RISK FACTORS FOR SURGICAL SITE INFECTION IN LARYNGEAL CANCER SURGERY

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SUMMARY – Surgical site infection (SSI) is a significant factor of morbidity and mortality in patients surgically treated for laryngeal carcinoma. The aim of this prospective study in 277 patients was to determine the incidence of SSI in patients surgically treated for laryngeal squamous cell carcinoma and to identify risk factors for development of SSI. Patients with previous chemotherapy and/or radiotherapy were excluded. All patients had tracheostomy postoperatively and received antibiotic prophylaxis with cephalosporin, aminoglycoside and metronidazole. The overall incidence of SSIs in our cohort was 6.5% (18 patients): 4 (22.22%) patients with superficial infections, 11 (61.11%) with deep infections and 3 (16.66%) with organ-space infections. The remaining infections included pneumonia (1 case) and Clostridium difficile colitis (2 cases). The median hospital stay in patients having developed SSIs was longer than in those without SSIs (33.5 vs. 16 days, p<0.001). By using univariate analysis American Society of Anesthesiologists score ≥3, duration of surgery longer than 120 minutes and National Nosocomial Infections Surveillance risk index ≥1 were found to be significantly associated with the occurrence of SSI. Age, sex, body mass index, history of smoking, underlying diabetes and preoperative length of stay were found not to be associated with SSI. The most frequently isolated microorganism was Klebsiella spp.

Key words: Surgical wound infection; Head and neck neoplasms – surgery; Head and neck neoplasms – complications; Laryngeal neoplasms – epidemiology; Risk factors

Introduction

Loco-regional control of laryngeal cancer and good survival outcome can be achieved through surgery and organ-preserving radiotherapy or chemo/radiotherapy with advantages and disadvantages of each modality of treatment. Surgical resection still remains the mainstay of curative treatment for head and neck malignancy.

One of the most common complications of surgery is surgical site infection (SSI) despite all sterility principles used. SSI is a significant factor of morbidity and mortality in patients surgically treated for laryngeal malignant disease.3 According to the Centers for Disease Control and Prevention (CDC) from Atlanta, SSI can be classified as incisional (superficial or deep) and organ/space.4 5 The National Research Council classifies operative site as clean, clean-contaminated, contaminated, and dirty/infected. Surgical site in oral cavity, pharynx and larynx represents a clean-contaminated surgical site due to the presence of normal flora.6 Bacteria colonizing oral cavity are an important factor in nosocomial infections.

In laryngeal cancer surgery, SSI leads to wound dehiscence, formation of pharyngo-cutaneous fistula, and in severe cases sepsis and death. It can prolong hospital stay, increase health care costs, delay speech
rehabilitation, oral nutrition and postoperative adjuvant therapy, which in turn may affect the overall prognosis. SSI may cause poor cosmetic results and have significant psychological effect on the patient affecting his/her quality of life. Several authors also found that patients with head and neck cancer with local or regional infection were more likely to have recurrent disease\(^8,9\).

Data on SSI in laryngeal and/or pharyngeal cancer surgery are not so numerous. Reports on the incidence of SSI in oncologic surgery for head and neck malignancy differ, ranging from 10\% to 45\%\(^9\)-14. Analyses of series of patients revealed a large number of risk factors for postoperative SSI in head and neck cancer surgery, such as various disease, patient and operative characteristics, preoperative radiotherapy or chemotherapy\(^15\).

The aim of this study was to assess the incidence of SSI in patients surgically treated for laryngeal squamous cell carcinoma at a tertiary health care institution and to identify risk factors for development of SSI.

**Patients and Methods**

This prospective study included a cohort of 277 patients with squamous cell carcinoma of the larynx confirmed by histopathology. All 277 patients underwent surgery as primary modality of treatment between February 2006 and December 2011 at the Ear, Nose and Throat Department, Military Medical Academy (MMA), Belgrade, Serbia. Infection control personnel collected general data on each patient under surveillance: age, gender, history of smoking, body mass index (BMI), presence of underlying diabetes mellitus, American Society of Anesthesiologists (ASA) score, as well as health care related data including duration of surgery, preoperative length of stay (LOS), length of hospital stay, and National Nosocomial Infections Surveillance (NNIS) System risk index.

