Operative blood loss and use of blood products after full robotic and conventional low anterior resection with total mesorectal excision for treatment of rectal cancer

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Abstract To date, no studies have investigated the estimated blood loss (EBL) after full robotic low anterior resection (R-LAR) in a case-matched model, comparing it with the conventional open approach (O-LAR). Forty-nine patients in the R-LAR and 105 in the O-LAR group were matched for age, gender, BMI (body mass index), ASA (American Society of Anesthesiology) class, tumor–node–metastasis (TNM) classification and UICC (Union for International Cancer Control) stage, distance of the lower edge of the tumor from the anal verge, presence of comorbidities, and preoperative hemoglobin (Hb). EBL was significantly higher in the O-LAR group ($P < 0.001$); twelve units of packed red blood cells were globally transfused in the O-LAR group, compared to one unit only in the R-LAR ($P = 0.051$). A significantly higher postoperative Hb drop (3.0 vs. 2.4 g/dL, $P = 0.015$) was registered in the O-LAR patients. The length of hospital stay was much lower for the R-LAR group (8.4 vs. 12.4 days, $P < 0.001$). The number of harvested lymph nodes (17.4 vs. 13.5, $P = 0.006$) and extent of distal margin (2.9 vs. 1.9 cm, $P < 0.001$) were significantly higher in the R-LAR group. Open surgery was confirmed as the sole variable significantly associated ($P < 0.001$) with blood loss (odds ratio = 4.41, 95% CI 2.06–9.43). It was a confirmed prognosticator of blood loss ($P = 0.006$) when a preoperative clinical predictive model was built, using multivariate analysis (odds ratio = 3.95, 95% CI 1.47–10.6). In conclusion, R-LAR produced less operative blood loss and less drop in postoperative hemoglobin when compared to O-LAR. Other clinically relevant outcomes were similar or superior to O-LAR.

Keywords Full robotic low anterior resection · Low anterior resection · Estimated blood loss · Hemoglobin · Transfusion

Introduction

Precise robotic movements and fine manipulation of tissues in a close and fixed operating field make rectal cancer surgery an important application of robotic surgery, and in fact robot-assisted low-anterior resection (R-LAR)—with either total or tumor-specific mesorectal excision (TME)—was reported by several authors as a technically feasible and oncologically safe procedure for treatment of rectal cancer [1–5]. As robotic views of the operating field during R-LAR procedures require a relatively bloodless field, R-LAR might be expected to lead to less operative blood loss than open conventional low anterior resection (O-LAR). This has some interest for clinicians, as it has been reported that allogenic blood transfusion might be associated with an increased risk of tumor recurrence after colorectal cancer surgery [6, 7]. Studies of blood loss after O-LAR have had variable results, with rates of perioperative transfusions ranging from 20 to 75% [8]. To date, some studies have reported estimated blood loss (EBL)
after R-LAR [9, 10], but no study has investigated this topic as a case-matched model, comparing open and robotic approaches. This study compares blood loss as measured by EBL, mean drop in hemoglobin levels with surgery, and blood product use in patients undergoing O-LAR or R-LAR in different periods of time at the same institution, maintaining the same guidelines for transfusion in the postoperative period. In addition, some clinically relevant data on early outcomes were investigated.

Methods

All patients undergoing R-LAR or O-LAR in this study were entered into a prospectively-managed database, along with their age, sex, diagnosis received (including pathologic stage), and data regarding preoperative chemo-radiation therapy performed, if any. Only tumors with the distal edge within 12 cm of the anal verge were considered for this study. Operative details included operating time, American Society of Anesthesiologists (ASA) class, body mass index (BMI), EBL, and complications, including readmission within 30 days of hospital discharge.

Standard surgical techniques—emphasizing the need for TME—were routinely applied during this study, as previously published elsewhere [4, 11]. A da Vinci ™ surgical robot was always used for this study (Intuitive Surgical, Sunnyvale, CA). Surgical specimens were routinely dissected by experienced pathologists not aware of the surgical technique used. Pathologic examination included disease tumor–node–metastasis (TNM) stage, number of lymph nodes harvested, and longitudinal and radial margins of resection using standard techniques; in some cases, depending on the pathologist’s judgement, clearing fixatives were used prior to the dissection.

