An evaluation of treatment results of emergency versus elective surgery in colorectal cancer patients

Bahattin Bayar¹, Kerim Bora Yılmaz², Melih Akıncı², Alpaslan Şahin³, Hakan Kulaçoğlu²

Objective: Colorectal cancer is still one of the most common causes of cancer related deaths in the world despite improvements in diagnosis and treatment modalities, and application of community-based screening methods. Symptoms of colorectal cancer are non-specific and usually manifest following local progression. A number of patients with advanced stage colorectal cancer present to emergency departments with obstruction as the first sign of disease without any previous symptoms. This presentation is an indication for emergency surgery that has a high rate of morbidity and mortality. In this study, we aimed to determine the factors associated with early diagnosis and survival by comparing postoperative results of colorectal cancer patients who underwent surgery under emergency or elective situation.

Material and Methods: Files of colorectal patients treated between 2009-2013 were retrospectively analyzed. Data on patient age, gender, operation type, intraoperative results, length of hospital stay, co-morbidities, postoperative complications and pathological results were evaluated and compared.

Results: There was no statistical difference between groups in terms of age, gender, and pathology results (p>0.05). The difference between groups in terms of postoperative length of hospital stay, presence of co-morbid diseases, pathological stage, and postoperative complications was statistically significant (p<0.05). Length of hospital stay, advanced stage on admission, complications such as surgical site infection, evisceration, and anastomosis leakage rates were higher in patients in the emergency surgery group.

Conclusion: Risk groups should be determined in order to diagnose colorectal cancer patients at an early stage while they are still asymptomatic, and this information should be incorporated into effective screening programs. This approach will be beneficial to treatment outcomes, complication rates, length of hospital stay, and survival and treatment results.

Keywords: Colorectal cancer, emergency surgery, elective surgery, complication, treatment results

INTRODUCTION

Colorectal cancer (CRC) is one of the most frequent cancers with more than one million people worldwide being diagnosed with CRC annually, which is the most common gastrointestinal tract cancer (1). The majority of these neoplasms are endoluminal adenocarcinoma derived from the mucosa, and over 95% of CRC patients benefit from surgery or colonoscopic interventions for premalignant polyps with early diagnosis (2). Despite advances in diagnosis and treatment and dissemination of community-based screening, colorectal cancer remains to be one of the main reasons of cancer-related deaths in the world (3).

Colorectal cancer occurs in three ways: hereditary, sporadic or familial. The hereditary form is characterized by family history, being seen at a young age, presence of specific type of tumors and defects (4). Sporadic colorectal cancers often occur without family history and are generally detected in the elderly population (60-80 years). Neoplastic polyps of the colorectum such as tubular and villous adenomas are precursor lesions and 95% of CRC arise from these adenomatous polyps (4, 5).

The initial symptoms are not specific for colorectal cancer, and it usually manifests when the disease progresses locally. The main symptoms detected in the majority of symptomatic patients are change in bowel habit, hematochezia, rectal fullness and abdominal pain (6, 7). However, some advanced stage colorectal cancer patients are admitted to the emergency department with signs of obstruction without any detectable symptoms prior to these findings. This presentation creates a need for emergency surgery with quite high rates of mortality and morbidity, and nearly 20% of patients are diagnosed with acute colonic obstruction (8).

This study aimed to determine the factors associated with early diagnosis and survival in colorectal cancer patients by comparing age, sex, intraoperative findings, and surgical procedures performed according to tumor location, length of hospital stay, patient characteristics and postoperative treatment results among CRC patients who underwent either elective or emergent surgery.
MATERIAL AND METHODS

After obtaining the necessary permission from the clinical research ethics committee of our hospital, records of patients treated for CRC at Dışkapı Ankara Training and Research Hospital General Surgery Department between January 2009 and August 2013 were retrospectively evaluated. The patients with missing data, and those with discrepancies between files, operation report, pathology and emergency department data were excluded from the study. Patients were divided into two groups as those undergoing elective or emergent surgery. Patients who were operated under emergency conditions, who were admitted to the emergency room due to complications of tumor and then having surgery were included.

