Original Article

Early versus delayed debridement for surgical site infection after oncological neurosurgery

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ABSTRACT

Background: There are no guidelines on the management of surgical site infection (SSI) in neurosurgery. This study sought to analyze whether early debridement improved survival compared to antibiotic therapy alone in patients with postcraniotomy infections after oncological neurosurgeries.

Methods: We retrospectively reviewed patient records from 2011 to 2019 to identify patients that had been reoperated for the debridement of SSI after brain tumor resection. If SSI was suspected but not clinically evident, the diagnosis was confirmed by cerebrospinal fluid (CSF) analysis or contrast-based imaging examinations. Immediately after diagnosis, broad-spectrum antibiotics were started for all patients.

Results: Out of 81 SSI cases, 57 underwent debridement. Two patients were reoperated 3 times, and three had two surgeries, resulting in a total of 64 procedures. The number of days between SSI diagnosis and surgical intervention did not influence mortality in both univariate and multivariable analyses (Hazard ratio [HR] 1.03, 95% CI 0.93–1.13). Early debridement (<24 h) did not influence rates of antibiotic prescription at discharge ($P = 0.53$) or hospital length of stay (LOS) ($P = 0.16$). Higher neutrophil-lymphocyte ratios (NLRs) were associated with the lower survival (HR 1.05, 95% Confidence interval [CI] 1.01–1.08). Multiple cutoffs were tested and values above 3.5 are more significantly associated with worse outcomes (HR 2.2; 95%CI 1.1–4.2).

Conclusion: Early debridement does not seem to influence the survival, rates of antibiotic at discharge, or hospital LOS of patients presenting with SSI after neurosurgery for intracranial tumors. High NLRs are strong predictors of worse prognosis in this population.

Keywords: Antibacterial agents, Brain neoplasms, Debridement, Surgical wound infections, Survival analysis

INTRODUCTION

Patients submitted to any operation are susceptible to surgical site infections (SSIs), defined as an infectious process arising until 30 days after the procedure without prosthetic material or 1 year if prosthetic material is implanted.[16] For craniotomies, the current evidence states that the risk of incurring in this postoperative complication ranges around 2.4–8%.[11,14,17] Even low-risk patients for cranial SSI, that is, non-emergency, clean, and short duration (<4 h) craniotomies, can suffer from these infections.[14] Furthermore, the dire financial consequences are occasionally

unaffordable for patients and the health-care system – the cost per SSI case has been estimated at around £10 000.[17]

Patients with brain tumors usually present one or more risk factors for postcraniotomy infection, namely, prolonged operative times, reoperations, sinus contamination, cerebrospinal fluid (CSF) leak, and radiation therapy.[11] The immune impairment and inflammation inherent to oncological conditions[5,13] can further facilitate the proliferation of bacteria. Oncological treatments themselves can predispose to infections – there are reports that patients treated with bevacizumab, for instance, can have rates of craniotomy infection as high as 35%.[7]

There is no concise guideline on the management of SSI in neurosurgery.[20] Therefore, the decision-making in SSI is often based on subjective judgments. The primary objective of this study was to analyze whether early debridement improved survival compared to antibiotic therapy alone in patients with postcraniotomy infections after oncological neurosurgeries. The secondary objective was to analyze possible prognostic markers.

MATERIALS AND METHODS

We retrospectively reviewed patient records from 2011 to 2019 to identify patients that had been reoperated for the debridement of SSI after brain tumor resection. Out of 81 SSI cases, 57 had undergone debridement. Patient data retrieved included age, gender, hospital length of stay (LOS), necessity of antibiotics at discharge, primary tumor site, and presence of metastasis (both intra and extracranial).

If SSI was suspected but not clinically evident, the diagnosis was confirmed by CSF analysis or contrast-based imaging examinations, such as head computed tomography or magnetic resonance imaging. Immediately after diagnosis, broad-spectrum antibiotics were started for all patients. Debridement consisted of wound exposure, collected samples for microbiological analysis, thorough irrigation with saline, removal of any devitalized tissue, with or without CSF leak repair, and removal of infected bones. It was indicated in case of persistent inflammatory signs on surgical site, worsening in laboratory work-up, persistent fever, or CSF leak. The interval between SSI diagnosis and surgical debridement was also recorded. All patients had undergone antibiotic prophylaxis with first generation cephalosporins in their previous surgeries.

