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# Risk Factors Associated with Postoperative Infection in Cancer Patients Undergoing Spine Surgery

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**OBJECTIVES:** To determine the rate of and main risk factors for postoperative infection in cancer patients who underwent spine surgery in the last 5 years in order to determine whether there is an association between postoperative infection and increased mortality during hospitalization.

**METHODS:** All cancer patients who underwent surgical procedures between January 2015 and December 2019 at a single hospital specializing in spine cancer surgery were analyzed. The primary outcome of interest was postoperative infection. Bivariate logistic regression was used to estimate the odds ratio and 95% confidence interval for each variable in relation to the occurrence of infection.

**RESULTS:** We evaluated 324 patients, including 176 men (54.3%) and 148 women (45.7%) with a mean age of 56 years. The incidence of postoperative infection was 20.37%. Of the 324 patients, 39 died during hospitalization (12%).

**CONCLUSIONS:** Surgical time greater than 4 hours, surgical instrumented levels greater than 6, and an Eastern Cooperative Oncology Group of 3 or 4 were associated with an increased risk of postoperative infection, but these factors did not lead to an increase in mortality during hospitalization.

**KEYWORDS:** Surgical Site Infection; Spine Tumor; Risk Factors; Postoperative Complication; Spinal Metastasis.

## INTRODUCTION

Surgical site infection is a frequent complication of spinal surgery. It occurs in approximately 10–20% of metastatic cancer patients undergoing surgery, which is higher than the expected 4% rate among patients undergoing spine surgical procedures in general (1-7). Because of the high costs of managing postsurgical complications, postoperative infection has a substantial negative effect on patient survival, quality of life, and the health care system (8-10).

It is therefore important to know the rates of and the main risk factors for postoperative infection for institutions to propose measures to minimize infections. Thus, the present study aimed to determine these in cancer patients undergoing spine surgery in the last 5 years and to determine whether there is an association between postoperative infection and increased mortality during hospitalization.

## MATERIALS AND METHODS

This was a retrospective study of all patients undergoing urgent or elective spine surgeries between January 2015 and December 2019. All procedures were performed in a single institution by the same three surgeons with extensive experience in oncology spine surgery. According to the institutional protocol for investigating bacterial colonization, the swab is collected if the patient meets the swab collection criteria, and all the necessary safety measures are followed. The inclusion criteria were as follows: patients diagnosed with primary spinal cancer or metastatic malignancy from other primary sites who underwent surgery in the last 5 years. We excluded patients with incomplete records.

The measures were standardized as follows: age measured in years, sex (male or female), diagnosis of the patient's basic pathology, and surgical time in hours (stratified between greater than 4 hours or $\leqslant$4 hours).

The primary outcome of interest was postoperative infection. The definition of infection used in the study was as follows: worsening of laboratory parameters (leukocytosis or leukopenia, bandemia greater than 10%), fever (defined as an axillary temperature equal to or greater than 37.8°C)



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(11-12), associated or not with a positive culture. Any cases of postoperative infection that occurred within 90 days were included. The following variables were also analyzed: levels of instrumentation, Eastern Cooperative Oncology Group (ECOG) performance status, Karnofsky score, American Society of Anesthesiologists (ASA) scale, Frankel scale, pretreatment ambulation, comorbidities, emergency or elective surgery, revised Tokuhashi score system, neoadjuvant therapies 30 days before surgery (chemotherapy, radiotherapy, corticosteroids); pre-operative hemoglobin, leukocyte, and lymphocyte levels; postoperative hemoglobin levels; and smoking history.

Qualitative data were described as absolute and relative frequencies, and quantitative data were described using summary measures (mean, standard deviation, median, minimum, and maximum) for all patients in the sample.

The occurrence of infection was described as a qualitative characteristic using absolute frequencies, and the association was verified using Chi-square tests or Fisher's exact tests. The quantitative characteristics were compared based on the presence of an infection using summary measures and compared using Student's t-test. Bivariate logistic regression was used to estimate the odds ratio and 95% confidence interval for each variable in relation to the occurrence of infection. The joint model was adjusted to include all variables that presented significance levels below 0.2 ($p < 0.20$) in the bivariate tests, with all the variables inserted (full model) being maintained in the final model.

