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Intraoperative packed red blood cell transfusion (iPRBT) and PCI-normalised iPRBT rates (iPRBT/PCI ratio) negatively affect short- and long-term outcomes of patients undergoing cytoreductive surgery and intraperitoneal chemotherapy — An analysis of 880 patients

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ABSTRACT

Background: Most studies on the effects of intraoperative packed red blood cell transfusions (iPRBT) on patients undergoing cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have shown deleterious outcomes. It is unclear if this is a result of the transfusion itself or because iPRBTs serve as a surrogate of more advanced disease.
Methods: A retrospective analysis of 880 patients treated from 1996 to 2017. The effect of any exposure to iPRBT as well as the effect of peritoneal cancer index (PCI)-normalised iPRBT rates (ratio of iPRBT/PCI) on patients short- and long-term outcomes (recurrence-free (RFS) and overall survival (OS)) were assessed. Equally, the prognostic effect of postoperative PRBTs was analysed and adjusted for.
Results: Of the 880 patients included, only 26.4% had no iPRBT whereas 59.2% of patients had no postoperative PRBT. Patients with no iPRBTs had significantly lower PCIs, less high-grade complications, shorter ICU and hospital length of stay, as well as improved RFS and OS. Furthermore, high PCI-normalised iPRBTs resulted in worse perioperative and long-term outcomes, with a median OS of 41 months vs. 103 months (5-year survival rate 36.6% vs. 66.1%; $p < 0.001$) and median RFS of 13 months vs. 30 months (5-year RFS rate 18.3% vs. 37.6% $p < 0.001$) compared to those with a low iPRBT/PCI ratio. This independent effect was confirmed upon multivariable Cox regression analysis which corrected for important confounders including complexity of procedures and postoperative PRBTs (adjusted HR [aHR] 2.04, 95%CI 1.36–3.04, $p = 0.001$ for OS; aHR 1.38, 95%CI 1.06–1.81, $p = 0.017$ for RFS). However, subgroup analysis (stratified by histopathologic disease entities) revealed that this independent prognostic effect was seen in high-grade mucinous appendiceal neoplasms, whereas PCI-normalised IPRBTs were not significantly prognostic in other histopathologic subgroups.
Conclusion: iPRBTs significantly and independently impact perioperative and long-term outcomes of patients undergoing CRS/HIPEC. However, this effect mainly seems to occur in patients with high-grade mucinous neoplasms, whereas it may only be of borderline prognostic significance in other patient groups. The development of blood-sparing protocols may help improve outcomes of patients undergoing this complex oncologic procedure.

Introduction

Recent years have seen an increased interest in both the positive and negative effects of intraoperative red-blood cell transfusions

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(iPRBT) in patients undergoing oncologic surgical therapy [1,2]. The negative include: increased postoperative infectious complications, tumour progression as well as reduced patient overall survival, as shown in colorectal, gastric, pancreatic, hepatic, lung, urologic and gynaecologic malignancies [1,3–10]. These effects are thought to be mediated through a transfusion-induced inflammatory and immune-modulatory effect (transfusion related immune-modulation, TRIM), which may then result in tumour progression [11]. Importantly, these deleterious effects can occur even after transfusion of just 1–2 units of blood [12] and are worse in those with increased transfusion requirements, suggesting a potential dose-dependent effect [13,14].

Cytoreductive surgery (CRS) with heated intraperitoneal chemotherapy (HIPEC) is an increasingly utilised treatment for selected patients with a variety of peritoneal surface malignancies [15–18]. It often requires complex, multi-visceral resections resulting in long operating times and over 70% of patients undergoing CRS/HIPEC require iPRBT [6,13,19,20]. The extent of disease burden is captured by calculating the peritoneal cancer index (PCI) [21], with higher scores reflecting more extensive disease. Thus, there is a correlation of iPRBT requirements and PCI, whilst others have also found iPRBT to correlate with operative duration [6,13,19,20,22], which itself is often a result of the underlying disease location and extent thus reflecting procedural complexity.

Almost all studies of CRS/HIPEC and iPRBT have shown a negative effect on patient overall (OS) and recurrence-free survival (RFS) [13,14,23]. The main limitation has been, however, that the independent effect of iPRBT on patient outcomes has remained unclear, as iPRBT itself may simply serve as a surrogate of more advanced disease states [13].

In this study, we performed an analysis of the impact of allogenic red blood cell transfusions on patients undergoing CRS/HIPEC at a high-volume institution. We examined the effect of any blood exposure (both intra- and postoperative) on short- and long-term patient outcomes, and aimed to determine the independent effect of iPRBT rates by correcting for patients PCI. This effect was further explored by performing a disease-specific examination of the potential prognostic effect of PCI-normalised iPRBT rates. The rationale behind this lay in a simple hypothetical question: “If two patients have the same PCI, but different iPRBT requirements – what is the exact effect of the allogenic blood exposure on their respective short- and long-term outcomes?”

Materials & methods

Treatment setting and patient selection

Data from all patients with peritoneal surface malignancies (PSM) managed at St George Hospital (Sydney, Australia) from February 1996 to June 2017 were collected in a prospectively maintained database. All patients consented to inclusion of their information and institutional ethics board approval was obtained.

Patients were thoroughly staged preoperatively and selected for treatment as previously described [24,25]. iPRBT data were collected by a dedicated database manager in two ways: first through retrospective chart review and from 2009 onwards by analysing the use of ordered and administered products as documented in each patient's electronical medical record system. Postoperative complications were graded according to the Clavien Dindo Classification [26].

With regards to unit-specific transfusion practices the transfusion triggers have been quite constant over the years that CRS/HIPEC has been performed and followed evidence-based guidelines particularly since the initial learning curve in the late 90s and early 2000s was overcome. The general intraoperative cut-off for packed red blood cell (PBRC) transfusions is 7.0 g/dL for previously healthy patients and 9.0 g/dL for patients with known ischaemic heart disease. Over time, transfusion protocols have been refined and are point-of-care guided (intraoperative INRs, TEGs/ROTEMs). Furthermore, for mass-transfusion situations our unit tends to adhere to the Queensland Mass-Hemorrhage protocol (https://www.health.qld.gov.au/__data/assets/pdf_file/0012/142320/f-pph-mhp.pdf) with variations at the discretion of the consultant anaesthetists of the day. Data on perioperative packed red blood cell transfusions were extracted from our hospitals electronic medical records and divided into those packed red blood cells given during the intraoperative period and those given postoperatively during a patient's hospital admission.

Study inclusion criteria

Only patients with PSMs undergoing their first CRS with no extra-abdominal disease, complete data on iPRBT, a PCI $\geq$1, and a completeness of cytoreduction score (CC-score) [21] of 0 or 1 were included for analysis. Patients with a CC-score $\geq$2 (n = 33, 3.6%) were excluded to allow for an analysis of the effect of iPRBT and postoperative PRBT in an oncologic optimally treated cohort.

Cytoreductive surgery (CRS) and intraperitoneal chemotherapy (IPC)

Upon laparotomy, extent of abdominal disease was recorded by calculation of the PCI as described by Jacquet and Sugarbaker [21]. CRS was performed as described by Sugarbaker [27]. CC-scores were recorded as an indication of residual disease [21]. Intraperitoneal chemotherapy was administered as described previously by this unit [28].