Clinical and laboratory baseline data were collected from the 1st day of SSI diagnosis. CSF cultures were analyzed to diagnose meningitis and imaging was analyzed to diagnose abscesses. Functional assessment was recorded according to the World Federation of Neurological Societies (WFNS) scale before and after surgery, and patients who were not deceased had their follow-up censored at their last outpatient appointment.

Leukocyte differential and neutrophil-lymphocyte ratio (NLR) were studied as possible predictors of survival. Due to the diversity of primary tumor sites (including hematologic neoplasia), the differentials were included as percentages. Primary central nervous system (CNS) tumors included glioblastoma multiforme, astrocytoma, and oligodendroglioma. Non-CNS tumors (metastases) included melanoma, non-small cell lung cancer, and clear cell carcinomas.

Data are presented as mean (standard deviation) for normally distributed variables, median (interquartile range, IQR) for other continuous variables, and frequencies (valid %) for categorical variables. Welch's, Wilcoxon's, and Chi-squared tests were used for comparison of means and frequencies, as appropriate based on the variable's nature. Survival was studied using Kaplan–Meier survival curves and Cox proportional hazards regressions. Age and metastatic diseases (vs. primary CNS tumor) were included in the multivariable models due to biological plausibility, because both were considered to influence overall survival.

Linearity and proportional hazards assumptions were verified both numerically graphically through Schoenfeld and Martingale residuals. Values of $P < 0.05$ were considered significant. Statistical analyses were performed using R (R Foundation for Statistical Computing. Vienna, Austria, 2018).

RESULTS

Patient characteristics

Over this period, 57 patients were operated for the debridement of SSI. Mean patient age was 52.0 (±13.7) years and 18 (31.6%) were female. Concerning the primary tumor site, 33 (57.9%) had CNS neoplasms, 19 (33.3%) had non-CNS solid neoplasms, 2 (3.5%) had hematologic neoplasms, and three metastatic carcinomas of unknown primary site (5.3%). All patients had either primary CNS tumors or metastatic lesions. Median preoperative WFNS score was 2 (IQR 2). Three patients (5.3%) had associated meningitis and 8 (14%) had intradural abscesses [Table 1].

Seven of the primary surgeries were in the posterior fossa (12.3%). Five patients underwent multiple debridements: two patients were operated three times and three had two debridements, resulting in a total of 64 procedures. The most commonly identified bacteria were methicillin-sensitive *Staphylococcus aureus* (MSSA), in 16 (28.1%) cases, followed by MSSA, in 15 (26.3%). In ten cases, culture reports were negative [Table 2], and eight patients had polymicrobial infection. Three patients (5.3%) evolved with chronic osteomyelitis (>6 weeks), all of them having undergone debridement in the first 24 h of infection.

Table 1: Patient characteristics.

Age (years)	51.1 (±13.8)
Female	18 (31.6%)
Primary tumor site	
CNS	33 (57.9%)
Other solid neoplasms	19 (33.3%)
Hematologic	2 (3.5%)
Unknown	3 (5.3%)
Metastasis	
Intracranial only	16 (28.1%)
Intracranial and systemic	4 (7%)
Preoperative WFNS	1 (2)
Intracranial abscess	8 (14%)
Meningitis	3 (5.3%)

Data are presented as mean (± standard deviation) for age, median (interquartile range) for pre-operative WFNS, and count (valid percentage) for the others. CNS: Central nervous system, WFNS: World Federation of Neurological Surgeons

Table 2: Most frequent microorganisms detected by culture.

