Effect of autologous blood transfusion on the rate of biochemical recurrence after radical prostatectomy

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explore the association between ABT and BCR. Cox regression models addressed
the association between ABT and BCR in univariate and multivariate analyses, after
adjusting for preoperative prostate specific antigen level, pathological Gleason sum,
extracapsular extension, seminal vesicle invasion and lymph node invasion.

RESULTS
Of all patients, 205 (15.4%) received perioperative ABT. The mean (median, range)
follow-up was 43.2 (40.9, 0.3–145) months. BCR was recorded in 347 (26.9%) patients and
the time to BCR was 25.2 (20.5, 0.3–107) months. Neither in univariate (P = 0.053) nor
in multivariate (P = 0.2) Cox regression analyses was ABT a statistically significant or
independent predictor of BCR.

CONCLUSION
Perioperative ABT does not predispose to a higher rate of BCR in patients after RP.

KEYWORDS
autologous blood transfusion, biochemical recurrence, prostate cancer, radical
prostatectomy

INTRODUCTION
Radical prostatectomy (RP) is the main treatment for clinically localized prostate
cancer [1]. After the introduction of the anatomical RP technique [2], the amount of
blood loss dramatically decreased [3,4]. Nonetheless, haemodynamic management
remains an important issue in the perioperative care of the patient
undergoing RP, as blood transfusion (BT), either homologous or autologous (ABT),
can be required. Several previous reports showed that BFs have a negative prognostic
impact in various cancers, including lung, oesophageal, colon and breast cancer [5–9].
These adverse outcomes include increased cancer recurrence, BT-associated reactions,
immunomodulation and/or infections [10,11].

BT-related transmission of infectious agents represents the main deterrent of homologous
blood products. Hepatitis B and C and HIV have been associated with homologous BT
[12]. Thus, ABT can be considered a valid alternative, as the use of AB virtually
eliminates infectious risks [12,13]. However, other risks might be associated with ABT,
including transmission of cancer cells in transfused blood. Indeed, reverse
transcriptase-PCR results show that millions of prostate cancer cells might be present in
AB units [14,15]. Previous reports evaluated the effect of ABT in the context of RP, but
their results are not universally accepted [16,17]. A recent report analysed the effect
of BT on the rate of biochemical recurrence (BCR) after RP [18]. However, the authors
did not consider the influence of ABT as an independent variable. Based on these
considerations, we examined the hypothesis that ABT might increase the risk of BCR in a
large European population treated with RP.

PATIENTS AND METHODS
Between January 1992 and July 2005, 4222 patients with biopsy-confirmed, clinically
localized prostate cancer had RP. Patients with either unavailable PSA data before
treatment (195, 4.5%), missing pathological Gleason scores (152, 3.5%), homologous BT
(46, 1.1%) or missing follow-up information (298, 7.0%) were excluded from the study.
Moreover, patients with an unknown neoadjuvant hormonal therapy status (313,
7.2%) were also excluded, as results from these men could confound the relationship
between ABT and BCR. Finally, we excluded an additional 1927 patients (45.5%), who had no pelvic lymphadenectomy, as in these men the complete pathological stage of the disease at RP was not known. All exclusions resulted in 1251 evaluable patients remaining.

The AxSYM PSA assay (Abbott Park, IL, USA) was used, and the PSA level was measured before a DRE and TRUS-guided biopsy. The clinical stage was defined according to the 1992/2002 American Joint Committee on Cancer staging classification [19]. All RP specimens were surface-inked and processed according to the Stanford protocol [20]. The Gleason grading system was used for histological tumour grading [21]. No patient received any type of hormonal manipulation either before or at any time during the study follow-up. In all patients the PSA values were measured quarterly in the first year, followed by biannual measurements in the second and annual measurements in the third year after RP. BCR was defined as a PSA value after RP of ≥0.1 ng/mL and increasing after an initial undetectable PSA value. The first PSA value of ≥0.1 ng/mL was used to define the time to BCR; patients with no evidence of BCR were censored at the last follow-up.

The probability of being BCR-free after RP was plotted using the Kaplan-Meier method, with the log-rank test used to compare the rate of BCR according to ABT status. Life-table analyses were used to determine the population of patients who were free of BCR at 2, 4 and 6 years after RP. Covariates consisted of pretreatment PSA level, extracapsular extension (ECE), seminal vesicle invasion (SVI), lymph node invasion (LNI) and pathological Gleason sum. All predictors, including ABT status, were used in univariate and multivariate Cox regression models addressing the association between ABT and BCR, and all tests were two-sided with a significance level set at 0.05.

