Clinical Series

Management of patients with liver cirrhosis and invasive bladder cancer: A case-series

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ABSTRACT

Liver cirrhosis is a major risk factor for increased mortality and morbidity in patients undergoing non-hepatic surgery with overall mortality rates as high as 45–50%. However, cirrhotic patients are often in need of surgical procedures including urological surgeries like cystectomies for muscle invasive bladder cancer. Data on the prognosis of these patients undergoing cystectomy for bladder cancer are scarce in the literature. In the present case-study, we describe the outcomes of 3 patients with liver cirrhosis who underwent radical cystectomy for muscle invasive bladder cancer. To the best of our knowledge, this is the first study reporting on this kind of urological surgery in patients with liver cirrhosis. Accordingly, we provide a review in the literature on prognosis and factors influencing the survival of cirrhotic patients who undergo surgical procedures.

Key words: liver cirrhosis, Child-Pough score, MELD score, urologic surgery, non-hepatic surgery, bladder cancer

INTRODUCTION

Liver cirrhosis is a major health problem, as according to World Health Organization (WHO), it accounts for 1.8% of all deaths in the European population. Indeed, liver cirrhosis is responsible for approximately 170,000 deaths/year in Europe including almost 50,000 deaths/year due to hepatocellular carcinoma.[1,2] However, apart from hepatocellular carcinoma, extra-hepatic malignancies also seem to develop more frequently and at an earlier age in patients with cirrhosis.[3-5] In this context, it is well known that cirrhotic patients carry an increased risk of several types of cancers namely, cancer of the lung, larynx, buccal cavity, pharynx, pancreas, urinary bladder, and kidney, which are usually associated with common habits of the patients like tobacco and alcohol abuse.[6-9]

The survival of non-hepatic cancer patients with accompanied liver cirrhosis varies according to the severity of liver dysfunction.[10,11] In more detail, the prognosis of patients with advanced cirrhosis (decompensated, Child-Pugh C cirrhosis) and concomitant extra-hepatic cancer depends mostly on the liver disease, while patients with compensated liver disease rather die from tumor-related complications. The latter patients are good candidates for specific anticancer treatment, as they might have a clinically relevant benefit in terms of survival.[12]

On the other hand, surgical treatment is frequently indicated in patients with cancer especially at early tumor stages, being in many cases, the only curative treatment option. However, in spite of the significant advances in surgical and intensive care management of the patients, liver cirrhosis is considered a major risk factor carrying an increased morbidity and mortality in cirrhotic patients undergoing any kind of surgery, as they can often decompensate because of both anesthesia and surgery.[12-15] Diverse scores and indexes have been used for predicting the outcome of patients preoperatively, among which the American Society of Anesthesiologists (ASA) score and the age-adjusted Charlson Comorbidity

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Index (aaCCI) are the most validated for the pre- and perioperative evaluation.[14-16] However, in cirrhotic patients, the Child-Pugh and the Model for End-Stage Liver Disease (MELD) scores seem to predict better the mortality after major abdominal surgery.[17-19]

Radical cystectomy accompanied by pelvic lymphadenectomy remains the most effective and widely used surgical intervention for muscle invasive bladder cancer (MIBC) and is considered the treatment of choice for these patients.[20] This operation is still associated with a rate of complications of about 27% and mortality of 0.8%.[21] Complications are generally due to the operation itself and to the host. Actually, the complications associated with the procedure are related to the extent of surgical extirpation and the need of intestinal reconstruction, whereas those related to the patient characteristics are dependent on the patient's age and the presence of the underlying comorbidities.[22] To date, there are very scarce data on the safety and outcome of radical cystectomy for MIBC in patients with liver cirrhosis. Therefore, we report herein the outcome of 3 patients with liver cirrhosis who underwent open radical cystectomy for MIBC and discuss risk factors of poor survival in these patients undergoing surgery.

Case 1

A 63-year-old Caucasian man, heavy smoker with known liver cirrhosis due to hepatitis B was presented in our department with intermittent macroscopic hematuria initiated 4 years ago. The abdominal CT revealed an exophytic bladder mass and transurethral resection biopsy revealed muscle invasive high grade urothelial carcinoma. CT of the thorax was normal. During the preoperational work-up the patient was classified as Child–Pugh B, with a MELD score of 12, ASA score III, aaCCI 5 and performance status (PS) 0 (Table 1). The preoperative laboratory tests are shown in Table 2. Radical cysto-prostatectomy with extended lymph node dissection and a cutaneous ureterostomy was performed under general anesthesia. The total operative time was 165 min with intraoperative transfusion of 1 unit of red cells. During the postoperative period, ascites developed; and during the 11th postoperative day, abdominal wound dehiscence with evisceration occurred, which led to a surgical correction but the patient soon after developed fever and secondary bacterial peritonitis. Despite intense antibiotic therapy, the patient finally passed away on the 16th day due to septicemia, hepatorenal syndrome and hepatic encephalopathy. The biopsy showed pT2N0M0 muscle invasive urothelial carcinoma.

