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Histopathological and perioperative factors influencing the length of hospital stay and patients' outcome after radical cystectomy for urothelial carcinoma

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Abstract

Introduction: Length of hospital stay (LOS) is considered as a key factor in estimating outcomes after radical cystectomy (RC) in urothelial carcinoma (UC) patients. We aimed to assess whether clinical perioperative (age, gender, type of urinary diversion technique) and histopathological factors [UC variant, primary tumor, node, metastasis (pTNM) staging] could be a determining factor for LOS, as well as its influence on overall survival (OS) in a single institution, retrospective cohort study. *Patients, Materials and Methods*: We included a total of 69 UC patients that had RC performed in our Department during November 2011 and October 2018. Regular LOS was considered arbitrarily up to 12 days. All factors were analyzed in relation to LOS, using the *chi*-square and the Mann–Whitney tests. Impact of LOS on survival was assessed using the Kaplan–Meier and the Cox regression methods. *Results*: Age was associated to increased LOS (p=0.042), as well as the type of urinary diversion (p=0.003). Patients with complex diversion were found more frequently in the prolonged LOS group (ileal conduit p=0.006, Mainz pouch p=0.15, Camey neobladder p=0.517). Histopathologically, N stage had a significant association to LOS (p=0.044). Survival analysis showed decreased survival in the prolonged LOS group (p=0.653). Cox regression found no influence of LOS (p=0.653), advanced age (p=0.518) or type of urinary diversion on OS. *Conclusions*: Advanced age, the complexity of urinary diversion and lymph node involvement were found as associated factors for prolonged LOS in RC patients. The impact of LOS on survival is uncertain, requiring larger, in-depth studies.

Keywords: length of hospital stay, cystectomy, carcinoma, transitional cell, disease-free survival.

Introduction

Radical cystectomy (RC) is the standard-of-care in localized muscle invasive urothelial carcinoma (UC), in accordance to the *Guidelines of the European Association of Urology* (EAU) [1]. It is suitable for patients with long life expectancy, with a good general status and without serious comorbidities – predictors of postoperative outcome [2].

Although RC with loco-regional lymphadenectomy is a standard procedure, the postoperative outcomes [including length of hospital stay (LOS)] can be influenced by a series of factors like advanced age (≥75 years), frailty and comorbidities [3, 4].

Management of patients with bladder cancer, and especially after RC is a heavy financial burden on the health system, starting from perioperative complications and their management and leading to regular postoperative visits and investigations [5]. LOS can be determined by the healing period specific for each patient, as well as the onset of complications that require adequate management (*e.g.*, surgical reinterventions, deep vein thrombosis, etc.) [6].

Histologically, UC can be classified in conventional UC, as well as UC variants, which can be found alone or in mixed combinations [7]. Traditionally, some UC variants (*e.g.*, micropapillary, sarcomatoid, plasmacytoid variants) were found as being more aggressive, with increased tumor (T) extension stage at presentation and increased risk of lymph node (N) metastasis, which could result in a more difficult surgical procedure and could influence LOS [8]. Adjustment for stage and grade showed that just the presence of variant UC alone was not a predictor for overall mortality in RC patients [9]. Still, recent studies showed that certain UC variants (*e.g.*, the small cell variant) had a negative effect on overall survival (OS) after RC [10].

Aim

We aimed to assess whether clinical and perioperative factors (age, gender, type of urinary diversion technique, concomitant nephrectomy) and histopathological factors (including UC type, pTNM stage) could influence LOS in a retrospective, single institution cohort study.

Patients, Materials and Methods

Selection of patients

All patients that had RC performed for UC in the

Department of Urology, Mureş County Hospital, Târgu Mureş, Romania, during November 2011 and October 2018, were screened for inclusion in the study.

The study protocol was approved by the Ethics Committee of the University of Medicine and Pharmacy of Târgu Mureş (Letter of Approval No. 195/24.10.2018).

Patients with RC performed for other diseases, bearing upper urinary tract UCs, with incomplete resection or lost to follow-up, were excluded from the study.

