

Journal of Comparative Medicine Research Reviews and Reports

Immediate Salvage Radical Cystectomy for Massive Hematuria in Muscle-Invasive Bladder Cancer: Feasibility, Safety, and Oncologic Outcomes

Bjane O*, Tmiri A, El Badr M, Kbiro A, Moataz A, Dakir M, Debbagh A, & Aboutaieb R.

Urology department, Ibn rochd hospital, faculty of medicine and pharmacy, Hassan II university, Casablanca, Morocco.

*Corresponding author: Bjane O, Urology department, Ibn rochd hospital, faculty of medicine and pharmacy, Hassan II university, Casablanca, Morocco.

Submitted: 25 March 2025 Accepted: 11 April 2025 Published: 17 April 2025

Citation: Bjane, O., Tmiri, A., El Badr, M., Kbiro, A., Moataz, A., Dakir, M., Debbagh, A., & Aboutaieb, R. (2025). Immediate Salvage Radical Cystectomy for Massive Hematuria in Muscle-Invasive Bladder Cancer: Feasibility, Safety, and Oncologic Outcomes. J of Comp Med Res Rev Rep, 2(2), 01-06.

Abstract

Objective: This study aimed to evaluate the feasibility, safety, and clinical and oncological efficacy of immediate salvage radical cystectomy in patients with muscle-invasive bladder cancer (MIBC) presenting with massive hematuria and acute anemia (Hb < 8 g/dL).

Materials and Methods: A prospective cohort of 15 patients underwent immediate open radical cystectomy with pelvic lymphadenectomy at the Urology Department of Casablanca University Hospital between January 2022 and December 2024. Preoperative clinical and demographic data, surgical parameters, and postoperative outcomes were analyzed. Functional status was assessed using the Karnofsky Performance Scale, ASA classification, Charlson Comorbidity Index, and Clavien-Dindo classification. Oncologic outcomes, including soft tissue surgical margins (STSMs) and cancer-specific survival, were evaluated. Follow-up included clinical, biochemical, and imaging assessments.

Results: All patients were male, with a mean age of 62.8 years and a mean BMI of 28.3. The mean Charlson Index was 3.6, and the median Karnofsky score was 65.6. Preoperative imaging revealed cT4 (13%), cT3b (47%), and cT3a (40%) disease, with 27% showing lymph node involvement. The mean operative time was 282 minutes, and the mean blood loss was 520 mL. All patients required transfusions (mean: 4.2 units preoperatively, 2.1 units postoperatively). Histopathology showed 93.3% high-grade transitional cell carcinoma and 6.66% squamous cell carcinoma. Positive surgical margins were observed in 20% of cases, with 6.66% STSMs positive. The cancer-specific survival rate was 60% at a median follow-up of 26 months.

Conclusion: Immediate salvage radical cystectomy is a feasible and safe intervention for MIBC with massive hematuria, providing life-saving hemostatic control and satisfactory oncologic outcomes. Despite limitations such as a small sample size and short follow-up, this approach is critical for high-risk patients. Further studies are needed to validate these findings.

Keywords: Bladder Cancer, Muscle-Invasive Bladder Cancer (Mibc), Radical Cystectomy, Salvage Cystectomy, Massive Hematuria, Soft Tissue Surgical Margins (Stsms), Oncologic Outcomes, Clavien-Dindo Classification.

Introduction

Bladder cancer is one of the most common cancers worldwide, ranking as the ninth most frequently diagnosed cancer, with over

380,000 new cases annually and more than 150,000 deaths each year. It exhibits a significant male predominance, with an estimated male-to-female ratio of 3.8:1.0 [1].

Radical cystectomy remains the gold standard treatment for muscle-invasive bladder cancer (stages T2 to T4) in most Western countries [2, 3]. Although this procedure significantly impacts patients' quality of life, it is associated with low mortality and an acceptable complication rate, making it a preferred therapeutic option in many institutions [4–6].

In some cases, salvage cystectomy is necessary, particularly for non-responding patients to conservative treatments, in cases of tumor recurrence after bladder resection, or for non-urothelial carcinomas. It can also be performed with a palliative intent to manage complications such as fistulas, persistent pain, or recurrent macroscopic hematuria [7, 8].

