



# Neoadjuvant therapy does not adversely affect the short-term outcome of critically ill cancer patients who underwent surgery

Xue-Zhong Xing, Hai-Jun Wang, Shi-Ning Qu, Chu-Lin Huang, Hao Wang, Zhen-Nan Yuan, Hao Zhang, Quan-Hui Yang

Department of Intensive Care Unit, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

**Contributions:** (I) Conception and design: XZ Xing; (II) Administrative support: XZ Xing; (III) Provision of study materials or patients: XZ Xing; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: XZ Xing; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

**Correspondence to:** Xue-Zhong Xing. Department of Intensive Care Unit, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China. Email: xingxuezhong@cicams.ac.cn.

**Background:** There were conflicting data regarding the effects of neoadjuvant therapy (NT) on the short-term outcomes of critically ill cancer patients. The aim of this study was to investigate whether NT adversely affect the short-term outcomes of critically ill cancer patients who underwent surgery.

**Methods:** This was a retrospective study which enrolled all critically ill cancer patients who admitted to intensive care unit (ICU) of Cancer Hospital of Chinese Academy of Medical Sciences and Peking Union Medical College between September 2017 and September 2018. Patients were divided into two groups: NT group and no NT (nNT) group. The primary outcome was ICU mortality rate. Propensity score analysis and Logistic regression analysis were used to investigate risk factors of ICU death.

**Results:** Hundred and twenty-eight patients received NT and 737 patients did not. The ICU mortality was higher in NT group than that in nNT group (3.9% vs. 1.4%,  $P=0.041$ ) before propensity score matching analysis. After matching, there were no significant difference in ICU mortality between NT group and nNT group. Univariable logistic analysis demonstrated that a history of coronary heart disease ( $P=0.008$ ), NT ( $P=0.041$ ), unplanned admission to ICU ( $P<0.001$ ), simplified acute physiology score (SAPS) 3 on ICU admission ( $P<0.001$ ), sequential organ failure assessment (SOFA) on ICU admission ( $P<0.001$ ), acute kidney injury ( $P<0.001$ ), and mechanical ventilation ( $P<0.001$ ) were predictive of ICU death in all 865 patients. Multivariable logistic regression analysis demonstrated that history of coronary heart disease ( $P=0.010$ ; OR =9.614; 95% CI, 1.731–53.405), SAPS 3 on ICU admission ( $P=0.026$ ; OR =1.070; 95% CI, 1.008–1.135) and SOFA on ICU admission ( $P=0.031$ ; OR =1.289; 95% CI, 1.024–1.622) were independent risk factors of ICU death, while NT was not predictive of ICU death ( $P=0.118$ ).

**Conclusions:** NT was not a risk factor for ICU death in critically ill cancer patients who underwent surgery.

**Keywords:** Neoadjuvant therapy (NT); cancer; critically ill

Submitted Oct 03, 2019. Accepted for publication Dec 17, 2019.

doi: 10.21037/tcr.2019.12.78

View this article at: <http://dx.doi.org/10.21037/tcr.2019.12.78>

## Introduction

Neoadjuvant therapy (NT) has been increasingly used in many potential operable solid tumors such as gastric cancer, colon cancer, lung cancer, and it leads to improved long-

term survival (1-3). It was not associated with increased postoperative complications and deaths in esophageal cancer, and even decreased the incidence of some morbidities of pancreatic cancer surgeries (4,5). However, other reports had

found that NT conferred no survival benefit over adjuvant therapy in lung cancer and pancreatic cancer patients (6,7). In some studies, NT was even related to the occurrence of pulmonary embolism (8), and reduced cardiopulmonary reserve (9), which may have adverse effect on the short term outcomes of cancer patients who underwent surgery.

Currently there are no studies regarding the effect of NT on the short-term outcome in critically ill cancer patients who underwent surgeries. Therefore, we performed this study in an academic cancer center which aims to investigate whether NT affects the short-term outcome in critically ill cancer patients who underwent surgery.