The NNIS System risk index was calculated on the basis of data related to the operation: wound contamination class, duration of surgery, and ASA score. The NNIS System index ranges from 0 to 3. Each of three risk indices is worth 1 point: contaminated or dirty surgical wound, ASA scores greater than 2, and duration of surgery greater than the 75\% percentile for a specific group of surgical procedures\(^16,17\).

Surgical procedures included partial and total laryngectomy with or without partial pharyngectomy, resection of the base of the tongue, and neck dissection according to the stage of the disease. We did not have patients with free flap reconstruction or major blood loss during surgery. All patients had tracheostomy postoperatively, temporary or permanent. Surgery was performed by four surgeons with more than 10-year experience in laryngeal surgery. Surgical site was shaved with razor the day before the surgery and disinfected with povidone-iodine preoperatively observing the general rules of sterility. All included patients received antibiotic prophylaxis with cephalosporin, aminoglycoside and metronidazole during the surgery, continuing for 4 days postoperatively. Surgical drain was removed on the third postoperative day. All patients were monitored at the Intensive Care Unit immediately after the surgery and transferred to the ENT Department on the next day.

Until discharge from the hospital, SSIs were assessed on a daily basis. For diagnosis of SSI, the CDC criteria were used\(^4,18\). The outcome of interest was defined as the presence of purulent discharge from the incision wound or tracheostoma, spontaneous dehiscence of the wound with signs of infection, or the presence of pharyngo-cutaneous fistula. In all cases of SSI, microbial smear was taken and immediate empirical antimicrobial treatment was started with correction of therapy according to the culture result. Drainage of infected wound and placement of nasogastric feeding tube (if needed) was performed.

Microbiological testing was performed at the MMA Institute of Medical Microbiology. Isolates were identified by routine methods\(^19\). Susceptibility testing was done according to the Clinical and Laboratory Standard Institute recommendations\(^20\).

Statistical analysis was performed using the SPSS 15.0 software (Chicago, Illinois, USA). Data are presented as mean ± SD, range (minimum, maximum) and count (%). The univariate relationship between each variable and SSI was analyzed with logistic regression. Only variables with p value less than 0.1 in univariate analysis and variables that could be a potential risk factor for infection were entered in the multivariate logistic regression model.
Results

Patients were stratified into two groups based on the presence or absence of SSI. The overall incidence of SSI and LOS were calculated in the two groups of patients. Patient characteristics and predictive factors related to SSI according to the univariate analysis are shown in Table 1.

Incidence of SSI

Eighteen (6.5%) of 277 patients that underwent laryngeal surgery for squamous cell carcinoma had SSI postoperatively. Out of 18 SSIs, there were four (22.22%) patients with superficial infections, 11 (61.11%) with deep infections and three (16.66%) with organ-space infections. The remaining infections included pneumonia (1 case) and *Clostridium difficile* colitis (2 cases).

Study population characteristics

The mean age of the study population was 59.48 (range 34 to 82, median 59.00) years. There were fewer females (n=31; 11.2%) than males (n=246; 88.8%).

Preoperative variable and SSI

When surgical procedures were grouped by ASA preoperative assessment score, there were 1.8% (5 patients) of surgical procedures with patient ASA score 1 and incidence rate of infection 0%; 87.4% (n=242) with ASA score 2 and incidence rate of infection 5.4%; 10.8% (n=30) with ASA score 3 and incidence rate of infection 16.7%; we did not have patients with ASA score 4 or 5. Univariate analysis showed the occurrence of SSIs to be significantly associated with ASA score ≥3 (p<0.05; OR 3.600). Age, sex, BMI, history of smoking and underlying diabetes were not associated with SSIs.

