Postoperative 30-Day Mortality After Colon Cancer Surgery: A Descriptive Case Series
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Citation

Abstract
Objective: To analyze postoperative 30-day mortality (PostopM) after colon cancer (CC) surgery and to propose perioperative measures that can decrease complications and death.
Patients and methods: Patients with CC who had undergone primary surgery at the Central Armed Forces Hospital (CAFH) in Montevideo, Uruguay, between 1989 and 2005 were identified. We included patients who died in the 30 days following surgery.
Results: 282 patients underwent surgery for CC in the mentioned period. Fourteen patients died in the 30 days following surgery (4.9%). Eight patients (57.1%) required urgent surgical management of bowel obstruction. The most common causes of death were anastomotic dehiscence and respiratory insufficiency/infections. PostopM occurred more frequently in emergency than in elective settings, especially in patients with left-sided tumors (p=0.01).
Conclusions: To our knowledge this is the first study that analyzes PostopM exclusively in patients with CC. Attention must be paid to minimize operative risk, in some cases by the use of non-surgical approaches (stents). Routine use of a standardized regimen of prophylactic antibiotics, thromboprophylaxis +/- physiotherapy can decrease morbidity/mortality.

INTRODUCTION
In Uruguay, colorectal cancer is the third most common cancer in men and the second in women, with adjusted rates of 3.83/100,000 and 26.41/100,000, respectively. Colorectal cancer is responsible for about 10% of cancer related deaths, being the third and second most lethal cancer in males and females, respectively.

About 90% of patients with colonic cancer (CC) need surgery at any time in the natural history of their disease. Although it is usually included in the palliative care of advanced cases, most of the surgeries are performed with curative intention.

Mortality after CC surgery depends on: patient's history and physiologic status, the tumor characteristics (presentation, extension of disease, etc.) and the treatment and its complications. Thirty-day mortality after colorectal cancer surgery, defined as death within 30 days after the operation, is not infrequently reported in studies. However, 30-day mortality as the primary endpoint of study has not been frequently analyzed in medical literature. We have found 12 studies in which postoperative mortality is the main outcome of study after colorectal cancer surgery.

None of those studies analyzed exclusively CC and all studied colon and rectal cancers as a group. Presentation, surgical management and postoperative complications may differ between colon and rectal cancer. The aim of this retrospective study is to analyze postoperative 30-day mortality after CC surgery and based on this analysis to propose perioperative measures that could eventually decrease the incidence of complications and death.

PATIENTS AND METHODS
Patients with pathologically confirmed CC who had undergone primary surgery at the Central Armed Forces Hospital (CAFH) in Montevideo, Uruguay, between December 1989 and December 2005 were identified.

From this population, patients that died in the 30 days following surgery were included in the study and their records were retrospectively reviewed. Thirty-day mortality was defined as death within 30 days after the operation.
Clinical, pathologic and evolutive characteristics of these cases were recorded, including: previous medical history, physiologic status, indication for surgery, preoperative care, tumor location, tumor stage, type of operation, postoperative evolution, complications and their management, and death cause. Patients were excluded from the analysis if they met any of the following criteria: patients without surgical treatment, previous surgery for CC, uncertain diagnosis of cancer, appendix carcinomas, or insufficient clinical data.

Tumors proximal or distal to the left angle of the colon were considered as right-sided or left-sided tumors, respectively. Staging was performed according to TNM UICC classification. In order to assign a risk level for surgery and anesthesia, patients were classified according to the American Society of Anesthesiologists (ASA) classes.

Data were recorded and analyzed using SPSS for Windows, version 10.0 (SPSS, Chicago, IL). The statistical comparative analysis was performed by chi-square test for qualitative data. Fisher’s exact test was used when the expected values in any of the cells of the table were below 5. Continuous, nonparametrically distributed variables were analyzed with the Mann-Whitney U test. Significance was taken as p < 0.05.

RESULTS

Between 1989 and 2005, 282 consecutive patients underwent surgical treatment for pathologically confirmed primary CC in the CAFH. In all these cases, some kind of prophylactic antibiotic therapy was indicated, although regimes varied widely. Venous thromboembolism prophylaxis with enoxaparine was used at anesthesia induction only in elective surgery. On the contrary, respiratory physiotherapy was not routinely used.

