

The impact of perioperative blood transfusion on survival outcomes in radical cystectomy patients

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The impact of perioperative blood transfusion (BT) on survival outcomes has been reported in several urological and non-urological surgeries (1,2). Considering bladder cancer (BCa) patients, radical cystectomy (RC) with bilateral pelvic lymph node dissection represents the standard of care in muscle invasive and recurrent high risk non-muscle invasive disease (3). However, this procedure is related to a high risk of perioperative complications accounting for 50–60% of patients (4). In perspective, almost 30–65% of them need a perioperative BT as a direct consequence of tumor characteristics and complexity of the surgery (5). Preliminary data suggests that perioperative BT might have an impact on survival outcomes in RC patients (5). Proposed theories to explain this relation includes the immunosuppressive effect that BT exert due to the presentation of large amounts of antigen and is known as transfusion-related immune modulation (6). Immune modulation is mediated by the suppression of cytotoxic cell and monocyte activity, leading to an increase in suppression of T-cell activity (7). This, together with the surgical manipulation may lead to the release of circulating tumor cells, resulting eventually in distant metastases. However, at the time, no consensus has been reached about the real immunosuppressive effect of BT in RC patients. In this regard, the effect of leukoreduced BT on survival outcomes in RC was tested by Chipollini *et al.* (8). They found no association between leukoreduced BT and worse survival outcomes in RC

patients supporting the idea that immunosuppressive effect might be the cause of worse survival outcomes and might be avoided with leukoreduction of BT. On the other hand, short follow up period (median: 27.5 months), absence of some pivotal pathologic characteristics in the multivariable model and absence of duration of blood storage limits partially these findings. In this regard, duration of blood storage has been described as an important factor in predicting risk of infection and overall morbidity in RC patients (9). Moreover, the only other report with leukoreduced BT reported worse perioperative morbidity and advance oncologic outcomes in patients who received BT when compared to those who non received any (10).

Other theories include the effect of a locally advanced disease on preoperative characteristics that might cause anemia related to chronic hematuria or influenced directly by the presence of micro-metastases not radiologically assessable that might influence through the effect of inflammatory cytokine activity preoperative parameters such as thrombocytosis (11), hemoglobin level (12) or C reactive protein (13). Of course, the presence of lower hemoglobin levels due the effect of locally advanced or metastatic tumors are linked to an increased probability to receive BT and to worse survival after surgery due to the more advanced disease when compared to patients without locally advanced or metastatic disease. Moreover, technical difficulties in patients with locally advanced disease might require a more destructive surgery that might be associated

with more blood loss and therefore to higher chance of receiving intraoperative or postoperative BT when compared to patients with less advanced disease.

Vetterlein *et al.* (14) recently reported data from the prospective multicenter radical cystectomy series (PROMETRICS), analyzing data on 679 patients treated with RC at 18 European centers in 2011. In their series, more than half patients received perioperative BT, and this occurrence was not associated with any survival difference when compared to patients who did not receive perioperative BT in the multivariable models. These results were not surprising, in fact authors as recognized in their discussion, have no data regarding timing of BT or preoperative anemia and therefore could not adjust the multivariable models for these parameters. Considering these limitations, these results are in line with previous findings, where perioperative BT has no impact on survival outcomes in RC patients when BT are considered all together (intraoperative and postoperative) or preoperative anemia is not considered as a part of the multivariable models (15-17).

Further studies observed that the timing in delivering BT has a pivotal impact on defining survival outcomes in RC patients. Specifically, only intraoperative BT has a detrimental effect on survival parameters when compared to patients who not received BT or received postoperative only BT (17,18). Abel *et al.* (17) reported data on 360 RC patients validated with a cohort of 1,770 RC patients. In both groups, most than 60% patients received BT, but only those who received intraoperative BT had worse survival outcomes when compared to those who received no BT or postoperative BT only. However, when analyzed the impact of intraoperative BT on different pattern, timing or rate of distant recurrence (those recurrence that might be related to an immunosuppressive effect), no increased risk was recorded for those patients when compared to those who not received intraoperative BT (19).

Blood characteristics and specifically Rh factor and ABO blood type have been also investigated as possible actors in the association between perioperative BT and survival outcomes in RC patients. It was proposed a possible role as the loci of ABO blood type is located on the chromosome 9q34 that represents a common site for genetic deletions in BCa (20). The majority of reports on this topic failed to observe any survival differences considering ABO blood type and Rhesus factor and survival outcomes in RC patients when adjusted for demographics, perioperative and pathologic characteristics (21-23).

Although rapidly growing, the literature regarding the impact of BT on oncological outcomes in RC need level 1 evidence to prove the real effect of BT on survival outcomes. In this setting, some strategies such as the use of tranexamic acid (24) or the robotic approach (25) might be of benefit to reduce the need of perioperative BT.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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