The revised Tokuhashi score system was compared across infection groups and mortality groups using the Student's t-test. We used IBM-SPSS for Windows version 22.0 software to compare the analysis, and Microsoft Excel 2010 software for data tabulation. The tests were performed at a significance level of 5%.

### Ethics

The study was approved by the Institutional Review Board and Ethics Committee, and informed consent was not necessary.

## RESULTS

In the present study, 324 patients were included and evaluated, including 176 men (54.3%) and 148 women (45.7%) with a mean age of 56 years. The incidence of postoperative infection was 20.37% (Table 1), and only one patient did not require surgical debridement. We excluded 41 patients (incomplete records). Of the 324 patients, 39 died during hospitalization (12%).

The main primary metastatic sites of neoplasia were the breast (15.7%), prostate (9.3%), kidney (8.6%), lung (7.4%), and colon (4.9%). The least common sites were the gallbladder (0.3%), uterus (0.3%), thymus (0.3%), penis (0.3%), and parotid (0.3%).

Table 2 shows that when isolated, only the surgical time greater than 4 hours, instrumented surgical levels greater than 6, and ECOG score of 3 or 4 were statistically associated with the occurrence of postoperative infection.

Table 3 shows that regardless of the other characteristics evaluated, the same three characteristics that were associated with the occurrence of infection remained statistically significant after adjustment, namely the surgical time ($p$=0.008), instrumented surgical levels ($p$=0.048), and ECOG score ($p$=0.008).

**Table 1** - Distribution of the characteristics evaluated in all patients.

| Variable | Description (n=324) |
|---|---|
| Sex (male), n (%) | 176 (54.3) |
| Age (years) | |
| Mean ± SD | 56.4 ± 12.6 |
| Median (min.; max.) | 58 (18; 84) |
| Surgical Time >4 h, n (%) | 49 (15.1) |
| Instrumented levels >6, n (%) | 33 (10.2) |
| ECOG, n (%) | |
| 0 | 35 (10.8) |
| 1 | 93 (28.7) |
| 2 | 59 (18.2) |
| 3 | 111 (34.3) |
| 4 | 26 (8.0) |
| ASA, n (%) | |
| I | 2 (0.6) |
| II | 193 (59.6) |
| III | 122 (37.7) |
| IV | 7 (2.2) |
| Karnofsky, n (%) | |
| Mean ± SD | 68.8 ± 19.2 |
| Median (min.; max.) | 70 (20; 100) |
| Frankel, n (%) | |
| A | 20 (6.2) |
| B | 17 (5.2) |
| C | 43 (13.3) |
| D | 55 (17.0) |
| E | 189 (58.3) |
| Metastasis, n (%) | |
| No | 74 (22.8) |
| Single | 65 (20.1) |
| Multiple | 185 (57.1) |
| Ambulation pretreatment, n (%) | 241 (74.4) |
| Corticosteroids, n (%) | 138 (42.6) |
| Neoadjuvant chemotherapy, n (%) | 8 (2.5) |
| Neoadjuvant radiotherapy, n (%) | 3 (0.9) |
| Hemoglobin pre-operative | |
| Mean ± SD | 11.6 ± 2.1 |
| Median (min.; max.) | 11.6 (5.5; 17.3) |
| Hemoglobin postoperative | |
| Mean ± SD | 10.4 ± 1.8 |
| Median (min.; max.) | 10.3 (6.5; 17.4) |
| Leukocytes pre-operative | |
| Mean ± SD | 9.5 ± 6.5 |
| Median (min.; max.) | 8.1 (1.6; 88.9) |
| Lymphocytes pre-operative >1000/mm$^3$, n (%) | 124 (38.3) |
| Hypertension, n (%) | 126 (38.9) |
| Diabetes mellitus, n (%) | 46 (14.2) |
| Peripheral vascular disease, n (%) | 12 (3.7) |
| Smoking, n (%) | 130 (40.1) |
| Type of surgery (urgency), n (%) | 49 (15.1) |
| Revised Tokuhashi score system | |
| Mean ± SD | 10.7 ± 2.3 |
| Median (min.; max.) | 11 (4; 15) |
| Death during hospitalization, n (%) | 39 (12) |
| Infection, n (%) | 66 (20.4) |

SD: standard deviation.

The revised Tokuhashi score system did not statistically differ between patients who presented with infection and those who did not ($p$=0.700), or between patients who survived and those who did not during hospitalization ($p$=0.162), as shown in Table 4.

