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The Impact of Perioperative Packed Red Blood Cell Transfusion on Survival in Epithelial Ovarian Cancer

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Abstract

Objective—Perioperative packed red blood cell transfusion (PRBCT) has been implicated as a negative prognostic marker in surgical oncology. There is a paucity of evidence on the impact of PRBCT on outcomes in epithelial ovarian cancer (EOC). We assessed whether PRBCT is an independent risk factor of recurrence and death from EOC.

Methods—Perioperative patient characteristics and process-of-care variables (defined by the National Surgical Quality Improvement Program) were retrospectively abstracted from 587 women who underwent primary EOC staging between January 2, 2003, and December 29, 2008. Associations with receipt of PRBCT were evaluated using univariate logistic regression models. The associations between receipt of PRBCT and disease-free survival and overall survival were evaluated using multivariable Cox proportional hazards models and using propensity score matching and stratification, respectively.

Results—The rate of PRBCT was 77.0%. The mean $\pm$ SD units transfused was 4.1 ± 3.1 U. In the univariate analysis, receipt of PRBCT was significantly associated with older age, advanced stage (IIIA), undergoing splenectomy, higher surgical complexity, serous histologic diagnosis, greater estimated blood loss, longer operating time, the presence of residual disease, and lower preoperative albumin and hemoglobin. Perioperative packed red blood cell transfusion was not associated with an increased risk for recurrence or death, in an analysis adjusting for other risk factors in a multivariable model or in an analysis using propensity score matching or stratification to control for differences between the patients with and without PRBCT.

Conclusions—Perioperative packed red blood cell transfusion does not seem to be directly associated with recurrence and death in EOC. However, lower preoperative hemoglobin was associated with a higher risk for recurrence. The need for PRBCT seems to be a stronger prognostic indicator than the receipt of PRBCT.

Keywords

Perioperative red blood cell transfusion; Ovarian cancer; Disease-free survival; Overall survival

Epithelial ovarian cancer (EOC) is the most lethal gynecologic cancer in the developed nations,¹ and perioperative care is a vital first step in EOC survival. Improvement in overall and disease-free survival (DFS) correlates with residual disease (RD) at the time of primary EOC cyto-reduction.^{2–6} However, cytoreductive surgery often requires multiorgan resection⁴ with variable amounts of estimated blood loss (EBL)^{7–9} and rates of perioperative packed red blood cell transfusion (PRBCT). Reported EBL during EOC surgery^{7–9} ranges from 200 to 1500 mL, with previously published PRBCT rates^{10–12} of 23% to 77%. To date, there is a single study that investigated PRBCT and EOC outcomes. De Oliveira et al¹¹ demonstrated that receipt of PRBCT was associated with a decrease in both time to recurrence and overall survival (OS); however, this study did not control for RD, a known independent predictor of poor oncologic outcomes.^{4–6} Thus, factors other than PRBCT receipt may be more influential in disease recurrence and survival.

Although the literature assessing the impact of PRBCT in EOC is sparse, the impact of PRBCT has been relatively well reported in colorectal, gastric, and gastroesophageal cancer.^{13–17} In colorectal cancer, disease recurrence seems to double among patients who receive PRBCT,^{13,14} regardless of whether the PRBCT is allogenic or autologous.¹⁵ In addition, in gastric cancer surgery, PRBCT is associated with the presence of larger tumors and advanced stage.¹⁸ However, when controlling for stage in gastric cancer, there does not seem to be a survival difference associated with receipt of PRBCT.¹⁸ This suggests that, at least, in gastric cancer, the receipt of PRBCT may be a surrogate for advanced stage and need for a more complex surgery, rather than a causative factor in worse prognosis.