Consecutive unselected patients undergoing R-LAR between January 2007 and December 2009 were matched with patients undergoing O-LAR in the same institution during a previous 3-year period—between January 2004 and December 2006—for age, gender, ASA class and comorbidity as denoted by the hospital coding system (Diagnosis Related Grouping). In the O-LAR group, only patients without a history of major laparotomy (except cholecystectomy, appendectomy, or gynecologic surgery by a lower abdomen incision) were considered for comparison with the R-LAR group. Preoperative values for hemoglobin level and the corresponding postoperative values taken routinely on the first and third day after surgery were gathered by reviewing the central laboratory computer software system, into which all laboratory results were routinely entered. In this way, the mean drop in hemoglobin levels with surgery was registered.

EBL was regularly recorded on the patient’s chart at the end of the surgical procedure by the anesthesiologist and scrub nurse; drainage containers, and number of sponges and gauze pads used were carefully assessed.

The number of units of blood transfused on the day of surgery, during the first 48 h after surgery, and for the duration of the patient’s hospital stay were determined from the central laboratory computer software system, and cross-checked with data contained in the patient’s cards.

The recommended standard transfusion trigger for the institution is to give red blood packed cells to patients with a Hb level lower than 7 g/dL, unless the patient has a history of cardiac disease or there is active bleeding. This policy did not change during the entire 6-year period of the study, between January 2004 and December 2009.

Data on postoperative course and complications were reported on hospital cards by the surgical team. In addition, an epidemiology nurse was in charge to regularly collect microbiology data with respect to nosocomial infections (surgical site infections, pneumonias, urine, and intravascular catheters).

All complications were registered, with the exception of those considered as deviations from the normal postoperative course without the need for pharmacologic treatment or surgical, endoscopic, and radiologic interventions, according to the classification method proposed by Clavien et al. [12].

Hospital discharge was subjected to pre-defined conditions, in agreement with institutional policy, including fully resumed oral feeding, recovered intestinal function, autonomous walking, and approval of responsible physician.

Statistical analysis

Summary statistics (counts, percentages, mean, median, standard deviation, min and max) for patients’ characteristics, pathologic findings and clinically relevant postoperative outcomes except blood loss were tabulated according to surgery type. Blood loss was summarized using mean, median, 5th and 95th percentiles, and box-plotted against type of surgery. Categorical variables were compared using Fisher’s exact test or the chi-square test. After checking the normality assumption (Kolmogorov–Smirnov test), continuous variables were compared using either the Wilcoxon two-sample test or the unpaired \( t \)-test as appropriate. Univariate and multivariate odds ratios with 95% confidence intervals were estimated in a logistic regression model after removing collinear predictors. All tests were considered statistically significant at \( \alpha = 0.05 \) and two-sided. All analyses were conducted using SAS 9.2 software (Cary, NC, USA).
Results

Forty-nine patients in the R-LAR and 105 in the O-LAR group could be fully matched for age, gender, BMI, TNM classification, and UICC (Union for International Cancer Control) stage, distance of the lower edge of the tumor from the anal verge, presence of comorbidities, and preoperative Hb. No patients received preoperative transfusions, as Hb values were found normal in all patients. ASA class III patients were significantly more prevalent in the open-surgery group, whereas the percentage of patients who underwent neoadjuvant preoperative chemo-radiation therapy was significantly higher in the robotic surgery group (Table 1).