## Methods

This was a retrospective study which enrolled all critically ill cancer patients who admitted to intensive care unit (ICU) of Cancer Hospital of Chinese Academy of Medical Sciences and Peking Union Medical College between September 2017 and September 2018. The study was compliant with the 1964 ethical Declaration of Helsinki and its revision. Informed consents were waived, owing to the non-interventional nature of the study.

The following data were extracted and analyzed: age, gender, preoperative co-morbidities including a diabetic mellitus, coronary heart disease, history of hypertension, and chronic obstructive pulmonary disease (COPD), body mass index (BMI), type of admission to ICU (planned or unplanned), simplified acute physiology score 3 (SAPS 3) and sequential organ failure assessment (SOFA) on the admission day of ICU, diagnosis of acute kidney injury (AKI) and sepsis during ICU, duration of ventilation, American Joint Committee on Cancer (AJCC) staging, ICU death, in-hospital death, ICU length of stay (LOS), and hospital LOS.

Patients were divided into two groups: NT group and no NT (nNT) group. NT was defined as patients underwent chemotherapy and (or) radiotherapy at least 3 months before surgery. SOFA score was determined as a total of points of six different systems, one each for the coagulation, neurological, hepatic, cardiovascular, renal, and respiratory systems (10). SAPS 3 was determined using variables within 1 hour after patient admitted to ICU (11). Sepsis was defined using the new sepsis definitions, which consisted of sepsis and septic shock (12). AKI was determined according to the absolute or relative change of serum creatinine or the change of urine output (13). AJCC staging was carried out according to AJCC Cancer staging manual (14).

The primary outcome was ICU mortality. Secondary

outcomes were duration of mechanical ventilation, ICU LOS, hospital LOS and in-hospital mortality.

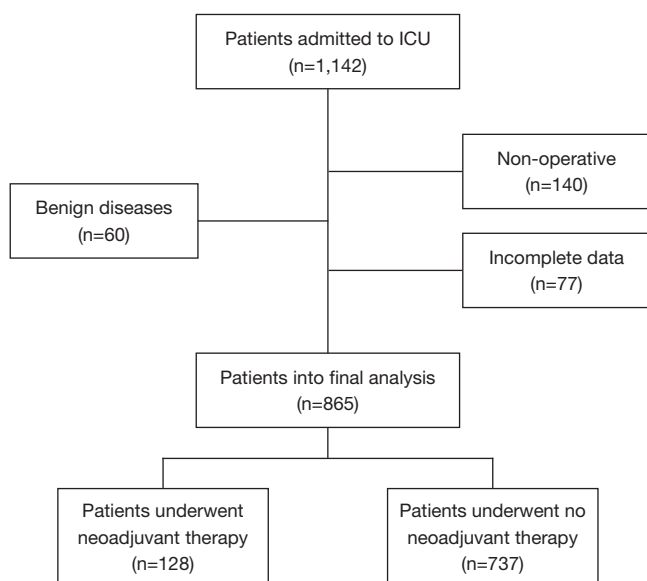
We used SPSS software for Windows, version 16.0 (SPSS Inc., Chicago, IL, USA) for statistical analysis. Categorical variables were presented as absolute numbers (percentages of frequency) and  $\chi^2$  test was used to compare the difference. Continuous variables are reported as mean  $\pm$  standard deviation and Student's *t*-test was used to compare the difference. In order to balance the confounding factors, we conducted propensity score matching analysis by the method proposed by Austin (15). First we did the logistic regression analysis that calculated propensity scores receiving NT as outcome with age, sex, co-morbidities (diabetic mellitus, coronary heart disease, hypertension, and COPD), BMI, AJCC staging and type of admission to ICU. We then excluded patients whose scores were lower than 0.05 (low chance having NT) and higher than 0.90 (high chance having NT). Then we analyzed patients with matching scores. Finally, we used univariable and multivariable logistic analysis to investigate the risk factors of ICU death. A P value less than 0.05 was defined as significant.

## Results

During the study period, there were a total of 1,142 admissions to ICU. After excluding 60 benign diseases, 140 non-operative cases, and 77 incomplete data, there were 865 patients who were enrolled into the final analysis (*Figure 1*).