RESULTS

The characteristics of the 1291 evaluable patients are shown in Table 1, with a graph of the variables shown in Fig. 1 to better show the similarities (pretreatment PSA level) and differences (pathological Gleason sum, ECE, SVI) in the distribution between ABT vs no BT groups; e.g. the PSA level was no different between the groups. Conversely, pathological Gleason sums showed different distribution rates of Gleason 7, which favoured the ABT group. Similarly, the ABT group had a lower prevalence of ECE. The rate of SVI was lower in ABT patients, albeit not statistically significantly. The mean (median, range) pretreatment PSA level was 10.6 (8.0, 1.0–49.8) ng/mL. The pathological Gleason sum was ≤6 in 37.3%, 7 in 60.0% and 8–10 in 27.2%. ECE, SVI and LNI were, respectively, recorded in 27.2%, 16.4% and 6.3% of the patients. The blood loss was 1090 (1000, 100–3000) mL. BCR after RP was recorded in 27.2%, 16.4% and 6.3% of the patients. The blood loss was 1090 (1000, 100–3000) mL. BCR after RP was recorded in 27.2%, 16.4% and 6.3% of the patients. Of all patients, 15.9% received ABT during or after RP, in this subgroup, BCR was found in 20.8%.

Figure 2A shows the Kaplan-Meier plot of overall BCR-free survival, and Fig. 2B stratifies BCR-free survival according to ABT status. The rate of BCR was higher in patients with ABT, but not quite statistically significantly (P = 0.053). The BCR-free rates at 2, 4 and 6 years are also shown in Fig. 2.

Table 2 shows the univariate and multivariate Cox regression models addressing the effect of ABT on BCR, after RP. Covariates were pretreatment PSA level, pathological Gleason sum, ECE, SVI and LNI. In the univariate analyses, ABT was not quite statistically significant (P = 0.053), but all covariates were statistically significantly associated with BCR (P < 0.001). In the multivariate fully adjusted models, ABT was not an independent predictor (P = 0.2), but all other covariates were independently associated with BCR (all P < 0.007).

DISCUSSION

Blood loss during RP has decreased dramatically in the last few years, due to refinements in surgical technique [4]. However, control of haemostasis during RP still represents a critical issue [22,23]. Despite the important improvements in the maintenance of haemostasis during RP, a significant proportion of patients are still at risk of blood loss. The most recent reports quantify the probability of blood loss that requires a BT at 9–19% [18,24,25]. In these

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall</th>
<th>No BT</th>
<th>ABT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%) patients</td>
<td>1291</td>
<td>1086</td>
<td>205</td>
<td>1.0</td>
</tr>
<tr>
<td>Age, years* (range)</td>
<td>62.6 (63)</td>
<td>62.7 (63)</td>
<td>61.6 (62)</td>
<td>0.001</td>
</tr>
<tr>
<td>Preoperative PSA level, ng/mL*</td>
<td>10.6 (8.0)</td>
<td>10.6 (7.9)</td>
<td>10.6 (8.1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Pathological Gleason sum, n (%)†</td>
<td>481 (37.3)</td>
<td>391 (36.0)</td>
<td>90 (43.9)</td>
<td>0.09</td>
</tr>
<tr>
<td>Blood loss, mL*</td>
<td>1090 (1000)</td>
<td>1075 (1000)</td>
<td>1169 (1000)</td>
<td>0.01</td>
</tr>
<tr>
<td>Time to BCR, months (log-rank)</td>
<td>25.2 (20.5)</td>
<td>25.2 (19.1)</td>
<td>25.7 (22.6)</td>
<td>0.053</td>
</tr>
</tbody>
</table>

NOTE: The test; †chi-square.

*—test; †chisquare.
patients, ABT might represent an alternative to homologous BT. Unfortunately, autologous blood can contain viable prostate cancer cells and this might increase the risk of BCR [14,15]. The use of intraoperative cell-saver devices has been examined for the possibility of prostate cancer cell transfusion [13,18]; these studies showed that the risk of BCR was not increased by using these devices, but the cell-saver studies are not directly comparable to studies in which ABT was used.

Therefore we formally analysed the exposure to ABT and its effect on BCR, specifically investigating the association between ABT and the rate of BCR in univariate and multivariate Cox regression models predicting BCR after RP. We hypothesized that ABT might increase the risk of BCR, due to re-infusion of circulating prostate cancer cells. We tested this hypothesis within a large contemporary group of 1291 men with clinically localized prostate cancer, treated with RP at a high-volume European centre. BCR was recorded in 26.9% of patients, with a mean time to BCR of 25.2 months. In univariate analyses, ABT was a borderline statistically significant predictor of BCR (P = 0.053). ABT had a protective effect, as shown by the BCR-free rates of 99.0%, 97.0% and 95.4%, vs 98.9%, 93.9% and 92.0% in, respectively, the ABT and no-BT groups at 2, 4 and 6 years after RP.

In multivariate models, ABT was not an independent predictor (P = 0.2) when all pathological predictors and pretreatment PSA level were also considered. Conversely, the pathological characteristics and pretreatment PSA level were independent predictors of BCR (all P < 0.007). Therefore, our results show that exposure to ABT does not increase the risk of BCR.

