Relationship between of short-course preoperative radiotherapy and serum albumin level and postoperative complications in rectal cancer surgery

Odnos između kratkotrajne preoperativne radioterapije i vrednosti albumina u serumu i postoperativnih komplikacija u hirurgiji karcinoma rektuma


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Abstract

Background/Aim. The identification of risk factors could play a role in improving early postoperative outcome for rectal cancer surgery patients. The aim of this study was to determine the relationship between short-course preoperative radiotherapy (RT), serum albumin level and the development of postoperative complications in patients after anterior rectal resection due to rectal cancer without creation of diverting stoma. Methods. This retrospective study included patients with histopathologically confirmed adenocarcinoma of the rectum with the clinical stage of T2-T4 operated on between 2007 and 2012. All the patients underwent open anterior rectal resection without diverting stoma creation. Preoperative serum albumin was measured in each patient. Tumor location was noted intraoperatively as the distance from the rectal carcinoma to the clinical stage of T2-T4 operated on between 2007 and 2012. All the patients underwent open anterior rectal resection without diverting stoma creation. Preoperative serum albumin was measured in each patient. Tumor location was noted intraoperatively as the distance from the inferior tumor margin and anal verge. Tumor size was measured and noted by the pathologist who assessed specimens. Some of the patients received short-course preoperative RT, and some did not. The patients were divided into two groups (group 1 with short-course preoperative RT, group 2 without short-course preoperative RT). Postoperative complications included clinically apparent anastomotic leakage, wound infection, diffuse peritonitis and pneumonia. They were compared between the groups, in relation to preoperative serum albumin level, patient age, tumor size and location. Results. The study included 107 patients (51 in the group 1 and 56 in the group 2). There were no significant difference in age ($p = 0.95$), gender ($p = 0.12$) and tumor distance from anal verge ($p = 0.53$). The size of rectal carcinoma was significantly higher in the group 1 than in the group 2 ($51.37 \pm 12.04\, \text{mm} \, vs \, 45.57 \pm 9.81\, \text{mm}$, respectively; $p = 0.007$). The preoperative serum albumin level was significantly lower in the group 1 than in the group 2 ($34.80 \pm 2.85\, \text{g/L} \, vs \, 37.55 \pm 2.74\, \text{g/L}$, respectively; $p < 0.001$). A significant correlation between the tumor size and the serum albumin level was found ($p = 0.042$). Overall, postoperative complications were observed in 13 (25.5%) patients in the group 1 and in 10 (17.8%) patients in the group 2 without significant difference between the groups ($p = 0.18$). A significantly lower level of serum albumin was found in patients with postoperative complications and in those who died. A significant difference in anastomotic leakage occurrence between groups was found ($p = 0.039$). Male gender and the lower level of serum albumin were significant predictors for anastomotic leakage occurrence ($p = 0.05$ and $p = 0.002$, respectively), but preoperative RT had no significant impact on it. Conclusions. A lower serum albumin level, but not short-course of preoperative RT, was significantly associated with postoperative complications development after rectal resection without diverting stoma.

Key words: rectal neoplasms; radiotherapy, adjuvant; surgical procedures, operative; treatment outcome; postoperative period; risk factors; serum albumin.

Apstrakt

Uvod/Cilj. Identifikacija faktora rizika mogla bi biti važna za poboljšanje ranog postoperativnog ishoda kod bolesnika operisanih zbog karcinoma rektuma. Cilj ove studije bio je da se odredi odnos između kratkotrajne preoperativne radioterapije (RT), vrednosti albumina u serumu i nastanka postoperativnih komplikacija kod bolesnika podvrgnutih prednjoj resekciji rekturnog karcinoma bez kreiranja protektivne stome. Metode. Ova retrospektivna studija obuhvata je bolesnike sa histološki potvrđenim adenokarcinomom rekturnog karcinoma i kliničkim stadijonom T2-T4, operiš-

