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ORIGINAL ARTICLE

Peri-operative blood transfusion in gastric cancer surgery: prognostic or confounding factor?

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ABSTRACT

Background and Purpose: The relationship between peri-operative blood transfusions (PBTs) and poor prognosis in gastric cancer (GC) patients is still debated. The aim of this study is to examine the real prognostic impact of PBTs in comparison to well-known prognostic factors.
Methods: We retrospectively analyzed a series of 224 patients who underwent surgery with curative intent for GC from January 1995 to December 2011. Among 224 patients, 46 (20%) required PBTs.
Results: The overall 5-year survival was 77% in non-transfused patients and 65% in patients who received PBTs ($p = 0.03$). PBTs did not further stratify any recognized prognostic category (such as pT or pN according to the 7th edition of the TNM staging system). Multivariate analysis including all known prognostic variables (both cancer- and non-cancer-related) did not select PBTs as an independent prognostic factor. Only pre-operative hemoglobin and albumin level, pT and operative time were significantly associated with the requirement for PBTs.
Conclusions: The study showed a worse prognosis for transfused patients, but PBTs seem a confounding factor more than a prognostic indicator, as they are obviously affected by other variables.

1. Introduction

Radical surgery with extended lymphadenectomy is the key point in gastric cancer (GC) treatment,[1] and this often induces a significant intra-operative blood loss and a related need for peri-operative blood transfusions (PBTs). Several authors in the last decade have analyzed the possible role of PBTs in the prognosis of GC patients. However the controversies on the relationship between blood transfusions and poor prognosis are still far from being resolved: although many studies do not support it, some authors state that it does exist.[2–16]

The present study considers a consecutive series of patients who underwent curative gastrectomy for GC in order to analyze the real prognostic impact of PBTs in comparison with well-known prognostic factors.

2. Patients and methods

Clinical data have been collected from case sheets. Between January 1995 and December 2011, 224 patients with non-metastatic GC underwent surgery with curative intent. Seventy-seven (34.4%) were females, and 147 (65.6%) were males; the mean age was 67.0±11.6 years. The mean intra-operative blood loss was 509±407 ml. All transfused patients received packed red blood cells, and peri-operative blood transfusions were defined as the administration of packed red blood cells within two weeks before and one month after surgery. PBTs were administered according to clinical criteria and on the basis of laboratory data: if cardiologic comorbidities were identified, patients with a hemoglobin level lower than 10 g/dl were pre-operatively transfused. A hemoglobin level lower than 8.5 g/dl represented itself an indication for PBTs, both pre- and post-operatively. In the analysis we considered the following factors: patient's age and gender; tumor location (1/3 proximal versus 2/3 distal); type of surgery (total versus subtotal gastrectomy), multivisceral resection, number of removed nodes, peri-operative blood transfusions; hemoglobin and albumin levels at admission, operative time, residual tumor (R), tumor diameter, Lauren's classification, grading of differentiation (G), and pT and pN classified according to the seventh TNM edition.[17] We retrospectively considered cancer-related death as the end-point to evaluate survival rates.

2.1. Statistical analysis

All variables were expressed as mean ± standard deviation (SS) or median and range. Where appropriate, continuous variables were categorized around their median value or a recognized cutoff. Survival was calculated from the day of surgery to January 2012. Patients who died from a non-cancer-related cause were censored

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Table 1
Clinical and pathological features. Overall survival rates and univariate analysis of the sample