Clinical and demographic data were retrieved from the patient files: age at surgery, gender, tumor staging, details on the surgery procedure itself (lymphadenectomy, type of urinary diversion, concomitant nephrectomy, etc.). The standard surgical procedure was RC with lymphadenectomy and one of the methods of urinary diversion (ureterostomy, ileal conduit or neobladder). Lymphadenectomy was not performed in palliative situations.

According to their age, patients were stratified into two groups, frail and non-frail. Frailty was defined as having an age of at least 75 years old or more.

Pathology

For each case included in the study, complete pathological data were retrieved from the histopathological reports. The following parameters were recorded: histological type of UC (conventional or other), associated carcinoma *in situ* (CIS), tumor (T) extension, lymph node (N) involvement, presence of distant metastases (M), positive surgical margins or concomitant prostate cancer.

Since the original interpretation had been performed either using the 2004 [11] or the 2016 [7] version of the *World Health Organization* (WHO) *Classification of Tumours of the Urinary System and Male Genital Organs*, the corresponding Hematoxylin–Eosin (HE)-stained slides for all the cases included in the study were re-evaluated in consensus by two experienced uro-pathologists (AB, AL), in accordance to the *2016 WHO Classification*. The cases were reclassified either as non-invasive papillary UC and/or infiltrating UC, the latter comprising conventional UCs, UCs with divergent differentiation (squamous, glandular and trophoblastic) or specific variants of UC (micropapillary, plasmacytoid, sarcomatoid, poorly differentiated UC) [8, 12].

TNM staging was assessed in accordance to the *American Joint Committee on Cancer* (AJCC) *Cancer Staging Manual, 8th edition* (2017) [13], as follows: pT1 tumor invading subepithelial connective tissue, pT2 tumor invading muscularis propria (Figure 1, a and b), pT3 tumor invading perivesical tissue (Figure 1, c and d), pT4 tumor invading any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall. N+ (lymph node metastasis) was defined as involvement of at least one regional lymph node (obturator, internal or external iliac) (Figure 1, e and f). M+ (distant metastases) cases were considered cases in which secondary, metastatic tumors were identified at the time of diagnosis or during the follow-up period.

Length of hospital stay (LOS)

LOS was defined as the period the patients were hospitalized following RC; it was calculated using the admission and discharge dates. Based on the available published data and similar studies from the literature [14], the patients were stratified into two groups by their LOS after RC: regular LOS <12 days and prolonged LOS ≥12 days. To our knowledge, no standard definitions of regular and prolonged LOS after RC do exist in the literature. Twelve days was considered as the "cut-off" value after revising the median LOS in previous published large studies [14–16].

Follow-up data

All RC patients were subjected to regular follow-up survey according to the *National Guidelines* issued by the Romanian Ministry of Health as well as the *Guidelines of the EAU* [1, 17]. Thus, all patients were invited for regular evaluations every three months (in the first two years), every six months in the third year and then yearly from the fourth year onward. Follow-up data were collected from the database of Romanian National Insurance System, as well as from the local databases of the Department of Urology and the Department of Oncology, Mureş County Hospital, Târgu Mureş.

Statistical analysis

Descriptive statistics with means and medians were performed for continuous variables. Comparison of continuous variables was performed using the non-parametric Mann–Whitney test or the Student's *t*-test, according to the results of normality assumption testing using the Shapiro–Wilk *W*-test. For categorical variables, comparison was performed using either Pearson's χ^2 (*chi*-square) test or Fisher's exact test. Survival analysis was performed using the Kaplan–Meier and the Cox regression methods. Statistical significance was set at $p<0.05$. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) Statistics 23.0 (IBM SPSS, IBM Corp, Armonk, NY, USA).

Results

Seventy-two (n=72) patients with RC performed for UC were registered in the Department of Urology, Mureş County Hospital, Târgu Mureş, over the study period. Out of these cases, three were excluded because of incomplete data (the patients were lost to follow-up). The remaining 69 cases were further analyzed and included in the study.