Statistical analysis

Continuous variables were compared using Student's t-, Wilcoxon rank-sum, one-way analysis of variance ANOVA and/or Kruskal-Wallis tests as appropriate. Where necessary, log-transformation of data was performed to achieve normal distribution. Differences between proportions derived from categorical data were compared using Pearson's χ^2-or Fisher's exact test where appropriate. Data are reported as median with inter-quartile range (IQR) unless denoted otherwise. The study adhered to a pre-determined statistical analysis plan. First, to determine a correlation between PCI and iPRBT, the number of transfusions per PCI group (0–5, 6–10, 11–15, 16–20, 21–25, 26–30, 31–35, >35) was plotted and Poisson regression performed with the number of iPRBTs as a dependent variable and PCI categories as predicting variables. Subsequently, each patient's ratio of iPRBTs to PCI was calculated to normalise the effect of PCI and generate an intra-patient index variable of allogenic blood product usage per volume of disease according to the following formula:

Number of units of packed red blood cells ÷ peritoneal cancer index

The resulting variable allowed for a depiction of the variation that may occur within patients who have the same PCI but different requirements for iPRBT (thus reflecting the complexity of the resulting surgical therapy/trauma) hereby allowing for a more independent analysis of the effect of iPRBT. The resulting numeric variable (iPRBT/PCI ratio) was then stratified by the overall cohort median, quartiles and quintiles (Group 1: 0–0.25, Group 2: 0.25–0.50, Group 3: 0.50–1.0, Group 4: 1.0–2.0, Group 5: >=2.0), to determine the whether a dose-response effect for PCI normalised iPRBT was present, as this has been suggested for iPRBTs alone [13]. To this end, the impact of PCI-normalised iPRBT rates on patient short- and long-term outcomes was determined. Stratified overall and recurrence free survival times were plotted using the Kaplan-Meier method and compared using the log-rank test. Uni- and multivariable Cox-regression analysis was performed to determine the independent impact of PCI-normalised iPRBT requirements on patient survival. Equally, Cox regression was used to explore the effect of iPRBT and PCI-normalised iPRBT in histopathologic subgroups (low-grade appendiceal mucinous neoplasms [LAMNs], high-grade appendiceal mucinous neoplasms [HAMNs], colorectal cancer [CRC], mesothelioma, ovarian and "other" cancer patients [including other entities such as gastric cancer, desmoplastic small round cell tumours etc.]). Furthermore, as the included data spans an over 20-year time-frame, during which improvements in surgical and anaesthetic techniques have occurred, a time-factor was included in all Cox-models to adjust for this potentially undocumented effect. This time-factor was determined by examining the rates of transfusion over-time as well as stratified by case-number to determine the time-point at which improvements in surgical technique, anaesthesia, pre-operative work-up etc. led to significant reductions in iPRBTs. Accordingly, it was determined that this occurred from 2011 onwards (data not shown) and thus the cohort was divided into those cases being performed prior to 2011 and those afterward.

Overall survival was defined as the time from CRS to date of last follow-up with death from any cause. Recurrence free survival was defined as time from CRS to recurrence at any site or death, depending on which occurred first. Only patients with complete data were included in the survival analyses. All p-values <0.05 were regarded as statistically significant and all analyses were performed using R Statistical Packages [29].

Results

Patient characteristics

From February 1996 to June 2017 1141 cytoreductive procedures were performed. Following the application of the studies exclusion criteria, 880 patients were included in the final analysis. An overview of patient demographic features is presented in Table 1.

Intraoperative packed red blood cell transfusion patterns and impact on patient outcomes

In total, 4631 units of packed red blood cells were transfused with a median of 4 units/case (range 0–46). Two-hundred and thirty-two patients (26.4%) had no iPRBT whatsoever. The median PCI of these patients was significantly lower at 8 (IQR 5–14) vs 9 (IQR 10–31, $p < 0.001$). Patients with no iPRBTs had significantly less high-grade complications (19.4% vs. 49.6%, $p < 0.001$) and shorter ICU as well as total hospital length of stay (15 vs. 23 days, $p < 0.001$). Similarly, these patients' overall survival (OS) as well as recurrence-free survival (RFS) was better than patients who received any iPRBT (median OS 103months vs 50months and median RFS 50months vs. 16 months, both $p < 0.001$; Supplementary Fig. 1A + B).

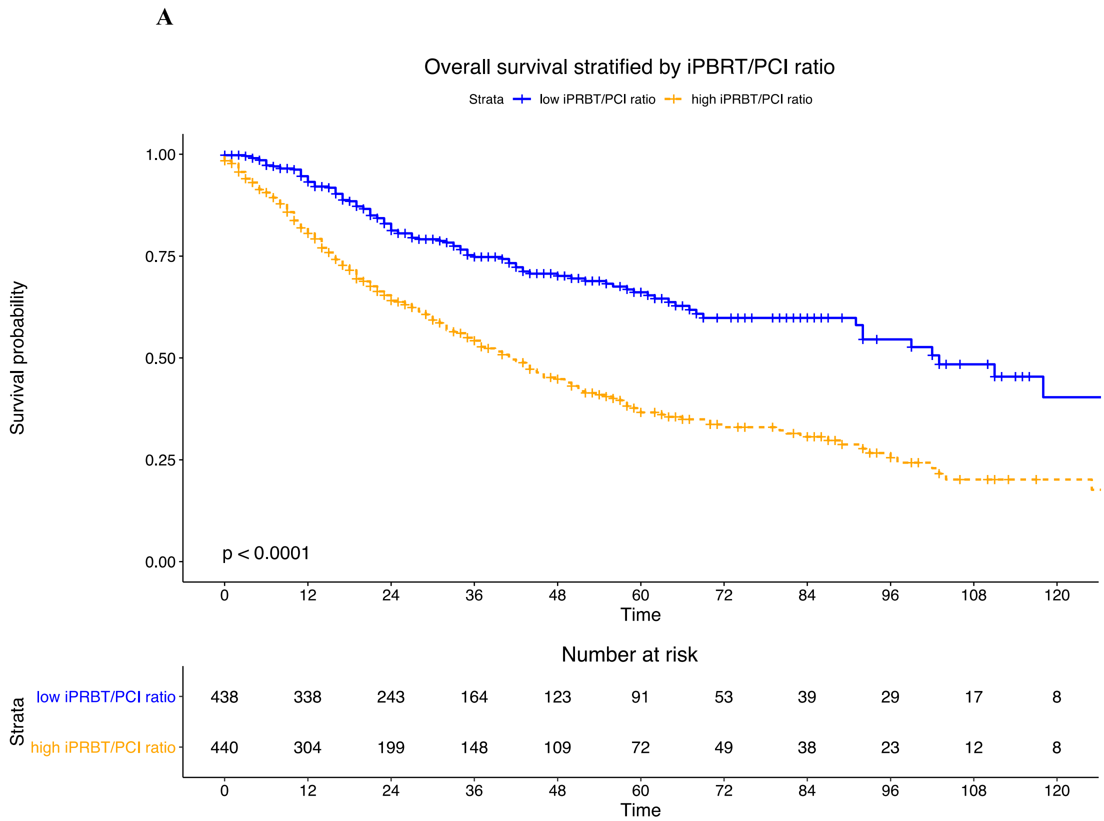
Correlation of iPRBT with PCI and PCI normalised iPRBT requirements

iPRBT correlated significantly with PCI. For example, patients with a PCI of 35 or higher received a median of 13.5 units (IQR 8–42), whereas patients with a PCI of 5 or lower had a median of 0 iPRBT (IQR 0–3, $p < 0.001$; Fig. 1). This incremental increase in iPRBT per PCI was confirmed upon regression analysis, whereby each increase in PCI by 5 points yielded a significant increase of approximately two units of packed red blood cells (data not shown). Despite this correlation of PCI with iPRBT rates, there was also visible disparities within PCI groups with regards to the amount of iPRBTs received (as reflected by the variation of iPRBT within each PCI group, Supplementary Fig. 2). In attempt to correct for this correlation and variability, the ratio of each patient's iPRBT to PCI was calculated. The median ratio for the whole cohort was 0.21 (IQR 0–0.4).

Table 1
Overview and comparison of baseline demographic features of patients included in the study.

