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The Relationship of Perioperative Blood Transfusion With Bladder Cancer Mortality In Radical Cystectomy Patients

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ABSTRACT

Background: Perioperative blood transfusion is correlated to adverse effects which lead to mortality on a few cases of patients with malignancy, especially kidney tumors. The objective of this study is to evaluate the relationship between blood transfusion timings and survival of patients with bladder cancer who undergo radical cystectomy and measure the differences in the outcomes between patients undergoing intraoperative blood transfusion and patients undergoing blood transfusion after surgery.

Methods: This research is a retrospective analytic study with a cohort design. Thirty patients with bladder tumors who performed radical cystectomy and did not undergo perioperative chemotherapy were included in the study data. Recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS) were analyzed by the Kaplan-Meier method and compared between groups with log-rank tests. Chi-square test was used for comparative evaluation of each group. Univariate and multivariate analyzes were performed to evaluate the relationship between clinical and pathological variables with risks such as RFS, CSS, and OS. P<.005 were considered statistically significant, and SPSS software was used for the entire analysis process.

Results: From a total of 29 patients who had a radical cystectomy, 22 patients received perioperative blood transfusion. The 17 patients had the transfusion intraoperatively while the rest had the transfusion after the operation. The mean of blood loss was 1491 cc and the mean of survival was 13.2 months. Intraoperative blood transfusion was associated with a significantly increased risk of disease recurrence (HR: 1.32; *P*=.034), bladder cancer mortality (HR: 1.65; *P*=.015), and all-cause mortality (HR: 12.38; *P*=.013).

Conclusions: Intraoperative blood transfusion is significantly associated with an increased risk of cancer mortality. Further investigation is needed to determine the biological mechanisms underlying patient outcomes.

INTRODUCTION

Perioperative blood transfusion is correlated to adverse effects which lead to mortality on a few cases of patients with malignancy, especially kidney tumors. The immunosuppressive effect of blood transfusion has been explained in other studies [2–4]. Additional mechanisms explaining the correlation between perioperative blood transfusion and poor outcomes on cancer include weakened host immunity caused by anesthesia drugs and opioids, also increased circulating released tumor cells caused by surgery. Those mechanisms have a great effect during surgery and potentially giving a poor outcome as long as the patient is administered to perioperative transfusion [4]. Because of this correlation, further studies are needed to obtain alternative transfusion strategies, including delaying blood transfusion, as a way to improve outcomes.

Radical cystectomy for bladder cancer is an appropriate model to observe whether the timing of blood transfusion is independently associated with disease recurrence and mortality [1]. In previous studies, perioperative blood transfusion was given to about 60% who underwent surgery and three studies showed a relationship of perioperative blood transfusion with bladder cancer-specific survival in patients undergoing radical cystectomy [5,6]. However, there is a lack of data that shows the importance of timing of blood transfusion, and it is not yet known whether there is a difference between blood transfusion during and after surgery.

METHODS

This study was a retrospective analytic study with a cohort study design. A total of 29 patients with bladder

tumors undergoing radical cystectomy and not administered to perioperative chemotherapy were included in the study data. This study data was taken in Dr. Sardjito Hospital from January 1, 2016, to December 31, 2017, and has been approved by the Ethics Committee, Faculty of Medicine Universitas Gadjah Mada (study number KE/FK/1300/EC/2019). The sample was taken using a consecutive sampling method.

All patients in Dr. Sardjito Hospital Yogyakarta who met inclusion criteria were included in the study sample. The inclusion criteria for cases consisted of having a medical record, aged ≥ 18 years old at diagnosis, having a clinical diagnosis of bladder cancer based upon radiographic, pathologic, or cytological findings alone or in combination with one another, having a radical cystectomy operation, and written informed consent obtained from the subject. The exclusion criteria consisted of having secondary cancer, not administered to perioperative chemotherapy, and having an inability to comply with the study.

Clinical and pathological variables include age, gender, preoperative hemoglobin level, TNM stage, and blood transfusion processes. Tumor stage and histological subtypes were not analyzed separately because most patients who undergo radical cystectomy have high-grade urothelial malignancies.

Perioperative blood transfusion is defined as the administration of packed red blood cells (PRC) either during surgery (intraoperatively) or during post-surgery (postoperative). Transfusion indications were based on the policies of the surgical team and anesthesia team without any standard criteria. Transfusion with other blood products was not recorded. The range of follow-up was between 0 and 20 months. The standard follow-up after radical cystectomy is every 3 months in the first 2 years after surgery, every half month for 3 years, and later once every year. Recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS) were analyzed between groups by using Kaplan-Meier analysis with log-rank statistics.

RESULTS

From a total of 29 patients who had a radical cystectomy, 22 patients received perioperative blood transfusion (**Table 1**). The 17 patients had the transfusion intraoperatively while the rest had the transfusion after the operation. The mean of blood loss was 1491 cc and the mean of overall survival was 13.2 months.

