Original article

Concurrent urologic and palliative care after cystectomy for treatment of muscle-invasive bladder cancer

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Abstract

Purpose: To characterize the effect of palliative care provided concurrently with usual urologic care for patients with bladder cancer undergoing cystectomy.

Materials and methods: Prospective, 6-month, serial cohort study comparing 33 participants receiving usual care with cystectomy for muscle-invasive bladder cancer, with 30 participants also receiving concurrent palliative care. Patients and family caregivers completed validated symptom assessment and satisfaction surveys preoperatively and at 2, 4, and 6 months postoperatively.

Results: The intervention group saw improvements in most symptom measures over the 6 months following cystectomy compared with the control group. Depression and anxiety decreased over the 6-month period for the intervention group patients but increased over this time among the controls ($P = 0.01$). Fatigue decreased to a minimum for the intervention group participants at 4 months, whereas it peaked at this time for control participants (0.002). Quality-of-life and posttraumatic growth scores followed a similar pattern, with scores peaking at 4 months for the intervention group whereas controls reported their lowest scores at this time ($P = 0.01$ and $P = 0.03$, respectively). Changes in pain scores did not reach statistical significance. Neither family caregiver burden nor patient satisfaction showed statistically significant changes over time.

Conclusions: Patients who received concurrent palliative care in addition to usual urologic care following radical cystectomy for muscle-invasive bladder cancer had better outcomes, including improved fatigue, depression, quality of life, and posttraumatic growth. Although further research on this topic is needed, our results suggest that providing palliative care services in addition to usual urologic care for patients with bladder cancer may significantly reduce postoperative symptoms. © 2015 Elsevier Inc. All rights reserved.

Keywords: Cystectomy; Bladder cancer; Symptoms; Distress; Palliative care

1. Introduction

Major professional organizations call for comprehensive cancer care to include palliative care [1,2]. A growing body of research demonstrates benefits in clinical outcomes, patient satisfaction, health care utilization, and cost for palliative care for patients with serious illness, including urologic cancers, regardless of prognosis [3–8]. In response to this persuasive research, the American Society for Clinical Oncology has called for palliative care consultation for all patients with cancer with metastatic disease or high symptom burden or both [2], and palliative care is recognized as integral to routine oncology care by the National Comprehensive Cancer Network and the Commission on Cancer.

Integration of palliative care into the routine treatment of bladder cancer has been limited. The American Urological Association recommends palliative care for some patients with advanced prostate cancer but offers no guidance regarding palliative care for patients with bladder cancer [9].

The European Association of Urology's monograph on palliative care includes a section on pain management for patients with bladder cancer [10].

Bladder cancer is the fifth most prevalent cancer in the United States, but its symptoms have not been well studied [11–16]. A recent study demonstrated that cystectomy to potentially cure bladder cancer did not improve presurgery symptom burden 6 months after surgery for a number of important symptoms and may have worsened others [17]. Bladder cancer and its treatment create significant distress, but symptoms may not be adequately assessed, and few interventions have been prospectively evaluated using validated instruments [17–19]. In particular, palliative care offered concurrently with surgical oncologic care for patients with bladder cancer being treated with curative intent has not been studied.

To assess the effect of concurrent palliative care in bladder cancer, we examined symptoms, quality of life, and satisfaction among patients undergoing cystectomy for muscle-invasive bladder cancer and receiving usual urologic care for 6 months postoperatively. We compared outcomes from this group with those from patients receiving concurrent palliative care.

2. Materials and methods

The study methodology for the usual urologic care group has been described previously [17]. For the study, 2 serial cohorts of patients at an academic comprehensive cancer center with histologically confirmed urothelial carcinoma who were scheduled to undergo radical cystectomy were recruited. The first cohort (control) included patients undergoing cystectomy during a 13-month period from 2009 to 2010. The second cohort (intervention) included patients undergoing cystectomy during a 15-month period from 2010 to 2012. Patients unable to complete study surveys in English and those with psychosis or cognitive impairment were excluded. All participants were asked to complete surveys before surgery and at 2, 4, and 6 months postoperatively. If participants identified a primary family caregiver at their initial visit, the caregiver was asked to complete surveys at the same time intervals.