The data in Table 1 showed no differences in the PSA distribution between the groups, with no statistical significance (P = 1.0) and by overlapping distributions (Fig. 1). The lack of statistically significant differences in PSA level or distribution implies that PSA level does not contribute to the observed difference in BCR between the ABT and the no-BT groups. Conversely, the situation differs for the other prostate cancer characteristics. Pathological Gleason sum, ECE and SVI, to varying extents, differed in the ABT and the no-BT groups, e.g. in the ABT group there was a smaller proportion of pathological Gleason sum 7 prostate cancer (54.1% vs 61.1%), fewer instances of ECE (21.0% vs 28.4%), and finally,
slightly fewer instances of SVI (16.1% vs 16.5%). Although not all of these differences were statistically significant or even of borderline significance, together they contribute to a more aggressive phenotype of the ABT population. The finding that more aggressive prostate cancers were associated with higher blood loss and greater rate of BT (ABT), is hardly surprising. Therefore without multivariate adjustment, the BCR rate in the ABT group would be expected to be somewhat more favourable than that of other patients. This was indeed the case (P = 0.053). However, can the borderline statistically significant BCR benefit be related to ABT or to differences in pathological variables? This was resolved by multivariate analyses controlling for pathological characteristics (Table 2), indicating that ABT had no bearing on BCR (relative risk 0.76, P = 0.2). These findings can be used to conclusively reject the hypothesis that ABT has either a positive or a negative effect on BCR. The results can also be used to assess the strength and the statistical significance of the effect of PSA level and tumour pathology on the rate of BCR, after accounting for ABT status. Here, the role is reversed, as all pathological characteristics and PSA level had a strong statistical effect on BCR rate.

Our results have important clinical implications. Some patients are at high risk of blood loss during RP. Large prostate glands, neoadjuvant hormonal therapy, extended lymphadenectomy, high body mass index, general anaesthesia and locally advanced disease have been identified as risk factors for increased perioperative blood loss [22,23]. ABTs have been shown to be better than homologous BT for reducing complications, including HIV, hepatitis B or C infection and T cell leukaemia [12]. Consequently, ABT might represent a safer alternative to homologous BT. Our results represent the first large-scale contemporary report of the safety of this approach for the rate of BCR.

The present findings are consistent with previously published reports that showed no statistically significant differences in recurrence rates after RP in patients who received ABT vs homologous BT [13,18,23]. In 309 patients, Ness et al. [23] recorded BCR in 24.5% of patients receiving homologous blood, vs 22.7% receiving ABT or no blood (P > 0.5). Also, Davis et al. [13] recently reported, in 408 evaluable patients, that when either cell-saver or ABTs were used, the risk of BCR was not increased. However, in that analysis only 14% of patients had no BT. As most patients (86%) were transfused, it might be difficult to detect the effect of BT. Paul et al. [18] also assessed the effect of BTs on BCR; of all patients included in their analyses, only 3.2% received ABT, and ABT had no effect on BCR. However, as 3.2% is a small proportion of the total, it might be equally difficult to detect a statistically significant effect of such a measure.

The present study differs from previous studies in the proportion of patients having ABT (15.4%), which is consistent with contemporary BT rates; it is higher than that of Paul et al. [18] (3.2%), yet substantially lower than that of Davis et al. [13] (86%). A BT rate of 15% allows a better examination of the true effect of ABT on BCR.

Despite its strength relative to the previous ABT studies, there are several limitations to the present study. We did not analyse the effect of the amount of transfused blood on BCR. Unfortunately, these data were not available in this relatively small group of patients. Paul et al. [18] addressed this outcome and showed that the number of transfused blood units did not affect the rate of BCR (P = 0.5). We did not consider surgical margins in the multivariate model, but the effect of positive surgical margins would be unlikely to change the virtually non-existent effect of ABT in that analysis [24–26]. The present study assessed the outcomes of patients from one centre; of these, most had favourable pathological disease characteristics. It is conceivable that including patients with more unfavourable prostate cancer might have resulted in a higher rate of ABT and could have affected the observed outcome. Moreover, we had no access to body mass index data; considering those could also have affected the multivariate relationship between ABT and BCR. Finally, generally patients were not exposed to neoadjuvant hormonal therapy and we did not perform extended lymphadenectomy. Both variables are known to predispose to blood loss, which could have also affected the results.

Despite these potential limitations we are confident that considering these variables would not have modified the effect of ABT on BCR, especially that ABT had a protective effect on BCR in the univariate analysis. This effect was dissipated completely once PSA level and pathological stage were considered. In conclusion, ABT has no effect on the rate of BCR, and thus when higher blood loss is anticipated, ABT represents a safe method which should not be avoided.

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CONFLICT OF INTEREST

None declared.

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Abbreviations: (A)BT, (autologous) blood transfusion; BCR, biochemical recurrence; RP, radical prostatectomy; ECE, extracapsular extension; SVI, seminal vesicle invasion; LNI, lymph node invasion.