Three hundred and twenty patients were included in the study, and they were compared with each other in terms of parameters such as age, gender, type of surgery, intraoperative findings, hospital length of stay, co-morbidities, postoperative complications and pathology results.

Statistical Analysis

The data were analyzed with “Statistical Package for the Social Sciences for Windows 17.0” (SPSS Inc., Chicago, IL, USA) statistical software package. Mann-Whitney U test was used for comparing the two groups. p values less than 0.05 were considered significant.

RESULTS

The demographic characteristics of the patients, co-morbidities, and hospital stay are summarized in Table 1. Indications for emergent operations were tumor perforation (9 patients), multiple intra-abdominal abscesses due to rectal cancer (one patient), sigmoid colon torsion due to a tumor (one patient), while the rest were operated for obstruction. Tumor location and type of surgery of the patients undergoing elective and emergency surgery are presented in Table 2.

There was statistically significant difference between the two groups in terms of co-morbidities (Table 1). There was at least one co-morbid disease in 88.9% of patients undergoing emergent operation, and the most common co-morbid diseases were hypertension and diabetes in 19 patients (21.1%). In the group undergoing elective surgery, the most common co-morbid disease was hypertension in 37 patients (16.1).

The most common location of the CRC in patients undergoing elective and emergency surgery was the rectosigmoid (Table 2). Peritoneal carcinomatosis was statistically more frequent in emergent cases as compared to elective surgery group (p<0.05). Synchronous tumors, anal canal tumors, recurrent and metastatic colorectal cancers constituted the other colorectal cancer group.

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Right hemicolecotomy, anterior resection, low anterior resection, segmental colon resection, and Miles operation were the most commonly performed surgeries in patients undergoing elective surgery, while sigmoid colon resection + Hartmann operation, loop colostomy alone and ileostomy were statistically more common in the group who underwent emergent surgery (p<0.001). Other operations included subtotal colectomy, by-pass operations for unresectable patients or patients with advanced stage disease, ileocecal resection, local excision, and debulking surgery.

Intraoperative findings are summarized in Table 3. Tumor perforation, adjacent organ invasion, liver metastasis, and peritonitis carcinomatosis were significantly more frequent in the group with emergency surgery as compared to elective surgery group.

The most common tumor type in histopathologic examination was adenocarcinoma in both groups (Table 4). There was statistically significant difference between the two groups in terms of the degree of tumor differentiation (p<0.001). While poor differentiation was more frequent in emergent cases;
well and moderate differentiation were more frequent in elective cases (Table 4) (p<0.001).

As outlined in Table 5, there was a statistically significant difference between the two groups in terms of TNM staging system. Stage 1, stage 2 and stage 3 disease were more common in elective patients, while patients with more advanced stages constituted the emergent group. The most common stage in elective cases was stage 2a with 46 patients (20%), while stage 1, stage 2 and stage 3 disease were more common in emergent cases (Table 4) (p<0.001).

The incidence of accompanying disease and high ASA score have been shown as independent risk factors for increased postoperative morbidity and mortality (18, 19). When additional diseases of the patients were evaluated, it was determined that 88.9% of the emergency surgery group and 71.7% of the elective surgery group had one or more co-morbid diseases. Co-morbid diseases were significantly more frequent in women than in men (17). In our study, it was detected 1.7 and 1.6 times more in men as compared to women in emergent and elective surgery groups, respectively, and was significantly higher than the rates in the literature.

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The analysis of postoperative complications revealed a statistically significant difference between the two groups (Table 6). More postoperative complications were observed in emergent cases as compared to the group undergoing elective surgery. Surgical site infection, atelectasis, evisceration, anastomotic leakage, and postoperative ileus were more common in the group who underwent emergency surgery. Surgical site infection was the most common postoperative complication in both groups. Rectovaginal fistula was observed in two patients with elective surgery in our study group.

There was a statistically significant difference between the two groups in terms of length of hospital stay (p<0.001). The average length of stay for elective and emergency surgery was 10 and 18 days, respectively (Table 1). A patient who underwent emergency surgery died on the second postoperative day.