Case 2

A 72-year-old Caucasian man, heavy smoker with history of alcoholism, current hepatitis B virus infection and right nephroureterectomy due to upper urinary tract urothelial tumor was presented in our clinic with macroscopic hematuria. The abdominal CT revealed bladder mass and following transurethral resection biopsy a muscle invasive, high grade, urothelial cancer was found. Preoperatively, liver cirrhosis was classified as Child-Pugh A, with MELD score 10, while the ASA score was III, the aaCCI 8 and PS 0 (Table 1). CT of thorax was normal. The preoperational laboratory work-up is shown in Table 2. Radical cysto-prostatectomy with extended lymphadenectomy and ileal conduit (Bricker) diversion was performed. The operation lasted 231 minutes and there were no intra-operative complications while no blood transfusion was required. Postoperative period was uneventful except for leaking ascites. Patient was discharged at the 10th postoperative day with antibiotic coverage. Biopsy specimen revealed a muscle invasive bladder pT2N0M0. During follow-up the patient was stable, without recurrence of ascites or development of other complications due to cirrhosis. However, in 9th month of follow-up, he developed bone metastatic disease, for which he received palliative radiotherapy. The patient died 36 months after surgery due to disseminated metastatic disease.

Case 3

A 69-year-old Caucasian man, heavy smoker, was admitted to our hospital with severe macroscopic hematuria. The patient had a 10 years history of cirrhosis due to hepatitis B. Urinary bladder ultrasound revealed an exophytic bladder tumor, abdominal and lung CT scans were negative for metastasis, while the transurethral resection biopsy revealed a muscle invasive, high grade, urothelial carcinoma. Preoperatively, the patient was classified as Child-Pugh

Table 1: Scores used as risk factor predictors of peri- and post-operative outcome in the 3 patients with cirrhosis who underwent radical cystectomy for muscle invasive bladder cancer

	Age (years)	CTP	MELD	ASA	CCI
Case 1	63	B	12	III	5
Case 2	72	A	10	III	8
Case 3	69	A	6	III	5

CTP: Child-Pugh classification; MELD: model for end-stage liver disease; ASA: American Society of Anesthesiologists physical status classification; CCI: Charlson comorbidity index.

Table 2: Preoperative laboratory data of the 3 cirrhotic patients who underwent radical cystectomy for muscle invasive bladder cancer

Preoperative values	Case 1	Case 2	Case 3
Hct (%)/Hg (g/dL)	28/9.1	38.6/12.8	38.7/12.8
WBC(/μL)	4,600	3,800	6,500
Platelets (/μL)	89,000	96,000	138,000
Glucose (mg/dL)	108	96	98
Urea (mg/dL)	36	94	32
Creatinine (mg/dL)	1.2	1.30	1.01
Creatinine clearance*(mL/min)	66	51	69
AST IU/L**	17	31	33
ALT IU/L**	10	21	42
γ-GT U/L**	54	56	48
ALP IU/L**	38	89	92
LDH UI/L	160	129	136
Total bilirubin (mg/dL)	0.74	0.75	0.85
Albumin (g/dL)	3.3	4.35	4.2
K (mmol/L)	4.3	4.4	4.8
Na (mmol/L)	136	143	138
Ca (mg/dL)	8.6	9.4	8.9
PT (s)	14.1	12.5	11.5
INR	1.20	1.07	1.02
aPTT (s)	30	27.3	31

*According to Cocroft-Gault formula, **AST < 40 UI/L, ALT < 35 UI/L, ALP < 120 UI/L, γ-GT < 40 UI/L.

Hct: hematocrit; Hg: hemoglobin; WBC: white blood cell; AST: aspartate aminotransferase; ALT: alanine aminotransferase; γ-GT: gamma glutamyl transferase; ALP: alkaline phosphatase; LDH: lactate dehydrogenase; INR: international normalized ratio; aPTT: activated partial thromboplastin time.

