6 (13)	7 (15.2)	1 (2.2)
6 mo	11 (78.6)	1 (7.1)	2 (14.3)	0
12 mo	9 (90)	0	1 (10)	0
24 mo	4 (66.7)	0	2 (33.3)	0
36 mo	3 (42.9)	2 (28.6)	2 (28.6)	0
Do you wear pads?				
Before treatment	39 (88.6)	4 (9.1)	0	1 (2.7)
6 mo	14 (100)	0	0	0
12 mo	8 (80)	1 (10)	0	1 (10)
24 mo	5 (83.3)	1 (16.7)	0	0
36 mo	6 (100)	0	0	0

No Grade 4 toxicity was reported. For dysuria, hematuria, and incontinence, approximately 88% of patients had no or Grade 1 side effect beyond 6 months. For urination frequency, 7% of patients had Grade 2 (i.e., interval between urination from 2 to 3 h), and 10% of patients had Grade 3 sequelae at 24 months.

Other treatment sequelae were evaluated: 1 patient reported late proctitis with minimal bleeding at each stool and 1 patient reported chronic diarrhea with more than four stools per day.

Sexual function was evaluated through only one question. Sexual activity was present in 56% of 43 evaluated patients before treatment and in 11 of 14 patients (79%) evaluated at 18 months.

DISCUSSION

A number of other treatment-related factors can influence potential GU toxicity, including total radiation dose, treatment volume, treatment modality (EBRT or brachytherapy), and treatment technique (3D-CRT, IMRT and image guidance).

The Massachusetts General Hospital study retrospectively documented normal urodynamic function for 24 of 32 long-term survivors (75%). These included flow symptoms in 6%, urgency in 15%, and control problems in 19% [5].

The evaluation of late effects with the LENT-SOMA scale by investigators confirms the good quality of bladder preservation for patients locally controlled without cystectomy, with no Grade 4 toxicity and only 10% Grade 3 toxicity (mainly urinary frequency). The self-assessment by patients is in agreement with the investigators' evaluation. At the time of the study, a specific module for urinary symptoms of the QLQC-30 questionnaire was not available, and a specific questionnaire was built, based on other published studies [6, 7].

Using this tool, 70% of patients maintained a good score for bladder function 12 months after treatment. In the first year after treatment, symptoms such as frequency, pain, and control problems

improved, probably owing to tumor disappearance. This good quality of bladder function was maintained up to 24 months, but thereafter deterioration was seen. The daily frequency was better at 6 and 12 months than before treatment, but at 36 months 5 of 7 patients had a urinary interval of 2 to 3 h. The same observation was made for nightly frequency of urination. The majority

of patients with pain on urination before treatment usually experienced an improvement, but in 37.7% at 6 months there was deterioration, and 14% had frequent pain at 36 months.

The Table lists the common acute and chronic side effects along with treatment options [3].

Toxicity		Treatment
Gastrointestinal	Enteritis	Acute Diarrhea: antidiarrheals, hydration, and high- or low-fiber diet. If refractory, regular IV fluids, test for <i>C. difficile</i>
		Chronic Diarrhea: fiber, probiotics, and avoidance of lactose Leakage: biofeedback, pelvic floor exercises Malabsorption: nutrition support, cholestyramine for bile salt deficiency, or low fat diet
		Proctitis Acute: topical hydrocortisone, steroid, or sucralfate enemas Chronic: argon laser, hyperbaric oxygen, vitamin A, and metronidazole
		Hemorrhoids Pain management; topical application of lidocaine and petroleum mixture
		Fistula or stricture Surgical evaluation
		Obstruction Bowel rest, may require surgery if refractory
Genitourinary	Cystitis Acute: hydration, antibiotics, NSAIDs, and anticholinergic agents Chronic: hyperbaric oxygen and intravesical endoscopic procedure	
	Fistula Surgical repair	
	Stricture Stent placement	
Sexual	Mucosal injury Hydrogen peroxide douche, hyperbaric oxygen, metronidazole, and oral or topical antifungal	
	Stenosis Vaginal dilator, benzydamine, and surgery	
	Menopause Hormone replacement, serotonin reuptake inhibitors	
	Infertility Fertility counseling before treatment	
	Erectile Dysfunction Phosphodiesterase inhibitors, vacuum erection devices, injections with prostaglandins, and penile implants	