## DISCUSSION

The spine is the third most common site of metastasis after the lung and liver. With the advancement of therapeutic

**Table 2** - Description of infections according to the characteristics evaluated and the results of unadjusted analyses.

| Variable | Infection | | OR | CI (95%) | | p |
|---|---|---|---|---|---|---|
| | No | Yes | | Inferior | Superior | |
| Sex, n (%) | | | | | | 0.552 |
| Female | 120 (81.1) | 28 (18.9) | 1.00 | | | |
| Male | 138 (78.4) | 38 (21.6) | 1.18 | 0.68 | 2.04 | |
| Age (years) | | | 1.00 | 0.98 | 1.03 | 0.806 |
| Mean ± SD | 56.3 ± 12.7 | 56.8 ± 12.4 | | | | ** |
| Median (min.; max.) | 58 (18; 84) | 59 (20; 81) | | | | |
| Surgical Time >4h, n (%) | | | | | | **0.002** |
| No | 227 (82.5) | 48 (17.5) | 1.00 | | | |
| Yes | 31 (63.3) | 18 (36.7) | 2.75 | 1.42 | 5.31 | |
| Instrumented levels >6, n (%) | | | | | | **0.016** |
| No | 237 (81.4) | 54 (18.6) | 1.00 | | | |
| Yes | 21 (63.6) | 12 (36.4) | 2.51 | 1.16 | 5.41 | |
| ECOG, n (%) | | | | | | **0.011** |
| 0, 1 and 2 | 158 (84.5) | 29 (15.5) | 1.00 | | | |
| 3 and 4 | 100 (73) | 37 (27) | 2.02 | 1.17 | 3.48 | |
| Karnofsky, n (%) | | | | | | 0.635 |
| 90 and 100 | 70 (81.4) | 16 (18.6) | 1.00 | | | |
| <90 | 188 (79) | 50 (21) | 1.16 | 0.62 | 2.18 | |
| ASA, n (%) | | | | | | 0.137 |
| I and II | 150 (76.9) | 45 (23.1) | 1.00 | | | |
| III and IV | 108 (83.7) | 21 (16.3) | 0.65 | 0.37 | 1.15 | |
| Frankel, n (%) | | | | | | 0.480 |
| A and B | 27 (73) | 10 (27) | 1.00 | | | |
| C | 36 (83.7) | 7 (16.3) | 0.53 | 0.18 | 1.56 | |
| D and E | 195 (79.9) | 49 (20.1) | 0.68 | 0.31 | 1.50 | |
| Metastasis, n (%) | | | | | | 0.192 |
| No | 58 (78.4) | 16 (21.6) | 1.00 | | | |
| Single | 47 (72.3) | 18 (27.7) | 1.39 | 0.64 | 3.02 | |
| Multiple | 153 (82.7) | 32 (17.3) | 0.76 | 0.39 | 1.48 | |
| Ambulation pretreatment, n (%) | | | | | | 0.730 |
| No | 65 (78.3) | 18 (21.7) | 1.00 | | | |
| Yes | 193 (80.1) | 48 (19.9) | 0.90 | 0.49 | 1.65 | |
| Corticosteroids, n (%) | | | | | | 0.251 |
| No | 144 (77.4) | 42 (22.6) | 1.00 | | | |
| Yes | 114 (82.6) | 24 (17.4) | 0.72 | 0.41 | 1.26 | |
| Neoadjuvant Chemotherapy, n (%) | | | | | | >0.999 |
| No | 251 (79.4) | 65 (20.6) | 1.00 | | | * |
| Yes | 7 (87.5) | 1 (12.5) | 0.55 | 0.07 | 4.56 | |
| Neoadjuvant Radiotherapy, n (%) | | | | | | >0.999 |
| No | 255 (79.4) | 66 (20.6) | 1.00 | | | * |
| Yes | 3 (100) | 0 (0) | & | | | |
| Lymphocytes pre-operative >1000/mm$^3$, n (%) | | | | | | 0.227 |
| No | 155 (77.5) | 45 (22.5) | 1.00 | | | |
| Yes | 103 (83.1) | 21 (16.9) | 0.70 | 0.40 | 1.25 | |
| Hypertension, n (%) | | | | | | 0.637 |
| No | 156 (78.8) | 42 (21.2) | 1.00 | | | |
| Yes | 102 (81) | 24 (19) | 0.87 | 0.50 | 1.53 | |
| Diabetes mellitus, n (%) | | | | | | 0.084 |
| No | 217 (78.1) | 61 (21.9) | 1.00 | | | |
| Yes | 41 (89.1) | 5 (10.9) | 0.43 | 0.16 | 1.15 | |
| Peripheral vascular disease, n (%) | | | | | | 0.135 |
| No | 246 (78.8) | 66 (21.2) | 1.00 | | | |
| Yes | 12 (100) | 0 (0) | & | | | |
| Smoking, n (%) | | | | | | 0.478 |
| No | 157 (80.9) | 37 (19.1) | 1.00 | | | |
| Yes | 101 (77.7) | 29 (22.3) | 1.22 | 0.71 | 2.11 | |
| Type of surgery, n (%) | | | | | | 0.251 |
| Elective | 216 (78.5) | 59 (21.5) | 1.00 | | | |
| Urgent | 42 (85.7) | 7 (14.3) | 0.61 | 0.26 | 1.43 | |
| Hemoglobin pre-operative | | | 1.00 | 0.88 | 1.14 | 0.974 |
| Mean ± SD | 11.6 ± 2.1 | 11.6 ± 2.2 | | | | ** |
| Median (min.; max.) | 11.7 (5.5; 17.3) | 11.2 (6.7; 15.8) | | | | |
| Hemoglobin postoperative | | | 0.91 | 0.78 | 1.06 | 0.178 |
| Mean ± SD | 10.5 ± 1.9 | 10.2 ± 1.5 | | | | ** |
| Median (min.; max.) | 10.3 (6.5; 17.4) | 10 (7; 14.4) | | | | |