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Colorectal cancer is a significant cause of morbidity and mortality and one of the most common malignant disease worldwide. The actual treatment regimen for rectal cancer is en-bloc surgical excision of affected segment of the bowel with tumor-specific mesorectal excision. The importance of circumferential lateral spread in local disease recurrence led to the introduction of total mesorectal excision (TME) by Heald in 1982, which ensures resection of the complete mesorectum. The adjuvant therapy, such as chemotherapy or irradiation, may be used for more advanced rectal cancers. Randomized studies have shown benefits of radiotherapy (RT) over surgery alone. Preoperative RT has some advantages over postoperative adjuvant RT that include: better local disease control, reduced therapeutic toxicity, increasing the possibility of sphincter preservation surgery, and better overall outcome in recently published studies. Short-course irradiation (25 Gy in 5 fractions) with immediate surgery is frequent regimen in the preoperative treatment of patients with resectable rectal cancer. However, there are concerns of neoadjuvant therapy effects on the early post-operative morbidity. Serum albumin has been considered as a marker of nutritional status, but a number of studies consider it as an inflammatory marker rather than indicator of nutrition. Studies have shown its predictive value in surgery for colorectal cancer. Tumor size, in particular the maximal horizontal tumor dimension, is an important prognostic parameter for patients with colorectal cancer. Whereas prognostic influence is strong within the colon, it appears to be of minor value within the rectum.

A number of possible complications and the risk of perioperative mortality burden patients undergoing resection for colorectal cancer. Despite advances in surgical techniques, better understanding of the impact on preoperative bowel preparation, prophylactic antibiotics and better postoperative care, colorectal surgery is associated with the mortality rate of 3% to 6% and morbidity of 20% to 40%. The fact that colorectal cancer is a disease of the elderly, with only 5% of cases recorded among those below 40 years of age, even further complicates outcome. The results of systematic review of the outcome of surgery for colorectal cancer in elderly patients showed a progressive increase of postoperative morbidity and mortality with advancing age. Wound infections, intra-abdominal abscesses, and/or anastomotic leakage are the most common complications. In literature data, there is a wide range of morbidity and mortality rates associated with anastomotic leakage. In the past, an incidence of anastomotic leakage varied from 3.4% to 40%. A clinical leakage rate after anterior rectal resection varies from 3% to 11%, and its occurrence depends on various factors. The advantages of diverting stoma after rectal resection are still under debate. Some authors propose creation of a diverting stoma only in low rectal resections, neoadjuvant chemoradiotherapy (CRT) and in patients with significant comorbidities, but others do not recommend a stoma at all. Late postoperative complications are functional derangements and incontinence, especially in patients with neoadjuvant RT. Sexual and bladder functions may also be affected due to injury of autonomic nerves. The identification of risk factors could play a role in improving early postoperative outcome. The literature (Medline, PubMed) has not conclusive data regarding postoperative complications between patients with and without short-course of preoperative RT without diverting stoma.

The aim of this study was to determine the relationship of preoperative serum albumin level and short-course preoperative RT with the development of early postoperative complications in patients with anterior rectal resection immediately after RT without creation of diverting stoma.

**Methods**

This retrospective study included patients with elective oncological resection for rectal adenocarcinoma between January 2007 and December 2012 at the Clinic for General Surgery, Military Medical Academy, Belgrade, Serbia. The study included all operated patients with histologically confirmed adenocarcinoma of the rectum with the clinical stage T2 to T4 (cT2-T4Nx disease) of the International American Joint Committee on Cancer (AJCC 6th edition) TNM classification who underwent anterior resection of rectal cancer without creation of a diverting stoma, or with short-course preoperative RT. Preoperative clinical staging was assessed by physical and per rectal examination, and by various imaging modalities (computed tomography scan, magnetic resonance imaging, endoscopic ultrasonad). The inferior tumor margin was located no farther than 15 cm from the anal verge, measured by sigmoidoscopy. Preoperative serum albumin level was measured in each patient and a value noted one day before surgery was included in the study. Short-course preoperative RT included the total dose of 25 Gy administered in 5 fractions during 5 days according to the International Commission on Radiation Units and Measurements guide- lines. In the patients who received short-course preoperative RT rectal resection was performed within 2 to 7 days after RT. Every patient received preoperative mechanical bowel preparation and antibiotic prophylaxis (metronidazol 500 mg and ceftriaxone 2 g). In all the patients standard oncological anterior resection of a rectum with TME (if tumor was located in the middle and low parts of the rectum), and partial mesorectal excision (if tumor was located in the upper part of the rectum) was performed by open approach with single or double stapling anastomosis technique, without the creation of diverting stoma. Pelvic contact drain was placed in each patient. Tumor location was noted intraoperatively as the distance from the inferior tumor margin to the anal verge. Tumor size was measured and noted by the pathologist who assessed specimens. The patients were divided into two groups (the group 1 with short-course preoperative RT followed by resection and anastomosis and the group 2 with resection and anastomosis without short-course preoperative RT). Postoperative complications included clinically apparent anastomotic leakage (the presence of stercoral contents to the pelvic contact drain), wound infection, diffuse peritonitis and pneumonia. If conservative treatment of the patients with anastomotic leakage failed, they were reoperated (Hartmann’s procedure in all of them). Postoperative complications were assessed between the groups, as well, in relation to preoperative serum albumin level, age, tumor size and tumor location.