In the multivariate analysis, intraoperative blood transfusion was associated with significantly increased risk of disease recurrence (HR: 1.32; *P*=.034), bladder cancer mortality (HR: 1.65; *P*=.015), and all-cause mortality (HR: 12.38; *P*=.013); otherwise, the postoperative blood transfusion was not associated with an increased risk of recurrence (*P*=.742), bladder cancer death (P=.74), or overall mortality (*P*=.454) (**Table 2**).

Table 1. Characteristics of patients who had bladder tumor and had radical cystectomy

Parameter	value	*P*
Mean of overall survival (SD)	13.2 (7.4)	
Gender		< .001
Man	26 (89%)	
Woman	3 (11%)	
Transfusion		
During operation	17	< .001
After operation	5	< .001
Mean of Blood Loss (SD)	1491 (135)	.200
Mean of Hb before surgery (SD)	11.5 (0.35)	.207

Hb: Hemoglobin

Table 2. Multivariate analysis of the survival of patients who had the radical cystectomy

Variable	Tumor Recurrence			Death from Bladder Cancer			All-cause Mortality		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Gender (ref.:female)	1.04	0.55-1.94	0.06	1.22	0.64-2.14	0.31	1.26	0.35-2.36	0.29
Amount of blood loss	1.03	0.78-1.35	0.36	1.12	0.94-1.34	0.062	1.14	0.94-1.16	0.044
Hb before operation	0.98	0.82-1.24	0.29	0.91	0.81-1.13	0.034	0.89	0.81-1.12	0.026
Blood Transfusion (ref.: no blood transfusion)									
Intraoperative	1.32	0.62-4.38	0.034	1.65	0.82-8.12	0.015	12.38	1.3-118	0.013
Postoperative	0.34	0.06-2.62	0.742	1.03	0.24-3.11	0.74	0.417	0.04-4.33	0.454

Hb: Hemoglobin

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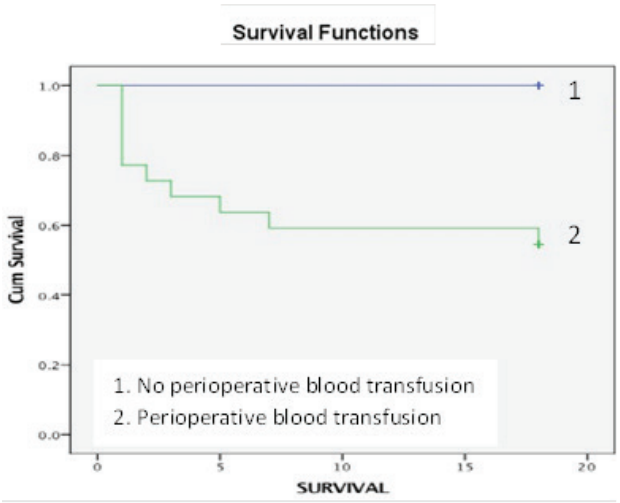

Figure 1. Kaplan-Meier curve for the survival of patients who had radical cystectomy

DISCUSSION

Our study obtained a significant difference in the age of lung cancer patients who received radiation with the occurrence of radiation pneumonitis with a *P*=043. A similar result was obtained by the study from Ivan et al. [3] which pointed out that increasing age would elevate the risk of radiation pneumonitis by 1.7 times with *P*<.0001. A study from Youngkyong et al. [4] found that age < 65 years or ≥ 65 years did not significantly cause radiation pneumonitis within 6 months (*P*=.363). The study from Kharofa et al. [5] stated that age > 70 years increased the risk of radiation pneumonitis with *P*=.01. However, this study did not explain the pathogenesis of the correlation between age and the event of radiation pneumonitis.

Our study found no significant differences between sex and the proportion of radiation pneumonitis (*P*=.34). This result was following the study from Youngkyong et al. [4] which also found that sex did not affect the event of radiation pneumonitis even though males experienced radiation pneumonitis more often (*P*=.224) [4]. Ivan et al. [3] stated that there were no significant differences between sex and the event of radiation pneumonitis. The study from Baker et al. [6] revealed that female sex increased the risk of radiation pneumonitis.

There were no differences in smoking history with the occurrence of radiation pneumonitis (*P*=.074). The different result was found in the study from Ivan et al. [3] which mentioned that smoking in irradiation was a protective factor with an odds ratio (OR) of 0.6 times and a *P*=.008. Patients with smoking history increased the risk by 0.7 times. Smoking history increased the event of radiation pneumonitis as a result of the pre-existing lung damage. Youngkyong et al. [4] stated that smoking history was not related to the incidence of radiation pneumonitis (*P*=.230). Some studies claimed that smoking history could increase the risk of radiation pneumonitis, but active smokers could protect the lung from radiation damage [7].