In addition to usual cystectomy care, the intervention group patients received palliative care consultation. This included a preoperative meeting or telephone consultation with a board-certified palliative care physician or nurse practitioner to orient the patient to the upcoming surgery and provide anticipatory guidance about symptom management and expectations for the postoperative course. Intervention patients also received an "Orientation to Bladder Cancer and Cystectomy" handbook and a "Prepare for Surgery" meditation audio CD. Intervention patients were visited in the hospital by the palliative care team after cystectomy to assist with symptom management and explain planned palliative care services. Intervention

patients received telephone or in-person consultations with the palliative care clinician monthly for 6 months postoperatively. The team included a palliative care physician and nurse practitioner with 0.05 clinical FTE each. Patient problems identified during these interactions with the palliative care team were addressed during the visit or follow-up calls, or it led to engaging the patient's surgeon. Surgeons were alerted to all palliative care activities. Recommendations typically included advice about management of symptoms, including pain, constipation, depression, and fatigue. Family caregivers were included in consultations at the patients' discretion.

The primary study outcome measures were changes from baseline in pain, fatigue, depression, anxiety, health-related quality of life, and spiritual well-being at 2, 4, and 6 months after enrollment. Baseline surveys were obtained in the week before surgery and, for intervention patients, before the first interaction with palliative care. Participants completed the following surveys at each of the time points: Brief Pain Inventory [20], Cancer Fatigue Scale, [21], the Hospital Anxiety and Depression Scale (HADS) [22], the Functional Assessment of Chronic Illness Therapy—Spirituality-12 [23], and the Functional Assessment of Cancer Therapy—General [24].

Secondary patient outcomes included posttraumatic growth, health care utilization, patient satisfaction, and family caregiver burden at 2, 4, and 6 months after enrollment. These outcomes were assessed with the Posttraumatic Growth Inventory [25], the Patient Satisfaction Questionnaire III [26], the Zarit Burden Inventory [27], and the FAMCARE survey [28].

Demographic information, pathology data, and postoperative health care utilization were assessed at each of the 4 time points by chart and electronic medical record review.

Statistical analysis of primary and secondary outcomes was performed using generalized estimating equations, and the correlation of repeated measures within subjects was accounted for via the robust standard used in generalized estimating equations. P values for the comparison in trends of each group over time were estimated using a difference-in-differences analysis. Significance was based on 2-sided $P \leq 0.05$. Survey results were adjusted for disease stage, bladder cancer treatment before cystectomy, multiple comorbidities, number of hospitalization, and hospitalization duration, as these variables had statistically significant differences between the intervention and control groups. All analyses were performed using the Intercooled Stata statistical software package (version 12.0; StataCorp LP, College Station, TX). Approval from the university's institutional review board was obtained for this study before data collection.

3. Results

3.1. Recruitment and enrollment

During the control study period, 57 patients underwent cystectomy, and all were assessed for participation in the

study. Of them, 14 were ineligible, and 10 declined to participate—7 listed "too busy" as the explanation for their refusal, 1 listed "health limitations," and 2 refusals were for unknown reasons. Therefore, 33 patients (57.9%) agreed and were enrolled. Of the original 33 control participants (66.6%), 22 completed the surveys at each time interval—8 (24.2%) were lost to follow-up and 3 died before the conclusion of the study (9.1%). There were no statistically significant survey response differences from patients lost to follow-up and those who completed the entire study. All 3 deceased patients died before the 2-month survey was completed.

Overall, 44 patients underwent cystectomy during the intervention period, and all but 5 were assessed for participation. Of them, 3 were ineligible and 6 declined to participate—1 listed "too busy" as the explanation for refusal, 2 listed "cost/insurance", and 3 refusals were for unknown reasons. Therefore, 30 patients (68.2%) agreed and were enrolled. Over the course of the study period, 24 of the original 30 prospective participants (80%) completed the surveys at each time interval. Of them, 2 participants (6.7%) were lost to follow-up and 4 died before the conclusion of the study (13.3%). Because there were minimal missing values in the surveys among the intervention groups, data from all 30 participants were included. There were no statistically significant survey response differences between the 2 patients lost to follow-up and those who completed the entire study. All 4 deceased patients died before the 4-month survey was completed.