Statistical analysis was performed with SPSS software (Statistical package for the social sciences version 18.0, Chicago, IL, USA). Mann-Whitney U-test, Student’s t-test and χ²-test were used to test the significance of differences between the two groups. Correlations between parameters were tested with Pearson’s correlation. Logistic regression was used to evaluate the influence of parameters on postoperative complications development. The results were expressed as median (range), mean ± standard deviation and number (%). P-values < 0.05 were considered statistically significant for all comparisons.

**Results**

Patient demographic data and clinical characteristic are listed in Table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (n = 51)</th>
<th>Group 2 (n = 56)</th>
<th>p value</th>
<th>Total (n = 107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67 (27–89)</td>
<td>66 (28–83)</td>
<td>0.95</td>
<td>73 (27–89)</td>
</tr>
<tr>
<td>Sex, male</td>
<td>31 (60.8)</td>
<td>42 (75.0)</td>
<td>0.115</td>
<td>73/34</td>
</tr>
<tr>
<td>Clinical tumor stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>2 (3.9)</td>
<td>9 (16.1)</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>T3</td>
<td>45 (88.2)</td>
<td>47 (83.9)</td>
<td></td>
<td>92</td>
</tr>
<tr>
<td>T4</td>
<td>4 (7.8)</td>
<td>0</td>
<td>0.007**</td>
<td>4</td>
</tr>
<tr>
<td>Tumor distance from the anal verge(cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 (4–15)</td>
<td>9 (5–15)</td>
<td>0.53</td>
<td>9 (4–15)</td>
<td></td>
</tr>
<tr>
<td>Tumor size (mm)</td>
<td>51.37 ± 12.043</td>
<td>45.57 ± 9.811</td>
<td>0.007*</td>
<td>51 (26–72)</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>34.80 ± 2.85</td>
<td>37.55 ± 2.74</td>
<td>&lt; 0.001*</td>
<td>36 (27–43)</td>
</tr>
</tbody>
</table>

Data are presented as median (range), mean ± standard deviation and number (%); *t-test for equality means, **χ²-test – statistically significant difference.

The study included a total of 107 operated patients due to rectal cancer, 51 with short-course preoperative RT (group 1) and 56 without it (group 2). The majority of patients had the T3 stage of rectal cancer in both groups, however only 4 (3.7%) patients had the T4 stage (all in the group 1) with a significant difference between the groups (χ²-test 7.777, p = 0.007). No significant difference in age (p = 0.95), gender (p = 0.115) and tumor distance from the anal verge (p = 0.53) between the groups was found.

The size of rectal carcinoma was significantly higher in the group 1 (51.37 ± 12.04 mm) than in the group 2 (45.57 ± 9.81 mm).
9.81 mm), \( p = 0.007 \). The preoperative serum albumin level was significantly lower in the group 1 than in the group 2 (\( t \)-test = -5.09, \( p < 0.001 \)).

Overall postoperative complications including anastomotic leakage (conservatively or surgically treated), wound infection, diffuse peritonitis and pneumonia were observed in 23 (21.5%) patients; in 13 (25.5%) patients in the group 1, and in 10 (17.8%) patients in the group 2 without significant difference between the groups (\( p = 0.18 \)). Postoperative complications are presented in Table 2.