**Table 2 -** Continued.

| Variable | Infection | | OR | CI (95%) | | p |
|---|---|---|---|---|---|---|
| | No | Yes | | Inferior | Superior | |
| Leucocytes pre-operative | | | 1.03 | 0.99 | 1.07 | |
| Mean ± SD | 9.2 ± 4.6 | 10.8 ± 11.1 | | | | |
| Median (min.; max.) | 8.1 (1.6; 33.5) | 8.2 (2.4; 88.9) | | | | |

Chi-square test; *Exact Fisher test; **t-Student 3 test; & Unable to estimate. OR: odds ratio; CI: confidence interval; SD: standard deviation.

**Table 3** - Joint model of the selected variables to explain the occurrence of postoperative infection.

| Variable | OR | CI (95%) | | p |
|---|---|---|---|---|
| | | Inferior | Superior | |
| Surgical Time >4h | 2.61 | 1.28 | 5.32 | **0.008** |
| Instrumented Levels >6 | 2.32 | 1.01 | 5.32 | **0.048** |
| ECOG (3 and 4) | 2.21 | 1.23 | 3.96 | **0.008** |
| ASA (III and IV) | 0.60 | 0.32 | 1.11 | 0.102 |
| Metastases | | | | |
| No | 1.00 | | | |
| Single | 1.47 | 0.63 | 3.43 | 0.372 |
| Multiple | 0.71 | 0.33 | 1.50 | 0.368 |
| Diabetes mellitus | 0.51 | 0.19 | 1.39 | 0.187 |
| Hemoglobin postoperative | 0.90 | 0.76 | 1.07 | 0.244 |

Multiple logistic regression (*full model*). OR: odds ratio; CI: confidence interval.

**Table 4** - Description of revised Tokuhashi score system according to the occurrence of infection and intrahospital mortality of patients and the results of comparisons.

| Variable | Revised Tokuhashi score system | | p |
|---|---|---|---|
| Infection | No | Yes | 0.700 |
| Mean ± SD | 10.6 ± 2.3 | 10.8 ± 2.3 | |
| Median (min.; max.) | 11 (4; 15) | 11 (4; 15) | |
| Death during hospitalization | No | Yes | 0.162 |
| Mean ± SD | 10.7 ± 2.2 | 10.2 ± 2.6 | |
| Median (min.; max.) | 11 (4; 15) | 10 (4; 15) | |

t-Student test. SD: standard deviation.

options and survival improvement among cancer patients, the need for surgical procedures for metastatic cancers in the spine is increasing, and thus, the number of postoperative complications is also increasing (13).

