Assessment of Perioperative Morbidity for Radical Cystectomy in Elderly Patients

length of stay (LOS), and onset of toleration of house diet. Multivariate analysis (ordered logistic regression) was used to correlate baseline status with peri- and postoperative morbidity.

Results

Thirty-two patients had no complications. Twenty patients (39 %) had at least one complication. 31 % had minor complications (Clavien score 1 or 2), and 8 % had a major complication (Clavien score ≥ 3a). Only one patient needed intervention for a surgical complication. After discharge, the 90-day complication rate was 11.5 % and the 90-day readmission rate was 9.6 %. Perioperative mortality rate was 0 %. 54 % tolerated house diet by one week. The mean LOS was 9.6 days. It was 3.5 days longer in case of complication. Multivariable statistical analysis was done using the method of ordered logistic regression and found that intolerance of house diet after one week was a risk factor for complication ($p = 0.02$). A Charlson score ≥ 1 ($p = 0.01$) and an ASA score ≥ 1 ($p = 0.03$) were risk factors for LOS ≥ 10 days.

Conclusion

These results suggest that RC can be performed safely in the elderly. Follow-up studies with larger patient populations may determine clearer predictors of outcome.

Keywords

Radical cystectomy, bladder cancer, elderly, morbidity, risk factor

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INTRODUCTION

Radical cystectomy (RC) is the standard treatment for muscle-invasive bladder cancer (MIBC) and for non-muscle-invasive bladder cancers for which intravesical therapy has failed. Historically, elder-age has often been quoted as one of the contraindications to RC. A recent study indicated that, of patients 80 years old or older, bladder cancer management included watchful waiting (7 %), radiotherapy alone (1 %), full or partial cystectomy (12 %), and transurethral resection (79 %). Patients 80 years old or older were less likely to be treated with extirpative surgery than their younger counterparts ($P < 0.0001$) [1]. In another study, of patients with muscle invasion, those age 75 years and older were less likely to undergo RC (14 %) compared with patients ages 55 - 64 years (48 %) and those ages 65 - 74 years (43 %) [2]. Is this assertion that elder age is a contraindication to undergoing RC supported by clinical research or is it an unfounded bias? This study aims to answer this question by addressing whether it really is age or comorbidity status that should be taken into account when considering RC in the elderly.

Some studies that suggest RC can indeed be safely performed in elderly and that there is a benefit for overall and specific survival. One study demonstrated that, among patients 80 years or older, radical cystectomy/partial cystectomy had the greatest risk reduction in death from bladder cancer (hazard ratio 0.3) and death from any cause (hazard ratio 0.4) among the primary treatment modalities ($P < 0.0001$) [1], especially for elderly people who have a life expectancy of more than two years [3]. In another study of over 1,000 patients, Donat et al. showed that for major complications, risk appeared to increase slightly up to age 65 years and then plateau. However, after adjusting for baseline characteristics (gender, BMI, prior abdominal surgery, prior chemotherapy, prior radiotherapy, American Society of Anesthesiologists (ASA) score, and abnormal creatinine status), risk of any complication was similar across all age groups [4]. For Gupta et al., there was no significant difference between septuagenarians and patients younger than 70 years old with regard to pathologic stage or length of hospital stay [5]. Chang et al. even suggests that radical cystectomy can be safely done in high-risk elderly patients (75+ years and ASA of 3-4) [6].

There is, however, controversy in the current literature, with several studies suggesting that age alone is a contraindication to RC. A population-based study identified age (>65 years old) as an independent predictor of complications ($p = 0.02$) and mortality ($p = 0.005$) [7]. For Tyrtzis et al., increased age was associated with greater hazard for 90-day morbidity [8]. In a study assessing the impact of comorbidity on perioperative radical cystectomy, Novotny et al. showed that age was an independent predictive factor for perioperative complications, which were significantly more frequent in the elderly group: 31 % (< 70 years old) versus 21.5 % (> 70 years old) with $p = 0.002$ [9]. The Boström et al. study also found that age (≥ 65) was a significant risk factor for major complications [10].

The current literature is difficult to draw recommendations from, due to variations in outcome measurements and inconsistency in definitions of complications and time periods. Of the studies in favor of performing RC in the elderly, Hollenbeck et al. only assessed mortality, not morbidity. They also only looked at elderly patients older than 80 years old and failed to include septuagenarians, like the Donat et al. study. Chang et al. only looked at high-risk patients (ASA 3 - 4) and patients older than 75 years old, failing to include patients with lower ASA scores and patients 70 - 75 year old. Furthermore, they included complications up to 6 month post-operatively, without any data on the perioperative period. They did look at ASA, sex, gender, transfusion requirement, pathological tumor stage, need for surgical intensive care unit admission and/or cardiac monitoring, hospital length of stay, major complications, and minor complications, but did not include the number of postoperative days to onset of toleration of house diet, BMI, or preoperative GFR in their analysis.