Variable	Number	Percentage	5-year survival (%)	p-value
Peri-operative blood transfusions				0.026
Yes	46	20.6	64.7	
No	178	79.4	77.0	
Age				0.518
⩽67	108	48.2	75.9	
>67	116	51.8	73.3	
Gender				0.544
M	147	65.6	74.3	
F	77	34.4	76.1	
Tumor location				0.961
1/3 proximal	47	21.1	74.6	
2/3 distal	176	78.9	74.8	
Albumin level at admission (g/dl)				0.037
>3.5	168	75.0	80.5	
⩽3.5	56	25	63.0	
Hemoglobin level at admission (g/dl)				0.113
⩾12	113	50.4	81.3	
<12	111	49.6	73.4	
R				<0.001
0	205	91.5	79.0	
1–2	19	8.5	38.7	
Type of gastrectomy				0.614
Total	104	46.4	74.5	
Subtotal	120	53.6	75.2	
Multivisceral resection				0.647
Yes	11	4.9	80.0	
No	213	95.1	75.3	
Number of lymph nodes removed				0.122
<16	92	41.1	72.0	
⩾16	132	58.9	58.9	
Operative time (min)				0.219
⩽180	104	46.4	80.0	
>180	120	53.6	74.7	
Tumor diameter (mm)				0.01
⩽40	138	61.6	83.4	
>40	86	38.4	63.1	
Lauren's classification				0.081
Diffuse	122	54.5	69.3	
Intestinal	102	45.5	81.8	
Grading				0.026
1	10	4.5	100	
2	95	42.4	82.1	
3	119	53.1	69.3	
pT				<0.001
1–2	92	41.1	87.0	
3–4	132	58.9	53.9	
pN				<0.001
0	99	44.2	94.8	
+	125	55.8	46.7	

at the time of death. Survival rates were calculated by the Kaplan–Meier method and log-rank test was used for univariate analysis. The Cox proportional hazard model was used for multivariate analysis, including only variables with $p < 0.1$ at log-rank test, with a backward elimination model for all covariates. Hazard ratio (HR) and 95% confidence interval (CI) were calculated in the model for each variable included. The regression model was controlled with goodness of fit tests; $p < 0.05$ was considered statistically significant. The differences among groups (PBTs versus other factors) were evaluated by non-parametric tests. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 13.0 for Windows©.

3. Results

The clinical and pathological sample characteristics, survival rates and the results of the univariate analysis are reported in Table 1. After a median follow up of 48 months, 50 patients (22.3%) had died from GC recurrence. Subtotal gastrectomy was performed in 120 cases (53.6%), and total gastrectomy in 104 (46.4%). Multivisceral

resection was required in 11 patients (4.9%) for suspected T4 tumors. Two hundred and thirteen patients (95.1%) underwent a limited lymphadenectomy (D1); a more extended lymphadenectomy (D2) was performed in 11 cases (4.9%). Overall survival at 12, 24, 36, 48 and 60 months was, respectively, 96.2%, 87.2%, 80.0%, 74.9% and 74.1%.

Patients without PBTs showed better 5-year survival rate than patients with PBTs (77.0% versus 64.7%, respectively, p = 0.026; Fig. 1).

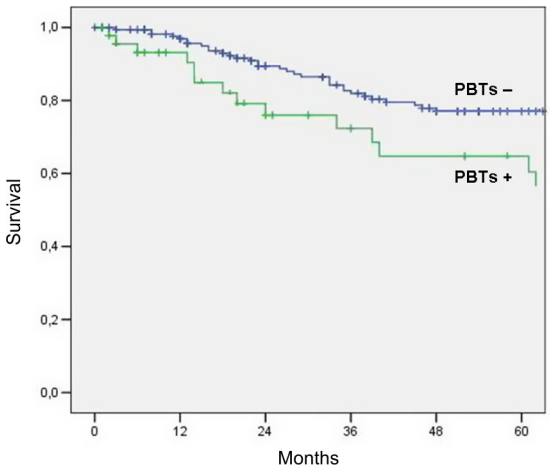

Fig. 1. Survival in transfused and in non-transfused patients.

Cox regression selected lymph node status as the only independent prognostic factor in our series (p < 0.001).

After univariate survival analysis, we revised survival of each pT and pN category according to need for PBTs without any relevant statistical significance (Table 2).

Table 2
5-year survival rates according to pT and pN stratified by need for PBT(s)

		5-year survival (%)	p-value
pT			
T1	Transfused	94.9%	0.682
	Non transfused	100%	
T2	Transfused	94.7%	0.655
	Non transfused	100%	
T3	Transfused	71.2%	0.645
	Non transfused	70.0%	
T4	Transfused	60%	0.069
	Non transfused	50%	
pN			
N0	Transfused	94.8%	0.363
	Non transfused	100%	
N1	Transfused	75.7%	0.340
	Non transfused	66.7%	
N2	Transfused	80.0%	0.178
	Non transfused	62.5%	
N3	Transfused	34.8%	0.207
	Non transfused	40.0%	

Hemoglobin level at hospital admission (< 12.0 g/dl versus ⩾12.0 g/dl, p < 0.001), albumin level at admission (⩽3.5 g/dl versus > 3.5 g/dl, p = 0.001), pT (T1–2 versus T3–4, p = 0.004), and operative time (⩽180 min versus > 180 min, p = 0.031) were the only factors significantly associated with the need for PBTs.