Table 1. Relationship between patient characteristics, predictive factors and surgical site infection

<table>
<thead>
<tr>
<th>Factor</th>
<th>Category</th>
<th>Patients with SSI (%)</th>
<th>Patients without SSI (%)</th>
<th>p value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≤59 years</td>
<td>7 (4.7)</td>
<td>142 (95.3)</td>
<td>0.196</td>
<td>1.907 (0.717-5.075)</td>
</tr>
<tr>
<td></td>
<td>&gt;60 years</td>
<td>11 (8.6)</td>
<td>117 (91.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>15 (6.1)</td>
<td>231 (93.9)</td>
<td>0.450</td>
<td>1.650 (0.450-6.055)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>3 (9.7)</td>
<td>28 (90.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>≤24.9</td>
<td>7 (5.6)</td>
<td>117 (94.4)</td>
<td>0.605</td>
<td>1.295 (0.487-3.445)</td>
</tr>
<tr>
<td></td>
<td>&gt;25</td>
<td>11 (7.2)</td>
<td>142 (92.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td>I, II</td>
<td>13 (5.3)</td>
<td>234 (94.7)</td>
<td>0.024</td>
<td>3.600 (1.185-10.932)</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>5 (16.7)</td>
<td>25 (83.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative LOS</td>
<td>≤2</td>
<td>6 (4.3)</td>
<td>134 (95.7)</td>
<td>0.139</td>
<td>2.144 (0.781-5.886)</td>
</tr>
<tr>
<td></td>
<td>&gt;3</td>
<td>12 (8.8)</td>
<td>125 (91.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>No</td>
<td>16 (6.2)</td>
<td>240 (93.8)</td>
<td>0.562</td>
<td>1.579 (0.338-7.383)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>2 (9.5)</td>
<td>19 (90.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>No</td>
<td>6 (4.9)</td>
<td>116 (95.1)</td>
<td>0.348</td>
<td>1.622 (0.591-4.455)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>12 (7.7)</td>
<td>143 (92.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of surgical procedure</td>
<td>≤119 min</td>
<td>7 (4.1)</td>
<td>162 (95.9)</td>
<td>0.054</td>
<td>2.624 (0.985-6.996)</td>
</tr>
<tr>
<td></td>
<td>&gt;120 min</td>
<td>11 (10.2)</td>
<td>97 (89.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNIS</td>
<td>0</td>
<td>12 (5.2)</td>
<td>219 (94.8)</td>
<td>0.057</td>
<td>2.737 (0.971-7.716)</td>
</tr>
<tr>
<td></td>
<td>1,2</td>
<td>6 (13.0)</td>
<td>40 (87.0)</td>
<td></td>
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</tr>
</tbody>
</table>

OR = odds ratio; CI = confidence interval; SSI = surgical site infection; BMI = body mass index; ASA = American Society of Anesthesiologists score; preoperative LOS = preoperative length of stay; DM = diabetes mellitus; NNIS = National Nosocomial Infections Surveillance risk index.
Healthcare-related data
The mean duration of surgical procedure was 107.02 minutes, varying from 40 to 240 minutes (100.00±38.139). Logistic regression analysis showed that duration of surgery longer than 120 minutes (p<0.05; OR 2.624) was a significant factor for developing SSI postoperatively.

Within the group of surgical procedures classified by the NNIS System risk index, there were 83.4% (n=231) of surgical procedures with risk index 0 and incidence rate of infection of 5.2%; 15.5% (n=43) with risk index 1 and incidence rate of 9.3%; and 1.1% (n=3) with risk index 2 and incidence rate of 66.7%; in our study, we did not have any patient with NNIS System risk index 3. Univariate analysis revealed that the occurrence of SSI was significantly associated with NNIS risk index ≥1 (p=0.057; OR 2.737).