However, performing an immediate salvage radical cystectomy in the context of acute massive hemorrhage due to muscle-invasive bladder cancer remains a rare and poorly documented clinical scenario in the literature. To our knowledge, this study is the first to report a case series of hemostatic cystectomies performed emergently to control massive hemorrhage related to bladder cancer.

The aim of this study was to evaluate the feasibility, safety, and clinical and oncological efficacy of this surgical strategy in the context of hemorrhagic emergencies. This approach poses particular challenges due to the often-precarious clinical condition of patients, the technical complexity of the procedure, and the generally poor oncological prognosis associated with advanced bladder cancers.

Materials and Methods

This study was conducted in the Urology Department of the Casablanca University Hospital between January 2022 and December 2024. We prospectively collected data from a cohort of 15 patients who underwent immediate open radical cystectomy with pelvic lymphadenectomy for muscle-invasive bladder cancer, causing massive hematuria, acute anemia (Hb < 8 g/dL), and an inability to delay surgery. Preoperative clinical and demographic characteristics (listed in Table 1), surgical data, and postoperative parameters were included. A retrospective study was conducted to evaluate operative data, intra- and postoperative complications, and oncologic outcomes, with a median follow-up of 26 months. A contrast-enhanced abdominal CT scan was performed for the clinical staging of bladder cancer.

Table 1: Patient Demographics and Clinical Characteristics.

Preoperative functional status was assessed using the Karnofsky Performance Status Scale [9], the American Society of Anesthesiologists (ASA) Classification System, the Charlson Comorbidity Index [10], and the Clavien-Dindo Classification of Surgical Complications [11]. We also evaluated operative time, blood loss and transfusion rate, length of stay in the intensive care unit, and total hospitalization duration.

Postoperative follow-up included clinical examination and biochemical assessment every 3 months during the first year, every 6 months during the second year, and annually thereafter. An abdominal ultrasound scan was performed one month after surgery to assess the upper urinary tract status following urinary diversion. Additionally, a thoraco-abdominal CT scan was performed at 3 and 9 months postoperatively, then annually or when clinically indicated. The tumor grade was determined by pathologists according to the 1973 WHO grading system [12], and the pathological stage was assigned based on the 2009 American Joint Committee on Cancer (AJCC) TNM staging system [13].

Oncologic outcomes were assessed based on soft tissue surgical margin (STSM) positivity, overall surgical margin positivity (including ureteral, urethral, and soft tissue), and cancer-specific survival. A positive STSM was defined as the presence of tumor cells in the inked areas of soft tissue on the radical cystectomy specimen.

Results

All patients were male, with a mean age of 62.8 years (ranging from 46 to 74 years) and a mean BMI of 28.3. (range 20–36). The mean Charlson Index was 3.6, and the median Karnofsky score was 65.6 (Table 1). All patients were classified as ASA grade 2, with only one patient classified as grade 4. Due to the patients' age, comorbidities were relatively common. The most frequent condition was hypertension, with an occurrence rate of 13% (2/15). A history of pulmonary tuberculosis was present in 6.66% of patients (1/15). A history of cholecystectomy was present in 13% (2/15). Hyperuricemia was observed in 6.66% (1/15), end-stage renal disease (ESRD) in 6.66% (1/15), and one patient had a history of inguinal hernia surgery, with an incidence of 6.66% (1/15) (Table 2).

Age (mean)	62,8 (46–74)
Sex M : F	100:0
BMI (mean)	28.3 (20–36)
Charlson Index (mean)	3,6 (2–10)
Karnofsky scale (median)	65,6 (60-90)
ASA (median)	2

Table 2: Comorbidities.

Hypertension	(2/15) 13%
Pulmonary tuberculosis	(1/15) 6.66%
Cholecystectomy	(2/15) 13%
Hyperuricemia	(1/15) 6.66%

End-stage renal disease (ESRD)	(1/15) 6.66%
Inguinal hernia surgery	(1/15) 6.66%
Others	(2/15) 13%

All patients presented with muscle-invasive bladder cancer on CT imaging: 2/15 (13%) were classified as cT4, 7 as cT3b (47%), and 6 as cT3a (40%). Clinical lymph node involvement was present in 4/15 cases (27%): 1 (6.66%) was cN3, 1 cN2, and 2 cN1. Metastases occurred in 2 patients (13%), with all cases being pulmonary metastases. The mean preoperative hemoglobin level was 6 mg/dL (2.4–8.9). The mean operative time was 282 minutes (195–390). The mean blood loss was 520 mL (300–700). The overall transfusion rate was 100%, with a mean of 4.2 blood units (275 mL per unit) per patient preoperatively and 2.1 units postoperatively.