4. Discussion

Detrimental effects of peri-operative blood transfusions on prognosis have been observed in cancer surgery for several solid tumors. [15,18–27] However, controversies do exist, as some regard the PBT-related deleterious effect as coincidental rather than causative. [28] The coincidental factors resulting in more blood loss and more transfusions might be related to tumor (size, depth of invasion, node involvement), patient (age, nutritional status, and comorbidity), or surgery (operative accident or difficult dissection). [13]

To date there is no suitable alternative for peri-operative blood loss replacement than blood itself. Although the exact mechanism is not known, it seems that PBTs increase the risk of disease recurrence in cancer patients. Heiss et al. [29] suggested that transfusions induce the development of a large number of residual tumor cells in the bone marrow, leading to worse survival. Maeta et al. [7] found a significantly lower survival in transfused patients, but they suggested that immunosuppression could have been due to surgical stress rather than to PBTs. Another possible mechanism to explain this association is the increase in morbidity related to post-operative septic complications in transfused patients. [30,31] This could be a consequence of immunomodulation induced by PBTs or could be related to the circumstances requiring PBTs, as is seen in gastric carcinoma. [32] The immunological mechanism is supported by some studies which report a better survival in transfused patients who underwent splenectomy, [8,33] although other authors reported different results, with non-significant difference in survival and a higher recurrence rate in patients who underwent gastric resection and splenectomy. [34]

All considered studies reported that PBTs are significant in univariate survival analysis, but when testing it as an independent prognostic factor in multivariate analysis, different authors found different results. Moriguchi et al., [4] in a large series, reported PBTs not to be an independent prognostic variable in gastric cancer patients, while Dhar et al. [13] found blood transfusion to be an independent prognostic factor associated with an adverse effect on the disease recurrence. Other studies [2,3,5] reported poorer prognosis in transfused patients, but they postulated this could be related to the more advanced stage of disease observed in transfused patients. A higher rate of peritoneal recurrence has been observed by Kamei et al. [10] in patients who required PBTs because of great intra-operative blood loss, confirming the importance of a clean and dry surgery.

In our study, we aimed to verify the role of PBTs in the prognosis of gastric cancer patients who underwent radical surgery, analyzing also variables not directly related to cancer. Actually, while univariate analysis confirmed the prognostic role of peri-operative administration of blood (p = 0.026) (Table 1, Fig. 1), multivariate analysis did not confirm that it is an independent prognostic factor. In fact, it was not able to further significantly stratify survivals of the pT and pN groups (Table 2).

Furthermore, we found that the need for PBTs was significantly associated with a single factor directly related to cancer (pT, p = 0.004) and with three non-cancer-related variables, that is, pre-operative (at admission) albumin and hemoglobin levels (p < 0.001 and p = 0.001, respectively) and operative time (p = 0.031).

Taking into consideration these results, we conclude that the need for PBTs is strongly related to the stage of the disease and also depends on other factors not strictly related to the disease. Hence, in gastric cancer according to our results (although limited by the retrospective design of the study) PBTs seem to be more a confounding factor than a prognostic factor.

5. Conclusion

Our analysis has not shown that peri-operative blood transfusion is an independent prognostic factor. Moreover, it seems to be related to several factors, directly and indirectly linked to the tumor stage, supporting the hypothesis that PBTs is a confounding rather than a prognostic factor in gastric cancer patients. Anyway, since at this stage there is no clear evidence on the immunological response to transfusion, we suggest to carefully administer PBTs minimizing at the same time intra-operative blood loss via a meticulous surgical technique.

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Disclosure statement
The authors have no conflicts of interest to declare.

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