Fourteen patients died in the 30 days following surgery, representing 4.9% of all the identified cases. Half of these patients were male. Median age at surgery was 77 years (range: 51–90). In 10 patients surgery was performed with curative intent while in 4 with palliative intent. Seven patients had right-sided tumors while in the other seven cases tumors were located in the left colon. Eight patients (8/14; 57.1%) required urgent surgical management of bowel obstruction (6 left-sided and 2 right-sided tumors). Advanced tumor stages (TNM III-IV) were seen in 5 patients (62.5%) with obstructing carcinomas. In 6 patients (6/14; 42.8%) elective surgery was performed, and in 3 of them advanced tumors were found. In 4 patients (4/6; 66.7%) a primary resection and anastomosis could be performed.

According to the ASA scale, 13 patients (13/14; 92.29%) were ASA class III while one patient was ASA class II. All patients urgently operated had an ASA score of III.

Table 1: Shows the characteristics of the 14 patients included.

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
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<tr>
<td>Sex</td>
<td>7</td>
<td>50%</td>
</tr>
<tr>
<td>Median age at surgery</td>
<td>77 (range: 51-90)</td>
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<tr>
<td>Surgery</td>
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<tr>
<td>Urgent</td>
<td>8</td>
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<tr>
<td>Elective</td>
<td>6</td>
<td>42.8%</td>
</tr>
<tr>
<td>Tumor location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right colon</td>
<td>7</td>
<td>50%</td>
</tr>
<tr>
<td>Left colon</td>
<td>7</td>
<td>50%</td>
</tr>
<tr>
<td>TNM stage</td>
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<td></td>
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<tr>
<td>I</td>
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<td>0</td>
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<tr>
<td>II</td>
<td>6</td>
<td>42.8%</td>
</tr>
<tr>
<td>III</td>
<td>4</td>
<td>28.6%</td>
</tr>
<tr>
<td>IV</td>
<td>4</td>
<td>28.6%</td>
</tr>
<tr>
<td>ASA score</td>
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<td></td>
</tr>
<tr>
<td>I-II</td>
<td>1</td>
<td>7.7%</td>
</tr>
<tr>
<td>III</td>
<td>13</td>
<td>92.3%</td>
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<tr>
<td>IV-V</td>
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<td>0</td>
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</tbody>
</table>

Characteristics of the 14 patients with CC that died in the 30 days after surgery.

Median survival after surgery was 16 days (range: 1-27). Five patients needed to be re-operated, two of them twice. In all cases, the indication for re-operation was anastomotic leakage.

All patients had one or more co-morbid associations that included morbid obesity, diabetes, hypoalbuminemia, chronic obstructive pulmonary disease (COPD), cardiac insufficiency, previous pulmonary embolism (PE), stroke, arrhythmia, arterial hypertension (HT), Parkinson disease
and concurrent second neoplasia.

The most common cause of death was anastomotic dehiscence in 8 cases, of which 6 had respiratory insufficiency due to respiratory infection and 3 developed sepsis. Two patients died due to respiratory insufficiency secondary to aspirative pneumonia, 1 as a consequence of metabolic acidosis, 2 patients of cardiac insufficiency and 1 after pulmonary embolism (Table 2).

**Figure 2**

<table>
<thead>
<tr>
<th>Table 2</th>
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<tbody>
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<td>7</td>
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</tbody>
</table>

**ANALYSES ACCORDING TO TUMOR LOCATION: RIGHT- VERSUS LEFT-SIDED CANCERS**

If the whole population of CC patients operated at the CAFH between 1989 and 2005 is considered (n 282), we found that 131 of them (46.5%) had left-sided tumors, and that 7 of them died in the postoperative period of interest (7/131 5.3%). None of the 38 patients with left angle or descendent colon tumors died in the 30 days after surgery; the 7 patients that died had sigmoid tumors (7/93 7.5%). Only one of the 58 patients with sigmoid tumors that had undergone elective surgery died in the 30 days after surgery (1/58 1.7%), while this was the outcome of 6 out of 35 that had urgent surgery (6/35 17.1%, p=0.01).