Dermatologic	Dermatitis Antihistamines, colloidal oatmeal, and aloe
	Desquamation Sitz bath, hyaluronic acid or calendula cream; hydrogel, silver sulfadiazine
	Telangiectasia Laser therapy
	Fibrosis Massage, physical therapy
	Ulceration Wound care, debridement, and biopsy for nonhealing lesions to rule out secondary malignancy
Hematologic	Anemia Consider transfusion if Hgb < 10 g/dL
	Neutropenia Infection precautions for ANC < 500
	Thrombocytopenia Consider holding radiation for < 40,000/ μ L
Bone	Osteopenia Vitamin D, calcium, exercise, bisphosphonates, SERMs, and estrogen
	Fracture Pain management, rest
	Necrosis Surgery

NSAIDs, nonsteroidal anti-inflammatory drugs

Special Considerations

Gastrointestinal Toxicity

Individuals with cancer concomitant with comorbidities such as diabetes, atherosclerosis, or inflammatory bowel disease are at increased risk of acute and late toxicity from radiation. Additionally, radiation-induced rectal bleeding may be exacerbated by anticoagulants. There is an increased frequency of side effects in patients with a history of abdominal surgery or receiving radiation in the adjuvant setting [8].

Les données sur la qualité de vie (QV) de l'étude PORTEC-1 ont montré une augmentation des symptômes intestinaux jusqu'à 15 ans après radiochimiothérapie concomitante, par rapport aux personnes ayant reçu seulement une chimiothérapie [9].

Anticoagulants and hematuria: Other patient factors also influence radiation toxicity. As with gastrointestinal bleeding, the use of anticoagulants may increase the incidence and severity of post-radiation

hematuria. Obesity and heavy smoking have also been documented as risk factors for bladder complications after radiotherapy. The ethnic factor: A recent study showed that Latin American patients had higher rates of grade>2 GI and GU toxicity compared to European patients [3].

In our trial the QoL reported by the patient was high. The overall QoL was maintained over 70% for all patients alive without relapse for 36 months. An improvement of the global bladder function was observed after treatment and was maintained at 36 months. Sexual function was preserved in 79% of the patients at 18 months and was higher after than before treatment.

Comparison of QoL after surgery for conservative treatment with radiotherapy has been reported in two retrospective studies. Henningsohn *et al.*, [10] evaluated 71 patients treated conservatively and 325 controls treated by cystectomy. After radiotherapy, 74% reported little or no distress from symptom from urinary function. Thirty-eight percent had had intercourse the previous month, and 57% reported they had ejaculated. In contrast, after surgery only 13% had had intercourse, and none had ejaculated. Caffo *et al.*, [7] carried out a retrospective study by mailing a questionnaire to 93 patients treated with radiation with or without chemotherapy or by cystectomy. The QoL after surgery was reduced by lack of sexual activity and a worsened physical condition. In contrast, social and recreational life was little affected. In patients treated conservatively, a low incidence of urinary symptoms and an acceptable sexual adjustment were found. The QoL of the conservatively treated patient was better than in the surgical patients.

Zietman *et al.*, [5] reported a study on patients with clinical Stage T2–T4 bladder tumor treated with TUR, radiotherapy and chemotherapy. They undertook a urodynamic study and a QoL study in 71 patients treated 6.3 years earlier; 49 patients were evaluated. Bladder symptoms were uncommon, distress from urinary symptoms was low, and the majority of men retained sexual function. Global health-related QoL was high, and the majority of patients retained good bladder function.