A, with MELD score 6, ASA score III, aaCCI5 and PS 0 (Table 1), while the laboratory work-up is shown in Table 2. Radical cysto-prostatectomy with extended lymph node dissection and ileal conduit (Bricker) was performed. The operative time was 255 minutes and no major intra-operative complications occurred. After surgery, the patient was transferred directly to the general urology floor with no need for the intensive care unit. During the postoperative period, no complications occurred; the drain was removed on the 6th post-operational day and patient was discharged on the 10th post-operative day. Pathology examination showed a pT3aN0M0 bladder tumor. The patient is still alive 24 months post-surgery, with no evidence of disease on imaging, while his liver disease is stable and well compensated.

DISCUSSION

In the present case-study, we describe the outcomes of 3 patients with liver cirrhosis who underwent radical cystectomy for muscle invasive bladder cancer. To the best of our knowledge, this is the first study reporting on this kind of severe urological surgery in patients with liver cirrhosis. It is well known that non-hepatic surgery in cirrhotic patients is challenging with a high mortality rate. Studies reporting morbidity and outcome in patients with cirrhosis undergoing non-hepatic surgery have shown variable results with in-hospital mortality rates ranging from 8.3% to 25% compared to 1.1% in non-cirrhotic patients.[13,23] The severity of liver disease, and secondarily, the nature of surgical procedure seem to be the most important factors of postoperative outcome.[24]

In cirrhotics, the hemodynamic impairment (increased cardiac output, splanchnic vasodilatation and decreased systemic vascular resistance) because of the loss of hepatic reserve usually result in inappropriate responses to surgical stress. Furthermore, these patients are at an increased risk of bleeding, infection, postoperative hepatic decompensation, including hepatic coma or death. In general, elective surgery is well tolerated in patients with Child-Pugh A cirrhosis, while it is permissive with good preoperative evaluation in patients with Child-Pugh B and is contraindicated in patients with Child-Pugh C cirrhosis.[13,23] In particular, mortality rates after major abdominal surgery were 10% for Child-Pugh A, 30% for Child-Pugh B and 76%–82% for Child-Pugh C cirrhosis.[24] Similarly, MELD score also predicts mortality after surgery and seems to correlate better with outcome. Thus, a MELD score 0–11 is associated with 5v10% 90-day mortality, a 12–25 score with 25–54% and scores above 26 with 90% postoperative mortality rate.[25] Teh *et al.*[25] concluded that the most important predictors of mortality are severity of liver disease as reflected by the MELD score, age

and comorbidities as determined by the ASA physical status classification. Indeed, in our study, the 2 patients with Child-Pugh A and low MELD scores did not have major peri- and post-operative complications, while the patient with Child-Pugh B and a higher MELD score died due to surgical complications, but also major disease decompensation (hepatorenal syndrome and hepatic encephalopathy).

On the other hand, the kind of surgical procedure is the second crucial determinant of postoperative outcome. The morbidity and mortality risks are the highest in patients undergoing cardiac surgery (up to 31% perioperative mortality) and open abdominal surgeries.[26] Abdominal surgery in particular, is more often complicated by hepatic ischemia, while the risk of intra-operative bleeding is increased due to the presence of portal hypertension. Moreover, perfusion may be impaired from anesthesia, which may also reduce the hepatic blood flow and decrease oxygen uptake by the liver.[27]

Radical cystectomy with extended lymphadenectomy is considered the standard treatment of muscle invasive bladder cancer with an overall 5-year survival up to 70% for pT2 disease.[16] However, the complications of the procedure, due to surgery itself as well as the urinary diversion, remain high.[16,28] Lughezzani *et al.*[29] in a large population-based competing-risks analysis of the survival of patients treated with radical cystectomy found that even after adjusting for bladder cancer pathologic stage, cancer-specific mortality was higher in older individuals than in younger ones. Our patients were > 60 years old but < 80 years with a 5 year cancer-specific mortality rate of around 30%[29] and all had PS 0, which is correlated with an excellent overall survival after radical cystectomy.[30] According to the aaCCI, which is recommended by the European Association of Urology guidelines[16] for assessing patients with muscle invasive bladder cancer before therapeutic decision making, the two patients with aaCCI 5 had a probability of survival of 0.8 at 2 years and the third with aaCCI 8 had a probability of survival of 0.35 at 2 years. Under this context, Abdollah *et al.*[31] in a population based study of 12,274 patients treated with radical cystectomy, showed that the postoperative mortality with a aaCCI ≥ 4 was around 12%. Finally, although nowadays laparoscopic surgery has been considered safe in patients with liver cirrhosis and may provide improved patient outcomes when compared to the open techniques,[32–34] we chose to perform radical cystectomy with open surgery, as there are no clear-cut guidelines for laparoscopy in this kind of surgical procedure in cirrhotic patients.[16,35]