In 5 cases, urinary diversion was performed using a Bricker procedure; for 4 patients, while for 10 patients, cutaneous ureterostomy was the only available option due to comorbidities, performance status, and age. No intraoperative complications occurred. Intensive care was required for 5/15 patients (33.3%), with a mean intensive care stay of 2 days (1–9).

Histopathological examination revealed high-grade transitional cell carcinoma in 93.3% of cases (14/15), and squamous cell carcinoma of the bladder was diagnosed in one patient. Pathological staging showed 4 cases of pT2b (26.6%), 3/15 (20%) of pT3a, 4/15 (26.6%) of pT3b, and 4/15 (26.6%) of pT4. Lymph node involvement was confirmed in 6 patients (40%): 3/15 were pN1, 2/15 pN2, and 1/15 pN3. A median of 16 lymph nodes (ranging from 7 to 26) was removed. Concomitant prostate cancer was present in 1 patient (6.66%). The overall positive surgical margin rate was 20% (3/15). Soft tissue surgical margins (STSMs) were positive in 1/15 cases (6.66%), localized in the lateral bladder wall. Clinical and pathological data are summarized in Table 3.

Table 3: Clinical and pathological data.

Grade		
High	15/15(100%)	
Concomitant CIS	0/15(0%)	
	cTNM	
T3a	6/15(40%)	
T3b	7/15(47%)	
T4	2/15(13%)	
N0	11/15(74%)	
N1	2/15(13%)	
N2	1/15(6,66%)	
N3	1/15(6,66%)	
M0	13/15(87%)	
M1	2/15(13%)	
	pTNM	
T2b	4/15(26,6%)	
T3a	3/15(20%)	
T3b	4/15(26,6%)	
T4	4/15(26,6%)	
N0	9/15(60%)	
N1	3/15(20%)	
N2	2/15(13%)	
N3	1/15(6,66%)	
M0	13/15(87%)	
Mx	2/15(13%)	
Mean lymph node removed	16 (7–26)	
Urir	narydiversion	
UCS	10/15(67%)	
Bricker	5/15(34%)	
Overall PSM	3/15(20%)	

Positive STSM	1/15(6,66%)
Concomitant prostate cancer	1/15(6,66%)

UCS: ureterocutaneostomy; PSM: positive surgical margins; STSM: softtissuesurgicalmargin.

All patients experienced at least one postoperative complication, with a total of 30 complications. According to the Clavien-Dindo classification, grade I and II complications were 14 (46.6%) and 11 (36.6%), respectively; 5 grade III complications (16.6%) occurred: nephrostomy drainage (grade IIIa) for urinary leakage from the ureteral anastomosis. No patient experienced a grade IIIb or grade IV complication.

Preoperative hydronephrosis was present in 60% of patients (9/15). Three months after surgery, 4/15 patients (25%) presented with hydronephrosis. The mean serum hemoglobin level at discharge was 8.74 g/dL (8.1–10.9). The mean hospital stay was 15.2 days (14–29). 6/15 patients (40%) were scheduled for adjuvant chemotherapy.

At a median follow-up of 26 months, the cancer-specific survival rate was 60 %: 6/15 patients died from bladder cancer after a mean postoperative period of 167 days (ranging from 90 to 330 days).

Discussion

Radical cystectomy with pelvic lymphadenectomy has been the gold standard treatment for muscle-invasive bladder cancer for several decades, providing local cancer control and improving long-term survival [2]. However, recently, for selected patients, some authors have proposed a bladder-preserving multimodal therapy, including transurethral resection of the bladder (TURB), external beam radiotherapy, and chemotherapy, as an effective alternative to radical cystectomy, aiming to preserve patients' quality of life while achieving promising oncologic outcomes [12, 13]. Thus, salvage radical cystectomy is performed when conservative treatment fails. In contrast, our study exclusively includes cases requiring immediate salvage radical cystectomy as a "rescue" treatment due to massive macrohematuria.