CONCLUSION

The analysis of the complications of radiotherapy has benefited in recent years from a more rigorous inventory integrating the notion of quality of life.

This evaluation, which was as exhaustive as possible, made it possible to refine the therapeutic strategies by taking advantage of technical progress in radiotherapy. Better control of dose-volume parameters and individual adjustments to radiotherapy planning has

thus made it possible to reduce the rate of severe complications.

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DISCLOSURES

The authors have declared no conflict of interest.

REFERENCES

1. Cox, J. D. (1995). Toxicity criteria of the radiation therapy oncology group (RTOG) and the European organization for research and treatment of cancer (EORTC). *Int J Radiat Oncol Biol Phys*, 31(5), 1341-1346.
2. US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. 2010. USA: National Institutes of Health, National Cancer Institute Google Scholar, 2015.
3. Nicholas, S., Chen, L., Choflet, A., Fader, A., Guss, Z., Hazell, S., ... & Viswanathan, A. N. (2017, October). Pelvic radiation and normal tissue toxicity. In *Seminars in Radiation Oncology* (Vol. 27, No. 4, pp. 358-369). WB Saunders.
4. Zietman, A. L., Shipley, W. U., & Kaufman, D. S. (1993). The combination of cis-platin based chemotherapy and radiation in the treatment of muscle-invasive transitional cell cancer of the bladder. *International Journal of Radiation Oncology* Biology* Physics*, 27(1), 161-170.
5. Chauvet, B., Felix-Faure, C., Davin, J. L., Choquet, C., Alfonsi, M., & Reboul, F. (1998). Results of long-term treatment of inoperable cancer of the bladder with cisplatin and concurrent irradiation: prognostic factors of local control and survival. *Cancer Radiotherapie: Journal de la Societe Francaise de Radiotherapie Oncologique*, 2, 85s-91s.
6. Dunst, J., Rödel, C., Zietman, A., Schrott, K. M., Sauer, R., & Shipley, W. U. (2001, January). Bladder preservation in muscle-invasive bladder cancer by conservative surgery and radiochemotherapy. In *Seminars in surgical oncology* (Vol. 20, No. 1, pp. 24-32). New York: John Wiley & Sons, Inc..
7. Mommsen, S., Jakobsen, A., & Sell, A. (1989). Quality of life in patients with advanced bladder cancer. A randomized study comparing cystectomy and irradiation--the Danish Bladder Cancer Study Group (DAVECA protocol 8201). *Scandinavian Journal of Urology and nephrology. Supplementum*, 125, 115-120.
8. Viswanathan, A. N., Lee, L. J., Eswara, J. R., Horowitz, N. S., Konstantinopoulos, P. A.,

- Mirabeau-Beale, K. L., ... & Wo, J. Y. (2014). Complications of pelvic radiation in patients treated for gynecologic malignancies. *Cancer*, 120(24), 3870-3883. +
- Loiudice, T., Baxter, D., & Balint, J. (1977). Effects of abdominal surgery on the development of radiation enteropathy. *Gastroenterology*, 73(5), 1093-1097.
9. Nout, R. A., van de Poll-Franse, L. V., Lybeert, M. L., Wárlám-Rodenhuis, C. C., Jobsen, J. J., Mens, J. W. M., ... & Creutzberg, C. L. (2011). Long-term outcome and quality of life of patients with endometrial carcinoma treated with or without pelvic radiotherapy in the post operative radiation therapy in endometrial carcinoma 1 (PORTEC-1) trial. *Journal of Clinical Oncology*, 29(13), 1692-1700.
10. Henningsohn, L., Wijkström, H., Dickman, P. W., Bergmark, K., & Steineck, G. (2002). Distressful symptoms after radical radiotherapy for urinary bladder cancer. *Radiotherapy and Oncology*, 62(2), 215-225.