Although most studies of PRBCT and cancer prognosis are within the gastrointestinal cancer literature, there are similarities to the surgical approaches required for these cancers and EOC staging. In addition, although there is limited data on the perioperative impact of PRBCT among women undergoing EOC cytoreduction, PRBCT administration has been identified as an independent risk factor of perioperative morbidity in cancer and benign surgery.^{10,19–21} Whether it is receipt of a transfusion, intraoperative blood loss, or clinical factors associated with PRBCT driving worse outcomes, such factors may be modifiable. Because minimizing blood loss and judicious use of PRBCT may impact DFS and OS among women with EOC, we examined the factors associated with PRBCT and the impact of PRBCT administration on survival and recurrence among women undergoing primary EOC cytoreduction.

METHODS

Patient Population

Women with EOC, primary peritoneal carcinoma, or fallopian tube carcinoma (all collectively referred to as “EOC” for this study) undergoing primary surgical staging and cyto-reduction at the Mayo Clinic in Rochester, Minn, during a 6-year period (January 2, 2003, to December 29, 2008) were included in this retrospective study. Patients were excluded if they underwent prior surgical diagnosis of their current cancer via laparoscopy or laparotomy, received neoadjuvant chemotherapy and were undergoing interval cytoreduction, were undergoing surgery for recurrent disease, had a nonepithelial malignancy, or had denied access to their medical records for research purposes. Mayo Foundation institutional review board approval was obtained.

Data Collection

Objective perioperative data were retrospectively collected, and variables defined by the American College of Surgeons’ National Surgical Quality Improvement Program platform, which contains more than 130 elements for analyzing patient risk factors and process-of-care variables,^{22,23} were abstracted. To assess the factors associated with receipt of PRBCT, patient risk factors, process-of-care variables, and disease-specific parameters were abstracted from patient charts by a trained, dedicated registered nurse abstractor. All surgical procedures performed in the process of staging and debulking were recorded, and surgical complexity scores were assigned on the basis of an established calculation protocol.²⁴ All elements of the American College of Surgeons’ National Surgical Quality Improvement Program and disease-specific parameters with a prevalence of 5% or greater and/or deemed to be clinically relevant were considered in this analysis.

Statistical Analyses

Statistical analyses were performed using the SAS software package version 9.2 (SAS Institute, Inc, Cary, NC). Univariate logistic regression models were fit to identify factors associated with the receipt of PRCBT. Associations with receipt of PRCBT were summarized by calculating odds ratios and corresponding 95% confidence intervals (CIs). The 2 outcome measures of interest were DFS and OS after the primary surgical cytoreduction for EOC. The Cox proportional hazards models were fit to take into account the timing of each outcome and the varying duration of patient follow-up. Factors were first evaluated separately in univariate Cox models, and factors with a *P* value of less than 0.20 were considered in the multivariable analysis. A parsimonious multivariable Cox model was obtained using stepwise and backward variable selection methods. Associations with the time-to-event outcomes were summarized by calculating hazard ratios (HRs) and corresponding 95% CIs.

Because PRBCT was not randomly assigned in this cohort, a multivariable analysis may not adequately control for confounding and bias. Therefore, we sought to use propensity score (PS) analyses to obtain a less biased estimate of the effect of PRBCT on each outcome (DFS and OS, respectively).²⁵ A PS was defined as the estimated probability of a patient receiving a PRBCT on the basis of demographics and process-of-care variables at the time of EOC

surgery. Propensity score values were estimated on the basis of a multivariate logistic regression model that included all of the factors listed in Table 1 because these factors were identified as being related to receiving PRBCT and related to the outcomes of interest. All 2-way interactions were investigated, and interactions with a *P* value of less than 0.20 were included in the final model. Before fitting the logistic model, missing values were imputed for the patients missing preoperative hemoglobin or creatinine. Missing values were not imputed for missing preoperative albumin because this was not considered to be missing at random.