Clinical and intraoperative data

Table 1 illustrates the clinical and intraoperative data that were analyzed in the present study. The patients' age ranged from 40 to 77 years, with a median value of 64 years. Most (n=63, 91.3%) of the patients were younger than 75 years old (non-frail group), while only six patients were older than 75 (frail group). The majority of patients were males (57 cases, 82.6%). For more than half of the cases (n=46, 66.7%), the surgical procedure was RC with lymphadenectomy. Cutaneous ureterostomy (n=49, 71%) was the predominant type of urinary diversion, followed by ileal conduit (Bricker) (n=14, 20.3%).

Pathological data

Morphological characteristics of the study cases are listed in Table 2. Histologically, most of the cases were conventional UCs (*n*=40 cases, 58%), followed by poorly differentiated UC (*n*=8 cases, 11.6%) and micropapillary UCs (*n*=7 cases, 10.1%). Other variants of UC were rare, plasmacytoid and glandular variant of UC accounting for three (4.3%) and two (2.9%) cases, respectively. With regard to the tumor (T) stage, more than half of the UC cases were pT3 (*n*=22 cases, 31.9%) or pT2 (*n*=18 cases, 26.1%), followed by pT4 (*n*=15 cases, 21.7%). Only 10 (14.5%) cases were pT1. Lymph node dissection was performed in 46 (66.7%) UC cases. Of these, 17 (24.6%) cases displayed lymph node involvement.

CIS was found in half of the cases (*n*=35 cases, 50.7%). Positive surgical margins were present in five cases: two poorly differentiated UCs, one plasmacytoid UC and two conventional UCs.