| Characteristic                              | Open-LAR          | Robotic-LAR        | P value* |
|---------------------------------------------|-------------------|--------------------|----------|
| Continuous variables                        | Mean ± SD         | Mean ± SD          |          |
| Age (years)                                 | 61.6 ± 11.7       | 59.5 ± 11.3        | 0.414    |
| BMI                                         | 24.9 ± 3.6        | 24.9 ± 4.0         | 0.956    |
| Distance from the anal verge (cm)           | 7.9 ± 3.4         | 6.9 ± 2.6          | 0.091    |
| Preoperative Hb (g/dL)                      | 13.5 ± 1.5        | 13.3 ± 1.5         | 0.392    |
| Categorical variables                       | N (%)             | N (%)              |          |
| Sex                                         |                   |                    |          |
| Female                                      | 42 (40.0)         | 22 (44.9)          | 0.601    |
| Male                                        | 63 (60.0)         | 27 (55.1)          |          |
| ASA class                                   |                   |                    |          |
| I                                           | 13 (12.5)         | 9 (18.4)           |          |
| II                                          | 51 (49.0)         | 38 (77.6)          | <0.001   |
| III                                         | 40 (38.5)         | 2 (4.1)            |          |
| Tumor stage (TNM)                           |                   |                    |          |
| T0                                          | 15 (14.3)         | 10 (20.8)          | 0.843    |
| T1                                          | 9 (8.6)           | 3 (6.3)            |          |
| T2                                          | 31 (29.5)         | 15 (31.2)          |          |
| T3                                          | 47 (44.8)         | 20 (41.7)          |          |
| T4                                          | 3 (2.9)           | 2 (4.2)            |          |
| Node stage (TNM)                            |                   |                    |          |
| N0                                          | 65 (61.9)         | 30 (62.5)          | 0.878    |
| 1                                           | 31 (29.5)         | 15 (31.2)          |          |
| 2                                           | 9 (8.6)           | 3 (6.3)            |          |
| Metastases stage (TNM)                      |                   |                    |          |
| M0                                          | 98 (93.3)         | 42 (91.3)          | 0.659    |
| 1                                           | 7 (6.7)           | 4 (8.7)            |          |
| UICC Stage                                  |                   |                    |          |
| I                                           | 23 (21.9)         | 12 (24.5)          |          |
| II                                          | 40 (38.1)         | 19 (38.8)          | 0.979    |
| III                                         | 35 (33.3)         | 15 (30.6)          |          |
| IV                                          | 7 (6.7)           | 3 (6.1)            |          |
| Neoadjuvant preop CT/RT                     | 55 (52.4)         | 36 (73.5)          | 0.013    |
| Presence of comorbidities                   | 40 (38.1)         | 21 (42.9)          | 0.574    |

* Two-sample two-sided Wilcoxon test, unpaired *t* test, chi-square or two-sided Fisher’s exact test as appropriate

EBL was significantly higher in the O-LAR group ($P < 0.001$); 75% of R-LAR patients did not experienced any clinically significant intraoperative blood loss, compared to 41% of the O-LAR group ($P = 0.001$), as shown in Table 2 and Fig. 1. Neither intraoperative transfusions nor deaths were observed in these series (Table 3). Six patients in the O-RAR and only one in the R-LAR group received transfusions in the postoperative period ($P = 0.432$); twelve units of packed red blood cells were transfused in the O-LAR group compared to one unit in the R-LAR patients ($P = 0.051$). A significantly higher postoperative Hb drop ($3.0$ vs. $2.4$ g/dL, $P = 0.015$) was registered in the O-LAR patients; postoperative complication rates did not differ significantly between the matched
groups, either for infectious or non-infectious complications. No patients in the R-LAR group experienced a conversion to laparotomy; two patients needed another operation, but bleeding was not the cause. Finally, the length of hospital stay was much lower for the R-LAR group (8.4 vs. 12.4 days, \( P < 0.001 \)). With respect to relevant pathologic findings, radial circumferential margins did not differ significantly between the groups (about 100% of free margin for both), whereas number of harvested lymph nodes (17.4 vs. 13.5, \( P = 0.006 \)) and extent of distal margin (2.9 vs. 1.9 cm, \( P < 0.001 \)) were significantly more favorable in the robotic group (Table 4).

Univariate analysis of blood-loss risk estimates was performed, taking into consideration a number of possible variables (Table 5). Only open surgery was confirmed to be significantly associated (\( P < 0.001 \)) with blood loss during the hospital stay (odds ratio = 4.41, 95% CI 2.06–9.43, compared with referenced robotic surgery). Open surgery was again confirmed as the only prognosticator of blood loss (\( P = 0.006 \)) when a preoperative clinical predictive model was built, using a multivariate analysis of blood-loss risk estimate (odds ratio = 3.95, 95% CI 1.47–10.6, compared with referenced robotic surgery) (Table 6).