Variable	All (n = 880)	Low iPRBT/PCI[a] ratio cohort (n = 438)	High iPRBT/PCI ratio cohort (n = 440)	P-value
Median age (IQR[a])	55 (46–64)	55 (45–65)	55 (46–63)	0.70
Male sex, n (%)	377 (43%)	212 (48)	164 [37]	<0.001
ECOG[a] (>=2), n (%)	123 (14%)	39 (9%)	84 (19%)	<0.001
ASA[a] Score [3,4], n (%)	499 (57%)	219 (57%)	278 (71)	<0.001
Histopathology[a], n (%)				<0.001
- LAMN	203 (23%)	126 (29%)	76 (17%)	
- HAMN	215 (24%)	109 (25%)	105 (24%)	
- CRCs	284 (32%)	124 (28%)	160 (36%)	
- Peritoneal mesothelioma	70 (8%)	38 (9%)	32 (7%)	
- Ovarian	41 (5%)	15 (3%)	26 (6%)	
- Others	76 [9]	26 (6%)	41 (9%)	
PCI (median, IQR)	15 [8–27]	15 [8–25]	15 [9–29]	0.07
CC-scores[a], n (%)				0.01
CC 0	633 (72%)	332 (76%)	300 (68%)	
CC 1	247 (28%)	106 (24%)	140 (32%)	
Preoperative CEA, μg/L	4 [2–20]	3 [2–10]	6 [2–32]	<0.001
Preoperative CA19.9, kU/L	16 (7–53)	13 [7–30]	23 (8–112)	<0.001
Preoperative albumin	38 [34–40]	38 [36–41]	36 [32–39]	<0.001
Preoperative Hb[a], g/L, median (IQR)	131 (119–142)	137 (129–146)	124 (110–135)	<0.001
Median number of packed red blood cells transfused (IQR)	4 (0–7)	0 (0–3)	7 [4–10]	<0.001
Operating duration (hours)	8 [6–10]	7.5 [6–9]	9 (7.5–11)	<0.001
HIPEC[a], n (%)	800 (91%)	388 (89%)	410 (93%)	0.02
EPIC[a], n (%)	358 (41%)	202 (46%)	156 (36%)	0.001
Postoperative PRBTs, mean (SD)	2 (5.5)	1.23 (3.4)	3.0 (6.9)	<0.001

[a] iPRBT: intraoperative packed red blood cell transfusion, PCI: peritoneal cancer index; IQR: interquartile range; ECOG: Eastern Cooperative Oncology Group performance score; ASA: American Society of Anaesthesiologists; LAMN: low-grade appendiceal mucinous neoplasms; HAMN: high-grade appendiceal mucinous neoplasms; CRC: colorectal cancer; CC-score: completeness of cytoreduction score; Hb: hemoglobin.



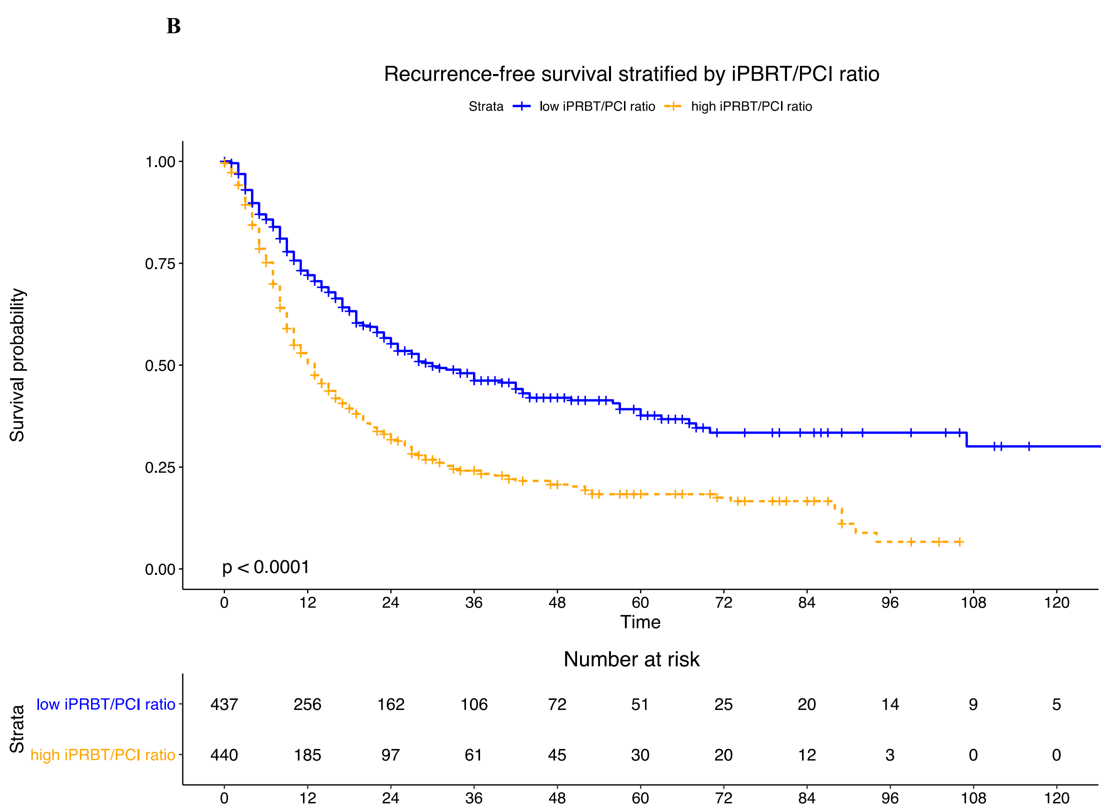


Fig. 1. Overall survival (1A) and recurrence-free survival (2B) of the whole cohort stratified by PCI-normalised intraoperative packed red blood cell transfusion rates (iPRBT/PCI ratio).

iPRBT/PCI ratio – comparison of patient baseline characteristics and short-term patient outcomes

A detailed comparison of patient baseline characteristics between the low vs. high iPBRT/ratio cohorts is provided in Table 1. In summary, patients with a high ratio were more likely to be males, had higher ECOG as well as ASA scores and were more likely to have colorectal cancer. Furthermore, preoperative serum tumour markers were more frequently elevated and higher in this group. Whilst the median preoperative haemoglobin levels were significantly lower in the high iPRBT/PCI cohort, they did not constitute preoperative anemia (i.e. <120 g/dl). Patients with a high ratio were transfused more units of blood per case and the median operative time was 1.5 h longer. Further, these patients had longer ICU and hospital length of stay and were more likely to experience high-grade postoperative complications. Notably, 13 of the 14 recorded postoperative deaths occurred in the high iPBRT/PCI cohort (Table 2).

Impact of PCI normalised iPRBT requirements on patient OS & RFS

The median overall survival (OS) of all patients was 61 months (95%CI 54–80 months) with an associated 3-, 5- and 10-year survival rate of 64.2% (95%CI 60.6–68.0%), 50.1% (95%CI 45.9–54.7%), and 29.2% (95%CI 23.1–37.1%) respectively. Stratified by the median, patients with a high iPRBT/PCI ratio exhibited significantly worse OS with 41months vs. 103months low iPRBT/PCI ratio patients (5-year survival rate 36.6% [95%CI 31.3–42.8%] vs. 66.1% [95%CI 60.3–72.4%]; $p < 0.001$; Fig. 1A). When stratified according to quintiles, patients in the lowest iPRBT/ratio group (group 1) had the best OS at 92 months compared to those in the highest group (group 5) at 18 months ($p < 0.001$; Supplementary Fig. 5). No differences in OS were seen for groups 2–4 (median OS 41, 40 and 41months, respectively).

The median RFS of all patients was 19 months (95%CI 17–22months) with an associated 3-, 5- and 10-year RFS of 35.1% (95%CI 31.6–39.1%), 27.8% (95%CI 24.2–32.0%), and 17.9% (95%CI 12.8–24.9%) respectively. Stratified by the median, patients with a high iPRBT/PCI ratio exhibited significantly worse RFS with 13 months vs. 30 months for low iPRBT/PCI ratio patients (5-year RFS rate 18.3% [95%CI 14.3–23.5%] vs. 37.6% [95%CI 32.0–44.3%]; $p < 0.001$; Fig. 1B).

Impact of underlying histopathology

As survival rates following CRS/HIPEC differ depending on the primary histopathological tumour type, we performed a separate survival analysis stratified by all histological entities as well as PCI normalised iPBRT rates.