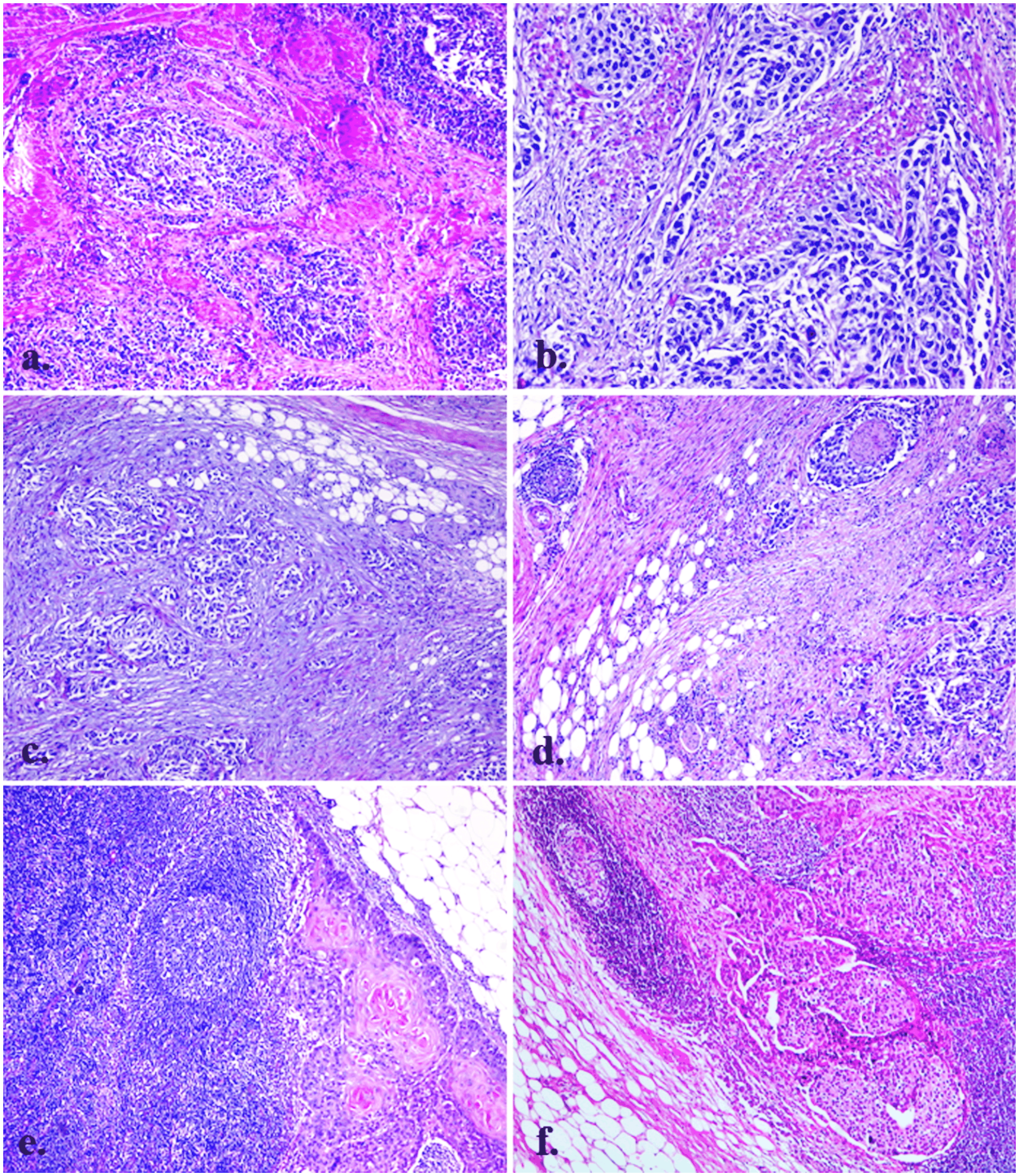

Figure 1 – ***TNM staging for UC cases, assessed in accordance to the AJCC Cancer Staging Manual, 8th edition (2017) [13]: (a and b) pT2 UC case, with tumoral tissue invading muscularis propria; (c and d) pT3 UC case, with tumoral tissue invading perivesical adipose tissue; (e and f) Two cases of UC with N+ lymph node metastasis. HE staining: (a, c–f) ×40; (b) ×100. AJCC: American Joint Committee on Cancer; HE: Hematoxylin–Eosin; TNM: Tumor, node, metastasis; UC: Urothelial carcinoma.***

Table 1 – ***Pre- and intraoperative data analyzed in the study in relation with LOS***

Variable	Median value or *n* (%) (minimum, maximum)	LOS <12 days	LOS ≥12 days	*p*-value
Age [years]	64 (40, 77)	58 (51, 71)	64 (40, 77)	0.042**
<75	63 (91.3%)	17 (24.6%)	46 (66.7%)	0.324*
≥75	6 (8.7%)	0	6 (8.7%)	
Gender				0.616*
Males	57 (82.6%)	14 (20.3%)	43 (62.3%)	
Females	12 (17.4%)	3 (4.3%)	9 (13%)	
Surgical procedure (radical cystectomy)				0.323*
With lymphadenectomy	46 (66.7%)	13 (18.8%)	33 (47.8%)	
Without lymphadenectomy	23 (33.3%)	4 (5.8%)	19 (27.5%)	
Concomitant nephrectomy				0.324*
Yes	6 (8.7%)	0	6 (8.7%)	
No	63 (91.3%)	17 (24.6%)	46 (66.7)	
Urinary diversion				0.003*
Cutaneous ureterostomy	49 (71%)	24 (34.8%)	25 (36.2%)	0.001*
Ileal conduit (Bricker)	14 (20.3%)	1 (1.4%)	13 (18.8%)	0.006*
Mainz pouch	4 (5.8%)	0	4 (5.8%)	0.15*
Ileal neobladder (Camey)	2 (2.9%)	0	2 (2.9%)	0.517*

LOS: Length of hospital stay; **Chi*-square/Fischer tests; **Mann–Whitney *U*-test; *p*<0.05.

