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

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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

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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. Inform consents were waived, owning 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 of 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 χ² test was used to compare the difference. Continuous variables are reported as mean ± 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±10.15 vs. 64.70±12.04, P<0.001), had more stage III to IV disease (35.03±12.37, P<0.001) and SOFA (3.60±2.84 vs. 2.61±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
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), 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
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 heterogeneity in patients in this study. There were cancer patients of different sites including cancer of head

| 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/m²)         | 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)        |            | 0.166 |
| Stage III–IV        | 88 (68.8)                       | 286 (38.8)                      | 84 (71.2)        | 80 (67.8)        |            |    |
| Type of ICU admission (%) | 0.010 |                     | 0.010            | 0.166 |            | |
| Planned admission   | 77 (60.2)                       | 527 (71.5)                      | 74 (62.7)        | 84 (71.2)        |            | 0.727 |
| 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.

| 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.
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.

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**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](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 owning to the observational nature of this study. The ethical number is NCC-2019C-162.

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