Upon univariable stratification the iPRBT/PCI ratio seemed to exert a prognostic effect on OS in LAMNs, HAMNs, peritoneal mesothelioma and other cancer types. Equally, a similar effect was seen in the same disease entities for RFS(Fig. 2A+2B). As previous reports from this unit have shown significantly worse survival outcomes for CRC patients requiring mass-transfusion [14], we explored the relationship of iPRBT in CRC patients further and found whilst the iPRBT/PCI ratio was not prognostic, there was a significant relationship between the amount of packed red blood cells transfused. OS decreased in a dose-dependent fashion, when patients were stratified into groups according to the amount of blood they were transfused during CRS/HIPEC (Supplementary Fig. 4).

Exploratory analysis of the interaction of preoperative anaemia and PCI-normalised iPRBTs

Increased iPRBT rates may not only be a function of the intraoperative tumour burden and associated surgical trauma, but also due to low preoperative haemoglobin values as well as iron stores in patients requiring CRS/HIPEC [13,19]. This was reflected in our baseline characteristics comparison. As such we assessed the interaction of preoperative anaemia (defined as a preoperative Hb value < 120 g/dl) and PCI-normalised iPBRT transfusion rates. We found that patients with preoperative anaemia and high iPRBT/PCI ratios had worse OS and RFS compared to patients who had normal preoperative haemoglobin values and low PCI normalised iPRBT rates (Fig. 3A+B).

Impact of postoperative PRBTs on short- and long-term patient outcomes

Postoperative transfusions are frequently required due to hemodilution, myelosuppressive effects of perioperative chemotherapy and the development of postoperative anemia. Assuming that the immunological effects of any exposure to packed red blood cells are similar we also analysed the impact of postoperative PRBT on patient outcomes. Overall, data regarding postoperative PRBT was available for 611 patients (69.4%). The median number of transfused units was 0 (mean 2 units, SD 5.45 units) and 249 patients (40.75) received at least one unit of packed red blood cells postoperatively. The mean number of postoperatively transfused units was significantly higher in the high PCI-normalised iPRBT group (2.98 vs. 1.23, $p < 0.001$). For subsequent outcome analyses, patients were stratified into those not requiring any postoperative PRBT vs. patients being exposed to any amount of postoperative PRBT ($n \geq 1$ unit). Additionally, patients were stratified into those having no postoperative blood transfusions, 1–2 units, 3–4 units and ≥ 5 units postoperatively.

With regards to short-term outcomes, patients receiving any postoperative blood had longer ICU & HDU length of stay (median 3 vs. 2 & 4 vs. 1 days, both $p < 0.001$, respectively) as well as a shorter overall hospital length of stay (median 28 vs. 16 days, $p < 0.001$). Equally, patients requiring postoperative PRBTs had significantly higher rates of grade 3/4 complications (65.5% vs. 24.0%, $p < 0.001$; Table 2).

Overall survival of patients receiving any postoperative blood transfusions was significantly shorter, compared to patients not receiving any postoperative PRBT (median 70 vs. 57 months, 5-year survival rate 58.3% [95%CI 50–67.9%] vs. 48.6% [95%CI 40.6–58.2%], $p = 0.003$; Supplementary Fig. 5A). However, no significant difference in RFS was observed (median 70 vs. 57 months, 5-year RFS rate 58.3% [95%CI 50–67.9%] vs. 48.6% [95%CI 40.6–58.2%], $p = 0.09$; Supplementary Fig. 5B).

Equally, when stratified into more refined transfusion groups (see above), then a dose-dependent negative OS effect could be seen (Supplementary Fig. 6A), whereas no effect on RFS was identifiable (Supplementary Fig. 6B). However, when postoperative transfusions were included in the multivariable Cox regression analyses for OS and RFS they were not an independent predictor of worse survival, whereas intraoperative PRBTs remained prognostic for OS in the total patient cohort (see below).

Uni- and multivariable Cox regression analysis – all patients

A summary of the findings from the uni- and multivariable Cox regression analysis for both OS and RFS is presented in Table 3. High PCI-normalised iPRBT rates were a significant independent predictor of worse OS and RFS in uni- and multivariable Cox regression

Table 2
Summary of short-term outcomes of all patients and stratified by intraoperative PRBTs, PCI-normalised PRBT rates and postoperative PRBT.