**DISCUSSION**

Age is an important risk factor for CRC, i.e. its prevalence increases with advancing age. More than 90% of CRC patients are diagnosed after the age of 50 (9). In large case series, it was found that it peaked at the 7th decade (9, 10). In our series, the mean age of patients with emergency and elective surgery was identified as 62 years. On the contrary, several studies have found that CRC patients undergoing emergent surgery are older than the group of patients with elective surgery (11, 12). The mean age of our series seems to be a little lower than the mean age of CRC (13, 14). However, the results are similar to other studies from our country (15, 16). Only 5% of patients with CRC are under 40 years of age. In our study, this rate was 6.9% in the elective surgery group, while this rate was 1.1% in the group who underwent emergency intervention. As we have seen in our series, patients over 40 years of age constitute the majority of CRC cases. We think these age-related findings are important to ensure provision of effective screening programs for CRC and early diagnosis, and to increase treatment effectiveness. Knowing the peak age of the disease in our country will be important in the development of screening programs.

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The CRC tumors were most commonly located in the rectosigmoid region followed by the left and right colon. However, the frequency of tumors in the proximal colon has been increasing in recent years (20, 21). In both groups, the most common tumor location was the rectosigmoid region (56.2% in the emergency group and 63.5% in the elective group). Following rectosigmoid region tumors, the most common tumors in both groups were right colon tumors (14.3% and 8.9%). When groups were compared, sigmoid colon tumors (25.6%) were more frequent in the group who underwent emergency intervention.

<p>| Table 3. Intraoperative findings of colorectal cancer patients with emergent or elective surgery |
|----------------------------------|---------------------|---------------------|---------------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Emergent (n=90)</th>
<th>Elective (n=230)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpable mass alone</td>
<td>8 (8.9%)</td>
<td>111 (48.3%)</td>
<td></td>
</tr>
<tr>
<td>Serosal involvement</td>
<td>25 (27.8%)</td>
<td>61 (26.5%)</td>
<td></td>
</tr>
<tr>
<td>Adjacent organ invasion</td>
<td>20 (22.2%)</td>
<td>30 (13.0%)</td>
<td></td>
</tr>
<tr>
<td>Tumor perforation</td>
<td>9 (10.0%)</td>
<td>1 (0.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peritonitis carcinomatosa</td>
<td>12 (13.3%)</td>
<td>8 (3.5%)</td>
<td></td>
</tr>
<tr>
<td>Mass + liver metastasis</td>
<td>3 (3.3%)</td>
<td>6 (2.6%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>13 (14.5%)</td>
<td>13 (5.7%)</td>
<td></td>
</tr>
</tbody>
</table>

| Table 4. Distribution of colorectal cancer patients with emergent and elective operation according to microscopic view and degree of differentiation |
|----------------------------------|---------------------|---------------------|---------------------|
|                                  | Emergent (n=90)     | Elective (n=230)    | p                   |
| Pathology                        |                     |                     |                     |
| Adenocarcinoma                   | 79 (87.8%)          | 201 (87.4%)         |                     |
| Mucinous adenocarcinoma          | 5 (5.6%)            | 14 (6.1%)           |                     |
| Signet ring cell carcinoma       | 2 (2.2%)            | 2 (0.9%)            | >0.05               |
| In situ carcinoma                | 1 (1.1%)            | 7 (3%)              |                     |
| Malignant epithelial tumor       | 1 (1.1%)            | 2 (0.9%)            |                     |
| Other                            | 2 (2.2%)            | 4 (1.7%)            |                     |
| Differentiation                  |                     |                     |                     |
| Well                             | 5 (5.6%)            | 42 (18.2%)          |                     |
| Moderate                         | 53 (58.8%)          | 164 (71.4%)         | <0.001              |
| Poor                             | 32 (35.6%)          | 24 (10.4%)          |                     |
Table 5. Staging of colorectal cancer patients with emergent or elective surgery according to TNM classification system