**Discussion**

Previous studies have already supported the feasibility and oncologic safety of robotic LAR, although their results were limited by the small number of cases representing the early phase of the learning curve [13]. Since the first reports of robot-assisted rectal cancer surgery, the advantages of the robotic approach were focused on better early postoperative outcomes compared with conventional open analogue procedures, including earlier recovery, less postoperative pain due to smaller incisions, and a shorter postoperative hospital stay [14]. Blood loss has not been investigated in depth until now, in spite of immunosuppression, an untoward effect of allogenic transfusion, which has been postulated to result in decreased tumor surveillance and detrimental outcome. In 1982, Burrows and Tartter first linked perioperative allogenic blood

### Table 2 Estimated blood loss in the open and robotic groups

| Blood loss | Open-LAR | Robotic-LAR | \( P \) value* |
|------------|----------|-------------|----------------|
| None, \( N \) (%) | 42 (41.2) | 36 (75.0) | <0.001 |
| Mean (5th, 95th percentiles) | 146.4 (0, 500) | 83.7 (0, 500) | 0.001 |
| Median | 100 | 0 |
| Min, max | 0, 2000 | 0, 1500 |

* Fisher’s two-sided test or Wilcoxon test as appropriate

### Table 3 Clinically relevant outcomes

| Outcome | Open-LAR | Robotic-LAR | \( P \) value* |
|---------|----------|-------------|----------------|
| Intraoperative transfusions | 0 | 0 | – |
| Death | 0 | 0 | – |
| Postoperative transfusions | | | |
| Patients, \( N \) (%) | 6 (5.7) | 1 (2.0) | 0.432 |
| Units, \( N \) | 12 | 1 | 0.051 |
| Surgical complications (30th postoperative day) | | | |
| Infectious | 15 (14.3) | 8 (16.3) | 0.189 |
| Non-infectious | 11 (10.5) | 10 (20.4) | |
| Both | 5 (4.5) | 0 | |
| Overall | 31 (29.5) | 18 (36.7) | 0.371 |
| Reinterventions (30th postoperative day) | 0 | 2 (4.1) | 0.100 |
| Length of hospital stay (days) mean \( \pm \) SD (median) | 12.4 \( \pm \) 3.2 (12.0) | 8.4 \( \pm \) 9.3 (7.0) | <0.001 |
| Post-operative Hb (g/dL) mean \( \pm \) SD (median) | 10.6 \( \pm \) 1.6 (10.8) | 11.0 \( \pm \) 1.4 (10.8) | 0.124 |
| Hb drop (g/dL) mean \( \pm \) SD (median) | 3.0 \( \pm \) 1.4 (2.9) | 2.4 \( \pm \) 1.6 (2.0) | 0.015 |

* Two-sample two-sided Wilcoxon test, unpaired \( t \) test, chi-square or two-sided Fisher’s exact test as appropriate
transfusion to the prognosis of colorectal malignancy [15]. More recently (2006), a Cochrane Collaboration Review [16] confirmed in an updated meta-analysis the hypothesis that perioperative blood transfusions have a detrimental effect on the recurrence of curable colorectal cancers; the authors concluded that carefully restricted indications for allogenic blood transfusion are necessary in this clinical setting, although a causal relationship cannot be claimed, due to the heterogeneity detected and the not yet completely defined impact of surgical technique [17].

To date, there is no uniform consensus on the relative blood loss when patients undergo low anterior resection for cancer using an open or a robotic approach, and that is true also for laparoscopic low anterior resection. While some studies found that EBL during minimally invasive colorectal resections was significantly lower than during analogue open procedures [18–21], others found the loss to be comparable [22, 23]. A possible reason could be the fact that most of these studies used EBL as the sole measure of blood loss during surgery, a parameter previously reported to be an inconsistent estimate of real blood loss [24, 25]. We used two additional measures to precisely define the blood loss related to surgery: postoperative hemoglobin level drop and overall use of blood products. Hemoglobin drop was much less in the robotic group, thus confirming the significant superiority of robot-assisted LAR in this clinical setting, whereas overall use of blood products showed a trend in favor of the R-LAR patients (12 vs. 1 units of packed red blood cells, \( P = 0.051 \)). In both univariate and multivariate analyses, conventional open surgery was confirmed as the sole variable significantly associated with blood loss; moreover, it was confirmed as a prognosticator of blood loss when a preoperative clinical predictive model was built.

