

# Effect of Allogeneic Intraoperative Blood Transfusion on Survival in Patients Treated With Radical Cystectomy for Nonmetastatic Bladder Cancer: Results From a Single High-Volume Institution

Marco Moschini,<sup>1,2</sup> Paolo Dell' Oglio,<sup>1</sup> Paolo Capogrosso,<sup>1</sup> Vito Cucchiara,<sup>1</sup> Stefano Luzzago,<sup>1</sup> Giorgio Gandaglia,<sup>1</sup> Fabio Zattoni,<sup>3</sup> Alberto Briganti,<sup>1</sup> Rocco Damiano,<sup>2</sup> Francesco Montorsi,<sup>1</sup> Andrea Salonia,<sup>1</sup> Renzo Colombo<sup>1</sup>

## Abstract

**Transfusion has been related to poor survival after surgery in several cancers. Recently, timing of transfusion has been proposed as crucial in the determination of poor survival expectancies after surgery, in fact, intraoperative but not postoperative transfusion were found to be related. We confirmed these findings in patients who underwent radical cystectomy because of bladder cancer; physicians should avoid use of transfusion intraoperatively.**

**Background:** Previous studies have demonstrated that perioperative blood transfusion (BT) is associated with a significantly increased risk of cancer recurrence and mortality after radical cystectomy (RC). Recently, it was shown for the first time that intraoperative transfusion has a detrimental effect on cancer survival. The aim of the current study was to validate this finding in a single European institution. **Patients and Methods:** The study focused on 1490 consecutive nonmetastatic bladder cancer patients treated with RC at a single tertiary care referral center between January 1990 and August 2013. Kaplan–Meier analyses and Cox regression analyses were used to assess the effect of timing of BT administration (no transfusion vs. intraoperative transfusion vs. postoperative transfusion vs. intraoperative and postoperative transfusion) on cancer-specific mortality (CSM), overall mortality (OM), and disease recurrence. **Results:** Mean age at the time of RC was 67 years. Overall, 322 (21.6%) patients received intraoperative BT and 97 (6.5%) received postoperative BT. At a mean follow-up time of 125 months (median, 110 months), the 5- and 10-year CSM rate was 846 (58%) and 715 (48%), respectively. In multivariable analyses patients who received intraoperative BT had greater risk of disease recurrence (hazard ratio [HR], 1.24;  $P < .04$ ), CSM (HR, 1.60;  $P < .02$ ), and OM (HR, 1.45;  $P < .03$ ). Conversely, this effect disappears with postoperative BT (all  $P > .2$ ). **Conclusion:** Our study confirms that intraoperative, but not postoperative BT, are related to a detrimental effect on survival after RC. These results should be taken into account by physicians to administer BT using the correct timing.

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## Introduction

Radical cystectomy (RC) with pelvic lymph node (LN) dissection (PLND) is the treatment of choice for muscle-invasive and high-risk

nonmuscle invasive bladder cancer (BCa) patients.<sup>1</sup> However, the 5-year overall life expectancy after surgery is not optimal ranging from 42% to 58%, according to stage of the disease and node

<sup>1</sup>Department of Urology, Urological Research Institute, Vita-Salute University, San Raffaele Scientific Institute, Milan, Italy

<sup>2</sup>Doctorate Research Program, Magna Graecia University of Catanzaro, Catanzaro, Italy

<sup>3</sup>Department of Urology, University of Padua, Padua, Italy

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Address for correspondence: Marco Moschini, MD, Department of Urology, University "Vita-Salute," San Raffaele Hospital, Via Olgettina, 60-20132 Milan, Italy  
Fax: +02-26435659; e-mail contact: [marco.moschini87@gmail.com](mailto:marco.moschini87@gmail.com)

status.<sup>2</sup> In this context, several biochemical or hematological parameters have been described as possible predictors of survival in BCa patients treated with RC.<sup>3-7</sup> Specifically, perioperative blood transfusion (PBT) has been recently proposed by several investigators as a possible predictor of poor survival expectance after RC,<sup>8-11</sup> that underlying hematological factors have a direct role in BCa. This effect was known and investigated in several other malignancies, including breast, larynx, colon-rectal, and prostate cancer.<sup>12-17</sup> Several mechanisms have been proposed to explain this effect, which include immunosuppressive effects from blood transfusion (BT),<sup>18</sup> a decreased host immunity caused by anesthetics and opioids,<sup>19</sup> and a release of increased numbers of circulating tumor cells caused by surgical manipulation.<sup>20</sup> None of the aforementioned studies evaluated the effect of the timing of BT (intraoperative vs. postoperative) in terms of outcomes after RC. In this context, Abel et al<sup>21</sup> in a multiinstitutional cohort of 360 patients, assessed whether individuals who received BT during their surgery had better outcomes compared with patients who received BT during their postoperative hospitalization. They validated their results in a validation cohort of 1770 patients, demonstrating that intraoperative transfusion but not postoperative transfusion was associated with lower survival expectances.