Age, general health status, and comorbidities influence the choice of initial treatment and the type of urinary diversion: for this reason, radical cystectomy is generally reserved for younger patients without significant comorbidities and with a good performance status [14]. In our series, the mean age was 62.8 years, the mean Charlson Comorbidity Index was 3.6, and the median Karnofsky Performance Scale was 65.6. All patients were classified as ASA grade 2, primarily due to acute anemia. Although each patient experienced at least one postoperative complication, major complications (defined as Clavien-Dindo grade III, IV, and V complications) occurred in 33.3% of cases. This result is comparable, though slightly higher, than that of larger series [5, 6], which can be partially explained by the small sample size of our study. Moreover, Hautmann et al. reported early complications (within 3 months post-surgery) in 58% of patients in a large monocentric series [15]. In two long-term studies and a population-based cohort study, perioperative mortality was reported to range between 1.2-3% at 30 days and 2.3-5.7% at 90 days [15-17]. However, in our series, no intraoperative complications occurred.

Recently, numerous authors have emphasized the significance of positive soft tissue surgical margins (STSMs) and their role as predictors of oncologic outcomes after radical cystectomy. In a large multicenter study, Novara et al. demonstrated that positive STSMs increased the risk of disease recurrence and cancer-specific mortality in patients with pT3Nany, pT4Nany, pTanyN0, and pTanyN+ disease [18]. Dotan et al. further showed that positive STSMs were associated with a higher rate of distant metastases, whereas Hadjizacharia et al. found that positive STSMs were linked to worsened overall mortality [19, 20]. The proportion of positive STSMs increases with higher clinical T stage, advanced pathological T stage, higher pathological grade, and the presence of lymph node metastases. Therefore, the frequency of positive STSMs may depend on tumor biology (size, extension, and aggressiveness) as well as surgical factors.

In our series, overall positive surgical margins were 20%, including ureteral, urethral, and soft tissue margins. Only one patient (6,66%) had a positive STSM. Despite the small sample size, this result is comparable to larger series. Herr et al. suggested that STSM rates should remain below 10% in all cases, below 15% for locally advanced tumors, and below 20% for salvage radical cystectomies [21]. Recently, in a cohort of 1100 patients, Hautmann et al. reported a 10-year cancer-specific survival rate of 67% following radical cystectomy, including all pT stages [22]. Culp et al. reported promising oncologic outcomes, with a 5-year cancer-specific survival rate of 83.5%, but their cohort included only patients with cT2 muscle-invasive bladder cancer without high-risk features (hydronephrosis, palpable mass, adjacent organ invasion, and lymphovascular invasion) who underwent radical cystectomy alone [23]. In a multicenter study of 1180 patients who underwent radical cystectomy for pT3-4 or pT0-4N1-3 disease, Power et al. reported 2-year and 5-year cancer-specific survival rates of 67% and 53%, respectively [24-26].

In our series, cancer-specific survival was 60% after a median follow-up of 26 months. This result is lower than in larger series, but this can be explained by our cohort, which included 17% pT2b, 33.3% pT3a, and 50% pT4 disease. Additionally, oncologic outcomes may be influenced by the small sample size of our study population. Given the high-risk disease profile of our cohort, the oncologic outcomes can be considered satisfactory.

The limitations of this study include its retrospective design, small sample size, and relatively short follow-up period, particularly regarding oncologic outcomes.

Conclusion

Immediate salvage radical cystectomy is a feasible and safe intervention for muscle-invasive bladder cancer with massive hematuria, offering life-saving hemostatic control and satisfactory oncologic outcomes. Despite limitations like a small sample size and short follow-up, this approach is critical for high-risk patients. Further studies are needed to validate these findings.

