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Urologic Oncology: Seminars and Original Investigations ▮ (2017) ▮▮▮–▮▮▮

UROLOGIC ONCOLOGY

Original article

Perioperative blood transfusion adversely affects prognosis after nephrectomy for renal cell carcinoma

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Received 11 February 2017; received in revised form 7 July 2017; accepted 5 September 2017

Abstract

Background: It has been previously suggested that perioperative blood transfusion (PBT) may induce adverse oncological outcomes following cancer surgery. The aim of the current study is to evaluate the effect of PBT on the prognosis of patients who underwent nephrectomy due to renal cell carcinoma (RCC).

Methods: Study included 1,159 patients who underwent radical nephrectomy or partial nephrectomy (PN) between the years 1987 and 2013. Univariate and multivariate models were used to evaluate the association of PBT with cancer-specific survival (CSS), disease-free survival, and overall survival (OS).

Results: Of 1,159 patients undergoing nephrectomy, 198 patients (17.1%) received a PBT. The median follow-up was 63.2 months. Risk factors for PBT included: lower preoperative hemoglobin ($P < 0.01$), size of the renal mass ($P < 0.05$), open surgical approach ($P < 0.01$), and capsular invasion. Receipt of a PBT was associated with significantly adverse disease-free survival (hazard ratio [HR] = 2.1, $P = 0.02$), metastatic progression (HR = 2.4, $P = 0.007$), CSS (HR = 2.5, $P = 0.02$), and OS (HR = 2.2, $P = 0.001$). In the current study, 582 patients underwent PN; of these, 87 (14.9%) required PBT. The association of PBT with outcome remained significant in this subgroup after controlling for patient and tumor-related variables with respect to metastatic progression (HR = 5.9, $P = 0.006$), CSS (HR = 5.8, $P = 0.007$) and OS (HR = 2.1, $P = 0.05$).

Conclusion: PBT is associated with reduced recurrence-free survival, CSS, and OS in patients undergoing nephrectomy for RCC. Worse oncological outcomes are also found in a separate analysis for patients undergoing PN.

Keywords: Renal cell carcinoma; Perioperative blood transfusion; Prognosis; Survival

1. Introduction

The effects of perioperative allogeneic blood transfusion (PBT) on morbidity, mortality, and disease recurrence following cancer surgery have previously been studied in several malignancies. Various studies in lung, patients with colorectal and hepatocellular cancer have demonstrated increased risk of tumor recurrence and disease specific mortality for patients who received PBT [1–3]. The reported association between blood transfusions and oncologic outcomes changed the nature (and the amount) of blood administration in many surgical disciplines. This link has increased awareness in recent years, as many surgeons are being more hesitant or even reluctant to administrate blood, unless it is clearly indicated. However, despite the apparent consensus, the correlation between blood transfusions and prognosis remains questionable in some malignancies. Focusing on urological malignancies, while the association between PBT and adverse oncological outcomes has been established in patients with bladder cancer [4,5], such correlation is much less clear in patients with upper tract urothelial carcinoma [6,7] or prostate cancer [8–11]. Specifically for renal cell carcinoma (RCC), in the last decades, few retrospective studies examined the association between PBT and recurrence or survival after nephrectomy.

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http://dx.doi.org/10.1016/j.urolonc.2017.09.006
1078-1439/

Although part of the studies suggested that PBT resulted in increased cancer recurrence and cancer-specific mortality [12,13], several suggested limited association with all-cause mortality [14] whereas others showed no significant associations with prognosis at all [15–17].

In view of these inconsistent findings, in the current study, we aimed to examine the incidence of PBT as well as the effect of positive margins on disease specific survival in patients undergoing curative surgery for RCC.