In conclusion, radical cystectomy in cirrhotic patients is challenging but feasible. As in any other surgical procedure, the degree of liver impairment seems to significantly influence postoperative mortality in cirrhotic patients. For this reason, patients should be evaluated preoperatively and carefully classified according to their cirrhosis stage, while other classifications such as aaCCI, probably predicts better the cancer-related mortality. However, further multicenter studies are needed in order to make clear suggestions for better therapeutic decision-making in this rare group of patients. We are currently undertaking such studies. Nevertheless, the optimal management of cirrhotic patients with bladder cancer requires deep knowledge of both diseases and an interdisciplinary approach.

Conflict of Interest

None declared.

REFERENCES

1. Zatoński WA, Sulkowska U, Mańczuk M, Rehm J, Boffetta P, Lowenfels AB, *et al.* Liver cirrhosis mortality in Europe, with special attention to Central and Eastern Europe. Eur Addict Res 2010; 16: 193–201.
2. Blachier M, Leleu H, Peck-Radosavljevic M, Valla DC, Roudot-Thoraval F. The burden of liver disease in Europe: a review of available epidemiological data. J Hepatol 2013; 58: 593-608.
3. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018; 69: 182-236.
4. Njei B, Rotman Y, Ditah I, Lim JK. Emerging trends in hepatocellular carcinoma incidence and mortality. Hepatology 2015; 61: 191–9.
5. Sorensen HT, Friis S, Olsen JH, Thulstrup AM, Mellemkjaer L, Linet M, *et al.* Risk of liver and other types of cancer in patients with cirrhosis: a nationwide cohort study in Denmark. Hepatology 1998; 28: 921–5.
6. Berman K, Tandra S, Vuppalanchi R, Ghabril M, Sandrasegaran K, Nguyen J, *et al.* Hepatic and extrahepatic cancer in cirrhosis: a longitudinal cohort study. Am J Gastroenterol 2011; 106: 899-906.
7. Dam MK, Flensborg-Madsen T, Eliasen M, Becker U, Tolstrup JS. Smoking and risk of liver cirrhosis: a population-based cohort study. Scand J Gastroenterol 2013; 48: 585–91.
8. Ratib S, Fleming KM, Crooks CJ, Walker AJ, West J. Causes of death in people with liver cirrhosis in England compared with the general population: a population-based cohort study. Am J Gastroenterol 2015; 110: 1149–58.
9. Gundling F, Seidl H, Schmidtler F, Löffler N, Strassen I, Wolf P, *et al.* Nonhepatic cancer in liver cirrhosis: a retrospective study of prevalence, complication rate after specific oncological treatment, follow-up and prognostic predictors of outcome in 354 patients with cirrhosis. Anticancer Res 2011; 31: 2931-2938.
10. Schuppan D, Afdhal NH. Liver cirrhosis. Lancet 2008; 371: 838–51.
11. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006; 44: 217–31.
12. Pinter M, Trauner M, Peck-Radosavljevic M, Sieghart W. Cancer and liver cirrhosis: implications on prognosis and management. ESMO Open 2016; 1: e000042.
13. del Olmo JA, Flor-Lorente B, Flor-Civera B, Rodriguez F, Serra MA, Escudero A, et al. Risk factors for nonhepatic surgery in patients with cirrhosis. World J Surg 2003; 27: 647-52.
14. Djaladat H, Bruins HM, Miranda G, Cai J, Skinner EC, Daneshmand S. The association of preoperative serum albumin level and American