References

- Global Burden of Disease Cancer Collaboration. (2017). Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: A systematic analysis for the Global Burden of Disease Study. JAMA Oncology, 3(4), 524–548. https://doi.org/10.1001/jamaoncol.2016.5688
- Witjes, J. A., Bruins, H. M., Cathomas, R., Compérat, E. M., Cowan, N. C., Gakis, G., ... & van der Heijden, A. G. (2021). EAU guidelines on muscle-invasive and metastatic bladder cancer. European Urology, 79(1), 82–104. https://doi.org/10.1016/j.eururo.2020.03.055.
- Stein, J. P., Lieskovsky, G., Cote, R., Groshen, S., Feng, A. C., Boyd, S., Skinner, E., Bochner, B., Thangathurai, D., Mikhail, M., Raghavan, D., & Skinner, D. G. (2001). Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. Journal of clinical oncology: official journal of the American Society of Clinical Oncology, 19(3), 666–675. https://doi.org/10.1200/ JCO.2001.19.3.666
- World Health Organization (WHO) Consensus Conference on Bladder Cancer, Hautmann, R. E., Abol-Enein, H., Hafez, K., Haro, I., Mansson, W., Mills, R. D., Montie, J. D., Sagalowsky, A. I., Stein, J. P., Stenzl, A., Studer, U. E., & Volkmer, B. G. (2007). Urinary diversion. Urology, 69(1 Suppl), 17–49. https://doi.org/10.1016/j.urology.2006.05.058
- Shabsigh, A., Korets, R., Vora, K. C., Brooks, C. M., Cronin, A. M., Savage, C., Raj, G., Bochner, B. H., Dalbagni, G., Herr, H. W., & Donat, S. M. (2009). Defining early morbidity of radical cystectomy for patients with bladder cancer using a standardized reporting methodology. European urology, 55(1), 164–174. https://doi.org/10.1016/j.eururo.2008.07.031.
- Novara, G., Catto, J. W., Wilson, T., Annerstedt, M., Chan, K., Murphy, D. G., Motttrie, A., Peabody, J. O., Skinner, E. C., Wiklund, P. N., Guru, K. A., & Yuh, B. (2015). Systematic review and cumulative analysis of perioperative outcomes and complications after robot-assisted radical cystectomy. European urology, 67(3), 376–401. https://doi.org/10.1016/j.eururo.2014.12.007
- Herr, H. W. (1992). Salvage cystectomy for recurrent bladder cancer after radiation therapy. Urologic Clinics of North America, 19(4), 789–795.
- Dotan, Z. A., Kavanagh, K., Yossepowitch, O., Kaag, M., Olgac, S., Donat, M., & Herr, H. W. (2007). Positive surgical margins in soft tissue following radical cystectomy for bladder cancer and cancer specific survival. The Journal of urology, 178(6), 2308–2313. https://doi.org/10.1016/j. juro.2007.08.023
- Mor, V., Laliberte, L., Morris, J. N., & Wiemann, M. (1984).
 The Karnofsky Performance Status Scale: An examination of its reliability and validity in a research setting. Cancer, 53(9), 2002–2007. https://doi.org/10.1002/1097-0142(1984 0501)53:9<2002::AID-CNCR2820530915>3.0.CO;2-#
- Charlson, M. E., Pompei, P., Ales, K. L., & MacKenzie, C. R. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of chronic diseases, 40(5), 373–383. https://doi.org/10.1016/0021-9681(87)90171-8