3.2. Baseline characteristics

Data on sociodemographic characteristics, treatment, and health care utilization of the control and intervention groups are summarized in Table 1. At baseline, the intervention group participants had more comorbidities ($P = 0.01$), had a higher average tumor stage ($P = 0.001$), and received more aggressive cancer treatment ($P = 0.001$). There were no significant group differences in the attending urologic surgeons. The groups had no differences in emergency room visits, but intervention group patients had more hospitalizations ($P = 0.001$) and a greater number of hospital days ($P = 0.001$). At 2 years postoperatively, the intervention group patients had a higher mortality ($P = 0.02$) than the control group patients.

3.3. Palliative care interventions

All active intervention patients received scheduled preoperative and postoperative consultations, except for 1 patient who could not be reached for the 4-month call. Most follow-up consultations were via telephone. Among the intervention group patients, most received education about how to use their prescribed analgesics; 7 (23.3%) received a prescription for a new medication from the palliative care clinician, mostly antidepressant medications, but also

including an opioid analgesic and a laxative. Only 1 (3.33%) intervention family caregiver initiated telephone calls to palliative care. All family caregivers of patients who died received bereavement calls from the palliative care clinician.

3.4. Symptom, quality-of-life, and satisfaction survey scores

Intervention group patients experienced higher levels of pain at baseline compared with the control group (Table 2). Although the comparison of the trends for the 2 groups over the 6-month postoperative period was not statistically significant ($P = 0.13$), the intervention group scores decreased ($P = 0.13$) whereas the control group scores increased significantly ($P = 0.03$) over time. The intervention group reported the lowest pain scores, whereas the control group reported the highest pain scores at 4 months.

Cancer fatigue scores over time were significantly different between the intervention and control groups (Table 2). The intervention group reported higher fatigue scores at the time of cystectomy, which decreased significantly over 6 months, whereas fatigue scores of the control group started lower and increased over time ($P = 0.002$). Intervention participants reported the lowest fatigue scores at 4 months after surgery, whereas control group participants reported the highest scores then.

HADS scores followed a similar statistically significant trajectory for the control and intervention groups (Table 2). Scores for the intervention group decreased over the course of 6 months, whereas the control group scores increased over time ($P = 0.01$). These changes were driven by the depression subscale of the HADS survey. The HADS scores of the intervention group initially would be categorized as "abnormal" but decreased to a "normal" range by 4 months. Control group participants had a mean score in the "normal" range initially but increased to a "borderline" score by 4 months postoperatively.

The Posttraumatic Growth Inventory demonstrated that patients in the intervention group experienced a trend toward personal and existential growth in the 6 months following surgery (Table 2). This trend was significant when compared with the results of the control group over time ($P = 0.03$).

Health-related quality of life, as measured by the Functional Assessment of Cancer Therapy-General, also improved over time for the intervention group (Table 2), whereas the control group's scores decreased slightly. The comparison of the trends between the 2 groups over time was statistically significant ($P = 0.01$).

The significant differences in the trends for fatigue, anxiety/depression, posttraumatic growth, and health-related quality of life remained significant when adjusted for sex, education level, disease stage, prior psychiatric diagnosis, religion, and diversion type.

Spiritual well-being did not change significantly in either study group. Patient satisfaction scores were high in both

Table 1
Characteristics, severity of illness, and utilization of control and intervention patients