<table>
<thead>
<tr>
<th>Stage</th>
<th>Emergent (n=90)</th>
<th>Elective (n=230)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>2 (2.2%)</td>
<td>36 (15.7%)</td>
<td></td>
</tr>
<tr>
<td>Stage 2a</td>
<td>8 (8.9%)</td>
<td>46 (20%)</td>
<td></td>
</tr>
<tr>
<td>Stage 2b</td>
<td>11 (1.1%)</td>
<td>29 (12.5%)</td>
<td></td>
</tr>
<tr>
<td>Stage 3a</td>
<td>4 (4.4%)</td>
<td>28 (12.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stage 3b</td>
<td>16 (17.8%)</td>
<td>31 (13.5%)</td>
<td></td>
</tr>
<tr>
<td>Stage 3c</td>
<td>22 (24.5%)</td>
<td>25 (10.9%)</td>
<td></td>
</tr>
<tr>
<td>Stage 4a</td>
<td>24 (26.7%)</td>
<td>15 (6.5%)</td>
<td></td>
</tr>
<tr>
<td>Stage 4b</td>
<td>12 (13.3%)</td>
<td>13 (5.7%)</td>
<td></td>
</tr>
<tr>
<td>In situ carcinoma</td>
<td>1 (1.1%)</td>
<td>7 (3.0%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 6. Frequency of postoperative complications in colorectal cancer patients with emergent and elective surgery

<table>
<thead>
<tr>
<th>Postoperative complication</th>
<th>Emergent (n=90)</th>
<th>Elective (n=230)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>8 (8.9%)</td>
<td>175 (76.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>82 (91.1%)</td>
<td>55 (23.9%)</td>
<td></td>
</tr>
<tr>
<td>Surgical site infection</td>
<td>24 (26.7%)</td>
<td>25 (10.9%)</td>
<td></td>
</tr>
<tr>
<td>Atelectasis</td>
<td>11 (12.2%)</td>
<td>13 (5.7%)</td>
<td></td>
</tr>
<tr>
<td>Evisceration</td>
<td>10 (11.1%)</td>
<td>1 (0.4%)</td>
<td></td>
</tr>
<tr>
<td>Anastomosis leak</td>
<td>8 (8.9%)</td>
<td>6 (2.6%)</td>
<td></td>
</tr>
<tr>
<td>Postoperative ileus</td>
<td>8 (8.9%)</td>
<td>3 (1.3%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>8 (8.9%)</td>
<td>2 (0.9%)</td>
<td></td>
</tr>
<tr>
<td>PTE</td>
<td>3 (3.3%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>DVT</td>
<td>1 (1.1%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>9 (10%)</td>
<td>5 (2.1%)</td>
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</tbody>
</table>

Colorectal cancer constitutes an important part of all colon-related emergencies. The treatment type varies depending on tumor location. A significant number of studies accepted the common one-step resection and primary anastomosis in all CRC patients with a right colon tumor undergoing elective or emergent surgical treatment for obstruction as standard, except for those who are at poor overall condition (22, 23). Resection and primary anastomosis (right hemicolectomy) was the most common operation for right colon tumors in our series, consistent with the literature.

Some researchers argued that resection and primary anastomosis can be safely used in emergent left colon resection (24, 25). Capasso et al. (26) compared resection and primary anastomosis for obstructive left colon cancer and Hartmann procedure for appropriate indications and by experienced surgeons in terms of postoperative mortality and complications, and argued that similar results were obtained. It is generally recommended to perform a step-wise surgery for left colon tumors because resection and primary anastomosis performed under emergency conditions on a dirty and severely dilated colon is considered quite risky. The biggest risk in such circumstances is anastomotic leak (27). Although there are opposing views in various publications, the most common emergent surgery technique for left colon cancer in our series was resection and Hartmann operation (18.9%). Seah et al. (28) have reached the conclusion that Hartmann procedure was beneficial in 85 emergent surgeries on elderly patients with medical problems, of which 45 had colorectal tumors. Ansaloni et al. (29) stressed that Hartmann procedure should be preferred to loop colostomy. As a result, we believe that the surgical treatment to be applied for acute left-sided tumors should be decided according to the patient’s general condition, the surgeon’s experience and the hospital’s conditions.