In the current study we aimed to assess the effect of intraoperative BT on survival after RC for BCa in a large contemporary European cohort of patients with nonmetastatic BCa treated at a tertiary referral center, to test the hypothesis that the intraoperative BT in our center increased the risk of disease recurrence, cancer-specific mortality (CSM), and overall mortality (OM).

## Patients and Methods

### Study Population

After institutional review board approval was obtained, we evaluated 1490 consecutive patients with nonmetastatic BCa treated with RC and bilateral PLND at a single tertiary care referral center between January 1990 and August 2013.

### Covariates

Preoperative patient characteristics were evaluated at admission for RC and included: age at time of surgery, sex, body mass index (BMI), Charlson Comorbidity Index ([CCI which was set to 0 vs. 1 vs.  $\geq 2$ ), preoperative hemoglobin (Hb) level, and anemic status. Tumor characteristics included pathological T stage (pT0-T2 vs. pT3 vs. pT4; classified according to the 2009 tumor, node, metastases classification<sup>22</sup>), carcinoma in situ, and surgical margin status. Perioperative BT was defined as transfusion of allogeneic red blood cells during RC or in the postoperative hospitalization. Administration of BT was based on the discretion of the treating physicians and stratified according intraoperative or postoperative administration. Anemic status was defined as a preoperative Hb value recorded as  $< 13$  g/dL for men and  $< 12$  g/dL for women, according to the World Health Organization (WHO) definition.<sup>23</sup>

Dedicated genitourinary pathologists examined all surgical specimens. All removed LNs were examined for the presence of nodal metastases. LN invasion was invariably defined as  $\geq 1$  metastatic LNs. Positive soft tissue surgical margin (PSTSM) was defined as

the presence of tumor at inked areas of soft tissue on the RC specimen.

Clinical and radiological follow-up consisted of a baseline visit at 3 to 4 months after surgery. Subsequently, the minimum follow-up consisted of at least 2 annual visits. Examinations included radiological imaging with computed tomography in all patients. In addition to physical examination with laboratory testing, intravenous pyelography, cystoscopy, urine cytology, urethral washings, and bone scan were carried out if indicated.

### Statistical Analyses

Descriptive statistics of categorical variables focused on frequencies and proportions. Means, medians, and interquartile ranges were reported for continuously coded variables. The Mann–Whitney test and  $\chi^2$  test were used to compare the statistical significance of differences in medians and proportions, respectively.

Our analyses consisted of different steps. First, Kaplan–Meier analyses were used to evaluate the effect of PBT on the recurrence, OM, and CSM rates in the overall population and after stratification according to the timing of PBT. Second, multivariable Cox regression analyses were used to test the relationship between receipt of transfusion and the risk of recurrence, CSM, and OM after adjusting for age, sex, CCI, PSTSM, pathological stage, number of positive nodes, number of removed nodes, adjuvant chemotherapy, and anemia status.

All statistical analyses were performed using SPSS version 22.0 (IBM Corp, Armonk, NY), with a 2-sided significance level set at  $P < .05$ .

## Results

### Baseline Characteristics

Clinical and pathological characteristics of patients included in the study are shown in Table 1. Overall, 580 patients (38.9%) received BT. Of these, 322 individuals (21.6%) received intraoperative BT, 161 individuals (10.8%) received intraoperative and postoperative BT, 97 individuals (6.5%) received postoperative BT. As expected, patients who received intraoperative and postoperative BT had lower preoperative Hb values, were more anemic, and lost more blood during surgery (all  $P < .001$ ). Moreover, patients who received BT had the higher rate of LNs removed and of positive surgical margin (all  $P < .02$ ). Finally, no statistically significant difference was detected in age, BMI, CCI, pathological T stage, Grade (WHO 1973), carcinoma in situ, number of positive nodes, or neoadjuvant or adjuvant chemotherapy, according to the timing of BT administration (all  $P > .1$ ).

### Survival Estimates

Mean (median) follow-up was 125.13 (110) months after surgery. Overall, the 5- and 10-year CSM survival-free rates were 58% and 48% (Figure 1A). After stratification according to the timing of BT administration (no transfusion vs. postoperative transfusion vs. intraoperative transfusion vs. intraoperative and postoperative transfusion), the 5- and 10-year CSM rates were 64% and 52% versus 60% and 60% versus 49% and 42% versus 50% and 40%, respectively ( $P < .001$ ; Figure 1B). Moreover, patients who received

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