1.1. Patients and methods

After obtaining institutional review board approval, we did a retrospective cohort study of 1,159 patients who underwent elective partial and RN for renal cancer, between the years 1988 and 2013. All operations were performed in the same surgical environment. All of the surgeries were performed by 5 senior surgeons who had performed at least 50 nephrectomies with each of the 2 surgical approaches (laparoscopic and open). Patient demographics and operative details were collected retrospectively. Clinicopathologic variables recorded included: age, gender, height, weight, and body mass index, comorbidities, preoperative hemoglobin (HB) levels, receipt of PBT, and number of units transfused. Operative variables included type of operation (i.e., open or laparoscopic). Pathological variables included capsular invasion, vascular invasion, renal pelvis invasion, perinephric fat extension, and tumor necrosis. Tumor stage was coded as a dichotomous variable, pT2 or less vs. pT3. Patients with benign histology (including metanephric adenomas, angiomyolipomas, oncocytomas, and others) were excluded from this analysis. Additional exclusion criteria included: patients with malignant tumors other than RCC (urothelial cell carcinoma, sarcoma, neuroendocrine tumor, squamous cell carcinoma, leiomyoma, and liposarcoma). And patients with metastatic disease upon diagnosis. PBT was defined as transfusion of allogenic red blood cells either during the day of operation or within the postoperative hospitalization. Notably, administration of PBT was based on the discretion of the treating physicians. No institutional standardized intraoperative or postoperative thresholds were used for transfusion. Transfusion with other blood products was not recorded. Follow-up was conducted according to accepted clinical practice at our institution. In general, follow-up consisted of physical examination, chest radiographs, and abdominal imaging every 6 to 12 months during the first 5 years and annually thereafter. Metastatic progression was defined as unequivocal imaging findings indicating distant organ involvement with or without a confirmatory diagnostic biopsy.

Statistical analysis was performed using univariate and multivariable logistic regression analyses to determine features associated with PBT. Outcomes measured include recurrence-free survival (RFS; local and distant), cancer-specific survival (CSS), and overall survival (OS). Survival was estimated as the time from nephrectomy to event using the Kaplan-Meier method and compared between cohorts with the log-rank test. Cox proportional hazard regression models were used to evaluate the association of the different PBT groups with outcomes, controlling for clinicopathologic variables. Survival analysis was performed to the entire cohort first (RN and PN), and next, to the PN group "alone." A $P < 0.05$ was considered statistically significant. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS, Version 22.0, Chicago, IL).

2. Results

Of the1,159 patients undergoing nephrectomy, 198 patients (17.1%) received a PBT (Table 1); the median number of units transfused was 2 (interquartile range: 1–3 units). Median follow-up after surgery was 63.2 months (interquartile range: 31.9–102.2; range: 6–322) during which time 165 (14.2%) patients had disease recurrence: 77 had local recurrence and 88 developed metastatic progression; 255 patients died, of whom, 55 died of renal cancer. Comparisons of the clinical and pathological features between patients who did and did not receive a PBT are shown in Table 1. Patients who received a PBT were more likely to be female ($P < 0.005$), with symptomatic presentation ($P < 0.001$) and a higher rate of adverse pathological features, including larger tumors ($P < 0.001$), high nuclear grade ($P < 0.001$), presence of tumor necrosis ($P < 0.001$), and capsular invasion ($P < 0.001$). In addition, patients who received a PBT were more likely to undergo open nephrectomy ($P < 0.05$). All variables found significantly related to receiving a PBT in the univariate analysis were introduced into a multivariable logistic regression analysis. On multivariate analysis, preoperative HB value ($P < 0.01$), size of the renal mass ($P < 0.05$), open surgical approach ($P < 0.01$), and capsular invasion remained associated with the need for PBT (Table 2). No significant difference in tumor histology was noted based on PBT status ($P = 0.14$). In addition, surgeon volume was found to be minimally associated with the rate of PBT ($P = 0.09$). Notably, receipt of a PBT was associated with significantly worse 5-year RFS (92% vs. 81%, $P < 0.01$), (Fig. 1) and metastatic free survival (93% vs. 79%, $P < 0.001$). Similarly, patients who received a PBT had adverse 5-year CSS (95% vs. 85%, $P < 0.001$) (Fig. 2) as well as adverse OS (81% vs. 73%, $P < 0.001$) compared with patients who did not receive perioperative BT (Fig. 3).

The association of PBT with outcome, controlling for patient and tumor-related variables is presented in Table 3. On the multivariate Cox model, receipt of a PBT remained associated with significantly increased risks of tumor recurrence (hazard ratio [HR] = 2., $P = 0.02$), metastatic progression (HR = 2.4, $P = 0.007$), death from RCC (HR = 2.5, $P = 0.02$), and all-cause mortality (HR = 2.2, $P = 0.001$). Advanced pathologic tumor stage and presence of tumor necrosis were also associated with