MSSA	16 (28.1%)
MRSA	15 (26.3%)
Enterobacter cloacae	5 (8.8%)
Staphylococcus spp. (coagulase negative)	4 (7.0%)
Pseudomonas aeruginosa	3 (5.3%)
Escherichia coli	2 (3.5%)
Klebsiella pneumoniae ESBL	2 (3.5%)
Morganella morganii	2 (3.5%)
Others	15 (26.3%)

The percentages refer to the number of patients in whom the microorganisms were identified divided by the total (*n*=57) and do not add up to 100% because some infections were polymicrobial. MSSA: Methicillin-sensitive *Staphylococcus aureus*, MRSA: Methicillin-resistant *Staphylococcus aureus*

Time between SSI diagnosis and debridement ranged from 0 to 17 days, but the median was 2 days (IQR 4.75). At discharge, the median WFNS score was 1 (IQR 2). Patients' median follow-up time was 326.5 days. During follow-up, 38 (66.6%) patients died. The median follow-up of these patients was 276 days (IQR 585.75) and five of them (8.8%) survived <30 days.

Early debridement

Time between infection diagnosis and debridement was first analyzed as a continuous variable [Table 3] and the number of days until surgical intervention did not influence mortality in both univariate (Hazard ratio [HR] 1.04, 95% Confidence interval [CI] 0.96–1.13) and multivariable analyses (HR 1.03, 95% CI 0.93–1.13), adjusted for age, presence of abscess, and metastatic disease [Figure 1]. This delay was also studied as a binary variable, using multiple time frames (24 h, 48 h, and 72 h), and debridement after these time limits also did not result in additional mortality risk in multivariable, adjusted for age, and metastasis (compared to primary CNS tumors) [Table 4].

Antibiotics were maintained at discharge for 25 patients (46.3%) and early (<24 h) debridement did not influence this rate ($\chi^2 = 0.40$, $P = 0.53$). The same was true for different time frames (48 h and 72 h, both $P > 0.4$). Median LOS was 21 days (IQR = 23.5) in general, 15 days (IQR = 14) for those who underwent debridement <24 h, 26 days (IQR = 30) for those who underwent debridement > 24 h, and 23.5 days (IQR = 20.75) for debridement >48 h. No differences were observed for any of the time frames: 24 h ($P = 0.16$) and 48 h ($P = 0.98$).

Hematologic parameters, NLR, and prognosis

Hematologic parameters were tested to identify potential outcome predictors of SSI after craniotomy for brain tumor resection. Among the differential leukocyte count, lower survival was observed in patients with a higher percentage of neutrophils (univariate, HR 1.03, 95% CI 1.003–1.05), whereas the opposite was true regarding lymphocytes (univariate, HR 0.95, 95% CI 0.92–0.97). Percentages of eosinophils, basophils, and monocytes did not influence survival.

Higher NLR predicted worse prognosis in the multivariable analyses, adjusted for age, and metastatic disease [Table 5]. As a continuous variable, it was associated with the lower survival (HR 1.05, 95% CI 1.01–1.08). Multiple cutoffs were tested [Figure 2]. Thresholds of 2, 2.5, and 3 did not significantly correlate with survival. NLR > 3.5 was associated with a HR of 2.2 (95% CI 1.1–4.2); for values > 4, the associated HR was 1.95 (0.98–3.9); for ratios > 4.5, HR 2.8 (95% CI 1.5–5.4); and for NLR > 5, HR 2.5 (95% CI 1.3–4.8) [Figure 3].

DISCUSSION

Our results demonstrate that early debridement does not seem to influence mortality for patients with SSI after craniotomies for brain tumor resection. There were also no differences regarding LOS at the hospital or necessity of antibiotics at discharge. The NLR is a robust prognostic marker in this population.

Multiple factors inherent to patients with cancer can predispose them to infections and potentially impair their ability to handle pathogens. These factors might be patient-related (advanced age, comorbidities, and functionality), disease-related (metastasis or bone marrow involvement), or treatment-related conditions (chemotherapy regimen and dosage).[18]

Table 3: Association between survival and time from diagnosis to debridement.