		Any intraoperative PRBT (total n = 880)			PCI-normalised iPRBT transfusion rates (total n = 880)			Any postoperative PRBT (total n = 611)		
All patients undergoing CRS/HIPEC (n = 880)	All	>= 1 iPRBT (n = 648)	No iPRBT (n = 232)	P-value	High iPBRT/PCI ratio (n = 440)	Low iPBRT/PCI ratio (n = 438)	P-value	>=1 postoperative PBRT (n = 249)	No postoperative PRBT (n = 362)	P-Value
Median ICU length of stay (days, IQR)	2 [3]	2.0 (2.0)	2.0 (2.0)	<0.001	2.0 (2.0)	2.0 (2.0)	<0.001	3.0 (3.0)	2.0 (2.0)	<0.001
Median HDU length of stay (days, IQR)	2 [5]	3.0 (6.0)	1.0 (4.0)	<0.001	3.0 (6.0)	2.0 (5.0)	0.005	4.0 (6.0)	1.0 (4.0)	<0.001
Median hospital length of stay (days, IQR)	20 [15]	23.0 (18.0)	15.0 (10.2)	<0.001	23.0 (19.0)	18.0 (12.2)	<0.001	28.0 (23.0)	16.0 (10.0)	<0.001
Grade III/IV complications (%)	363 [41]	318 (87.6)	45 (12.4)	<0.001	228 (62.8)	135 (37.2)	<0.001	163 (65.2)	87 (34.8)	<0.001
In hospital death, n (%)	14 (1.6)	14 (100.0)	0 (0.0)	0.02	13 (92.9)	1 (7.1)	0.001	7 (100.0)	0 (0.0)	0.001
Low-grade appendiceal mucinous neoplasms (n = 203)										
Median ICU length of stay (days, IQR)	2.0 (2.0)	2.0 (2.0)	2.0 (1.5)	0.015	3.0 (3.0)	2.0 (1.0)	0.034	2.0 (4.0)	2.0 (2.0)	0.016
Median HDU length of stay (days, IQR)	5.0 (4.0)	5.0 (4.0)	4.0 (3.0)	0.179	5.0 (4.5)	5.0 (4.0)	0.393	6.0 (3.0)	5.0 (3.0)	0.007
Median hospital length of stay (days, IQR)	23.0 [14]	24.0 (15.0)	18.0 (12.5)	<0.001	25.0 (20.5)	21.0 (12.0)	0.002	28.0 (22.0)	19.0 (9.0)	<0.001
Grade III/IV complications (%)	87 (42.9)	71 (81.6)	16 (18.4)	<0.001	46 (52.9)	41 (47.1)	<0.001	31 (59.6)	21 (40.4)	<0.001
In hospital death, n (%)	2 (1.0)	2 (100.0)	0 (0.0)	0.313	2 (100.0)	0 (0.0)	0.067	1 (100.0)	0 (0.0)	0.22
High-grade appendiceal mucinous neoplasms (n = 215)										
Median ICU length of stay (days, IQR)	2.0 (2.0)	3.0 (3.0)	1.0 (1.0)	<0.001	3.0 (4.0)	2.0 (2.0)	<0.001	3.0 (3.0)	2.0 (2.0)	<0.001
Median HDU length of stay (days, IQR)	3.0 (5.0)	4.0 (5.0)	1.0 (2.8)	<0.001	4.0 (6.0)	2.0 (5.0)	0.001	4.0 (5.0)	1.5 (4.0)	<0.001
Median hospital length of stay (days, IQR)	24 (20.0)	27.0 (20.0)	11.5 (5.0)	<0.001	30.0 (21.0)	19.0 (14.2)	<0.001	32.5 (22.8)	16.0 (10.2)	<0.001
Grade III/IV complications (%)	197 (49.8)	103 (96.3)	4 (3.7)	<0.001	66 (61.7)	41 (38.3)	<0.001	66 (78.6)	18 (21.4)	<0.001
In hospital death, n (%)	5 (2.3)	5 (100.0)	0 (0.0)	0.292	4 (80.0)	1 (20.0)	0.165	2 (100.0)	0 (0.0)	0.18
Colorectal cancer (n = 284)										
Median ICU length of stay (days, IQR)	2.0 (2.0)	2.0 (2.0)	2.0 (2.0)	0.133	2.0 (2.8)	2.0 (2.0)	0.105	2.0 (3.0)	2.0 (2.0)	0.029
Median HDU length of stay (days, IQR)	1.0 (2.0)	1.0 (4.0)	0.0 (1.0)	<0.001	1.0 (4.0)	0.0 (2.0)	0.002	2.0 (3.2)	0.0 (2.0)	<0.001
Median hospital length of stay (days, IQR)	17.0 (12.0)	20.0 (13.0)	15.0 (9.0)	<0.001	20.0 (13.0)	16.0 (10.0)	0.019	22.5 (20.5)	15.0 (8.0)	<0.001
Grade III/IV complications (%)	98 (34.5)	78 (79.6)	20 (20.4)	0.003	63 (64.3)	35 (35.7)	0.041	35 (50.0)	35 (50.0)	<0.001
In hospital death, n (%)	2 (0.7)	2 (100.0)	0 (0.0)	0.335	2 (100.0)	0 (0.0)	0.209	2 (100.0)	0 (0.0)	0.034
Peritoneal mesothelioma (n = 70)										
Median ICU length of stay (days, IQR)	2.0 (1.75)	2.0 (2.0)	2.0 (1.2)	0.478	2.0 (3.0)	2.0 (1.0)	0.239	3.0 (3.0)	2.0 (2.0)	0.067
Median HDU length of stay (days, IQR)	2.0 (4.0)	2.0 (5.0)	0.0 (2.0)	0.037	2.5 (3.2)	0.0 (2.8)	0.003	4.0 (4.0)	0.0 (2.0)	<0.001
Median hospital length of stay (days, IQR)	17.5 (13.75)	20.0 (16.2)	13.0 (6.5)	<0.001	25.0 (13.0)	15.0 (9.5)	0.003	28.0 (15.0)	12.0 (6.0)	<0.001
Grade III/IV complications (%)	30 (42.9)	28 (93.3)	2 (6.7)	0.005	21 (70.0)	9 (30.0)	<0.001	11 (64.7)	6 (35.3)	0.008
In hospital death, n (%)	2 (2.9)	2 (100.0)	0 (0.0)	0.435	2 (100.0)	0 (0.0)	0.118	1 (100.0)	0 (0.0)	0.22
Ovarian Cancer (n = 41)										
Median ICU length of stay (days, IQR)	2.0 (1.0)	2.0 (1.0)	2.0 (1.5)	0.603	2.0 (2.0)	2.0 (0.5)	0.257	4.0 (7.8)	2.0 (0.8)	0.072
Median HDU length of stay (days, IQR)	1.0 (4.0)	1.0 (4.0)	3.0 (1.5)	1.00	1.0 (3.5)	3.0 (4.0)	0.584	2.5 (4.5)	1.5 (3.0)	0.294
Median hospital length of stay (days, IQR)	21.0 (21.0)	21.0 (21.2)	16.0 (15.5)	0.98	22.0 (22.5)	17.0 (15.5)	0.821	39.0 (44.0)	14.5 (6.5)	0.001
Grade III/IV complications (%)	15.0 (36.6)	15 (100.0)	0 (0.0)	0.172	11 (73.3)	4 (26.7)	0.317	10 (76.9)	3 (23.1)	0.008
In hospital death, n (%)	1 (2.4)	1 (100.0)	0 (0.0)	0.776	1 (100.0)	0 (0.0)	0.442	1 (100.0)	0 (0.0)	0.309
Other histopathologic entities (n = 67)										
Median ICU length of stay (days, IQR)	2.0 (2.0)	2.0 (3.0)	2.0 (1.0)	0.027	2.0 (2.0)	2.0 (1.0)	0.026	2.0 (2.0)	2.0 (2.0)	0.341
Median HDU length of stay (days, IQR)	2.0 (4.0)	2.0 (4.0)	2.0 (4.0)	0.95	2.0 (4.0)	1.0 (4.0)	0.368	3.0 (4.5)	1.0 (2.2)	0.123
Median hospital length of stay (days, IQR)	19.0 (14.0)	21.5 (20.2)	15.0 (8.5)	0.002	22.0 (19.0)	15.0 (9.5)	0.005	35.0 (22.5)	15.0 (9.0)	<0.001
Grade III/IV complications (%)	26 (38.8)	23 (88.5)	3 (11.5)	0.015	21 (80.8)	5 (19.2)	0.009	10 (71.4)	4 (28.6)	<0.001
In hospital death, n (%)	2 (3.0)	2 (100.0)	0 (0.0)		2 (100.0)	0 (0.0)		0 (–)	0 (–)	–

*(i)PRBT: intraoperative packed red blood cell transfusion, PCI: peritoneal cancer index; IQR: interquartile range; Complication grading according to Clavien-Dindo classification.

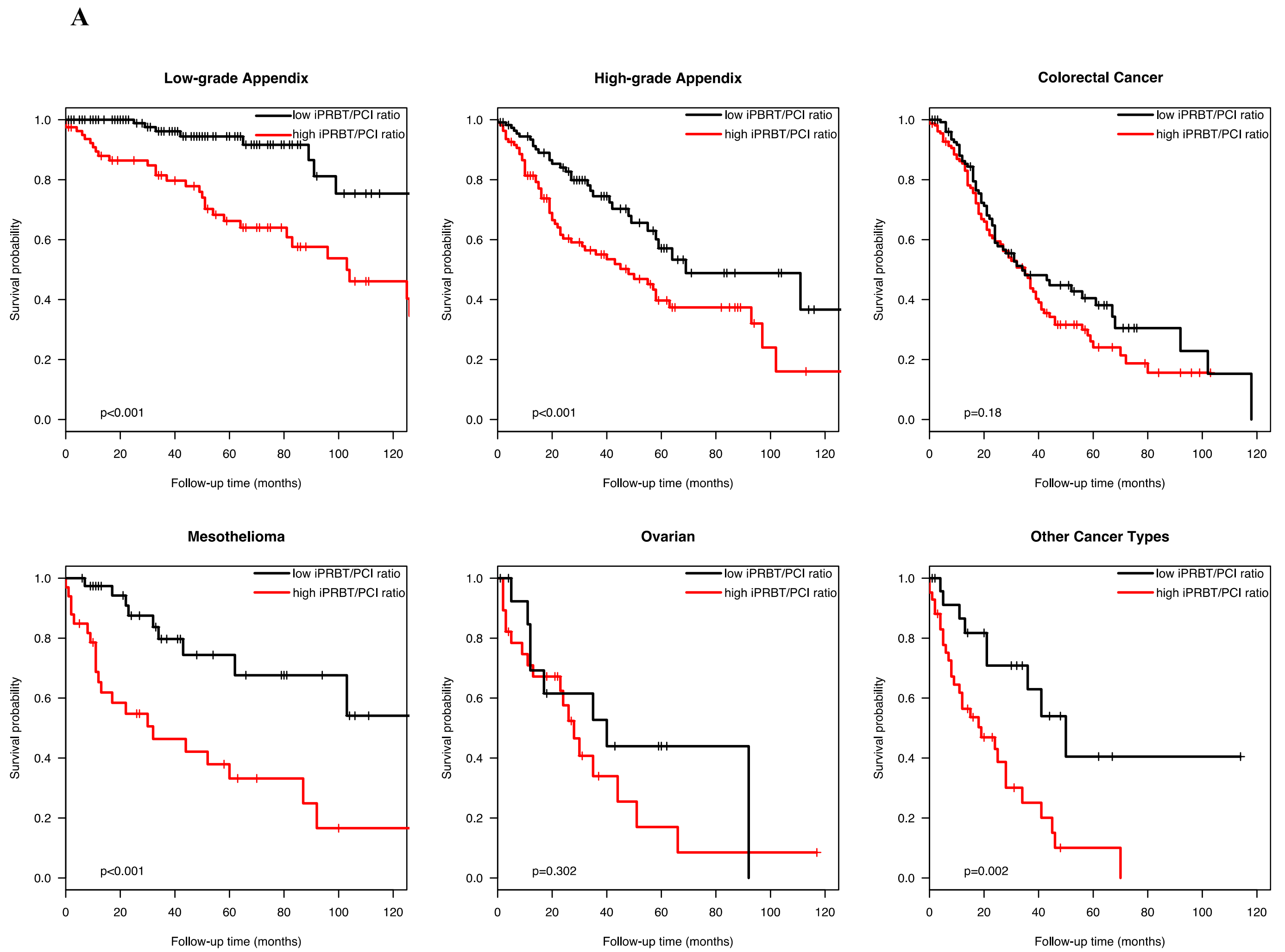


Fig. 2. Overall survival (2A) and recurrence-free survival (2B) of histological subtypes stratified by PCI-normalised intraoperative packed red blood cell transfusion rates (iPRBT/PCI ratio).

analyses which corrected for important confounders including complexity of procedures as well as postoperative PRBTs (adjusted HR [aHR]2.04, 95%CI 1.36–3.04, p = 0.001 for OS; aHR 1.38, 95%CI 1.06–1.81, p = 0.017 for RFS).