Of the studies that suggest RC is contraindicated in the elderly, the Elting et al. study did not have a timed endpoint (they assessed mortality based on admission and length of hospital stay) and did not asses comorbidity in patients greater than 80 years old. The Tyrtzis study and the Bostrom et al. study were conducted at medium volume academic centers, with low mean annual volume of RC and therefore the data might not be as broadly applicable. Novotny et al. classified patients into two groups (ASA score ≤ 2 and ≥ 3) before statistical analysis, instead of using each individual score on a continuum for an

ordered logistic regression. Also, only complications within 30 days of surgery were included.

Because of these deficiencies in the literature and conflicting clinical suggestions, many providers are left with the difficult task of deciding whether or not to provide RC to patients without a standardized set of guidelines. Furthermore, many elderly patients may not be receiving RC treatment that they need.

Our study addresses these deficiencies in the literature and assesses the risk factors for major complications and mortality that are important in decision-making for providers considering RC in elderly patients with bladder cancer. This study was targeted to the perioperative period and was done at a tertiary care center, included three standardized classification systems (Age-adjusted Charlson Comorbidity Index (ACCI), ASA score, and Clavien-Dindo Classification of Surgical Complications), and included the full 90-day post-surgery complication rates in the analysis. Septuagenarians were included in the study and each individual ASA score on a continuum was used for an ordered logistic regression during analysis. This study reflects the experience of a tertiary care center and provides clinical data that will improve healthcare delivery to patients with bladder cancer.

Summary of Author Contributions to this Study: Several contributors were involved in creation, design, implementation, and finalization of this project. Elizabeth Wendel participated in and contributed to initial discussions about the general design of the study and acquired funding for this project. She was responsible for chart review, collection of data, analysis and interpretation of data, and writing all sections of the paper. She also conducted a search of the current literature and, for the introduction section, wrote a background review relevant to the study. In addition, she was responsible for making revisions to the final paper. Dr. Vincent Meyer made revisions to the initial drafts of the paper and contributed to study design. He assisted with data collection and data interpretation. He also designed data collection tools for the electronic medical record system in order to facilitate efficiency during the chart review phase of this study. Dr. Michael O'Leary was responsible for conception and design of the project. He also made revisions to the paper and acquired funding to conduct

this study. Nathaniel Hevelone designed and implemented the statistical analysis plan for data interpretation. Specifically, he ran multivariate statistical analysis using the method of ordered logistic regression on the data collected. Dr. Adam Kibel revised the draft paper and offered suggestions for further study. Dr. Jerome Richie revised the draft paper. Dr. Janet Mullington provided feedback and advice for the draft paper.

PATIENTS AND METHODS

This was a retrospective study of 52 patients greater than 70 years old undergoing RC for bladder cancer at Brigham and Women's Hospital from 1995 to 2011. Comorbidity factors, as measured by age, ASA score, Age-adjusted Charlson Comorbidity Index (ACCI), BMI, preoperative GFR were analyzed. Perioperative morbidity was defined as any complication during hospitalization or subsequent 90-day follow-up. The ACCI was downsized to 0 for patients in their seventies without comorbidity. Symptomatic tumors were defined by weight loss, ureteral obstruction with a decreased renal function, gross hematuria complicated by anemia or retention, pelvic pain, or urgency not relieved by medical treatment. The indications for RC were muscle invasive disease and non-muscle invasive disease refractory to intravesical immunotherapy.

We analyzed perioperative complications using the Clavien-Dindo Classification of Surgical Complications [11,12], the length of stay (LOS) in days, and onset of toleration of house diet. In defining post-surgical ileus, we chose emesis associated with abdominal distension and/or nasogastric tube placement. Bacterial colonization or non-febrile UTI and perioperative complications discovered after surgery were not counted as complications. Early cancer recurrence rate was not studied. Multivariate analysis (ordered logistic regression) was used to correlate baseline status with peri- and postoperative morbidity.

RESULTS

Patient characteristics are listed in Table 1. The mean age was 76.4 years (range 70 - 93). The mean BMI was 25.7 (range 20 - 31). The mean ACCI score was 1.84 (range 0 - 5). Every patient underwent an ileal conduit procedure, except one who underwent

ureterostomy because of ureteral transitional cell carcinoma, which necessitated a nephroureterectomy associated with the cystectomy.

Twenty patients (39 %) had at least one complication. Eight patients had several complications. Severity of complications and LOS associated are listed in Table 2. One patient had a small urinary leak on an obstructed ureteral stent, which was resolved with unclogging. The only surgical complication was a small bowel leak closed by primary repair without stomy. Peroperative complications discovered after surgery were postural nerve palsy, an obturator nerve palsy, and dysphagea due to intubation with left vocal cord paresis. After discharge, the 90-day complication rate was 11.5 % and the 90-day readmission rate was 9.6 %.