Variable	Control Group ($n = 22$) Number (%)	Intervention Group ($n = 30$) Number (%)	P value
Mean age	68.3, range: 45–84 y	67.4, range: 46–82 y	0.47
Male	19 (86.4)	23 (76.7)	0.071
Marital status			0.87
Married	16 (72.7)	20 (66.7)	
Separated	2 (9.1)	5 (16.7)	
Single	1 (4.5)	3 (10.0)	
Widowed	3 (13.6)	2 (6.67)	
Family caregiver identified	19 (86.4)	26 (86.7)	0.40
Education level			0.74
Middle	1 (4.5)	1 (3.3)	
High School	7 (31.8)	10 (33.3)	
College	7 (31.8)	12 (40.0)	
Graduate school	7 (31.8)	7 (23.3)	
Religion			0.24
Other	2 (9.1)	1 (3.3)	
Christian	13 (59.1)	25 (83.3)	
Buddhist	4 (18.2)	0 (0)	
None	3 (13.6)	4 (13.3)	
Muslim	0 (0)	0 (0)	
Jewish	0 (0)	0 (0)	
Multiple comorbidities	20 (90.9) (mean = 3.5, range: 1–8)	28 (93.3) (mean = 4.3, range: 1–10)	**0.01**
Three most common comorbidities			
Hypertension	11 (50)	20 (66.7)	
Dyslipidemia	11 (50)	15 (50.0)	
Coronary artery disease	6 (27.3)		
GERD		10 (33.3)	
Prior diagnosis of anxiety or depression or both	5 (22.7)	6 (20.0)	0.22
Prior treatment			**0.001**
TURBT	22 (100)	10 (33.3)	
TURBT + Intravesical therapy	9 (40.9)	7 (23.3)	
TURBT + Neoadjuvant chemotherapy	4 (18.2)	11 (36.7)	
TURBT + other		2 (6.7)	
Diversion method			0.82
Neobladder	7 (31.8)	10 (33.3)	
Ileal conduit	15 (68.2)	20 (66.7)	
Tumor stage			**0.001**
In Situ	1 (4.6)	2 (6.7)	
Stage 1	6 (27.3)	2 (6.7)	
Stage 2	9 (40.9)	11 (36.7)	
Stage 3	4 (18.2)	2 (6.7)	
Stage 4	2 (9.1)	13 (43.3)	
Postoperative health care utilization			
Mean Number of Bladder Cancer Program visits	2.3	Unknown	
Emergency Department visits	7 (32% of patients had ED visits)	11 (36.7% of patients had ED visits)	0.31
Number of subsequent hospitalizations	5 (22.7% of patients were hospitalized)	11 (36.7% of patients were hospitalized)	**0.001**
Median number of days in hospital for subsequent hospitalizations	1.8	4	**0.001**
Postoperative mortality			
6 Months	0	1 (3.3%)	0.32
1 Year	0	3 (10%)	0.80
2 Years	0	5 (17.9%)	**0.02**