Table 2 – ***Morphological and follow-up characteristics analyzed in the study in relation with LOS***

Variable	Median value or *n* (%) (minimum, maximum)	LOS <12 days	LOS ≥12 days	*p*-value
UC types				
Conventional UC	40 (58%)	8 (11.6%)	32 (46.4%)	0.294*
Poorly differentiated	8 (11.6%)	2 (2.9%)	6 (8.7%)	0.638*
Squamous	5 (7.2%)	0	5 (7.2%)	0.323*
Sarcomatoid	1 (1.4%)	0	1 (1.4%)	0.754*
Micropapillary	7 (10.1%)	3 (4.3%)	4 (5.8%)	0.352*
Plasmacytoid	3 (4.3%)	0	3 (4.3%)	0.372*
Glandular	2 (2.9%)	0	2 (2.9%)	0.565*
Miscellaneous	3 (4.3%)	1 (1.4%)	2 (2.9%)	0.578*
TNM staging				
T stage				0.348*
T0-Ta-Tis	4 (5.8%)	0	4 (5.8%)	
T1	10 (14.5%)	3 (4.3%)	7 (10.1%)	
T2	18 (26.1%)	2 (2.9%)	16 (23.2%)	
T3	22 (31.9%)	7 (10.1%)	15 (21.7%)	
T4	15 (21.7%)	5 (7.2%)	10 (14.5%)	
N stage				
Nx (not performed)	23 (33.3%)			
N0	29 (42%)	5 (10.9%)	24 (52.2%)	0.044*
N+	17 (24.6%)	8 (17.4%)	9 (19.6%)	
M stage				
M0	59 (85.5%)	13 (18.8%)	46 (66.7%)	0.248*
M1	10 (14.5%)	4 (5.8%)	6 (8.7%)	
Presence of CIS				0.833*
CIS positive	35 (50.7%)	9 (13%)	26 (37.7%)	
CIS negative	34 (49.3%)	8 (11.6%)	26 (37.7%)	
Positive surgical margins				
Absent	64 (92.8%)	15 (21.7%)	49 (71%)	0.59*
Present	5 (7.2%)	2 (2.9%)	3 (4.3%)	
Follow-up data				
Alive	33 (47.8%)	7 (10.1%)	26 (37.7%)	0.527*
Deceased	36 (52.2%)	10 (14.5%)	26 (37.7%)	

CIS: Carcinoma *in situ*; LOS: Length of hospital stay; TNM: Tumor, node, metastasis; UC: Urothelial carcinoma; **Chi*-square/Fischer tests; *p*<0.05.

Follow-up data

Distant metastases were documented in 10 (14.5%) patients with UC: three patients already had distant metastases at the time of surgery and seven patients developed distant metastases during the follow-up period. Metastases were found at various sites: lung, liver, ovary, brain and peritoneum.

OS ranged from 0 to 85.1 weeks, with a median value of 20 weeks. Further division of the patients in the regular and prolonged LOS revealed no statistically significant difference in survival between the two groups (p=0.83).

At the last clinical assessment, 33 (47.8%) patients were alive, while 36 (52.2%) patients had deceased.

Associations of LOS to clinical, intraoperative and pathological factors

LOS ranged from six to 37 days, with a median of 17 days. Our data demonstrated a statistically significant difference in the median age of patients between the regular and prolonged LOS groups. Thus, prolonged LOS patients had a higher median age (64 years), when compared to patients with regular LOS (58 years) (p=0.042).

There was no statistically significant difference in LOS in relation to gender (p=0.616), frailty (p=0.324), performing of loco-regional lymphadenectomy (p=0.323) or concomitant nephrectomy for unilateral hydronephrosis (p=0.324).

When analyzing the type of urinary diversion procedure, patients with cutaneous ureterostomy were more likely to be less hospitalized (regular LOS group), compared to patients with other types of urinary diversions (ileal conduit – Bricker, Mainz pouch and ileal neobladder – Camey) that were only rarely hospitalized less than 12 days (regular LOS group only one case) and more frequently associated with prolonged LOS. The differences were statistically significant (p=0.003).

We further inquired whether the histological subtype of UC could lead to differences in LOS. No statistically significant differences were found between regular and prolonged LOS groups of patients with conventional UC (p=0.294), poorly differentiated UC (p=0.638) and micropapillary UC (p=0.352), respectively. Although our study included only five and three patients with squamous and plasmacytoid variant of UC, respectively, all these patients were associated with a prolonged LOS (p=0.323 and p=0.372, respectively) (Table 2).