The overall postoperative mortality rate was 5.6% (6 patients). In the group 1, five (9.8%) patients died in the postoperative period during hospitalization. Four of them died as consequences of postoperative complications (diffuse peritonitis), and one as consequences of acute pulmonary thromboembolism and respiratory failure. In the group 2 one (1.8%) patient died as consequences of severe pneumonia complicated by sepsis in the postoperative period. In a patient with anastomotic leakage and diffuse peritonitis who died a handsewn suture on anastomosis was placed and diverting ileostomy was created as the second operation, with a subsequent Hartmann’s procedure as the third operation. In the other 3 patients with anastomotic leakage and diffuse peritonitis who died the Hartmann’s procedure was the second operation. No significant difference was found in the mortality rate between the groups (\( p < 0.001 \)). Anastomotic leakage was observed in 12 (23.5%) of the patients (group 1), while conservative treatment was successful in 5 of them. Seven patients with anastomotic leakage (group 1) required reoperation (Hartmann’s procedure in all of them). Four of those patients died of diffuse peritonitis (\( p = 0.101 \)). There was a significant difference in anastomotic leakage occurrence between the groups (\( p = 0.039 \)). There were no patients with anastomotic leakage who required reoperation in the group 2 vs 7 patients in the group 1 with a significant difference (\( \chi^2 = 8.224, p = 0.004 \), but without differences in conservatively treated anastomotic leakage between the groups (\( \chi^2 = 0.024, p = 1.0 \)).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (n = 51)</th>
<th>Group 2 (n = 56)</th>
<th>( p ) value</th>
<th>Total (n = 107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anastomotic leakage – surgically treated</td>
<td>7 (13.7)</td>
<td>0</td>
<td>0.004</td>
<td>7 (6.5)</td>
</tr>
<tr>
<td>Anastomotic leakage – conservatively treated</td>
<td>5 (9.8)</td>
<td>5 (8.9)</td>
<td>0.98</td>
<td>10 (9.3)</td>
</tr>
<tr>
<td>Diffuse peritonitis</td>
<td>4 (7.8)</td>
<td>0</td>
<td>0.048</td>
<td>4 (3.7)</td>
</tr>
<tr>
<td>Wound infection</td>
<td>14 (27.5)</td>
<td>8 (14.3)</td>
<td>0.092</td>
<td>22 (20.5)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5 (9.8)</td>
<td>2 (3.6)</td>
<td>0.254</td>
<td>7 (6.5)</td>
</tr>
</tbody>
</table>

\( p \) – values are calculated for \( \chi^2 \)-test.

There were 22 (20.6%) patients with wound infection; 14 (27.5%) patients in the group 1 and 8 (14.3%) patients in the group 2 without a significant difference between the groups (\( p = 0.92 \)). Although there were more patients with postoperative pneumonia in the group 1, no significant difference between the groups was found (\( p = 0.254 \)). A significantly lower serum level of preoperatively measured albumin was found in the group 1 than in the group 2, \( p < 0.001 \). No significant correlation between preoperative level of serum albumin, patients age, tumor cT stage and tumor distance from the anal verge was found, while a significant correlation between tumor size and the serum albumin level was found (\( p = 0.042 \)). Male gender and a lower level of serum albumin were significant predictors of anastomotic leakage occurrence (\( p = 0.05 \) and \( p = 0.002 \), respectively), while short-course preoperative RT had no significant impact on it (Table 3).

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Sig. (p)</th>
<th>( \text{Exp}(B) )</th>
<th>95% C.I. for ( \text{Exp}(B) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>0.543</td>
<td>0.647</td>
<td>0.159</td>
</tr>
<tr>
<td>Gender</td>
<td>0.054</td>
<td>0.186</td>
<td>0.034</td>
</tr>
<tr>
<td>Tumor distance from the anal verge</td>
<td>0.170</td>
<td>0.809</td>
<td>0.598</td>
</tr>
<tr>
<td>Serum albumin level</td>
<td>0.002</td>
<td>0.691</td>
<td>0.549</td>
</tr>
</tbody>
</table>

\( \text{Exp}(B) \) – estimated odds ratio in binary logistic regression models.
The variability is 38% (Negelkerke R Square), calibrated ( Hosmer and Lemeshow test \( X^2 = 5.318; p = 0.723 \)) with classification power of 86%.

**Discussion**

TME is the standard surgical treatment for rectal cancer in the distal two-thirds, and partial mesorectal excision for tumors in the proximal part of the rectum \(^3, 4, 7\). After implementation of short-course preoperative RT or long-course...
protein turnover can lead to cancer cachexia. In tumor stages T2-T4 and potentially curative resections (R0), short-course preoperative RT followed by immediate surgery could provide a lower local or systemic recurrence rate with acceptable risks of the occurrence of postoperative complications. Also, the advantages of this regimen of neoadjuvant RT are lower costs and patient convenience, especially in older patients, such as in our study population. There were two reasons why some patients with advanced clinical T stage in our study population did not receive short-course preoperative RT: rectal cancer in the upper third of the rectum and the absence of tumor penetration throughout the mesorectal fascia confirmed by endoscopic ultrasound and/or magnetic resonance imaging. Although there were a lot of patients in our retrospective review who did not receive short-course preoperative RT, it was a relatively small number if compared to the number of all the operated patients for rectal cancer in our institution in a 3-year duration period.

