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Comment

Blood Transfusion, Radical Cystectomy, and Cancer Recurrence: A New Look at an Old Story. Comment on Ladner et al. Perioperative Blood Transfusion Is Associated with Worse Survival in Patients Undergoing Radical Cystectomy after Neoadjuvant Chemotherapy for Muscle-Invasive Bladder Cancer. *Soc. Int. Urol. J.* 2024, 5, 202–213

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Radical cystectomy can be a morbid operation. Complications are common and many patients require a blood transfusion [1]. Whilst enhanced recovery [2] and robotic surgery are improving outcomes, numerous challenges remain. These challenges include the use of blood transfusions in pre-operatively anaemic patients or in those with significant blood loss during surgery. Concerns regarding the safety of transfusions, and observed higher risks of cancer recurrence, were initially raised over 40 years ago [3]. Whilst authors suggest that the suppressive effect of exogenous blood may impact the immune system's ability to detect (and remove) circulating cancer cells, there are direct associations between a more advanced tumour stage and a greater blood loss (and the need for transfusions) that could prove confounding. Systematic reviews detail many reports have low methodological rigor and missing data [4], although many teams favour the use of pre-operative iron supplements in 'at risk' patients [5].

Whilst much is known in colorectal cancer, the picture in bladder cancer is less clear. Within this issue of the journal, Ladner et al. build upon our knowledge by focusing upon the specific issue of blood transfusions and cancer recurrence after neoadjuvant chemotherapy and radical cystectomy [6]. The authors report an impressive international multi-centre retrospective review of patients who underwent neoadjuvant chemotherapy and open radical cystectomy. Patients were treated at one of nineteen hospitals in Europe and North America between 2000 and 2013. As with all retrospective multicentre reports, the authors faced challenges with data accuracy and completeness. The team found transfusion rates were high (64% of patients required transfusion, with a median of 3 units) and that perioperative blood was associated with a worse overall survival (even in multivariate analysis that included tumour stage and sex).

As readers, we should absorb these findings, consider their implications in our practices, and also question some of the observations. Examples of take-home messages include that women were more likely to receive a transfusion and so perhaps need a better pre-operative work up (with lower thresholds for iron transfusions). The same was also true for patients who received MVAC or ddMVAC, when compared to gemcitabine and cisplatin/carboplatin. However, conversely, there were some concerning issues that give pause for thought. The transfusion rate was higher than expected or seen in prospective rigorous datasets [1]. This may reflect real-world observations, variations in practice [7], or potential selection during case entry. Around half of the initial 1865 patients were excluded, primarily due to missing transfusion data, and so it is plausible that those without blood

were less likely to have a clear transfusion outcome (yes or no) in the notes. Of note, rates of missing data varied dramatically between centres. We should also wonder about the nature of the cohort. Whilst the participants and their tumours appear similar to many contemporary series, almost 40% had died within 2 years of surgery (as shown in the overall survival in Figure 2 [4]). This rate is worse than older retrospective cohort reports [8] or contemporary RCTs [9] and so perhaps points to a more aggressive disease or less fit patients than many of us see.

As with all retrospective data, the true value lies in comparisons with our own contemporary practice [10]. As the authors rightly conclude, much is changing in cancer care and cystectomy pathways. We can all agree that avoiding blood transfusion is an important goal, not least from the risks of viral infections, transfusion reactions, and (possibly) higher rates of cancer recurrence. The rise in robotic cystectomy use should undoubtedly reduce transfusions rates [9], but current ERAS pathways for radical cystectomy do not mention pre-operative measures to address anaemia [11]. This issue needs highlighting in updated guidelines. We should pay special attention to high-risk cohorts (e.g., women, more advanced cancers, those receiving neoadjuvant MVAC, and those anaemic in clinic), embrace strategies that minimise transfusion needs, and observe how these findings change in a landscape with a wider use of systemic immunotherapies.

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