Multivariate statistical analysis was done using the method of ordered logistic regression. The mean LOS was 9.6 days (range 5 - 25). It was 3.5 days longer in case of complication (Table 2). It was also longer for patients ≥ 80 years old (8.2 vs.13.7 days, OR = 0.16; 95 % CI = 0.03 - 0.79; p = 0.02). 28 patients (54 %) tolerated house diet by one week. An age ≥ 80 years old was a risk factor for taking longer than one week before tolerating house diet (OR = 0.03; 95% CI = 0.003 - 0.265; p = 0.001). There was no significant decrease in renal function in patients who were ≥ 80 years old (p = 0.9).

Type of complication, risk factors for perioperative complication, and risk factors for LOS greater than ten days are detailed in Table 3, Table 4, and Table 5, respectively.

DISCUSSION

These results suggest that RC can be performed safely in the elderly. Of all the patients, 92 % had either minor or no complications. The only significant risk factors for a longer length of stay were related to comorbidity (ASA score, ACCI). The intolerance of house diet after one week was associated with perioperative complication, but was more a consequence than being a risk factor, especially in case of ileus. In defining post-surgical ileus, we chose the parameters of emesis associated with abdominal distension and/or

nasogastric tube placement. Therefore, there might have actually been more patients than recorded who had ileus. Another definition of ileus is intolerance of oral intake by postoperative day five with a lack of bowel activity. This definition seems too strict for elderly because there are several other factors that can interfere like anorexia or dysphagea. Therefore, we differentiated between patients who were able to tolerate solid food before and after one-week post surgery. The real ileus rate would be between those two figures.

A limitation of the study is that some patient medical files were found to be incomplete and missing co-morbidity data. For example, the albumin values before and after RC were not available for most of the patients (however, its dosage would be systematic before RC). Furthermore, some patients might have had co-morbidities that have yet to be diagnosed. But almost all studies on morbidity and mortality of RC are retrospective and heterogeneous. The number of patients in our study is mid-tier in comparison to the literature. Table 6 summarizes the complication and mortality rates in the literature. Our complication rate is within the literature range, and our major complication and mortality rates are under the literature values.

The reported frequency of complications after RC in elderly patients is very heterogeneous. Our two most frequent complications (ileus and infection) were the same as in most studies, which ranges from 16 % to 40 % for infection and 2 % to 32 % for ileus [5]. We had no wound dehiscence (0 % vs. 2-11 %), and the rate of disorientation and wound infection was lower than the literature (2 % vs. 5-20 % and 2 % vs. 2-21 %, respectively). However, our rate of atrial fibrillation was higher (8 % vs. 2-8 %).

The reviewed LOS values are listed in Table 6. There is no data about how patients were managed during hospital stay and which factors were significant. Our 9.6 days LOS was the second lowest in the literature. It was 24 days for Gamé et al., but European patients are not usually managed in an ambulatory fashion, especially with catheter removal [13].

In conclusion, these results suggest that RC can be performed safely in the elderly. It seems that they are a high-risk group mostly due to their comorbidities instead of their age, but it is still the best option and remains a standard. Follow-up studies with larger patient populations may determine clearer predictors of outcome.

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APPENDIX

Table 1. Patient characteristics, surgical and pathological characteristics

	# of Patients (n_{total} =52)	(%)
Gender		
Female	15	(29)
Male	37	(71)
Age (years)		
70-79	39	(75)
≥ 80	13	(25)
Body Mass Index (BMI)		
< 25	11	(21)
25-30	15	(29)
≥ 30	2	(4)
Missing	24	(46)
Preoperative Glomerular Filtration Rate (GFR) (ml/min)		
≥ 60	35	(67)
60-30	14	(27)
< 30	3	(6)
Symptomatic tumor?		
No	36	(69)
Yes	16	(31)
Clinical stage		
T – Primary tumor		
CIS (Carcinoma In Situ)/0	1	(2)
1	9	(17)
2	35	(67)
3	3	(6)
4	4	(8)
N – Lymph nodes		
0	52	(100
1	0	
Pathology		
Low grade	4	(8)
High grade	46	(88)
Adenocarcinoma	2	(4)
Neoadjuvant chemotherapy?		
No	46	(88)
Yes	6	(12)
Type of urinary diversion		
Conduit	51	(98)

Ureterostomy	1	(2)
Pathological stage		
T – Primary tumor		
CIS/0	6	(12)
1	3	(6)
2	17	(33)
3	18	(35)
4	8	(15)
N – Lymph nodes		
0	39	(75)
1	6	(12)
2	3	(6)
X (Lymphatic vessel invasion could not be assessed)	4	(8)
Surgical margin classification		
R0 (No residual tumor)	51	(98)
R+ (R1: microscopic or R2: macroscopic residual tumor present)	1	(2)