General characteristics of 865 patients are presented in *Table 1*. There were 128 patients who received NT and 737 patients who received nNT. Before propensity score matching, patients in NT group were younger ( $60.08 \pm 10.15$  vs.  $64.70 \pm 12.04$ ,  $P < 0.001$ ), had more stage III to IV disease ( $68.8\%$  vs.  $38.8\%$ ,  $P < 0.001$ ) compared with patients in nNT group. There were no significant differences in gender, co-morbidities and BMI between these two groups. There were more ICU deaths in NT group compared with nNT group ( $3.9\%$  vs.  $1.4\%$ ,  $P = 0.041$ ) (*Table 2*). There were more unplanned admissions to ICU ( $39.8\%$  vs.  $28.5\%$ ,  $P = 0.01$ ) more mechanical ventilations ( $52.3\%$  vs.  $36.4\%$ ,  $P = 0.001$ ) in NT group than those in nNT group. Patients in NT group were more severe as reflected by higher SAPS 3 ( $41.77 \pm 13.35$  vs.  $35.03 \pm 12.37$ ,  $P < 0.001$ ) and SOFA ( $3.60 \pm 2.84$  vs.  $2.61 \pm 2.70$ ,  $P < 0.001$ ).

After matching, the general characteristics of patients including age, gender, co-morbidities, BMI, unplanned admissions to ICU and tumor staging were similar between



**Figure 1** Flow chart of the study.

two groups (*Table 1*). There were no significant differences in secondary outcomes including duration of mechanical ventilation, ICU mortality, in-hospital mortality, ICU LOS and hospital LOS between NT group and nNT group (*Table 2*).

For all 865 patients, univariable logistic analysis demonstrated that a history of coronary heart disease ( $P=0.008$ ), NT ( $P=0.041$ ), unplanned admission to ICU ( $P<0.001$ ), SAPS 3 on ICU admission ( $P<0.001$ ), SOFA on ICU admission ( $P<0.001$ ), AKI ( $P<0.001$ ), and mechanical ventilation ( $P<0.001$ ) were risk factors of ICU death (*Table 3*). Multivariable logistic regression analysis demonstrated that a history of coronary heart disease ( $P=0.010$ ; OR =9.614; 95% CI, 1.731–53.405), SAPS 3 on ICU admission ( $P=0.026$ ; OR =1.070; 95% CI, 1.008–1.135) and SOFA on ICU admission ( $P=0.031$ ; OR =1.289; 95% CI, 1.024–1.622) were independent risk factors of ICU death, while NT was not ( $P=0.118$ ).

## Discussion

In this study, we used two statistical methods to analyze the data and found that in critically ill cancer patients who underwent surgery, NT was not a risk factor for ICU death.

In our study, ICU mortality was increased in patients who received NT before propensity score matching analysis. Sabra *et al.* found that NT was associated with the occurrence of pulmonary embolism in esophageal cancer patients (8). Yendamuri *et al.* demonstrated that 30- and 90-day mortality were increased in advanced staged non-small cell lung cancer.

In their study, the risk of 30- and 90-day mortality in stage II was 1.11- and 1.28-fold respectively compared with stage I lung cancer, and was 1.19- and 1.53-fold respectively in stage III, and 1.72- and 2.99-fold in stage IV (16). In our study, more patients in NT group had stage III–IV cancer (68.8% *vs.* 38.8%), which may account for increased ICU mortality and hospital mortality in patients who received NT compared with patients who did not receive NT. After controlling confounder factors including age, tumour staging, the ICU mortality was similar between NT group and nNT group in this study.

In addition, other postoperative complications such as septic shock, AKI were also similar between two groups, and there were no significant differences in secondary outcomes including duration of mechanical ventilation, ICU LOS and hospital LOS. Combined literatures and our results, we concluded that NT was safe, and it did not lead to increment of postoperative complications rates or 30-day mortality (4).