Disease specific uni- and multivariable Cox regression analysis

Uni- and multivariable Cox regression analysis for OS and RFS was performed for each specific histopathologic patient subgroup (LAMN, HAMN, CRC, ovarian cancer, primary peritoneal mesothelioma & "others"). The results are presented in Supplementary Tables 1–12. In summary, after adjusting for significant confounders, PCI-normalised iPRBTs were only a significant independent negative prognostic factor for overall survival in high-grade mucinous appendiceal neoplasms (aHR 2.11, 95%CI 1.26–3.53, p = 0.004) and of borderline independent prognostic significance in low-grade mucinous appendiceal neoplasms (aHR 2.80, 95%CI 0.88–8.96, p = 0.083), colorectal cancer (aHR 1.68, 95%CI 0.90–3.14, p = 0.101) and "other" histologic entities undergoing CRS/HIPEC (aHR 4.42 95%CI 0.89–22.11, p = 0.070). With regards to recurrence-free survival, the iPRBT/PCI ratio was again significantly independently prognostic in HAMNs (aHR 1.78, 95%CI 1.10–2.88, p = 0.020), whereas no independent prognostic effect could be documented for other histopathologic groups.

Discussion

Cytoreductive surgery with intraperitoneal chemotherapy is an established treatment option for selected patients with peritoneal metastases from various intra-abdominal tumours. Whilst many factors influence the short- and long-term outcomes of patients undergoing CRS/HIPEC, recent studies have explored the negative effect of iPRBT in these patients [13,14,23]. Until now, however, it has remained unclear whether increased transfusion requirements are a causative factor of deleterious patient outcomes or the result of a more aggressive disease presentation [13,14,22,23]. In this study, we show that iPRBT is associated with a more aggressive disease presentation, but that correcting for this by developing a novel intra-patient index variable of transfusion requirements per extent of disease reveals, that iPBRTs are an independent, negative prognostic factor for both short- and long-term patient outcomes. However, whilst the initial analysis suggests that this is relevant to all patient groups, our subgroup multivariable analyses suggest, that this is of particular relevance to patients with HAMNs. We

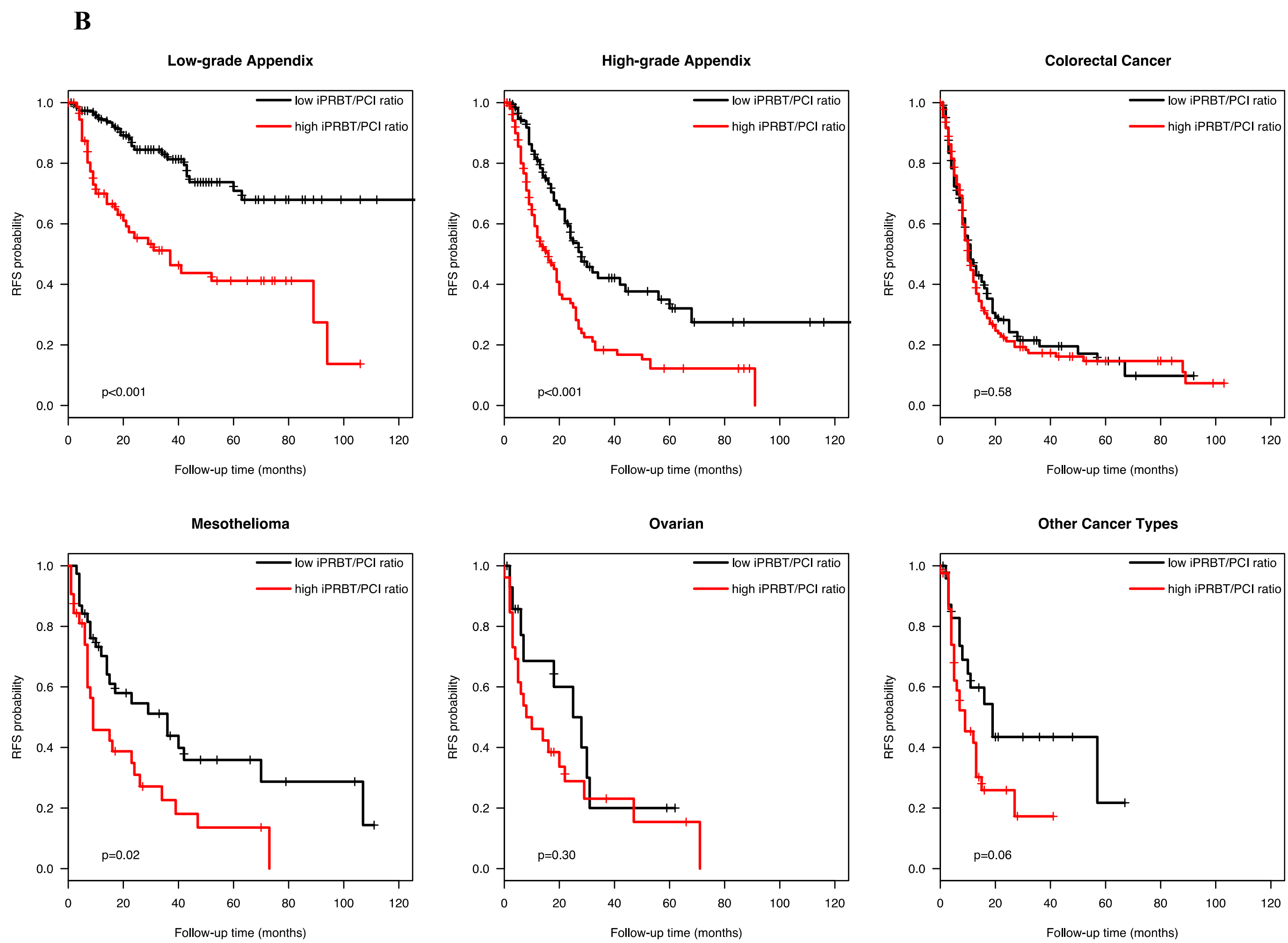


Fig. 2. (*continued*).

believe these data support calls for the development of blood-sparing strategies in patients undergoing CRS/HIPEC, particularly in patients with mucinous neoplasms of the appendix [13].

In this study, the median transfusion requirement per patient was four units, with 26.4% of patients having no intraoperative packed red blood cells. These findings are similar to other reports [13,19,20,23] and like other reports, transfusion patterns were also associated with the unit's learning curve (data not shown) [13,19,23]. Irrespective of this, this high transfusion rate contrasts other GI malignancy resections, and underscores the extensive surgical trauma that occurs during CRS/HIPEC. The requirement to perform both extensive and complex resections during CRS/HIPEC to achieve complete cytoreduction can often be anticipated by a patient's PCI and is also reflected by the fact that the median number of organs resected was 5 in our cohort of patients. As such, many studies, including ours, have found an association of higher PCIs and increased transfusion requirements [13,14,19,20,22,23,30,31]. This is particularly relevant to survival analyses, as PCI is an important prognostic marker for most malignancies treated by CRS/HIPEC [32] and to our knowledge none of the previous studies on iPRBT have corrected for the interaction of PCI and iPRBT. By accounting for this association, however, we believe our data indicate that iPRBT independently can affect CRS/HIPEC patient short- and long-term outcomes. This is of particular relevance, as postoperative transfusions whilst associated with short-term outcomes were not of prognostic significance.