Concerning pTNM staging, a statistically significant difference was found in LOS values in relation to N stage (p=0.044). No statistically significant differences were found in LOS in relation to T (p=0.348) or M stage (p=0.248). Further on, no statistically significant differences were found in LOS in relation to CIS (p=0.833), the presence of positive surgical margins (p=0.59) or follow-up data (patient alive or deceased) (p=0.527) (Table 2).

Associations of LOS to overall survival (OS)

Analysis concerning the impact of LOS on the OS (using the Kaplan–Meier method) revealed a decreased survival in the prolonged LOS group, although not statistically significant (p=0.947) (Figure 2a). A decreased OS rate was also documented in the frail group, compared to the no-frail group, also not statistically significant (p=0.513) (Figure 2b).

Survival analysis using Cox regression found no influence of prolonged LOS on the OS rate (p=0.653), as well as an age higher than 75 years old (p=0.518). Further, on the technique deployed for urinary diversion had no statistically significant impact on survival (Table 3).

Discussions

Current developments in postoperative care offer the possibility to reduce LOS and improve patient recovery. Such an example is enhanced recovery after surgery (ERAS), both a pre- and postoperative patient support protocol that has promising results in RC patients [6]. Based on ERAS principles, LOS is a risk factor for poor postoperative results, hence the necessity for its reduction [6].

We performed a single-center, retrospective cohort study aiming to assess the clinical, perioperative and histopathological factors that could influence LOS and, subsequently, the outcomes of surgery.

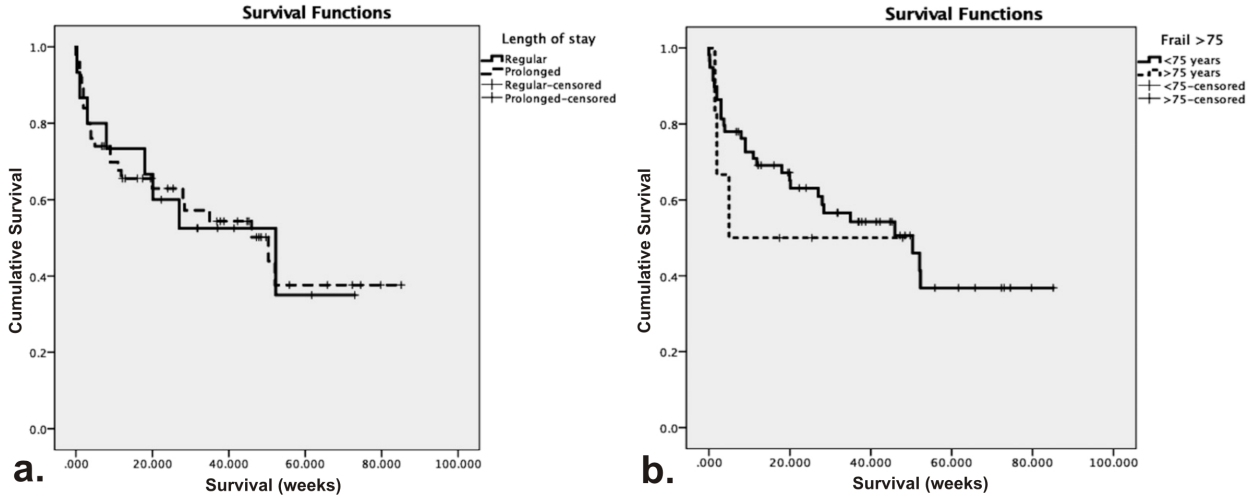

Figure 2 – ***Survival analysis using the Kaplan–Meier method showing the impact of LOS (a) and frailty (b) on overall survival. LOS: Length of hospital stay.***

Table 3 – ***Cox regression aimed at assessing the impact of age, frailty, as well as the different types of urinary diversion techniques on overall survival***

	Hazard ratio	*p*-value	95% CI for Exp(B)	
			Lower	*Upper*
Prolonged LOS	1.006	0.653	0.407	1.757
Frail (≥75 years)	1.485	0.518	0.447	4.932
Type of urinary diversion				
Ureterostomy	0.846	0.653	.407	1.757
Ileal conduit	0.742	0.467	.331	1.661
Mainz pouch	1.159	0.841	.275	4.888
Camey neobladder	0.046	0.429	.000	94.346

CI: Confidence interval; LOS: Length of hospital stay.