Median age of all patients with sigmoid cancer was 64 years (range: 30-91), while considering only the 7 patients that died postoperatively, it was 76 years (range: 63-90) (p=0.012). The type of surgeries performed in the patients that died were: Hartmann’s surgery in 3 cases, colostomy only in 2 cases, segmental colectomy with primary anastomosis in 2 cases. Identified mortality causes in patients with left-sided tumors were: anastomotic dehiscence in 4 cases, cardiac failure in 1 case, metabolic imbalance in 1 case and aspirative pneumonia in the remaining one.

One hundred and fifty-one patients of the whole population of 282 cases had right-sided cancers (53.4%). Thirty-two patients had undergone urgent surgery and 119 elective surgery. Seven patients with right-sided cancers died in the 30 days after surgery (7/151 4.6%), 2 of them after urgent surgery (2/32 6.3%) and 5 after elective surgery (5/119 4.2%, p=0.60). The types of surgery in these patients were: resection and primary anastomosis in 5 cases (4 elective surgeries and 1 emergency surgery), and resection with colostomy in 2 cases (1 elective surgery and 1 emergency surgery).
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Median age of all patients with right-sided tumors was 65 years (range: 26-96), while the patients that died had a median age of 78 years (range: 51-83) (p=0.039). These patients had comorbidities like chronic anemia, history of cardiovascular diseases, hypoalbuminemia, obesity, and there was a case of concurrent second neoplasia (chronic lymphoid leukemia) as contributory factor. Death causes in these patients were: anastomotic dehiscence in four cases, pulmonary embolism in one patient, cardiac failure in one and aspirative pneumonia in another one.

DISCUSSION AND CONCLUSIONS

Short-term mortality following surgical treatment for colorectal cancer can be considered mainly an indicator of patient’s comorbidities and physiological status, as well as of other factors like operative urgency and surgeon expertise.

In the present study, 4.9% of the patients that had surgery for the management of a colonic carcinoma died in the 30 days following surgery in a 16-years period. Other authors who reported 30-day mortality as the main endpoint of their studies showed that mortality in this period of time ranged between 1.0% and 11.9%. A study performed in the United States showed that postoperative mortality after colonic resection for cancer was 2.3%, but it included 9 hospitals with wide mortality variability between these institutions (from 0.8 to 15.4%). In this study, the participating institutions performed between 13 and 427 colonic resections per institution during the 2 years analyzed. In our series, the average of surgeries per year is 17. Although this figure may not seem impressive, it is similar to the one observed in small American institutions. Besides, it must be considered that despite the long period of time analyzed, all cases were managed by the same surgical and anesthetic team with same practices and similar expertise. The surgeons performing all these procedures (elective and urgent ones) were members of the coloproctology department and therefore specialized in colorectal surgery.

The effect of the number of surgeries performed in each institution on the evolution of the patients is controversial. A German study that included 2,293 patients operated in 75 different hospitals classified each institution considering the number of colonic resections performed annually. Prospective analysis of the outcome of the patients included did not reveal differences in the mortality rate in the 30 days post-resection. However, a larger number of surgeries per institution related to fewer complications and an increase in the indication of prophylactic antibiotics.

A study performed in the United States that included 9,739 patients that had undergone surgery for resection of colorectal carcinomas showed that most of the surgeons (81%) and hospitals (58%) were included in the group of low annual volume of patients per surgeon (≤5) and low annual volume of surgeries per institution (up to 40), respectively. In this study, a larger number of patients per surgeon was associated with a lower perioperative mortality, shorter hospital stay and lower costs. Hospitals with a low volume of patients, in which a large number of surgeons performed few colonic resections per capita, had worse outcomes in this study.

During the last decades we have witnessed several improvements in surgical and anesthetic technique as well as in pre- and postoperative care. The impact of these improvements in postoperative mortality is unknown. A study has suggested that there have been some favorable temporal changes in 30-day mortality after colorectal cancer surgical resection.