However, we found that the PCI-normalised iPRBT requirements were not prognostic across all peritoneal surface malignancies treated by our unit. Of relevance was the finding that in CRC and ovarian malignancies, the ratio of iPRBT/PCI did not segregate patients with worse OS/RFS from each other upon univariable Kaplan-Meier analysis. This is intriguing, as in high-grade appendiceal mucinous neoplasms, for example, PCI-normalised iPRBTs were particularly prognostic and of independent importance following correction for other confounders, a finding similarly supported by other groups [13]. However, the interpretation of these subgroup specific findings remain difficult, particularly as we saw a dose-dependent effect of iPRBT on CRC survival and the negative impact of iPRBT on CRC outcomes has been widely documented [33–35]. A potential explanation may be, that from 2012 onwards we instituted an upper PCI limit of 15 for our CRC CRS/HIPEC procedures thus skewing our results in favour of lower volume disease. This is also reflected by the significantly lower iPRBT requirement in our CRC patients (median 2, IQR 0–5) when compared to the other treated PSMs (data not shown). However, further data are required to better elucidate the independent prognostic impact of iPRBT on specific histologic subgroup patient outcomes as the present analysis may have been limited by fairly small subgroup patient numbers and thus more extensive exploratory subgroup analyses were not possible.

A particularly intriguing finding was that postoperative transfusions did not exert the same prognostic effect as iPRBT. Whilst

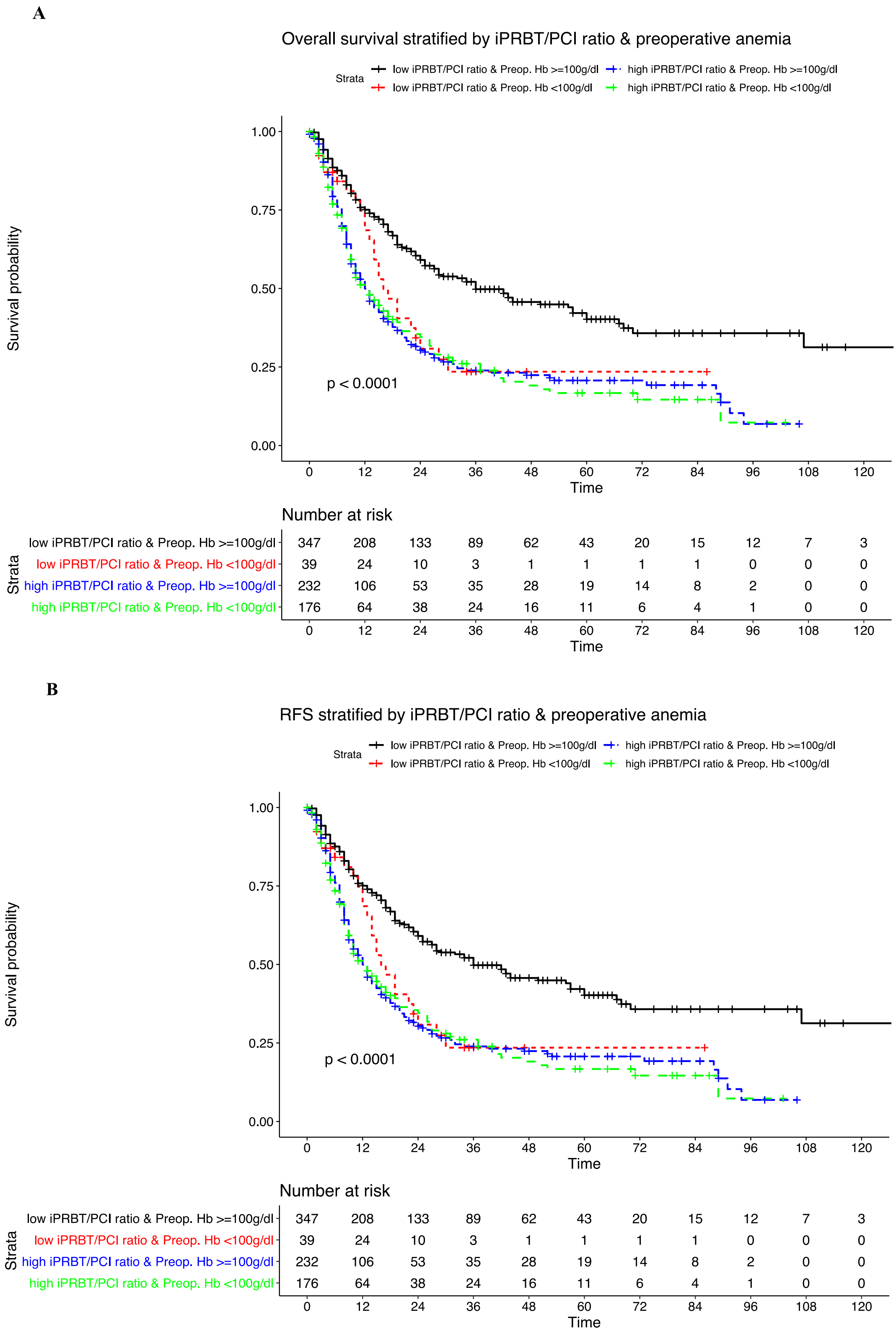


Fig. 3. Overall survival (1A) and recurrence-free survival (2B) of the whole cohort stratified by PCI-normalised intraoperative packed red blood cell transfusion rates (iPRBT/PCI ratio) as well as the presence of preoperative anemia defined as a haemoglobin concentration of <120 g/dl.

Table 3
Uni- and multivariable Cox regression analysis of factors predicting overall and recurrence free survival of all included patients.