	Coefficient	SE	HR (95% CI)	*P* value
Univariate				
Days to debridement	0.04	0.03	1.04 (0.96-1.13)	0.31
Multivariable				
Age	0.01	0.01	1.01 (0.99-1.03)	0.16
Abscess	0.29	0.46	1.34 (0.62-2.90)	0.37
Metastasis	0.15	0.37	1.17 (0.58-2.35)	0.66
Days to debridement	0.03	0.05	1.03 (0.93-1.13)	0.58

Cox proportional hazards regressions modeled to study whether time between diagnosis of craniotomy site infection and surgical debridement influenced mortality in patients with cancer. Broad-spectrum antibiotic therapy was always instituted immediately at the time of infection diagnosis. Time was included as a continuous variable (number of days). Metastasis is included in comparison to primary CNS tumors. SE: Standard error, HR: Hazard ratio, CI: Confidence interval

Table 4: Different time periods of clinical treatment.

	24 h	48 h	72 h
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Univariate			
Time	1.47 (0.73–2.98)	1.18 (0.59–2.36)	1.01 (0.49–2.07)
Multivariable			
Time	1.58 (0.80–3.13)	1.17 (0.60–2.25)	0.99 (0.49–1.99)
Age	1.01 (0.99–1.04)	1.01 (0.99–1.03)	1.01 (1.00–1.03)
Metastasis	1.16 (0.60–2.24)	1.10 (0.56–2.14)	1.07 (0.54–2.13)
Wald test	3.5 (3 d.f.)	2.24 (3 d.f.)	2.44 (3 d.f.)
P value	0.3	0.5	0.5

Different time periods between infection diagnosis and surgical debridement were studied in multivariable Cox proportional hazards regressions. Clinical treatment with antibiotics was attempted at varying time frames until debridement. All three models were adjusted for age and metastasis, and none of the covariates significantly influenced the outcome. SE: Standard error, HR: Hazard ratio, CI: Confidence interval

Figure 1: Kaplan–Meier curves for different time periods between infection diagnosis and debridement. Surgical debridement occurred at various different time periods from clinical diagnosis of surgical site infection (SSI). The curves represent cumulative survival for patients who underwent debridement <24 h after SSI diagnosis (full line), >24 h (dashed line), >48 h (dotted line), and >72 h (dash-and-dot line). Vertical dashes represent censored data. There were no significant differences in survival among groups (log-rank, all *P* > 0.05).

Debridement timing

While risk factors and prophylaxis are better studied and standardized,[14] the management of established infections is somewhat controversial. Antibiotics are mandatory, but surgical debridement is indicated based on subjective or experience-based criteria. Even for bone flap infections, a growing body of evidence proposes more conservative approaches such as salvaging the flap; therefore, avoiding a second surgery might be beneficial for patients in terms of SSI management and treatment of cancer – early start of adjuvant chemo and radiotherapy.[3,6,20,21]

Because surgical debridement was taken at many different timings, we analyzed this time-interval under two different perspectives to answer the same question: is it safe to start clinical treatment as first-option treatment for SSI?

The continuous analysis [Table 3] failed to demonstrate that a longer period until surgical debridement could change mortality. The dichotomized analyses point in the same direction [Table 4] demonstrating that 24, 48, or 72 h of
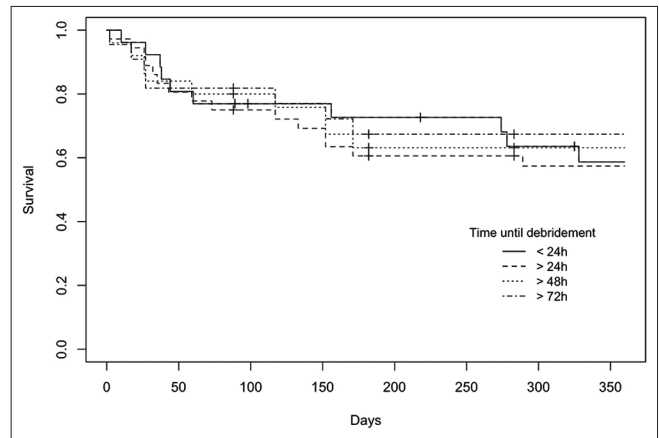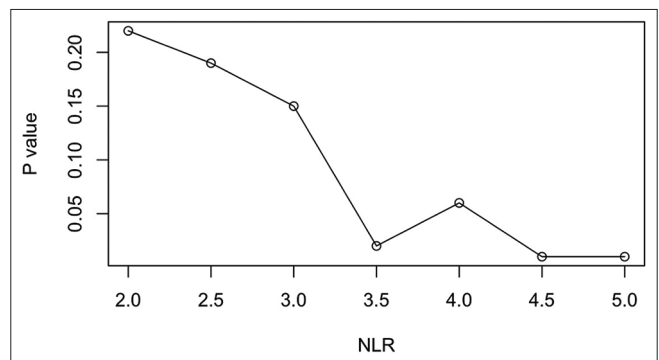