In our study, we have found that age is an important prognostic marker. Median age of patients that died postoperatively is more than a decade higher than the median age of all patients as a whole, even when different tumor locations are considered. This finding was consistent with that described in other reports.

We are aware of the fact that the reduced number of patients included in our analysis limits the identification of significant differences in the outcomes of patients in relation with tumor location (right- versus left-sided tumors). However, the descriptive analysis of these subgroups is of clinical interest and can reveal interesting data. In the present study, the absence of mortality in patients with tumors located in the descendant colon or left angle is noticeable. As in reported data, no difference in mortality was observed between patients with left- and right-sided cancers (5.3% vs. 4.6%; p = 0.8).

However, when considering tumor location in relation with surgical opportunity, interesting observations were made. Colonic carcinomas present with obstruction in 8-29% of the cases, and this is the most common cause of urgent surgery in patients with CC. Emergency surgery for occlusive colorectal carcinoma carries high rates of morbidity and mortality, and this is evidenced in our study in which 8 of the 14 (57.1%) patients that died in the
30-day period after surgery were urgently operated due to a colonic obstruction. Thus, postoperative mortality proved to occur more often in emergency than in elective settings. Postoperative mortality was a third higher in patients with right-sided tumors that needed urgent surgery than in patients operated electively (6.3% versus 4.2% respectively). This effect is even more noticeable and statistically significant in patients with sigmoid cancers, in which urgent surgery was associated with a 10-fold increase in the risk of death in the postoperative period (1.7 versus 17.1%). In some cases, one possible explanation for the higher mortality in the urgently operated patients may be related to the fact that “on call” surgeons, not necessarily experienced in colorectal surgery, perform urgent surgeries whereas experienced coloproctology surgeons perform surgeries in elective cases. In our case, this explanation is not plausible considering, as mentioned above, that all cases were managed by members of the coloproctology department.

When analyzing postoperative mortality in the emergency setting, it must also be considered that factors closely correlated with the emergency surgery, such as advanced age, comorbidities and advanced stage of disease, can confound the risk incurred by the emergency procedure itself. Usually, these tend to be patients at an increased risk for emergency surgery. In patients with a colonic obstruction, bowel resection and even surgical decompression with a colostomy may be a major source of morbidity, and increase the time of hospitalization, need for further medical care, and sometimes reduces quality of life.

Almost two-thirds of the patients with colonic obstruction in our study were found to have advanced tumors (stage III-IV). Other authors also have reported that colonic obstruction is usually a manifestation of advanced disease and as such it can be effectively prevented with the widespread use of appropriate CC primary and secondary prevention strategies. In regions in which CC screening strategies are applied as recommended, a stage migration has been observed and less advanced cancers are diagnosed. In Uruguay, as in many other regions of the World, colorectal cancer screening strategies are not widely used and therefore advanced colon cancers are frequently diagnosed. In these cases, not only the probability of cure is lower than in early stages, but also the chance of postoperative complications and death after surgery, especially when several risk factors co-exist (i.e. advanced age, comorbidities).

Different factors (i.e. tumor location, urgency, surgical risk, colonic distension and lack of adequate bowel preparation) influence therapeutic choice in colonic obstruction surgery. Resection followed by primary anastomosis is generally accepted as the treatment of choice for obstructing right-sided cancers. In our study, this was the therapeutic option in 1 of 2 patients with occlusive tumors located in this portion of the colon. Hartmann's procedure was performed in 3 patients with obstructive carcinoma of the left colon, and this has been reported to be the most common type of surgery in this setting. In 50% of these patients restoration of the colon continuity is never performed. Resection and primary anastomosis in left-sided tumors is usually reserved for carefully selected patients.

Patient's comorbidities and physiological status are known determinants of outcome after colorectal cancer resection. The value of the ASA score has been underlined in some papers. The use of this scoring system and/or the APACHE II score has been recommended in patients with occlusive tumors to decide whether to perform primary resection or not.