The PSs were used in 2 ways: stratification and matching. Using the stratification approach, the patients were stratified into 5 strata on the basis of their PS values. The stratum boundaries were defined on the basis of the quintiles for the distribution of PS values common to both the PRBCT and non-PRBCT groups; the patients with a PS value outside the stratum boundaries were excluded. The goal of the stratification was to have a balance in the factors between the PRBCT and non-PRBCT groups. Within each stratum, the balance in the factors between the non-PRBCT and PRBCT patients was assessed by evaluating the standardized difference for each factor. Upon finding adequate balance, within each stratum, the impact of PRBCT on each outcome (DFS and OS) was estimated by the HR derived from fitting the Cox proportional hazards model. The HR estimates were combined across the 5 strata using an inverse-variance weighted mean. Using the matching approach, each non-PRBCT patient (smaller group) was matched to a PRBCT patient using a greedy matching algorithm, matching the logit of the PS using calipers with a width of 0.1 to the SD of the logit of the PS. Upon evaluating the standardized differences for each factor and finding adequate balance, the impact of PRBCT on the outcome was estimated by the HR obtained from fitting a stratified Cox proportional hazards model, stratifying on the matched pairs.

RESULTS

Patient Demographics

There were 587 patients who underwent primary surgical cytoreduction for EOC between January 2, 2003, and December 29, 2008. The mean age was 64 years, 430 (73%) had serous histologic diagnosis, 347 (59%) had intermediate surgical complexity, and 136 (23%) had high surgical complexity. There were 91 women (16%) with stage I disease; 37 (6%), stage II; 353 (60%), stage III; and 106 (18%), stage IV. At the time of surgery, 316 (53.8%) were debulked to microscopic RD and 184 (31.3%) were debulked to 1 cm or less but measurable disease. Thus, 500 (85.2%) received an optimal cytoreduction by contemporary definition. The overall cohort demographics have been previously published.¹⁰

Of the 299 patients (50.9% of the cohort) who recurred, the median time to recurrence was 1.1 years (interquartile range [IQR], 0.7–1.6 years). There have been 319 deaths (54.3%) in this cohort. The median time from diagnosis to death was 2.0 years (IQR, 0.8–3.3 years). Among the 268 patients who were alive at the time of this publication, the median follow-up was 2.9 years (IQR, 0.7–4.9 years).

Frequency of PRBCT and Factors Associated With PRBCT

Overall, 452 (77%) received a PRBCT. Of the 452 women transfused, 146 (32%) were transfused only intraoperatively (mean, 2.9 U; range, 1–12 U), 99 (22%) were transfused only postoperatively (mean, 2.3 U; range, 1–9 U), and 207 (46%) had both intraoperative and postoperative transfusions (mean, 5.8 U; range, 2–28 U). The cohort demographics according to receipt of PRBCT are listed in Table 1. Those who received a PRBCT were older and were more likely to have stage IIIA disease or higher, undergo splenectomy, have high surgical complexity, and have serous histologic diagnosis. The patients receiving a PRBCT were also more likely to have RD at the end of their cytoreduction. In addition, those who were transfused had more than twice the mean EBL (1136.8 vs 454.1 mL), nearly 1 hour longer surgery (mean, 266.2 vs 208.1 minutes), and lower preoperative hemoglobin (mean, 12.5 vs 13.6 g/dL) than those who were not transfused (Table 1).

Evaluation of Factors Associated With Recurrence and Death

Among the entire cohort, the following factors were associated with an increased risk for recurrence on univariate analysis: receipt of PRBCT (HR, 1.96 [95% CI, 1.43–2.68]; $P < 0.001$), older age (1.15 [1.03–1.29] per 10-year increase in age; $P = 0.01$), stage IIIA or higher (5.99 [3.82–9.39]; $P < 0.001$), splenectomy (1.90 [1.39–2.61]; $P < 0.001$), greater surgical complexity (high, 1.58 [1.10–2.27], and intermediate, 0.75 [0.53–1.06], vs low [referent]; $P < 0.001$), higher EBL (1.14 [1.07–1.22] per 500-mL increase; $P < 0.001$), serous histologic diagnosis (2.40 [1.73–3.34], vs nonserous; $P < 0.001$), and higher RD (4.20 [2.95–5.98] for >1 cm and 2.95 [2.26–3.86] for ≤ 1 cm, vs microscopic [referent]; $P < 0.001$). Lower preoperative hemoglobin (1.08 [1.04–1.13] per 0.5-g/dL decrease; $P < 0.001$) and lower preoperative albumin (1.36 [1.18–1.57] per 0.5-g/dL decrease; $P < 0.001$) were also associated with an increased risk for recurrence.