Table 2
Control and intervention group outcomes

Survey	Time point	Average score (95% CI)		P value for score trend		P value for comparison of trends	Adjusted comparison P values*
		Control	Intervention	Control	Intervention		
Brief Pain Inventory	Initial visit	4.0 (0–8.0)	17.4 (8.2–26.7)	**0.03**	0.13	0.09	0.13
	2 Months	9.2 (3.8–14.6)	26.2 (14.3–38.0)				
	4 Months	11.3 (1.0–18.6)	8.9 (0.2–17.6)				
	6 Months	9.8 (1.9–17.6)	11.4 (4.0–18.8)				
Cancer Fatigue Scale	Initial Visit	18.6 (17.0–20.2)	34.3 (30.0–38.5)	0.12	**0.02**	**0.002**	**0.002**
	2 Months	18.0 (15.9–20.2)	34.3 (30.2–38.4)				
	4 Months	21.8 (18.7–24.9)	28.7 (25.0–32.3)				
	6 Months	21.0 (17.2–24.8)	29.7 (25.7–33.7)				
Hospital Anxiety and Depression Scale	Initial visit	7.6 (5.1–10.0)	9.8 (7.6–11.9)	0.37	**0.02**	**0.01**	**0.01**
	2 Months	6.6 (4.3–8.9)	10.5 (8.1–12.8)				
	4 Months	8.4 (6.0–10.7)	7.3 (4.9–9.6)				
	6 Months	8.4 (6.0–10.8)	7.2 (4.8–9.6)				
Depression Subscale	Initial visit	3.2 (2.1–4.3)	4.1 (3.0–5.3)	0.11	**0.01**	**0.003**	**0.004**
	2 Months	3.3 (2.2–4.5)	5.4 (4.1–6.7)				
	4 Months	4.4 (2.8–5.9)	3.6 (2.2–5.0)				
	6 Months	4.4 (2.8–6.0)	3.0 (1.8–4.2)				
Anxiety Subscale	Initial visit	4.3 (2.8–5.1)	5.6 (4.3–7.0)	0.85	**0.02**	0.21	0.27
	2 Months	3.3 (2.1–4.5)	5.1 (3.7–6.5)				
	4 Months	3.8 (2.4–5.0)	3.7 (2.6–4.7)				
	6 Months	4.0 (2.7–5.3)	4.2 (2.7–5.7)				
FACIT-SP	Initial visit	36.8 (33.7–40.0)	46.5 (43.4–49.6)	0.22	0.07	0.12	0.13
	2 Months	37.1 (33.8–40.4)	45.2 (41.5–48.9)				
	4 Months	35.4 (30.7–40.0)	48.9 (45.8–52.1)				
	6 Months	35.1 (31.5–38.8)	47.0 (42.7–51.3)				
FACT-G	Initial visit	88.0 (81.8–94.3)	80.7 (75.3–86.1)	0.22	**0.002**	**0.01**	**0.01**
	2 Months	86.9 (80.9–92.9)	76.7 (70.2–83.3)				
	4 Months	83.7 (75.6–91.8)	88.3 (82.6–94.0)				
	6 Months	84.6 (77.2–92.1)	88.1 (981.2–94.9)				
PTGI	Initial visit	13.4 (9.4–17.5)	13.9 (10.0–17.7)	0.97	**0.0004**	**0.02**	**0.03**
	2 Months	17.0 (12.7–21.2)	18.5 (14.9–22.0)				
	4 Months	13.1 (8.0–17.1)	21.9 (18.4–25.3)				
	6 Months	14.6 (10.9–18.2)	19.6 (15.6–23.6)				
PSQ-18	Initial visit	4.2 (3.8–4.5)	4.1 (3.8.0–4.3)	0.73	0.75	0.57	0.63
	2 Months	4.0 (3.8–4.3)	4.1 (3.8–4.4)				
	4 Months	4.0 (3.7–4.3)	4.3 (4.0–4.5)				
	6 Months	4.1 (3.8–4.4)	4.2 (3.9–4.4)				
FAMCARE	Initial visit	63.1 (57.8–67.8)	54.5 (46.3–62.8)	0.42	0.06	0.16	0.14
	2 Months	66.8 (61.9–70.8)	60.1 (54.8–65.3)				
	4 Months	62.3 (53.5–70.3)	65.1 (58.8–71.3)				
	6 Months	67.5 (62.5–71.9)	63.9 (55.4–72.4)				
ZBI	Initial visit	6.6 (4.0–9.4)	6.9 (4.4–9.4)	0.73	0.68	0.78	0.78
	2 Months	8.8 (5.0–13.3)	10.3 (7.4–13.1)				
	4 Months	7.8 (4.7–11.0)	8.2 (5.4–10.9)				
	6 Months	6.2 (3.3–9.8)	8.7 (5.3–12.2)				

P values in BOLD are statistically significant.
*Adjusted for sex, education level, disease stage, prior psychiatric diagnosis, religion, and diversion type.

groups and remained statistically unchanged over the course of the study period.

3.5. Family caregivers

Overall, 16 of the 19 control group patient caregivers (84.2%) and 20 of the 26 intervention group caregivers (76.9%) completed surveys at each study interval. In addition, 3 control group caregivers (15.8%) and 6 intervention group caregivers (23.1%) completed only the initial survey or the initial and 2-month surveys because they were caregivers to patients who died or were lost to follow-up. Caregivers for both groups reported little to no burden, and scores did not change significantly over time. Peak

caregiver burden occurred at 2 months postoperatively for both groups. The difference in trends between the groups was not statistically significant ($P = 0.78$). Family caregiver satisfaction did not change significantly over time for either group ($P = 0.14$).