Figure 2: Significance of different NLR thresholds. Significance of multiple neutrophil-lymphocyte ratios (NLR) in multivariable models adjusted for age and presence of metastasis (compared to primary CNS tumors). NLR becomes a robust predictor of worse prognosis for values > 3.5, although the NLR > 4.0 slightly missed the established significance threshold (*P* = 0.058).

Table 5: Neutrophil-lymphocyte ratio as a predictor of survival.

	Coefficient	SE	HR (95% CI)	*P* value
Univariate				
Neutrophil (%)	0.02	0.01	1.03 (1.003–1.05)	0.03*
Eosinophils (%)	0.03	0.04	1.03 (0.95–1.11)	0.50
Basophils (%)	−0.45	0.58	0.64 (0.20–2.06)	0.45
Lymphocytes (%)	−0.05	0.02	0.95 (0.92–0.97)	< 0.01*
Monocytes (%)	−0.02	0.04	0.98 (0.90–1.07)	0.65
Neutrophil-lymphocyte ratio				
Continuous	0.04	0.02	1.05 (1.01–1.08)	0.03*
>2	0.68	0.60	1.97 (0.7–5.8)	0.22
>2.5	0.50	0.45	1.65 (0.8–3.5)	0.19
>3	0.44	0.37	1.6 (0.85–2.8)	0.15
>3.5	0.77	0.36	2.2 (1.1–4.2)	0.02*
>4	0.67	0.34	1.95 (0.98–3.9)	0.06
>4.5	1.04	0.37	2.8 (1.5–5.4)	<0.01*
>5	0.93	0.36	2.5 (1.3–4.8)	<0.01*

Cox proportional hazards regressions analyzing leukocyte differential counts and NLR as predictors of survival. The analyses of the NLR were adjusted for age and metastasis (compared to primary CNS tumors). SE: Standard error, HR: Hazard ratio, CI: Confidence interval, NLR: Neutrophil-lymphocyte ratio
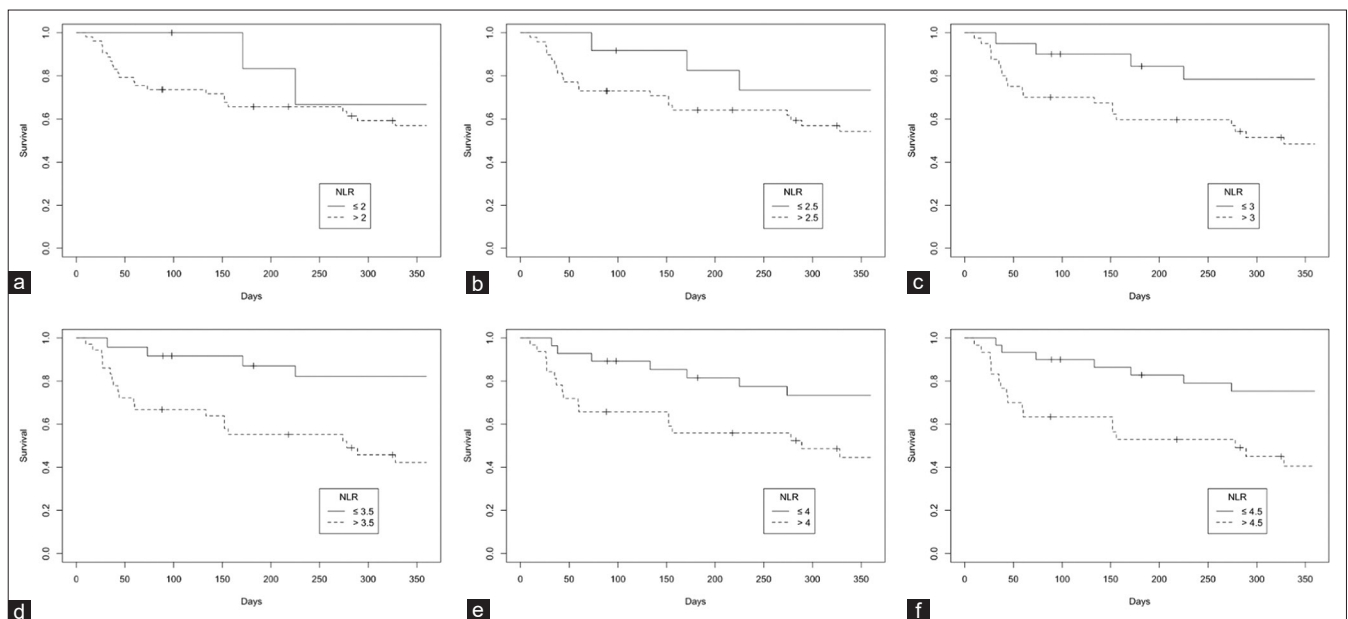