In multivariate analyses, advanced stage (IIIA), undergoing splenectomy, the presence of RD, and lower preoperative hemoglobin were identified as independent predictors associated with an increased risk for recurrence (Table 2). Packed red blood cell transfusion administration was not identified as a significant predictor of recurrence using stepwise and backward variable selection, and its HR was 1.01 (95% CI, 0.71–1.43; $P = 0.96$) after adjusting for the 4 factors above.

When analyzing OS, the following factors were identified as associated with an increased risk for death on the basis of univariate analyses: receipt of PRBCT (HR, 1.75 [95% CI, 1.31–2.33]; $P < 0.001$), older age (1.35 [1.22–1.48] per 10-year increase; $P < 0.001$), stage IIIA or higher (4.59 [3.00–7.03]; $P < 0.001$), splenectomy (1.57 [1.17–2.12]; $P = 0.003$), higher EBL (1.09 [1.03–1.16] per 500-mL increase; $P = 0.002$), serous histologic diagnosis (1.40 [1.07–1.84], vs nonserous; $P = 0.02$), higher preoperative creatinine (1.71 [1.13–2.59] per 1-mg/dL increase; $P = 0.01$), lower preoperative hemoglobin (1.08 [1.04–1.12] per 0.5-g/dL decrease; $P < 0.001$), lower preoperative albumin (1.55 [1.36–1.76] per 0.5-g/dL decrease; $P < 0.001$), and presence of RD (4.21 [3.13–5.66] for ≥ 1 cm and 2.39 [1.85–3.08] for < 1 cm, vs microscopic [referent]; $P < 0.001$). Intermediate surgical complexity (0.71 [0.54–0.95], vs low [referent] vs high (1.10 [0.79–1.52]; $P = 0.002$) was associated with a decreased risk for death.

In the multivariate analyses, older age, advanced stage (IIIA), lower preoperative albumin, and presence of RD were identified as independent predictors of an increased risk for death (Table 3). Packed red blood cell transfusion administration was not identified as a significant predictor using stepwise and backward variable selection, and its HR was 1.09 (95% CI, 0.81–1.47; $P = 0.56$) after adjusting for the 4 factors above.

Impact of PRBCT on Recurrence and Death Using Propensity Scores

The distribution of PSs for those with and without a PRBCT is depicted in Figure 1. The PS stratification approach was limited to 124 non-PRBCT patients and 209 PRBCT patients ($n = 333$ total patients) whose PS values were within the strata boundaries defined by the range common to both groups. The PS stratification analysis showed a 12% relative reduction in recurrence-free survival in the patients receiving a PRBCT; however, this effect did not reach statistical significance (Table 4; HR, 0.88; 95% CI, 0.59–1.30; $P = 0.51$). The HRs were generally consistent across the second, third, and fourth strata; within the last stratum, the results are difficult to interpret because of the small sample size of the PRBCT group. The PS matching approach was based on 113 matched pairs and yielded a 37% relative increase in recurrence-free survival in the patients receiving a PRBCT; however, this effect did not reach statistical significance (HR, 1.37; 95% CI, 0.76–2.47; $P = 0.29$).

For the outcome of OS, the PS stratification analysis yielded a nonsignificant 10% relative reduction (Table 5) in OS in the patients receiving a PRBCT (Table 5; HR, 0.90; 95% CI, 0.62–1.30; $P = 0.58$). The PS matching approach yielded a 12% relative increase in OS in the patients receiving a PRBCT; however, this effect did not reach statistical significance (HR, 1.12; 95% CI, 0.65–1.92; $P = 0.68$).