4. Discussion

In our study of patients with muscle-invasive bladder cancer treated with cystectomy, patients who received concurrent palliative care in addition to usual care had better postoperative outcomes over 6 months, including improved fatigue, depression, quality of life, and posttraumatic growth. Changes for fatigue and anxiety/depression showed a statistically significant difference among intervention patients, with decreasing fatigue and anxiety/depression postoperatively, whereas control patients demonstrated increasing fatigue and anxiety/depression. Intervention patients reported their lowest levels of fatigue 4 months postoperatively, whereas control patients reported their maximal fatigue at this time point. Similarly, quality of life improved for intervention patients but decreased for control patients postoperatively. The change in posttraumatic growth over time was greater for intervention patients than for control patients.

Prior research has shown significant symptoms among patients following cystectomy for muscle-invasive bladder cancer [17], but symptom and quality-of-life outcomes with palliative care consultation have not previously been assessed in this patient population. However, the improvements seen in our study are consistent with prior studies of concurrent palliative care offered along with routine oncologic care for patients with lung and prostate cancer [7,8], as well as other cancers and noncancer diagnoses [3]. Although improved satisfaction, more dramatic improvements in pain, and improved mortality have been seen in other palliative care studies, our research did not demonstrate this [3,7].

Notably, the palliative care intervention studied here was not intensive. Most consultations were done by telephone, few treatments were initiated, there was limited involvement with family caregivers, and there was no involvement of palliative care social workers or chaplains. This may explain the lack of improvement in spiritual well-being and family caregiver outcomes. It is notable, then, that numerous significant improvements were found even with a relatively limited intervention, suggesting that full palliative care intervention teams might lead to more profound improvements.

Our study has several limitations. This is a relatively small study and may have been underpowered to demonstrate all the potential effects from added palliative care. The control group in particular did not include the full 29 patients sought. The study included a single institution, which may limit generalizability. Although the survey instruments used are well-validated, no cystectomy-specific scales were used. We did not assess costs for this study, though the clinical palliative care work described here likely could be included in the existing practice capacity of many cancer center palliative care programs. Although we observed benefits from palliative care, our study was not able to identify which elements of the palliative care intervention (communication, education, medication, etc.) were responsible for the observed impacts.

Importantly, our study was not randomized. Owing to unavoidable limitations from contamination of the control group within a randomized trial design at a single institution with a limited number of providers, we chose to study serial cohorts with the first cohort receiving usual care. However, our nonrandomized design allowed for the possibility of confounding variables that may have influenced our results. Our control and intervention groups demonstrated a number of notable baseline differences. The intervention group had more advanced bladder cancer, had greater comorbidities, and more pain and fatigue at baseline. The difference in baseline severity of illness between the groups likely explains the differential health care utilization and 2-year mortality differences observed. It is possible that our statistical adjustment for disease stage, bladder cancer treatment before cystectomy, multiple comorbidities, number of hospitalization, and hospitalization duration may not have controlled for all confounding variables. Finally, it is possible that the intervention group, with greater baseline pain and fatigue, received greater symptom benefit from cystectomy than did the control group. However, this possibility is unlikely given our prior published findings that cystectomy does not tend to improve patients' symptoms and may actually worsen pain [17]. Given that nearly all patients undergoing cystectomy at our institution were included in each cohort, it is unknown why the intervention group had patients with greater burden of illness. We are not aware of any administrative, policy, or referral changes at the institution that might account for this. However, assessment of *trends* in symptom change allowed us to show differences between the intervention and control group experiences. Symptom changes over time went in opposite directions for the intervention and control patients, with intervention group symptoms improving and control symptoms worsening following cystectomy.

5. Conclusions

In our study, concurrent palliative care provided improved outcomes for patients with bladder cancer treated with cystectomy. To address the limitation inherent in our study design, subsequent studies might pursue a multisite, randomized, controlled trial of usual urologic care for patients with muscle-invasive bladder cancer undergoing cystectomy compared with the addition of concurrent, robust palliative care. Even before such a

proposed randomized trial can be accomplished, our results might justify consideration of providing palliative care concurrently with usual urologic care for patients undergoing cystectomy and for at least 6 months thereafter. Such care would comply with recommendations of professional organizations committed to improving the care of patients with bladder cancer and holds the promise of decreasing the morbidity of surgical treatment.

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