Early and late surgical complications are more frequent in patients with CRC than those operated due to benign causes. This is attributed to the deterioration of the immune system, which may be specific to cancer, as well as fecal contamination. Several studies have found the rates of morbidity and mortality in emergent colorectal surgery as 15-50% and 6-15%, respectively. These rates are reported as 4-14% and 1-7% in elective CRC surgery operations, respectively (30-32). The postoperative complication rate in our patients with emergent surgery was 91.1%, while this rate was 23.9% in the group with elective surgery, and the morbidity rate was higher in emergent patients. This high rate was consistent with several other studies (30-33). This high percentage is attributed to patients’ comorbidities and presence of situations that increase surgical risks such as electrolyte imbalance and dehydration as well as operating on dilated and dirty colon, which are all thought to contribute to complication rate.

One of the most feared major complications of colorectal surgery is anastomotic leakage. It leads to an increase in postoperative morbidity, length of hospital stay, and surgical site infection as well as adversely affecting mortality rate (34). It is generally accepted that the risk of anastomotic leakage after intrapelvic surgery should be kept below 10%, and in recent series this risk has been reported at even lower levels (<3%) (35). This rate is particularly high in rectal cancer. For example, the Sweden National Study determined symptomatic anastomotic leakage rate after rectal surgery as 12% (36). The rate of anastomotic leakage varies in different series from 0.5% to 30%, and its rate is higher in emergent surgery than in elective surgery (34-37). In our study, colorectal anastomotic leakage rate was 8.9% in the group with emergency surgery, and was higher as compared to the group with elective surgery. The anastomotic leak rate in the elective surgery group was detected to be 2.6%, and was at an acceptable level based on the literature.

Paralytic ileus is seen more frequently in laparotomies performed below the transverse mesocolon with a rate of 1.5% after right hemicolectomy and 3% after left colon and rectal surgery (38). In our study, the rate of postoperative ileus in emergency surgery (8.9%) was found to be higher than the group with elective surgery. Postoperative ileus leads to distension, nausea, vomiting, and an increase in intra-abdominal pressure that leads to evisceration and evagination in return. Menteş et al. (15) found the postoperative ileus rate to be 3%
in a study of 200 cases with colorectal surgery. In our study, postoperative ileus rate in the group with elective surgery (1.3%) was lower than the rates reported in other studies.

Colorectal surgery patients are at high risk for surgical site infections (SSI) (39). The rates of SSI in large series has been reported as approximately 1.5 to 3.9% for clean wounds, 3-4% for clean-contaminated wounds, 8.5 to 15.2% for contaminated wounds, and 21.3 to 41% for dirty wounds (40). Itatsu et al. (41) have reported the SSI rate as 11.7% in a prospective study on 1980 patients. Tang et al. (42) found the SSI rate in elective colorectal surgery as 10%. In our series, the SSI rate in the elective surgery group was found as 10.9% similar to other studies, while in the emergency surgery group, the SSI rate was 26.7%. It is stated in the literature that the SSI rate increases 1.69 times for malignant neoplasms and 1.9-2.65 times for emergency procedures (40). In addition, SSI rate has been shown to increase 1.1-fold with every three-day admission. These factors may have contributed to a higher rate of infection in CRC patients who underwent emergency intervention in our study. There are only a few researchers opposing these findings. Nguyen et al. (43) stated that SSIs are less frequent in emergency procedures due to the longer preoperative admission in elective cases.

Mechanical bowel preparation and appropriate use of prophylactic antibiotics is known to decrease the incidence of SSI. The SSI rate was reported to decrease from 35.2% to 20% by using a single dose of prophylactic antibiotic therapy (43). In another study, it was observed that SSI rate increased in patients without prophylactic antibiotic administration. Parallel to the specified studies, the low rate of SSI in the group with elective surgery in our study can be linked to the conduct of routine bowel preparation, although controversial, antibiotic prophylaxis, the low rates of anastomotic leakage and of tumor perforation and shorter hospital length of stay.

Evisceralion is a postoperative complication with high rates of mortality and morbidity. Technical deficiencies, COPD, infection, intra-abdominal pressure increase, and malnutrition as well as emergency surgery are considered among risk factors for the development of evisceralion in many studies (44). The evisceralion rate of elective surgeries in our study group was found to be 0.4%. The evisceralion rate reaches 4% in some series (45). The evisceralion rate in patients who underwent emergency intervention was seen to be quite high with 11.1%.