Packed Red Blood Cell Transfusion and Splenectomy

Within the whole cohort, 76 patients (12.9%) underwent splenectomy, and all but 1 received PRBCT. The most common indication for splenectomy was disease involvement (85.5%). The remaining cases (14.5%) were secondary to splenic bleeding. Among those who had a splenectomy, 71 (93.4%) had a PS value outside the strata boundaries (>0.964) and were thus excluded from the PS stratification approach. Therefore, the results from the PS analyses are essentially not applicable to patients who undergo a splenectomy.

DISCUSSION

A large proportion (77%) of the women undergoing primary EOC cytoreduction and staging received PRBCT; however, receiving a perioperative transfusion does not seem to impact recurrence or OS. As would be anticipated, advanced stage, greater surgical complexity, higher EBL, lower preoperative hemoglobin, and longer operative times were associated with an increased likelihood of transfusion. The patients who underwent splenectomy were more likely to receive PRBCT; given that 85% of all splenectomies were performed for disease involvement of the spleen, this relationship likely represents higher initial disease burden and resultant higher surgical complexity. Interestingly, splenectomy was also independently associated with worse DFS. Although splenectomy may be a surrogate for a

more extensive disease, systemic immunologic modulation may also play a role, and this warrants further investigation.

Older age, advanced stage, presence of RD, and lower preoperative albumin were identified as independent predictors of worse survival in women diagnosed with EOC; all of these factors are also associated with receipt of PRBCT. Although De Oliveira and colleagues¹¹ previously demonstrated decreased EOC survival associated with PRBCT administration, RD was not considered as a potential variable influencing outcome in that study. When controlling for RD, we did not find an association between PRBCT receipt and DFS or OS. In addition, PS analyses failed to show a survival impact associated with receipt of PRBCT.

However, although PRBCT receipt was not an independent predictor of worse DFS or OS, having a lower pre-operative hemoglobin level did independently portend worse DFS. Prior non-EOC studies have also implicated PRBCT in a causal relationship with worse oncologic outcomes.^{15,17} However, our findings raise the question as to whether it is transfusion receipt or transfusion need that is the stronger prognostic factor. In 1999, Obermair and colleagues²⁶ investigated the impact of preoperative hemoglobin levels in EOC patients. They found decreased survival in those with stage I or II disease who were anemic (<12 g/dL) compared with those with normal hemoglobin levels. This suggests that preoperative anemia is a harbinger of either more aggressive or less responsive disease or that red blood cell (RBC) dysfunction occurs before disease intervention and impacts response to treatment. Fragile RBCs leak angiogenic and cell growth factors, such as epidermal growth factor, vascular endothelial growth factor, and fibroblast growth factor, which have been shown to enhance cancer metastasis^{27,28}; such factors may influence EOC behavior and outcomes.

Among other gynecologic cancers, lower preoperative hemoglobin in surgically resectable early-stage cervical cancer has also been linked to worse prognosis.²⁹ However, receipt of perioperative RBC transfusion in the setting of radical hysterectomy for early-stage cervical cancer does not seem to impact recurrence or OS.^{30,31} In addition, although erythropoietin seems to increase the risk for thromboembolic events in cervical cancer,³² its use does not seem to be detrimental to DFS or OS in either cervical^{33,34} or ovarian cancer³⁵ survival. Whether erythropoietin administration or other interventions, such as iron infusion, before surgery can decrease the transfusion rate during primary debulking is unknown. However, the causes of preoperative anemia, the functional aspects of RBCs, and the intervention strategies in women with a new diagnosis of EOC warrant further investigation.