Figure 3: Kaplan–Meier curves for different NLR cutoffs. Survival curves for different neutrophil-lymphocyte ratios (NLR) cutoffs: 2.0 (a), 2.5 (b), 3.0 (c), 3.5 (d), 4.0 (e), 4.5 (f). In cases of SSI, NLR becomes a significant predictor of worse prognosis above 3.5.

antibiotic treatment alone before debridement does not seem to influence survival.

Even though the majority of patients underwent to debridement surgery, we believe that initial antibiotic course has several advantages for these patients. The early systemic inflammatory response is diminished; therefore, patients are often operated on better clinical conditions. Antibiotics trial can also attenuate a significant portion of SSI leading to less invasive surgical procedures. Our records demonstrated that almost 30% were managed with clinical treatment avoiding unnecessary surgical risks.

Inflammation and prognosis

Inflammation plays a critical role in both oncological and infectious diseases.[12] In this context, the NLR is an inflammatory biomarker whose elevation has been linked to poor prognosis in a myriad of conditions, including pneumonia, coronary artery disease, and cancer.[1,8-10] This

easily obtainable value has been shown to correlate strongly with prognosis in patients with glioma.[2,4,5]

Our results have demonstrated that high NLR at the 1st day of SSI diagnosis is a strong predictor of worse prognosis for patients with SSI after surgeries for intracranial tumors. Bao *et al.*[5] have reached an optimal cutoff of 2.50 as outcome predictor for gliomas. On the other hand, Templeton *et al.*[19] reported a median cutoff of 4.0 in a meta-analysis of one hundred studies on the association between NLR and overall survival of patients with solid tumors. In our analysis of SSI, only values above 3.5 were significantly correlated with higher mortality. There is a clear trend toward higher HRs and stronger significance of the coefficients as the NLR assumes growing values [Figure 2 and Table 5].

Strengths and limitations

Our paper has limitations. The sample size is relatively small, with 57 patients and 64 procedures, and patients can be heterogeneous within the wide clinical spectrum of SSI. Other important outcome measures need additional assessment, such as morbidity, time until infection resolution, or cost analyses. Furthermore, the retrospective design also brings potential biases, such as incomplete records and possible unknown confounders. Indeed, this matter should ideally be tested on a randomized trial to draw definitive conclusions.

However, a study of over 2600 craniotomies for tumors resulted in only 39 debridement's.[15] Therefore, our results are still representative of clinical experience from a high-volume oncologic center; additionally, to the best of our knowledge, this is the first study to compare early debridement with antibiotic therapy for SSI after oncological craniotomies.

CONCLUSION

Early debridement does not seem to influence the survival, rates of antibiotic at discharge, or hospital LOS of patients presenting with SSI after neurosurgery for intracranial tumors. In this setting, delayed debridement based on sound clinical judgment can be considered safe. High NLRs are strong predictors of worse prognosis in this population.

Ethical approval

For this type of study, formal consent is not required.

Declaration of patient consent

Patients' consent not required as patients' identities were not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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