Surgical site infection is the main postoperative complication of spine surgery, and these infections lead to high levels of morbidity, high levels of mortality, and high costs for the health care system (8-10). In the present study, the incidence of surgical site infection was 20.37%, which is consistent with the findings of similar studies (5,13). Several risk factors are associated with a higher incidence of postoperative infection including obesity, diabetes mellitus, multiple comorbidities, smoking, a poor nutritional condition, pre-operative radiotherapy, levels of instrumentation, and surgical time (3,4, 6,14,15).

In the present study, the vast majority of procedures were performed in a single stage, with the exception of a few (sacrectomies). When necessary, staged procedures were performed with a 1-week time difference. Regardless of the other characteristics evaluated, patients with a surgical time greater than 4 h had a 2.61-fold higher chance of infection than patients with shorter surgical time; patients with more than six surgical instrumented levels had a 2.32-fold higher chance of infection than patients with lower levels, and patients with an ECOG score of 3 or 4 had a 2.21-fold higher chance of infection than patients with an ECOG score of 0, 1, or 2. These findings are consistent with the results of previous studies (3,4,6,14,15). We used the ECOG and Karnofsky scores since they were also necessary for the assessment of the revised Tokuhashi score system.

However, in the population studied, the presence of diabetes mellitus, smoking, and lymphopenia was not associated with an increased incidence of infection. In addition, the use of corticosteroids, radiotherapy, chemotherapy, and an inability to walk in the 30 days prior to surgery were not related to the increased occurrence of surgical site infection. These findings differ from those of previous studies (4,6,14,16-18). Possible explanations for the fact that diabetes and smoking did not change the infection rate may be that patients after a diagnosis of metastatic cancer change their lifestyle or have better control of blood glucose and hematological parameters in outpatient clinics or during hospitalization.

Another important point to be highlighted is that the occurrence of postoperative infection was not associated with increased mortality during hospitalization, and there was no decrease in the revised Tokuhashi score system, which aims to predict mortality. The score system consists of

the analysis of six variables: the general condition, number of extraspinal metastatic foci, number of metastases in the vertebral body, metastases to other internal organs, primary site of malignancy, and palsy. The score ranges from to 0-8 (prognosis $<6$ months), –9-11 ($\geqslant 6$ months), and –12-15 ($\geqslant 1$ year) (19). A possible reason for not increasing mortality in the context of infection can be the fact that all postoperative infections were promptly diagnosed and addressed early, in order to try to minimize negative impacts on survival.

The strengths of the current study include the quality of the statistical analyses used and the performance of all procedures in a single institution by the same surgeons with extensive experience in oncological spine surgery. The limitations of the current study include its retrospective nature, lack of stratification by groups of pathologies or specific procedures, and a limited sample size. Other limitations include the fact that there was no stratification by age, nor differentiation between primary or metastatic cancer, and the aspects of quality of life were also not evaluated. Additionally, no adjuvant therapies were evaluated in the postoperative period except neoadjuvant therapies.

It should be noted that the best strategy to prevent surgical site infection is to know the risk factors for infection, modify the risk factors when possible, and act in a preventive manner.

## CONCLUSIONS

Surgical time greater than 4 hours, surgical instrumented levels greater than 6, and ECOG 3 or 4 showed a statistically significant association with the risk of postoperative infection, but these factors did not lead to increased mortality during hospitalization.

## AUTHOR CONTRIBUTIONS

Tavares-Júnior MCM designed the study, collected and analyzed the data, performed the procedures, and wrote and performed the final review of the manuscript. Cabrera GED performed a final review of the manuscript. Teixeira WGJ analyzed the data and literature, performed the procedures, and reviewed the manuscript. Narazaki DK performed the final review of the literature and project, analyzed the data, performed the procedures, and reviewed the manuscript. Ghilardi CS analyzed the data, performed a final review of the literature and project, performed the procedures, and reviewed the manuscript. Marcon RM analyzed the data, performed the final review of the literature and project, and reviewed the manuscript. Cristante AF analyzed the data, performed the final review of the literature and project, and reviewed the manuscript. Barros-Filho TEP analyzed the data, designed the study, performed a final review of the literature and project, and performed a final review of the manuscript.

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