Clinically, the findings in this study may be of value in preoperative EOC staging and cytoreduction counseling. More than 43% of the patients in this study had PSs of greater than 0.96, which represents a group of patients at such high risk for requiring PRBCT that the univariate analyses of the 5 strata in the PS stratification analysis do not apply to them. The knowledge that 77% of the women undergoing primary debulking will require transfusion may enhance the risk/benefit discussion. In addition, given the high rate of transfusion, providers should be prepared to manage rare but serious transfusion-related sequelae such as hemolytic reactions, transfusion-related acute lung injury, and transfusion-related immune reactions.^{36–38}

The limitations of this study include the fact that more than three quarters of the cohort received a PRBCT and that the other clinical factors associated with both EOC outcomes and the need for transfusion may have outweighed the influence of PRBCT. Given the multiple tumor and perioperative factors associated with PRBCT receipt, the use of PSs to match and to stratify patients into strata of similar baseline factors allowed more balanced outcome comparisons between those who received a transfusion and those who did not. However, the lack of substantial overlap in the PSs between the PRBCT and non-PRBCT patients resulted in small sample sizes within the strata. This study is also retrospective, and the usual limitations for retrospective analyses also apply.

The strengths of this study include the use of well-documented perioperative variables that have been shown to influence EOC survival, the large overall cohort of patients, and inclusion of separate approaches for the data analysis. Inclusion of all stages of disease makes the findings generalizable to any patient presenting for surgical consultation with suspected primary EOC.

In conclusion, the rate of PRBCT among women undergoing primary EOC staging and/or cytoreduction is substantial. Nevertheless, preoperative anemia seems to be a more significant factor affecting prognosis than is receipt of PRBCT. Further analyses at the molecular level of the causes of preoperative anemia and RBC function in EOC, as well as possible intervention strategies, are warranted.

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FIGURE 1. Distribution of the PSs for the patients who did (top panel, n = 452) and did not (bottom panel, n = 135) receive a PRBCT.

TABLE 1

Patient demographics and baseline characteristics according to PRBCT receipt

Characteristic	No PRBCT (n = 135)	PRBCT (n = 452)	OR (95% CI)	P
Age at surgery, y				
Mean (SD)	61.4 (11.3)	64.5 (11.7)	1.25 (1.06–1.48)*	0.008
Stage				<0.001
I or II	61 (45.2%)	67 (14.8%)	Reference	
IIIA	74 (54.8%)	385 (85.2%)	4.74 (3.09–7.26)	
Splenectomy				0.001
No	134 (99.3%)	377 (83.4%)	Reference	
Yes	1 (0.7%)	75 (16.6%)	26.63 (3.67–193.17)	
Surgical complexity				<0.001
Low	41 (30.4%)	63 (13.9%)	Reference	
Intermediate	90 (66.7%)	257 (56.9%)	1.86 (1.17–2.95)	
High	4 (3.0%)	132 (29.2%)	21.48 (7.37–62.59)	
EBL, mL				
Mean (SD)	454.1 (240.0)	1136.8 (841.7)	6.46 (4.25–9.84)*	<0.001
Histologic diagnosis				<0.001
Nonserous	55 (40.7%)	102 (22.6%)	Reference	
Serous	80 (59.3%)	350 (77.4%)	2.36 (1.57–3.55)	
Preoperative hemoglobin, g/dL				<0.001
n	134	447		
Mean (SD)	13.6 (1.2)	12.5 (1.4)	1.38 (1.27–1.50)†	
Preoperative creatinine, mg/dL				
n	134	446		
Mean (SD)	0.9 (0.2)	0.9 (0.3)	2.44 (0.98–6.08)*	0.05
Preoperative albumin, g/dL				
n	59	243		
Mean (SD)	4.1 (0.6)	3.8 (0.6)	1.48 (1.12–1.96)†	0.006
Preoperative albumin, g/dL				0.06
Missing	76 (56.3%)	209 (46.2%)		
>3 g/dL	56 (41.5%)	217 (48.0%)	Reference	
3 g/dL	3 (2.2%)	26 (5.8%)	2.24 (0.65–7.66)	
Operative time, min				
Mean (SD)	208.1 (81.4)	266.2 (95.9)	1.58 (1.36–1.83)*	<0.001
RD				<0.001
Microscopic	97 (71.9%)	219 (48.5%)	Reference	
Measurable, 1 cm	22 (16.3%)	162 (35.8%)	3.26 (1.97–5.41)	
Measurable, >1 cm	16 (11.9%)	71 (15.7%)	1.97 (1.09–3.56)	