		Overall Survival		Recurrence-free survival	
		Univariable HR (95%CI, p-value)	Multivariable HR (95%CI, p-value)	Univariable HR (95%CI, p-value)	Multivariable HR (95%CI, p-value)
Age	Mean (SD)	1.00 (0.99–1.01, p = 0.723)	1.00 (0.98–1.01, p = 0.491)	1.00 (0.99–1.00, p = 0.313)	1.00 (0.99–1.00, p = 0.401)
Sex	F	–	–	–	–
	M	1.06 (0.85–1.31, p = 0.622)	1.09 (0.78–1.53, p = 0.617)	1.07 (0.90–1.28, p = 0.452)	1.12 (0.88–1.42, p = 0.367)
ECOG status	ECOG 0-1	–	–	–	–
	ECOG 2-3	1.60 (1.22–2.10, p = 0.001)	1.37 (0.89–2.12, p = 0.151)	1.22 (0.95–1.56, p = 0.126)	0.89 (0.63–1.26, p = 0.510)
Serum albumin levels	>=38.0 g/L	–	–	–	–
	<38.0 g/L	1.33 (1.07–1.66, p = 0.011)	1.01 (0.71–1.45, p = 0.942)	1.26 (1.06–1.51, p = 0.010)	1.03 (0.81–1.32, p = 0.787)
Diagnosis	LAMN	–	–	–	–
	HAMN	3.47 (2.27–5.31, p < 0.001)	2.91 (1.43–5.93, p = 0.003)	2.60 (1.91–3.55, p < 0.001)	3.11 (1.98–4.87, p < 0.001)
	CRC	5.89 (3.94–8.80, p < 0.001)	12.03 (5.33–27.16, p < 0.001)	4.47 (3.34–5.98, p < 0.001)	11.50 (6.87–19.24, p < 0.001)
	Mesothelioma	3.26 (1.96–5.43, p < 0.001)	3.86 (1.59–9.38, p = 0.003)	2.91 (1.99–4.26, p < 0.001)	3.75 (2.15–6.54, p < 0.001)
	Ovarian Cancer	6.66 (3.88–11.44, p < 0.001)	11.15 (4.69–26.48, p < 0.001)	3.89 (2.51–6.04, p < 0.001)	9.40 (5.04–17.54, p < 0.001)
	Others	8.26 (5.07–13.46, p < 0.001)	8.88 (3.52–22.38, p < 0.001)	4.00 (2.65–6.05, p < 0.001)	9.08 (4.77–17.30, p < 0.001)
Signet ring cells	no signets	–	–	–	–
	signets present	2.76 (2.05–3.70, p < 0.001)	3.19 (2.11–4.83, p < 0.001)	1.65 (1.25–2.17, p < 0.001)	1.54 (1.09–2.16, p = 0.013)
Preoperative anemia	Hb ≥ 120 g/L	–	–	–	–
	Hb < 120 g/L	1.80 (1.40–2.31, p < 0.001)	1.38 (0.95–2.01, p = 0.089)	1.49 (1.21–1.83, p < 0.001)	1.21 (0.92–1.60, p = 0.163)
PCI	Mean (SD)	1.00 (0.99–1.01, p = 0.688)	1.02 (0.99–1.04, p = 0.252)	1.01 (1.00–1.01, p = 0.115)	1.03 (1.01–1.05, p < 0.001)
Operative time (hours)	Mean (SD)	1.05 (1.01–1.09, p = 0.009)	1.09 (0.98–1.21, p = 0.126)	1.07 (1.04–1.11, p < 0.001)	1.10 (1.02–1.18, p = 0.015)
Number of organs resected	<= 5 organs	–	–	–	–
	>5 organs	1.26 (1.00–1.58, p = 0.048)	1.34 (0.93–1.94, p = 0.120)	1.23 (1.02–1.48, p = 0.027)	1.07 (0.81–1.42, p = 0.635)
Completeness of cytoreduction score	CC 0	–	–	–	–
	CC 1	1.20 (0.95–1.51, p = 0.122)	1.18 (0.73–1.90, p = 0.509)	0.98 (0.81–1.19, p = 0.867)	0.93 (0.67–1.31, p = 0.692)
Postoperative morbidity	<3	–	–	–	–
	>= 3	1.57 (1.27–1.95, p < 0.001)	1.35 (0.95–1.91, p = 0.098)	1.41 (1.18–1.68, p < 0.001)	1.39 (1.08–1.80, p = 0.011)
iPRBT/PCI ratio	low transfusion ratio	–	–	–	–
	high transfusion ratio	2.30 (1.83–2.89, p < 0.001)	2.04 (1.36–3.04, p = 0.001)	1.92 (1.61–2.30, p < 0.001)	1.38 (1.06–1.81, p = 0.017)
Postoperative PRBT	any postop. PRBT	–	–	–	–
	no postop. PRBT	0.63 (0.47–0.85, p = 0.003)	0.91 (0.63–1.31, p = 0.605)	0.83 (0.67–1.03, p = 0.086)	1.16 (0.89–1.52, p = 0.280)
Case grouping	after 2011	–	–	–	–
	before 2011	1.42 (1.12–1.81, p = 0.004)	0.96 (0.67–1.38, p = 0.838)	0.87 (0.72–1.04, p = 0.123)	0.57 (0.43–0.75, p < 0.001)

HR = hazard ratio; 95%CI = 95% confidence interval; ECOG = Eastern Cooperative Oncology Group (ECOG) Performance Status Score; LAMN = low-grade appendiceal mucinous neoplasms, CRC = colorectal cancer, HAMN = high-grade appendiceal mucinous neoplasms; PCI = peritoneal cancer index; CC score = completeness of cytoreduction score; (i)PRBT = (intraoperative) packed red blood cell transfusions.

postoperative transfusions were associated with poor short-term patient outcomes, this finding should be interpreted with caution, as it is not clear if the PRBT in the postoperative setting caused these outcomes or were simply the result thereof. The explanations of why postoperative transfusions may not have the same long-term prognostic impact compared to iPRBT remain elusive, but other groups have reported similar findings [23].

In general, however, the mechanisms by which packed red blood cell transfusions exert a negative effect on patient outcomes have been widely discussed [1,2,11,36]. Of particular relevance to oncologic patients and the negative long-term outcomes is the observation, that PRBT may lead to an impaired immune-response thus altering tumour and microenvironement interactions resulting in increased risks of cancer dissemination as well as recurrence [36]. The exact mechanism, by which this so-called transfusion-related immunomodulation (TRIM) leads to these effects whilst widely discussed are inconsistently defined. It is thought the macrophages play a central role in mediating the immunomodulation caused by transfused red blood-cells, as they are centrally involved in erythrophagocytosis. Equally, it is possible that one of the potential possible causes related to the development of infections in patients with multiple PRBTs during or after a major surgery, is because of possible decreased function of natural killer cells and other antigen-presenting cells (APCs), reduced cell-mediated immunity, and increased regulatory T cells activity following exposure to allogenic blood. In the context of CRS/HIPEC, the association of iPRBT with increased infective (intra-abdominal) and other postoperative complications is of relevance, as high-grade complications have a pronounced negative prognostic effect [37] – a finding which is also supported by our data. This may also explain, why postoperative transfusions were not as prognostic as iPRBTs. Irrespective of the exact mechanism, new data supporting a dose-dependent relationship of iPRBT and CRS/HIPEC patient survival [13,14], and the present study showing that even exposure to just one unit of packed red blood cells negatively impacts patient outcomes, underscore the importance of developing trials evaluating blood-sparing treatment protocols and medically justifiable transfusion triggers. These aspects remain important in lieu of the herein elucidated synergistic effect of preoperative anaemia and iPRBT and other studies showing that structured transfusion protocol development can lead to significant reduction in transfusion requirements during CRS/HIPEC [19].

However, the present analysis has limitations. First, the ratio of iPRBT to PCI is an abstract concept and may be difficult to interpret. Whilst it helps elucidate the independent impact iPRBTs have on CRS/HIPEC patients, we acknowledge that it's use – from a practical point of view – is limited. Furthermore, whilst PCI is a widely-used score for determining disease extent, it has its limitations, including not accounting for the complexity of resections required depending deposit locations. As such, we support the view of Nizri et al. [13], that particularly low-volume transfusions should be replaced with aggressive, balanced volume resuscitation attempts. Secondly, increased iPRBT requirements should be interpreted in the context of substantial blood loss and the co-occurring coagulopathy. As such, the present study cannot determine, if it is iPRBTs themselves or also other blood products such as FFPs, cryoprecipitate, platelets and/or single factor substitutions that contribute to the deleterious patient outcomes. However, previous studies have included FFPs in their analyses, and these have often been determined as non-significant contributors to patient outcomes [20,22,30,42]. Further, the current study suggests that the independent prognostic effect of PCI-corrected iPRBT rates may not be equal across all histopathological subgroups. Equally, the extensive subgroup analyses performed in the present study should be interpreted with caution as they represent multiple retesting of the null-hypothesis and are thus at risk of data-dredging. Finally, as a retrospective analysis our study is also limited by the number of anaesthetic teams involved in each patient's management which may have resulted in non-uniform transfusion triggers, despite them having been quite constant over the years during which CRS/HIPEC has been performed at our unit. However, over time, our transfusion protocols have become refined and are point-of-care guided (intraoperative INRs, TEGs/ROTEMs) and this is an aspect not specifically accounted for in the present analysis, despite having aimed to correct for these changes over time by incorporating a "time-factor" in the multivariable analyses.

To conclude, the present study shows that elevated intraoperative blood loss and the associated requirement for iPRBT is independently associated with a plethora of negative short- and long-term outcomes for patients undergoing CRS/HIPEC. Beyond meticulous dissection and haemostasis, surgeons and anaesthetists may be able to influence a variety of factors associated with increased and decreased intraoperative blood loss. Thus, our and other unit's data support the call for the development of novel blood-sparing management protocols to control intraoperative blood loss and reduce unnecessary transfusions, hereby mitigating the risks of deleterious outcomes of patients undergoing these complex procedures.

Conflicts of interest

Nothing to declare.

Author contributions

OMF, NAA, MAK, DLM conception, design, acquisition, analysis and interpretation of data. OMF statistical analysis and interpretation of data. All authors drafting and revising of article content and final approval of manuscript prior to submission.

Conflicts of interest statement

The authors have no conflicts to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.07.031.

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