Older patients were more likely to be found in the prolonged LOS group. This is in accordance to the results obtained by Pietzak *et al.*, who also reported an association between older age and prolonged LOS [14]. By considering just age as a sign of frailty, we found no statistically significant difference in LOS. However, Palumbo *et al.* found that patients older than 75 had had an increased risk of prolonged LOS [relative risk (RR) 1.06, $p<0.001$]. They also reported that frailty, together with a Charlson Comorbidity Index (CCI) ≥2 were also independent factors for predicting prolonged LOS [3]. Similarly, Mazzone *et al.* also found age as predictor of longer LOS [RR 1.002, 95% confidence interval (CI) 1.001–1.003] [4].

We found no statistically significant association between gender and LOS, as both the male and female patients were in similar proportions in the prolonged LOS group, when compared to the regular LOS one. This differs from the findings of Cárdenas-Turanzas *et al.*, who found female gender ($p=0.015$) as a predictor for prolonged LOS [18].

The technique of urinary diversion proved to be a factor influencing LOS ($p=0.003$). In our cohort, most patients were found in the prolonged LOS, regardless of the type of urinary diversion. This was not reported by Pietzak *et al.*, who did not find a statistically significant relation between the type of urinary diversion and LOS ($p=0.11$) [14]. Chang *et al.* also reported no influence of urinary diversion type on LOS, although the types of urinary diversion that they deployed differed (no cutaneous ureterostomy patients were found in their cohort) [15].

No statistically significant differences among regular and prolonged LOS groups of patients in terms of tumor histology were demonstrated by our results. As expected, the histological subtype of UC does not seem to influence the LOS [19].

We demonstrated a statistically significant association between N+ status and prolonged LOS ($p=0.044$). Lymph node involvement could be related to an increased risk of developing lymphocele or prolonged drainage, which could be associated to prolonged LOS. Similarly, Pietzak *et al.* reported an association between the occurrence of both major or minor lymphocele and LOS [14].

Using the Kaplan–Meier technique, a lower OS was demonstrated in the prolonged LOS group. This could be partially be explained by the onset of potential complications that are responsible for prolonged LOS. This is in accordance to the study of Yamashita *et al.*, who demonstrated that high-grade complications were responsible for worsening of recurrence-free survival [hazard ratio (HR) 2.11; 95% CI 1.07–4.15, $p=0.03$] and cancer-specific survival (HR 2.74; 95% CI 1.05–7.14, $p=0.039$) [20].

Study limitations

Our study has several limitations. First, it is a retrospective study, with all the inconveniences. Apart from this, not all patient information relevant to LOS were available for analysis, including the number of ileus days, the period until removal of nasogastric tube and surgical drains, as well as time to onset of minor complications (*e.g.*, lymphocele). The study may also be influenced by incomplete information concerning readmissions (*e.g.*, time to readmission, cause of readmission – complication or other, cause of death when it occurred). However, to our knowledge, this is the first study aiming to assess the impact of perioperative and morphological factors on the LOS in patients with RC for UC in a Romanian population.

Conclusions

To sum up, advanced age, complex urinary diversion techniques (ileal conduit, Mainz pouch or Camey neobladder) and lymph node involvement were associated to prolonged LOS in RC patients performed for UC. The histological subtype of UC does not seem to influence the LOS. Although not reaching a statistically significant value, our results have demonstrated a decreased OS rate among the patients in the prolonged LOS group, compared to the patients in the regular LOS group. Further, larger in-depth studies are required to document the impact of LOS on the OS rate in patients with RC for UC.

Conflict of interests

None to declare.

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