Interestingly, oncology outcomes were also in favor of the robotic group, as witnessed by a higher number of harvested lymph nodes and a higher extent of free distal margin in the surgical specimens, thus confirming previous observations of our and other groups [13]. These results have been obtained while maintaining a comparable rate of surgical perioperative complications and a much lower hospital stay in the R-LAR group.

There are several limitations of this study that deserve some mentions. First, this is not a randomized trial, and therefore it could suffer from the typical limitations of observational-descriptive studies. Nevertheless, this is the first study specifically addressing the topic of blood loss and use of blood products in robotic low anterior resection, by means of a comparison between two quite large series of case-matched patients undergoing the same oncology procedure (low anterior resection) by the same surgical team, using a conventional open and a full robotic approach in the same institution and in a consecutive period of 6 years (three per group). During this study period, practice of care, perioperative management, and, in particular, transfusional policies did not change in our institution.

Another point to be noted is matching, since a potentially important difference between the groups was the higher prevalence of ASA class 3 in the open surgery one. This could reflect possible changes in the attitude and judging of attending anesthesiologists, to whom patients’ ASA classification is routinely given, as the anesthesiology team differed during the study periods, unlike the surgical one. However, our multivariate analysis is adjusted for all patients and tumor characteristics of prognostic relevance, and it excluded ASA class as a variable possibly associated with blood loss.

The higher prevalence in the robotic arm of patients who underwent preoperative neoadjuvant treatment (73.5% vs. 52.4%, \( P = 0.013 \)) is worth of further comment. Use of preoperative neoadjuvant chemo-radiation therapy became a standard option in our institution for locally advanced disease, preoperatively staged as any T, N positive or ≥ T3, any N, and this explains the higher prevalence of these cases in the second group (R-LAR), treated since 2007. A large previous trial, using a conventional open approach, reported that patients randomly assigned to preoperative radiation therapy lost more blood than those assigned to surgery alone (median blood loss 1,000 vs. 900 mL; \( P < 0.001 \)) [26]. Our data do not confirm these results: firstly, no differences were detected between preoperative chemo-radiation and immediate surgery groups in terms of EBL; moreover, median EBL for open surgery was only 100 mL, and zero mL for the robotic group. These findings probably reflect a significant and general improvement in surgical techniques, since these reference surgical data come from a national study concluded in the late 1990s; moreover, they underline the superiority of the robotic technique applied to LAR also in “difficult"
Table 5 Univariate blood-loss risk estimates

| Risk factor                  | Odds ratio (95% CI) | P value *          |
|------------------------------|---------------------|--------------------|
| Surgery                      |                     |                    |
| Robotic                      | Reference           |                    |
| Open                         | 4.41 (2.06, 9.43)   | <0.001             |
| Sex                          |                     |                    |
| Male                         | Reference           |                    |
| Female                       | 0.54 (0.28, 1.04)   | 0.067              |
| Age (years)                  |                     |                    |
| <62a                         | Reference           |                    |
| >62                          | 0.74 (0.39, 1.41)   | 0.360              |
| BMI                          |                     |                    |
| ≤25a                         | Reference           |                    |
| >25                          | 1.65 (0.87, 3.15)   | 0.125              |
| Distance anal verge (cm)     |                     |                    |
| ≤7a                          | Reference           |                    |
| >7                           | 0.64 (0.34, 1.23)   | 0.183              |
| Surgery time (min)           |                     |                    |
| ≤223a                        | Reference           |                    |
| >223                         | 0.78 (0.40, 1.50)   | 0.448              |
| Lymph nodes                  |                     |                    |
| ≤14a                         | Reference           |                    |
| >14                          | 0.54 (0.29, 1.05)   | 0.068              |
| Ostomy                       |                     |                    |
| No                           | Reference           |                    |
| Yes                          | 0.61 (0.32, 1.16)   | 0.132              |
| ASA                          |                     |                    |
| I                            | Reference           |                    |
| II                           | 1.46 (0.56, 3.83)   | 0.443              |
| III                          | 2.52 (0.86, 7.39)   | 0.093              |
| Neoadjuvant CT/RT            |                     |                    |
| No                           | Reference           |                    |
| Yes                          | 0.90 (0.47, 1.73)   | 0.762              |
| UICC Stage                   |                     |                    |
| I                            | Reference           |                    |
| II                           | 0.63 (0.27, 1.49)   | 0.291              |
| III                          | 0.47 (0.19, 1.13)   | 0.092              |
| IV                           | 0.70 (0.17, 2.88)   | 0.621              |
| TNM                          |                     |                    |
| T0–T1                        | Reference           |                    |
| T2                           | 1.33 (0.50, 3.58)   | 0.568              |
| T3–T4                        | 0.60 (0.24, 1.52)   | 0.280              |
| Comorbidities                |                     |                    |
| No                           | Reference           |                    |
| Yes                          | 0.58 (0.30, 1.12)   | 0.106              |