Society of Anesthesiologists (ASA) score on early complications and survival of patients undergoing radical cystectomy for urothelial bladder cancer. BJU Int 2014; 113: 887-93.
15. Boorjian SA, Kim SP, Tollefson MK, Carrasco A, Cheville JC, Thompson RH, *et al*. Comparative performance of comorbidity indices for estimating perioperative and 5-year all cause mortality following radical cystectomy for bladder cancer. J Urol 2013; 190: 55-60.
16. Alfred Witjes J, Lebret T, Compérat EM, Cowan NC, De Santis M, Bruins HM, *et al*. Updated 2016 EAU Guidelines on muscle-invasive and metastatic bladder cancer. Eur Urol 2017; 71: 462-75.
17. Hackl C, Schlitt HJ, Renner P, Lang SA. Liver surgery in cirrhosis and portal hypertension. World J Gastroenterol 2016; 22: 2725-35.
18. Lopez-Delgado JC, Ballus J, Esteve F, Betancur-Zambrano NL, Corral-Velez V, Mañez R, *et al*. Outcomes of abdominal surgery in patients with liver cirrhosis. World J Gastroenterol 2016; 22: 2657-67.
19. Neeff HP, Streule GC, Drognitz O, Tittelbach-Helmrich D, Spangenberg HC, Hopt UT, *et al*. Early mortality and long-term survival after abdominal surgery in patients with liver cirrhosis. Surgery 2014; 155: 623-32.
20. Herr HW, Faulkner JR, Grossman HB, Natale RB, deVere White R, Sarosdy MF, *et al*. Surgical factors influence bladder cancer outcomes: a cooperative group report. J Clin Oncol 2004; 22: 2781–9.
21. Novotny V, Hakenberg OW, Wiessner D, Heberling U, Litz RJ, Oehlschlaeger S, *et al*. Perioperative complications of radical cystectomy in a contemporary series. Eur Urol 2007; 51: 397-401.
22. Novotny V, Hakenberg OW, Froehner M, Zastrow S, Leike S, Koch R, *et al*. Systematic assessment of complications and outcome of radical cystectomy undertaken with curative intent in patients with comorbidity and over 75 years of age. Urol Int 2013; 30: 195-201.
23. Bhangui P, Laurent A, Amathieu R, Azoulay D. Assessment of risk for non-hepatic surgery in cirrhotic patients. J Hepatol 2012; 57: 874–84.
24. Waddell T, Verheij M, AllumW, Cunningham D, Cervantes A, Arnold D. Gastric cancer: ESMO-ESSO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013; 24: 57-63.
25. O'Leary JG, Friedman LS. Predicting surgical risk in patients with cirrhosis: from art to science. Gastroenterology 2007; 132: 1609–11.
26. Teh SH, Nagorney DM, Stevens SR, Offord KP, Therneau TM, Plevak DJ, *et al*. Risk factors for mortality after surgery in patients with cirrhosis. Gastroenterology 2007; 132: 1261-9.
27. O'Leary JG, Friedman LS. Predicting surgical risk in patients with cirrhosis: from art to science. Gastroenterology 2007; 132: 1609–11.
28. Gakis G, Efstathiou J, Lerner SP, Cookson MS, Keegan KA, Guru KA, *et a*l. ICUD-EAU International Consultation on Bladder Cancer 2012: radical cystectomy and bladder preservation for muscleinvasive urothelial carcinoma of the bladder. Eur Urol 2013; 63: 45–57.
29. Lughezzani G, Sun M, Shariat SF, Budäus L, Thuret R, Jeldres C, *et al*. A population-based competing-risks analysis of the survival of patients treated with radical cystectomy for bladder cancer. Cancer 2011; 117: 103-9.
30. Weizer AZ, Joshi D, Daignault S, Kinnaman M, Hussain M, Montie JE, *et al*. Performance status is a predictor of overall survival of elderly patients with muscle invasive bladder cancer. J Urol 2007; 177: 1287-93.
31. Abdollah F, Sun M, Schmitges J, Thuret R, Djahangirian O, Jeldres C, *et al*. Development and validation of a reference table for prediction of postoperative mortality rate in patients treated with radical cystectomy: A population-based study. Ann Surg Oncol 2012; 19: 309–17.
32. Zhan XL, Ji Y, Wang YD. Laparoscopic splenectomy for hypersplenism secondary to liver cirrhosis and portal hypertension. World J Gastroenterol 2014; 20: 5794-5800.
33. Acalovschi M. Gallstones in patients with liver cirrhosis: Incidence, etiology, clinical and therapeutical aspects. World J Gastroenterol 2014; 20: 7277-85.
34. Twaij A, Pucher PH, Sodergren MH, Gall T, Darzi A, Jiao LR. Laparoscopic vs open approach to resection of hepatocellular carcinoma in patients with known cirrhosis: Systematic review and meta-analysis. World J Gastroenterol 2014; 20: 8274-81.
35. Springer C, Mohammed N, Alba S, Theil G, Altieri VM, Fornara P, *et al*. Laparoscopic radical cystectomy with extracorporeal ileal neobladder for muscle-invasive urothelial carcinoma of the bladder: technique and short-term outcomes. World J Urol 2014; 32: 407-12.

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