There are no strong evidences that diverting stoma prevents anastomotic leakage, however, it is certain that it reduces septic complications resulting from anastomotic leakage and the overall postoperative mortality rate. We included only patients with rectal resection and no diverting stoma in order to evaluate the impact of short-course preoperative RT and the serum albumin level on early postoperative complications.

In our study the overall postoperative mortality rate was high (5.6%, 6 patients), but 4 of them died because of anastomotic leakage and subsequent diffuse peritonitis. Comparing the results of the Stockholm I trial that showed mortality rate of 8% in the preoperative RT group vs 2% in the group without preoperative RT, we can agree that the TME for rectal cancer after short-course preoperative RT does not lead to an increase in the postoperative mortality rate. In the Stockholm III trial a mortality rate in patients with short-course preoperative RT followed by immediate surgery was 0.8%, whereas in 75 patients with anterior rectal resection a stoma was created in 41% of them. In our study only patients without diverting stoma creation were included.

Malnutrition in patients with rectal cancer is caused by several factors. Cancer-induced higher metabolism, reduced dietary intake and body nitrogen loss due to increased whole protein turnover can lead to cancer cachexia. Hypoalbuminemia is accepted to be a good malnutrition indicator in many studies involving the patients with cancer. Also, low serum albumin level is associated with poor tissue healing, decreased collagen synthesis in surgical wounds including gastrointestinal anastomosis. Explanation for why tumor size, but not the stage, is relevant to hypoalbuminemia still remains unknown. It is possible that large tumors cause more gastrointestinal symptoms, leading to poor nutritional intake and/or partial gut obstruction. Our findings showed a significant correlation between the tumor size and the serum albumin level, but the preoperative level of serum albumin did not correlate with age, tumor cT stage and tumor distance from the anal verge. Also, statistical analysis showed that lower level of serum albumin and tumor size were significant risk factors for postoperative complications following rectal cancer surgery. A preoperative serum albumin level was significantly lower in patients who developed postoperative complications. A significantly lower serum albumin level and larger size of rectal cancer in the group 1 may contributed to the occurrence of anastomotic leakage in addition to irradiation related toxicity in this group of patients.

It was reported that a significant difference was not found between patients with immediate surgery and patients with delayed surgery after short-course preoperative RT in terms of postoperative complications and reoperations. However, the patients with immediate surgery after short-course preoperative RT had a higher rate of postoperative complications. In our study, there were no patients in the group 2 who required reoperation. An increase in the anastomotic leakage rate after preoperative RT was observed by several authors, both after short-course and after long-course preoperative RT. A two to three fold increase in the incidence of anastomotic leakage is generally reported after RT which is roughly the result of our study, also.

In gastrointestinal reconstructions after rectal resections, a significant difference in anastomotic leakage was not found in comparison between handsewn and stapled technique, but the level of anastomosis was important predictive factor for leakage, as confirmed in our study. We found that tumor distance from the anal verge influenced development of anastomotic leakage in all the patients (p = 0.026). Surgical site infection, including wound infection in open colorectal surgery varies from 2% to 25% with a higher incidence rate in rectal surgery. The preoperative RT, steroids and stoma creation are associated with a higher rate of surgical site infection in rectal resection.

Also, low serum albumin level may facilitate wound infection development. Although we had more patients with wound infection in the group 1 than group 2 (27.5% vs...
14.3%, respectively, but there was no significant difference between groups. Comparing our results with the results of the Stocholm III we had same incidence rate of wound infection. However, a higher incidence rate of wound infection in the Stockholm III trial of 28% vs the overall incidence rate of wound infection of 20.6% in our patients could be contributed by both preoperative irradiation and stoma existence.

The results of this study indicate that there was a significantly increased rate of postoperative complications in the patients with lower serum level of albumin preoperatively.

The rate of postoperative complications was also increased in the patients with short-course preoperative RT, but without a statistical significance.

The main disadvantage of this study is a relatively small number of patients and the lack of data including operation duration, blood loss and blood transfusion which may affect the occurrence of early postoperative complications.

**Conclusion**

Short-course preoperative radiotherapy did not significantly increase the rate of postoperative complications, but a significantly higher rate of anastomotic leakage occurred in the male patients and in the patients with a lower level of serum albumin. The patients with a lower serum albumin level had a significantly higher rate of postoperative complications.

**REFERENCES**