- 11. Dindo, D., Demartines, N., & Clavien, P. A. (2004). Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Annals of surgery, 240(2), 205–213. https://doi.org/10.1097/01.sla.0000133083.54934.ae
- 12. Epstein, J. I., Amin, M. B., Reuter, V. R., & Mostofi, F. K. (1998). The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. Bladder Consensus Conference Committee. The American journal of surgical pathology, 22(12), 1435–1448. https://doi.org/10.1097/00000478-199812000-00001L. H. Sobin, M. Gospodariwicz, and C. Wittekind, TNM Classification of Malignant Tumours. UICC International Union Against Cancer, Wiley-Blackwell, 7th edition, 2009.
- Shipley, W. U., Kaufman, D. S., Zehr, E., Heney, N. M., Lane, S. C., Thakral, H. K., ... & Tester, W. J. (2002). Selective bladder preservation by combined modality protocol treatment: Long-term outcomes of 190 patients with invasive bladder cancer. Urology, 60(1), 62–67. https://doi.org/10.1016/S0090-4295(02)01617-1
- 14. Rödel, C., Weiss, C., & Sauer, R. (2005). Organ preservation by combined modality treatment in bladder cancer: The European perspective. Seminars in Radiation Oncology, 15(1), 28–35. https://doi.org/10.1016/j.semradonc.2004.09.006.
- Miller, D. C., Taub, D. A., Dunn, R. L., Montie, J. E., & Wei, J. T. (2003). The impact of co-morbid disease on cancer control and survival following radical cystectomy. The Journal of Urology, 169(1), 105–109. https://doi.org/10.1016/S0022-5347(05)64041-4
- Hautmann, R. E., de Petriconi, R. C., & Volkmer, B. G. (2010). Lessons learned from 1,000 neobladders: The 90-day complication rate. Journal of Urology, 184(3), 990–994. https://doi.org/10.1016/j.juro.2010.05.020
- 17. Stein, J. P., & Skinner, D. G. (2006). Radical cystectomy for invasive bladder cancer: Long-term results of a standard procedure. World Journal of Urology, 24(3), 296–304. https://doi.org/10.1007/s00345-006-0084-8
- Porter, M. P., Gore, J. L., & Wright, J. L. (2011). Hospital volume and 90-day mortality risk after radical cystectomy: A population based cohort study. World Journal of Urology, 29(1), 73–77. https://doi.org/10.1007/s00345-010-0553-2
- 19. Novara, G., Svatek, R. S., Karakiewicz, P. I., Skinner, E., Ficarra, V., Fradet, Y., ... & Shariat, S. F. (2010). Soft tissue surgical margin status is a powerful predictor of outcomes after radical cystectomy: A multicenter study of more than 4400 patients. Journal of Urology, 183(6), 2165–2170. https://doi.org/10.1016/j.juro.2010.02.005
- Dotan, Z. A., Kavanagh, K., Yossepowitch, O., Kaag, M., Olgac, S., Donat, S. M., & Herr, H. W. (2007). Positive surgical margins in soft tissue following radical cystectomy for bladder cancer and cancer-specific survival. The Journal of Urology, 178(6), 2308–2313. https://doi.org/10.1016/j. juro.2007.08.024
- Hadjizacharia, P., Stein, J. P., Cai, J., & Miranda, G. (2009).
 The impact of positive soft tissue surgical margins following radical cystectomy for high-grade, invasive bladder cancer. World Journal of Urology, 27(1), 33–38. https://doi.org/10.1007/s00345-008-0301-2

- Herr, H., Lee, C., Chang, S., & Lerner, S. (2004). Standardization of radical cystectomy and pelvic lymph node dissection for bladder cancer: A collaborative group report. Journal of Urology, 171(5), 1823–1827. https://doi.org/10.1097/01.ju.0000120227.56467.ca
- Hautmann, R. E., de Petriconi, R. C., Pfeiffer, C., & Volkmer, B. G. (2012). Radical cystectomy for urothelial carcinoma of the bladder without neoadjuvant or adjuvant therapy: Long-term results in 1100 patients. European Urology, 61(5), 1039–1047. https://doi.org/10.1016/j.eururo.2012.01.060
- 24. Culp, S. H., Dickstein, R. J., Grossman, H. B., Millikan, R. E., Dinney, C. P., Bochner, B. H., ... & Kamat, A. M. (2014).

- Refining patient selection for neoadjuvant chemotherapy before radical cystectomy. The Journal of Urology, 191(1), 40–47. https://doi.org/10.1016/j.juro.2013.07.086
- 25. Power, N. E., Kassouf, W., Bell, D., Fairey, A., Chin, J., Izawa, J., ... & Cagiannos, I. (2012). Natural history of pT3–4 or node-positive bladder cancer treated with radical cystectomy and no neoadjuvant chemotherapy in a contemporary North American multi-institutional cohort. Journal of the Canadian Urological Association, 6(6), E217–E223. https://doi.org/10.5489/cuaj.11272
- 26. Cochetti, G., Barillaro, F., Boni, A., & Mearini, E. (2015). Immediate Radical Cystectomy for Massive Bleeding of Bladder Cancer. BioMed research international, 2015, 154392. https://doi.org/10.1155/2015/154392

Copyright: ©2025 Bjane O, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.