Although the propensity scores matching analysis had advantages over conventional regression modeling, and it is a well option for the analysis of data of non-randomized intervention trials (17), regression model is still a commonly used statistical method to control confounder factors. In this study, we also used the regression model to investigate whether NT was a risk factor of ICU death. In our study, although univariable logistic analysis showed that NT was associated with increased odds of ICU death, multivariable logistic regression analysis demonstrated that a history of coronary heart disease, SAPS 3 score on ICU admission and SOFA on ICU admission were risk factors of ICU death, while NT was not. Our results were consistent with Sabra *et al.*, that NT did not adversely affect 30-day death in cancer patients after esophagectomy. In Sabra *et al.* study, they also used multivariable logistic regression by data of American College of Surgeons National Surgical Quality Improvement Program (8).

However, controversy exists regarding the benefit of NT on the short-term outcome of cancer patients who underwent surgeries. Yendamuri *et al.* examined the impact of NT on the short-term and long-term survival in lung cancer patients with the National Cancer Database (16). They found that 30-day (3% *vs.* 2.6%;  $P<0.01$ ) and 90-day mortality (6.5% *vs.* 4.9%;  $P<0.01$ ) was higher in patients who received NT than patients who underwent upfront surgery after univariable and multivariable logistic analysis. However, follow up of the study demonstrated superior long-term survival in NT group than that in upfront surgery group. This paradox phenomenon deserves further study.

Several limitations should be noted in this study. First, the

**Table 1** Characteristics of neoadjuvant therapy in critically ill cancer patients before and after propensity scoring matching

Clinical variables	Before propensity scores matching			After propensity scores matching		
	NT group (n=128)	nNT group (n=737)	P value	NT group (n=118)	nNT group (n=118)	P value
Age (years)	60.08±10.15	64.70±12.04	<0.001	59.94±10.01	60.52±11.35	0.680
Male (%)	39 (30.5)	251 (34.1)	0.676	85 (72.0)	77 (65.3)	0.262
Hypertension (%)	11 (8.6)	89 (12.1)	0.427	39 (33.1)	37 (31.4)	0.781
Coronary heart disease (%)	15 (11.7)	113 (15.3)	0.255	7 (5.9)	9 (7.6)	0.605
Diabetic mellitus (%)	1 (0.8)	13 (1.8)	0.288	11 (9.3)	13 (11.0)	0.667
COPD (%)	39 (30.5)	251 (34.1)	0.416	0	1 (0.8)	0.316
BMI (kg/m <sup>2</sup> )	24.39±5.22	24.03±3.58	0.341	24.39±5.22	24.55±3.78	0.780
AJCC staging (%)			<0.001			0.572
Stage 0–II	40 (31.2)	451 (61.2)		34 (28.8)	38 (32.2)	
Stage III–IV	88 (68.8)	286 (38.8)		84 (71.2)	80 (67.8)	
Type of ICU admission (%)			0.010			0.166
Planned admission	77 (60.2)	527 (71.5)		74 (62.7)	84 (71.2)	
Unplanned admission	51 (39.8)	210 (28.5)		44 (37.3)	34 (28.8)	
SAPS3 score on ICU admission	41.77±13.35	35.03±12.37	<0.001	41.62±13.42	33.24±11.35	<0.001
SOFA score on ICU admission	3.60±2.84	2.61±2.70	<0.001	3.42±2.55	2.58±2.79	0.017
Septic shock (%)	6 (4.7)	31 (4.2)	0.804	5 (4.2)	4 (3.4)	0.734
Acute kidney injury (%)	5 (3.9)	22 (3.0)	0.580	5 (4.2)	5 (4.2)	1.000
Mechanical ventilation (%)	67 (52.3)	268 (36.4)	0.001	59 (50.0)	49 (41.5)	0.191

NT, neoadjuvant therapy; nNT, no neoadjuvant therapy; COPD, chronic obstructive pulmonary disease; BMI, body mass index; AJCC, American Joint Committee on Cancer; SAPS 3, simplified acute physiology score; SOFA, sequential organ failure assessment.