* Median value

* Two-sample two-sided Wilcoxon test, unpaired t test, chi-square or two-sided Fisher’s exact test as appropriate

Table 6 Multivariate blood-loss risk estimates—pre-operative clinical predictive model

| Risk factor                  | Odds ratio (95% CI) | P value |
|------------------------------|---------------------|---------|
| Surgery                      |                     |         |
| Robotic                      | Reference           |         |
| Open                         | 3.95 (1.47, 10.6)   | 0.006   |
| Sex                          |                     |         |
| Male                         | Reference           |         |
| Female                       | 0.57 (0.25, 1.30)   | 0.179   |
| Age (years)                  |                     |         |
| ≤62                          | Reference           |         |
| >62                          | 0.55 (0.25, 1.23)   | 0.147   |
| BMI                          |                     |         |
| ≤25a                         | Reference           |         |
| >25                          | 1.29 (0.60, 2.79)   | 0.513   |
| Distance from anal verge (cm) |                     |         |
| ≤7a                          | Reference           |         |
| >7                           | 0.50 (0.19, 1.26)   | 0.136   |
| Surgery time (min)           |                     |         |
| ≤223a                        | Reference           |         |
| >223                         | 1.18 (0.48, 2.93)   | 0.712   |
| ASA                          |                     |         |
| I                            | Reference           |         |
| II                           | 1.45 (0.47, 4.42)   | 0.518   |
| III                          | 2.02 (0.55, 7.46)   | 0.292   |
| Neoadjuvant CT/RT            |                     |         |
| No                           | Reference           |         |
| Yes                          | 0.78 (0.32, 2.27)   | 0.596   |
| UICC Stage                   |                     |         |
| I                            | Reference           |         |
| II                           | 0.56 (0.20, 1.57)   | 0.273   |
| III                          | 0.42 (0.14, 1.26)   | 0.120   |
| IV                           | 0.67 (0.14, 3.20)   | 0.618   |

* Median value

patients, such as those who underwent chemo-radiation neoadjuvant treatment. With respect to this issue, it is noteworthy to point out that we always applied—in both groups—one or more sheets of regenerated oxidized cellulose (Tabotamp® or Tabotamp Fibrillar®, Johnson & Johnson, Pratica di Mare, Rome, Italy) in case of residual bleeding after mesorectal excision, usually coming from small sacral and coccygeal interrupted venules. This is a
fairly common finding in pretreated rectal cancer patients, where the presacral Waldayer’s fascia is frequently involved in a thick, fibrous post-radiation tissue, and sacrococcygeal venules cannot be easily identified.

In conclusion, this study specifically evaluated whether robotic LAR reduces estimated intraoperative blood loss, postoperative Hb drop, and use of blood products when compared with carefully matched open LAR cases. Robotic LAR was found to lead to significantly less operative blood loss and less postoperative Hb drop, together with much lower use of blood products (P = 0.051) in these patients. Other clinically relevant outcomes—like length of hospital stay and pathologic findings—were found similar or superior to open LAR.

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