There were no significant differences in the performance status/PS of lung-cancer patients at the time of radiation with the proportion of radiation pneumonitis (*P*=.171). Youngkyong et al. [4] found that PS ≤ 1 or ≥ 2 was not related to the incidence of radiation pneumonitis (*P*=.130). The study from Takeyuki et al. [8] stated that PS was not related to the event of radiation pneumonitis. The diagnosis was made in this study using a CXR or thoracic CT scan in 2-week to 1-month post-radiation.

Our study obtained a significant difference between the occurrence of pneumonitis at radiation doses ≤ 4,000 and > 4,000 (*P*=.036). No significant difference was found in the radiation fraction with the event of radiation pneumonitis (*P*=.171). The radiation dose and fraction influenced the exudation process of protein material to the alveoli which promotes damage in air exchange. The results of this study were similar to the study from Joanne et al. [9] which found a significant difference between the radiation dose in a median of 4,800 cGy compared to 3,750 cGy with the incidence of radiation pneumonitis (*P*=.001). Joanne et al. [9] stated that the radiation fraction was also significantly different in the event of radiation pneumonitis (*P*=.013). Youngkyong et al. [4] pointed out that the dose < 7500 cGy or ≥ 7500 cGy was not related to the occurrence of radiation pneumonitis with a *P*=.165.

Chemotherapy regimens that were given sequentially and concurrently with radiation consisted of carboplatin and paclitaxel (66.6%), carboplatin and etoposide (26.6%), and gefitinib alone (1.77%). The chemotherapy regimens of carboplatin and paclitaxel were administered sequentially while the regimens of both carboplatin and etoposide or gefitinib alone were administered concurrently. The administration of irradiation and chemotherapy generated interferon β (IFNβ) and inflammatory mediators which caused an increase in cytotoxic radiation in the lung [10]. Lung cancer patients who received chemotherapy before radiation had a significant difference from those without chemotherapy for the incidence of radiation pneumonitis (*P*=.027). The study from Takeyuki et al. [8] found that there were no significant correlations between chemotherapy and radiation pneumonitis with a *P*=.222. This was due to the number of patients who received chemotherapy, which was less than 50% of the total study sample. Youngkyong et al. [4] obtained that the history of chemotherapy was not related to the incidence of radiation pneumonitis (*P*=.531).

The histologic types of lung cancer in this study were divided into two groups namely adenocarcinoma

and squamous cell carcinoma. The results of our study were similar to the results of the study from Takeyuki et al. [8] which also stated that there were no significant differences between the histologic types of lung cancer and the prevalence of radiation pneumonitis (*P* = .638). Youngkyong et al. [4] pointed out that histologic types of lung cancer did not correlate with the incidence of radiation pneumonitis. Following our study, Parashar et al. [11] also stated that there were no significant correlations between the histologic types of lung cancer and the occurrence of radiation pneumonitis.

Our study showed that there were no significant differences between the stage and the event of radiation pneumonitis (*P*=.669). In our study, the lung-cancer stage was divided into two groups which were III and IV. Youngkyong et al. [4] divided the stage of lung cancer into two groups namely I-IIB and IIIA-IV. The results obtained were that the stage was not related to the incidence of radiation pneumonitis with a *P*=.741. The study from Takeyuki et al. [8] found that there were no correlations between the stage and the prevalence of radiation pneumonitis (*P*=.211).

The diagnosis of radiation pneumonitis in our study was based on CXR in 1-month post-radiation. The criteria for chest radiograph was only divided into 2 categories: those with signs of radiation pneumonitis and those without signs of radiation pneumonitis. There were 13 CXRs found to have signs of radiation pneumonitis. Those 13 CXRs with radiation pneumonitis consisted of five with the feature of hazy ground-glass opacities, five with both hazy ground-glass opacities and fibrosis, and three with the feature of fibrosis. There is a theory which states that hazy ground glass opacities may disappear without sequelae if the lung damage is still limited. In some cases of severe lung damage, the opacities could develop into fibrosis [12]

The results of this study showed that the proportion of lung cancer patients who developed radiation pneumonitis at Persahabatan Hospital was 39.4%. The radiation technique used was Cobalt 60 (Co60). Youngkyong, et al. [4] stated that the proportion of lung cancer patients who experienced radiation pneumonitis at 1-month post-radiation was 13.2%. This study determined the proportion of radiation pneumonitis using CXR, thoracic CT scan, and CTCAE. The radiation technique used was different from our study, namely linac-based intensity-modulated radiotherapy. This radiation technique reduced normal lung tissue volume exposure and had a high accuracy which followed breathing patterns so that the radiation effect was reduced.

CONCLUSIONS

Intraoperative blood transfusion is significantly associated with an increased risk of recurrence, cancer mortality, and overall mortality. However, this study has a limitation of small sample size and wide CI. Further investigation is needed to determine the biological mechanisms underlying patient outcomes..

DECLARATIONS

Competing of Interest

The authors declare no potential conflicts of interest..

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