Several other tools have been developed to predict the risk of postoperative complications and mortality in colorectal cancer patients. The Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity (POSSUM) and its variants (including Colorectal-POSSUM) have been validated as scoring tools for the prediction of postoperative complications and mortality. Fazio et al. have developed a mathematical model with the intention of predicting 30-day mortality after colorectal cancer surgery. This model considers the following characteristics: patient age, ASA score, operative urgency, operative intent (curative?noncurative) and Dukes stage of tumor, and has proved to accurately predict postoperative death.

In our study, all but one patient had an ASA score of III. Other authors have demonstrated that higher ASA scores are associated with unfavorable outcome. Patients with ASA score ≥ III have a risk of postoperative mortality significantly higher than patients with ASA I or II. By definition, patients with ASA score III have a severe systemic disease that is not incapacitating. In colorectal cancer patients, this situation is usually a consequence of the tumor and its complications (i.e. colonic obstruction). Infection, dehydration and acid-base disorders are frequently seen in patients with obstructive tumors and can be the reason for a high ASA score. It must be considered that
those disorders are reversible in most cases, and that their preoperative treatment can lead to a surgery in better conditions, a decrease in the ASA score, and therefore a reduction of the risk of postoperative death. In patients with colonic obstruction and a high surgical risk it seems reasonable to postpone major surgery to allow a better control of other co-morbid factors with the objective of reducing operative and postoperative risk.

In the last two decades several non-surgical approaches for the management of occlusive cancers have been developed. The primary goal of these approaches is to avoid the need of emergency surgical treatment in non-stabilized patients. These alternatives include balloon dilation, ablative methods (cryotherapy, electrocoagulation, laser photocoagulation) and colonic stenting (using expandable or selfexpanding stents). Endoluminal stenting is a minimally invasive technique with low rate of major complications and a rate of success of 75-96%. In patients who are candidates for potentially curative surgery, it results in good cleansing of the colon and allows for stabilization of clinical conditions in high-risk patients allowing for a secondary planned radical procedure under better conditions. In the palliative setting it is capable of adequately resolving the obstruction obviating colostomy. A randomized study revealed that colostomy is only slightly less expensive (only 6.9%) than stenting. Other comparative study showed that colonic stent was associated with a lower mean cost per patient. Therefore, stents are a reasonable alternative to colostomy (especially in inoperable or high-risk patients - i.e. those with ASA score ≥ III-), achieving similar results with less morbidity, psychological repercussion and daily-life impact. In our series, no patient was treated preoperatively with a non-surgical technique for the management of colonic obstruction. We are aware of the fact that it can be difficult to extrapolate the mortality reported in our study with the mortality which may be expected by avoiding surgery in obstructing lesions by the use of endoluminal stents. In developing countries such as Uruguay, the use of these devices is frequently limited due to their cost. What health administrators from developing regions of the World must understand is that by the use of these “expensive” stents, several other costs can be avoided and that globally, as mentioned above, colonic stent is associated with similar costs to colostomy.

A serious postoperative complication in CC patients is anastomotic leakage. It is associated with an increase in 30-day mortality in comparison with patients without this complication. In our series, anastomotic leakage was the main cause of death (8/14 cases). Some authors reported a higher rate of suture dehiscence after primary resection and anastomosis, especially in left-sided tumors but also in right-sided cancers. This seems to be supported by our study since 4 out of 8 patients with right-sided carcinomas died due to anastomotic leakage. Those who had elective surgery and suffered postoperatively from suture dehiscence had contributory risk factors as obesity, hypoalbuminemia, and again an elevated ASA score.

The incidence of respiratory infection turned out to be particularly elevated in our series, favoring the development or complicating the course of anastomotic leakage in all the patients that had this complication. Perioperative prophylactic respiratory physiotherapy and adequate management of postoperative pain are simple but effective and economic measures that can decrease the incidence of respiratory complications, especially in smokers and patients with chronic obstructive pulmonary disease. Besides, 2 patients died due to an aspirative pneumonia. Bronchial aspiration constitutes an anesthetic complication that frequently determines severe respiratory complications that require mechanic ventilation and/or admission to an intensive care unit. Mortality in patients with bronchial aspiration can reach 5% and abdominal emergency surgery secondary to a bowel obstruction can raise its rate.