**Table 2** Short term outcome of neoadjuvant therapy in critically ill cancer patients before and after propensity scoring matching

Clinical variables	Before propensity scores matching			After propensity scores matching		
	NT group (n=128)	nNT group (n=737)	P value	NT group (n=118)	nNT group (n=118)	P value
Duration of mechanical ventilation	0.94±1.90	0.75±1.91	0.315	0.75±1.32	0.93±2.30	0.467
ICU length of stay (d)	3.12±3.16	3.12±3.63	0.982	3.11±2.94	3.28±4.36	0.727
Hospital length of stay (d)	17.59±9.33	16.70±12.24	0.438	17.93±9.20	17.06±15.7	0.603
ICU death (%)	5 (3.9)	10 (1.4)	0.041	4 (3.4)	2 (1.7)	0.408
Hospital death (%)	5 (3.9)	10 (1.4)	0.041	4 (3.4)	2 (1.7)	0.408

NT, neoadjuvant therapy; nNT, no neoadjuvant therapy; ICU, intensive care unit.

results were from a single center, and the sample is relatively small, further multicenter large sample studies are in need to clear up the role of NT on short-term outcome in critically

ill cancer patients who underwent surgeries. Second, there is a high heterogeneities in patients in this study. There were cancer patients of different sites including cancer of head

**Table 3** Univariable and multivariable logistic analysis of risk factors of ICU death in critically ill cancer patients before propensity scores matching

Clinical variables	Univariable analysis			Multivariable analysis	
	ICU death (n=15)	ICU alive (n=850)	P value	P value	RR (95% CI)
Age (years)	60.87±9.02	64.00±11.94	0.781		
Male (%)	9 (60.0)	565 (66.5)	0.599		
Hypertension (%)	6 (40.0)	284 (33.4)	0.592		
Coronary heart disease (%)	5 (33.3)	95 (11.2)	0.008	0.010	9.614 (1.731–53.405)
Diabetic mellitus (%)	0	128 (15.1)	0.103		
COPD (%)	0	14 (1.6)	0.616		
BMI (kg/m <sup>2</sup> )	23.63±3.11	24.09±3.87	0.674		
AJCC staging (%)			0.799		
Stage 0-II	9 (60.0)	482 (56.7)			
Stage III-IV	6 (40.0)	368 (43.3)			
Neoadjuvant therapy (%)	5 (33.3)	123 (14.5)	0.041	0.118	3.502 (0.728–16.852)
Type of ICU admission (%)			<0.001	0.990	
Planned admission	0	604 (71.1)			
Unplanned admission	15 (100.0)	246 (28.9)			
SAPS3 on ICU admission	71.20±15.07	35.40±11.80	<0.001	0.026	1.070 (1.008–1.135)
SOFA on ICU admission	10.53±3.94	2.62±2.51	<0.001	0.031	1.289 (1.024–1.622)
Septic shock (%)	2 (13.3)	35 (4.1)	0.080		
Acute kidney injury (%)	3 (20.0)	24 (2.8)	<0.001	0.169	3.373 (0.597–19.059)
Mechanical ventilation (%)	15 (100.0)	320 (37.6)	<0.001	0.991	

ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; BMI, body mass index; AJCC, American Joint Committee on Cancer; SAPS 3, simplified acute physiology score; SOFA, sequential organ failure assessment.

and neck, cancer of thorax, cancer of abdomen. However, the main endpoint was ICU death in our study, and short-term outcome of cancer patients mainly depend on the disease severity, but not the type of primary tumor, because the nature of cancer biologics might not significantly affect short-term outcomes but long-term survival (18). Third, intraoperative variables were not included in this study, as intraoperative esophagectomy surgical Apgar score is a risk factor of major morbidity in patients who underwent open esophagectomy in our previous study (19).

In conclusion, we found that NT was not a risk factor of ICU death in critically ill cancer patients who underwent surgery. Owing to the beneficial effect of NT on long term survival in cancer patients, intensivists should make every effort to treat each critically ill cancer patient who underwent NT.

## Acknowledgments

*Funding:* This study is supported by special fund of management study of Cancer Hospital of Chinese Academy of Medical Sciences (LC2017D06).

## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2019.12.78>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately

investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Investigational review board of Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, China approved the research and informed consent was waived owing to the observational nature of this study. The ethical number is NCC-2019C-162.

*Open Access Statement:* This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

## References

- Miao ZF, Liu XY, Wang ZN, et al. Effect of neoadjuvant chemotherapy in patients with gastric cancer: a PRISMA-compliant systematic review and meta-analysis. *BMC Cancer* 2018;18:118.
- Dehal A, Graff-Baker AN, Vuong B, et al. Neoadjuvant Chemotherapy Improves Survival in Patients with Clinical T4b Colon Cancer. *J Gastrointest Surg* 2018;22:242-9.
- Blumenthal GM, Bunn PA Jr, Chaft JE, et al. Current Status and Future Perspectives on Neoadjuvant Therapy in Lung Cancer. *J Thorac Oncol* 2018;13:1818-31.
- Mungo B, Molena D, Stem M, et al. Does neoadjuvant therapy for esophageal cancer increase postoperative morbidity or mortality?. *Dis Esophagus* 2015;28:644-51.
- Marchegiani G, Andrianello S, Nessi C, et al. Neoadjuvant Therapy Versus Upfront Resection for Pancreatic Cancer: The Actual Spectrum and Clinical Burden of Postoperative Complications. *Ann Surg Oncol* 2018;25:626-37.
- Tao X, Yuan C, Zheng D, et al. Outcomes comparison between neoadjuvant chemotherapy and adjuvant chemotherapy in stage IIIA non-small cell lung cancer patients. *J Thorac Dis* 2019;11:1443-55.
- Sohal DPS. Adjuvant and neoadjuvant therapy for resectable pancreatic adenocarcinoma. *Chin Clin Oncol* 2017;6:26.
- Sabra MJ, Smotherman C, Kraemer DE, et al. The effects of neoadjuvant therapy on morbidity and mortality of esophagectomy for esophageal cancer: American college of surgeons national surgical quality improvement program (ACS-NSQIP) 2005-2012. *J Surg Oncol* 2017;115:296-300.
- Thomson IG, Wallen MP, Hall A, et al. Neoadjuvant therapy reduces cardiopulmonary function in patients undergoing oesophagectomy. *Int J Surg* 2018;53:86-92.
- Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996;22:707-10.
- Moreno RP, Metnitz PG, Almeida E, et al. SAPS 3--From evaluation of the patient to evaluation of the intensive care unit. Part 2: Development of a prognostic model for hospital mortality at ICU admission. *Intensive Care Med* 2005;31:1345-55.
- Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315:801-10.
- Kellum JA, Lameire N, KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). *Crit Care* 2013;17:204.
- Amin MB, Edge S, Greene F. editors. *AJCC cancer staging manual*. Springer, 2017.
- Austin PC. Propensity-score matching in the cardiovascular surgery literature from 2004 to 2006: a systematic review and suggestions for improvement. *J Thorac Cardiovasc Surg* 2007;134:1128-35.
- Yendamuri S, Groman A, Miller A, et al. Risk and benefit of neoadjuvant therapy among patients undergoing resection for non-small-cell lung cancer. *Eur J Cardiothorac Surg* 2018;53:656-63.
- Benedetto U, Head SJ, Angelini GD, et al. Statistical primer: propensity score matching and its alternatives. *Eur J Cardiothorac Surg* 2018;53:1112-7.
- Kiehl MG, Beutel G, Böll B, et al. Consensus statement for cancer patients requiring intensive care support. *Ann Hematol* 2018;97:1271-82.
- Xing XZ, Wang HJ, Qu SN, et al. The value of esophagectomy surgical apgar score (eSAS) in predicting the risk of major morbidity after open esophagectomy. *J Thorac Dis* 2016;8:1780-7.

**Cite this article as:** Xing XZ, Wang HJ, Qu SN, Huang CL, Wang H, Yuan ZN, Zhang H, Yang QH. Neoadjuvant therapy does not adversely affect the short-term outcome of critically ill cancer patients who underwent surgery. *Transl Cancer Res* 2020;9(1):294-299. doi: 10.21037/tcr.2019.12.78