Table 2. Complication rate and length of stay (LOS) for ≥ 70 years old patients undergoing radical cystectomy

	Clavien score	Patients, *n*	(%)	Mean LOS (days)	LOS Interval
No complication	0	32	(61)	8.2	[5 ; 15]
Minor complication	1 or 2	16	(31)	10.2	[5 ; 22]
Major complication	≥3a	4	(8)	17.8	[7 ; 25]

Table 3.Type of complication for ≥ 70 years old patients undergoing radical cystectomy

	Patients, *n*	(%)
Medical complication		
Ileus	9	(17)
Infection	7	(13)
Urinary	1	(2)
Pneumonia	2	(4)
C.difficile diarrhea	2	(4)
Wound cellulitis	1	(2)
Unknown	1	(2)
Atrial fibrillation	4	(8)
Transfusion for blood loss	3	(6)
Acute pulmonary edema	2	(4)
Confusion	1	(2)
Acute tubular necrosis	1	(2)
Urinary leakage	1	(2)
Surgical complication		
Small bowel leakage	1	(2)

Table 4. Risk factors for perioperative complication

Subgroup	Percent	OR	95% CI	p-value
Age ≥ 80 years	5/13 (38.5%)	1.000	[0.275 ; 3.634]	1.000
Gender (female)	4/15 (26.7%)	1.213	[0.128 ; 1.780]	0.271
ASA score ≥ 1	10/34 (29.4%)	0.333	[0.102 ; 1.092]	0.070
ACCI ≥ 1	13/33 (39.4%)	0.897	[0.280 ; 2.876]	0.856
BMI ≥ 25	4/17 (23.5%)	1.219	[0.215 ; 6.922]	0.823
Glomerular Function rate < 60 ml/min	6/17 (35.3%)	1.222	[0.367 ; 4.069]	0.744
Neoadjuvant chemotherapy	1/6 (16.7%)	3.518	[0.380 ; 32.581]	0.268
Symptomatic tumor	14/37 (37.8%)	1.095	[0.321 ; 3.740]	0.885
Toleration of house diet after one week	15/24 (62.5%)	0.130	[0.037 ; 0.465]	**0.002**

Table 5. Risk factors for length of stay more than ten days

Subgroup	Percent	OR	95% CI	p-value
Age ≥ 80 years	9/9 (100%)	>999.999	[<0.001 ; >999]	0.9543
Gender (female)	7/11 (63.6%)	2.8	[0.650 ; 12.064]	0.1671
ASA score ≥ 1	15/26 (57.7%)	6.136	[1.101 ; 34.211]	**0.0385**
ACCI ≥ 1	14/22 (63.6%)	0.143	[0.031 ; 0.663]	**0.0129**
BMI ≥ 25	7/12 (58.3%)	1.19	[0.190 ; 7.456]	0.8522
Glomerular Function rate < 60 ml/min	5/9 (55.6%)	0.6	[0.132 ; 2.724]	0.5081
Neoadjuvant chemotherapy	2/4 (50%)	0.833	[0.104 ; 6.646]	0.8634
Symptomatic tumor	9/22 (40.9%)	1.651	[0.440 ; 6.200]	0.4579
Toleration of house diet after one week	14/14 (100%)	<0.001	[<0.001 ; >999]	0.9391

Table 6. Overview of reported perioperative mortality and complication rates in elderly patients undergoing radical cystectomy

Author	Period	*n*	Age (years)	Urinay diversion	Overall complication rate	Major complication rate	Mortality	Mean or median LOS (day)
Boström et al. **[10]**	1986–2005	258	≥65	Ileal conduit, neobladder	34%	11%	2.7%	20
Chang et al. **[6]**	1994-2000	44	≥75	Ileal conduit, ASA 3-4	22.7%	4.5%	0%	7
Clark et al. **[14]**	1971-1997	364	≥70	Ileal conduit, neobladder, 70-79 year rates	37%	-	4%	11
Donat et al. **[4]**	1995-2005	1142	≥80	Ileal conduit, neobladder	55%	17%	-	10
Gamé et al. **[13]**	1993-1999	25	≥75	Ileal conduit, neobladder	64%	-	4%	22
Gupta et al. **[5]**	1992-2002	41	≥70	Ileal conduit, neobladder	29.7%	-	7.3%	11
Novotny et al. **[9]**	1993-2010	365	≥70	Ileal conduit, neobladder	31%	15%	0.6%	-
Sogni et al. **[15]**	2000-2004	85	≥75	Ileal conduit rates	21.7%	-	5.6%	15.3
Tyritzis et al. **[8]**	2000-2009	81	≥75	Ileal conduit, neobladder, cutaneous ureterostomies	43.2%	-	3.7%	13