Although the need of prophylactic antibiotics is indisputable in colorectal surgery in order to reduce the rate of postoperative infectious complications, the optimal regimen and duration of antibiotic prophylaxis is still on debate. It is not possible to recommend one standard regimen and several of the plans studied seem to be equally effective. The use of a single preoperative dose of antibiotics has been evaluated in several studies and evidence indicates that it is as effective as the regimen of multiple doses and has practical advantages in eliminating the need for postoperative antibiotics. In our series, several schedules of prophylactic antibiotics have been used. No wound infections were reported as cause of death or comorbid condition in the patients that died. Infectious complications derived from suture dehiscence (the most common cause of death in our series) obviously can not be effectively prevented with prophylactic schedules.

For patients having surgery for cancer, the risk of venous thromboembolism (VTE) may be as high as 50% without prophylaxis. VTE was directly responsible for one out of
14 deaths in our series, and considering its high frequency in cancer patients, it could have been subclinically present in others, eventually aggravating their condition.

Despite the overwhelming evidence of the benefit of VTE prophylaxis and availability of published guidelines, practice among cancer surgeons, especially in developing countries, is far from being standardized or homogeneous. The most commonly used prophylactic regimens consist of a single preoperative injection of heparin (unfractioned UFH or low molecular weight LMWH) followed by subcutaneous injections starting within 12-24 hours after surgery and continued for few days during patients' stay in hospital. In our series, prophylaxis with LMWH was employed in every patient electively operated but was routinely used only in the preoperative setting. Some studies suggest that extended prophylaxis with LMWH provides an additional thromboprophylactic effect without increasing the risk of hemorrhage.\textsuperscript{48}

Two large randomized trials in patients undergoing elective, curative surgery for colorectal cancer have demonstrated that UFH and LMWH are equivalent in terms of efficacy and safety,\textsuperscript{49,50} the latter being more convenient in terms of ease of administration, patient comfort and control. Recently, Alcalay et al. have demonstrated that VTE reduces survival among patients with colorectal cancer.\textsuperscript{51}

Although not usually employed in Uruguay and not having been as thoroughly studied as heparins, pneumatic compression devices have demonstrated to effectively prevent thromboembolic complications in cancer patients after surgery, being especially indicated in patients in whom there is high risk of hemorrhagic complications.\textsuperscript{52} Some studies suggest that the combination of the mechanical method and UFH or LMWH could be better than heparin alone.\textsuperscript{53}

Based on the above, a prophylactic regimen that includes UFH, LMWH or pneumatic compression devices (or a combination of the mechanical method and heparin) must be routinely indicated in patients undergoing surgery for CC, considering the risks associated with the surgical procedure itself, the neoplastic disease and other factors that are frequently present in CC patients (i.e. age, prolonged immobilization). In developing countries, use of UFH is a cost-effective alternative to the more convenient and widely used LMWH.

In conclusion, in our retrospective study we have found a postoperative 30-day mortality rate after colon cancer surgery of 4.9%, similar to the one observed in other series from more developed countries. Although the number of surgeries per year in our institution is low, the good results achieved in terms of 30-day postoperative mortality can be partially explained by the similar practices and expertise of the surgical and anesthetic team. Anastomotic leakage was identified as the most common cause of death in our series. Of notice, most of the patients that died in the 30 days after colonic surgery had potentially avoidable fatal events as aspirative pneumonia, other not specified respiratory infections and VTE. Urgent colonic resection, especially in elderly patients and/or patients with high surgical risk (i.e. ASA score $\geq 3$) is associated with considerable risk of death. The use of preoperative risk stratification tools can result in a better selection of patients for surgery and therefore a reduction in risk of death. Increasing attention needs to be paid to minimizing operative risk by careful preoperative assessment, optimization of underlying comorbidities, and monitoring numerous physiologic variables during the intraoperative and postoperative period. In high risk patients with colonic obstruction, endoscopic stenting has good results with low risk of complications and we believe this procedure should be used more frequently than it actually is, with the intention of reducing postoperative complications and death. Furthermore, wider use of adequate and standardized prophylactic measures for the most common postoperative complications (i.e. infections, thromboembolic) is essential to achieve better surgical results.

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