Patients who had surgery for CRC are mostly at a high-risk group for deep vein thrombosis (DVT) due to having cancer, undergoing major surgery, and often being over 40 years old. If prophylaxis is not applied in these cases then the risks of pulmonary embolism (PE) and DVT can reach up to 3% and 40%, respectively (46). In our study, PE was not detected in the elective surgery group, and was detected as 3.3% in emergent cases.

In our series, tumor related complications were more common in emergency cases according to tumor pathologic features. When evaluated according to tumor stage, we identified that the rate of stage 3b, stage 3c and stage 4 tumors was higher in emergent patients, with 74 patients within 90 cases (82.2%). This rate was 36.6% in elective cases with 84 patients within 230 cases. In their study comparing pathologic data of CRC patients with emergency and elective operations, Ghazi et al. (47) found that the patients who were operated under emergency conditions presented at more advanced stages (advanced T and N, stages 3 and 4) and had more aggressive histopathology findings. In another study by Merkel et al. (12) examining the results of elective and emergency colorectal surgery, the rate of distant metastasis was significantly higher in the group with emergency surgery. In addition, emergency surgery was stated to be an independent prognostic factor for cancer-related survival (relative risk 1.6) and distant metastases (relative risk 1.8). Villar et al. (48) stated that local invasion and distant metastasis rates was higher in obstructing tumors as compared to those without obstruction. Similar to published studies, the distant metastasis rate was higher in the group who underwent emergency intervention in our series. The rate of patients with stage 4 disease was 40% in patients with emergency surgery, while 17.4% in the group with elective surgery.

Peritoneal carcinomatosis is detected more in emergency cases, and the associated risk factors for its development include right colon cancer, advanced T and N stage, and poor differentiation (49). Considering these risk factors, the high rate of peritoneal carcinomatosis in our emergent cases is reasonable.

Histologic grade of tumors is important for the evaluation of tumor behavior, prognosis and treatment selection. Adenocarcinomas are graded according to the tumor cell’s organization similarity to normal epithelial cells. When the degree of tumor differentiation was evaluated between the two groups, poor differentiation was significantly greater in the group who underwent emergency intervention (10.4% vs. 35.6%). There are many studies showing that the degree of differentiation and histologic grade of the tumor affect prognosis (50).

CONCLUSION
The role of the center where the study was carried out within emergency and trauma services resulted in high numbers of patients treated under emergency conditions. The increase in complications should be considered according to inclusion of more patients with emergent operations.

Colorectal cancer is of importance both because it is the third most common cancer among all cancers and because of the increase in its frequency. The biggest risk factor for sporadic CRC is age, and the disease is characterized by an increase in incidence with age. Being diagnosed at advanced stages adversely affects several parameters such as the type of surgery, period of hospitalization, complications, and patient survival.

Despite screening programs for colorectal cancer, emergency admissions and surgical procedures in emergency conditions remain high. Surgical operations for patients with impaired metabolic status due to mechanical obstruction do not only carry risks for patients but also yield inadequate results. In our study comparing the postoperative treatment results of patients with emergency and elective surgery for CRC, postoperative morbidities were more frequent in patients with emergency surgery.

It is observed that the disease remains asymptomatic for a long period and patients remain undiagnosed. The treatments performed under emergency conditions should be evaluated not only for the associated risks but also in terms of their effect...
on health related costs. Long hospital stay, cost related to the management of complications, and medical therapy should be considered.

From the clinician's point of view, early diagnosis of patients by effectively adopting screening programs particularly to risk groups will positively affect treatment efficacy and survival results. Thus, we believe that the problems encountered during postoperative treatment will be decreased, and treatment costs will be reduced with shorter hospital length of stay.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Ankara Dişkapı Yıldırım Be- yazıt Training and Research Hospital.

**Informed Consent:** Data were collected retrospectively and informed consent cannot be collected.

**Peer-review:** Externally peer-reviewed.


**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study has received no financial support.

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