* Odds ratio per 10-year increase in age, 500-mL increase in EBL, 60-minute increase in operative time, and 1-mg/dL increase in pre-operative creatinine.

[†] Odds ratio per 0.5-U decrease in preoperative hemoglobin and albumin. OR, Odds ratio.

TABLE 2

Multivariate analysis of variables independently associated with risk for EOC recurrence

Characteristic	HR (95% CI)	P
Stage		<0.001
I or II	Reference	
IIIA	3.81 (2.36–6.16)	
Splenectomy		0.035
No	Reference	
Yes	1.42 (1.02–1.97)	
Preoperative hemoglobin, g/dL	1.05 (1.01–1.10)*	0.025
RD		<0.001
Microscopic	Reference	
Measurable, ≤ 1 cm	1.87 (1.41–2.47)	
Measurable, >1 cm	2.78 (1.93–4.01)	

* Hazard ratio per 0.5-g/dL decrease.

TABLE 3

Multivariate analysis of variables independently associated with death in women with EOC.

Characteristic	HR (95% CI)	P
Age, y	1.27 (1.14–1.40)*	<0.001
Stage		<0.001
I or II	Reference	
IIIA	3.05 (1.92–4.83)	
Preoperative albumin		0.003
>3 g/dL	Reference	
3 g/dL	2.15 (1.36–3.38)	
RD		<0.001
Microscopic	Reference	
Measurable, 1 cm	1.47 (1.12–1.94)	
Measurable, >1 cm	2.75 (2.01–3.75)	

* Hazard ratio per 10-year increase in age.

TABLE 4

Association of PRBCT with DFS within the PS strata

Propensity Score Strata (Range; Sample Size[*])	HR (95% CI)	P
Strata 1 (0.084–0.349; 43 and 20)	0.91 (0.35–2.37)	0.84
Strata 2 (0.350–0.552; 39 and 27)	1.39 (0.61–3.14)	0.43
Strata 3 (0.553–0.780; 24 and 41)	1.15 (0.52–2.54)	0.72
Strata 4 (0.781–0.903; 9 and 55)	0.56 (0.24–1.33)	0.19
Strata 5 (0.904–0.964; 4 and 56)	0.45 (0.15–1.31)	0.14
Combined	0.88 (0.59–1.30) [†]	0.51

^{*} Number of non-PRBCT and PRBCT patients, respectively. The numbers are less than in the analysis of OS because some patients were missing information on recurrence.

[†] The estimates were combined across the 5 strata using an inverse-variance weighted mean.

TABLE 5

Association of PRBCT with OS within the PS strata

Propensity Score Strata (Range; Sample Size[*])	HR (95% CI)	P
Strata 1 (0.084–0.349; 45 and 21)	1.08 (0.43–2.71)	0.87
Strata 2 (0.350–0.552; 40 and 27)	1.27 (0.60–2.70)	0.54
Strata 3 (0.553–0.780; 25 and 41)	0.82 (0.40–1.66)	0.57
Strata 4 (0.781–0.903; 10 and 57)	0.95 (0.43–2.09)	0.91
Strata 5 (0.904–0.964; 4 and 63)	0.41 (0.14–1.18)	0.10
Combined	0.90 (0.62–1.30) [†]	0.58

* Number of non-PRBCT and PRBCT patients, respectively.

[†] The estimates were combined across the 5 strata using an inverse-variance weighted mean.