The median preoperative LOS was 4.42 days, range 0 to 48 days. Preoperative LOS for patients with SSI was 6.06 days and for patients without SSI 4.31 days, with no statistically significant difference between these two groups of patients.

The median LOS was 17 days (19.04±10.394), range 6 to 71 days. Hospital stay was longer in patients that developed SSIs than in those without SSIs (p<0.001). The median LOS was 33.50 (37.22±15.528) days in patients that acquired SSI and 16.00 (17.78±8.662) days in patients without SSI.

ASA and duration of surgery as significant factors in univariate analysis were analyzed by multivariate logistic regression analysis, which did not recognize either of them as a statistically significant predictor for SSI (Table 2).

Microorganisms
Microorganisms were isolated in 16 (88.9%) of 18 patients with recorded SSIs. Among these, one species was isolated in 68.75% (n=11), 2 species in 31.25% (n=5) and 3 species in 0% (n=0) of patients with SSIs. The most frequently isolated microorganisms were Klebsiella spp. (25%; 4/16), Streptococcus spp. (18.75%; 3/16), Pseudomonas aeruginosa (12.5%; 2/16) and Pseudomonas spp. (12.5%; 2/16), followed by Enterobacter, Enterococcus spp., Morganella spp., Acinetobacter, Stenotrophomonas and Staphylococcus aureus with one case of infection each (6.25%; 1/16).

Discussion
Surgical site infection is one of the most common nosocomial infections in hospital patients in Serbia. The severity of SSI varies from mild to life threatening.

The overall SSI incidence in this prospective study of surgically treated laryngeal cancer patients was 6.5%. The incidence of SSI in patients undergoing head and neck surgery for malignant disease has been reported to be as high as 45%. Suljagic et al. report an overall SSI incidence in head and neck surgery of 3%, Ogihara et al. on 10.0%, Cunha et al. on 10.9% and Lee et al. on 18.4%. Most of them included clean surgical procedures such as neck dissection, thyroidectomy or salivary gland excision. Contamination of surgical site is recognized as a risk factor for SSI along with patient characteristics, type of surgery and other factors. By penetrating into bacterial colonized mucosal surfaces, laryngeal and pharyngeal surgery presents a clean-contaminated surgical procedure according to the National Research Council operative-site classification. Operative exposure of the larynx and pharynx may lead to surgical site colonization and infection.

Reported data on SSI incidence in laryngeal and/or pharyngeal cancer surgery vary among different authors from 4.8% to 58%. A large number of studies included patients with previous chemotherapy and/or radiotherapy, blood loss and free flap reconstruction, recognizing them as risk factors for developing SSI. A small number of SSI in this study was probably due to our selection of patients with no previous radiotherapy, chemotherapy or tracheostomy. Comparing to Cunha et al. with 100% of deep incisional infections, 61.11% of our SSIs were deep infections.

Table 2. Multivariate logistic regression analysis

<table>
<thead>
<tr>
<th></th>
<th>p</th>
<th>OR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>ASA</td>
<td>0.180</td>
<td>3.231 (0.582-17.954)</td>
</tr>
<tr>
<td>Duration of</td>
<td>0.090</td>
<td>2.399 (0.871-6.604)</td>
</tr>
<tr>
<td>operation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNIS</td>
<td>0.985</td>
<td>0.985 (0.193-5.028)</td>
</tr>
</tbody>
</table>

OR = odds ratio; CI = confidence interval; ASA = American Society of Anesthesiologists score; NNIS = National Nosocomial Infections Surveillance risk index.
Besides SSI, Ogihara et al.\textsuperscript{10} and Cunha et al.\textsuperscript{15} report on respiratory infections, meningitis and urinary infections after head and neck tumor surgical procedures, whereas in our study we had two patients with \textit{Clostridium difficile} colitis and one case of pneumonia, which can be life threatening\textsuperscript{30}.

We identified significant risk factors for developing SSI in patients undergoing laryngeal or laryngopharyngeal cancer surgery. By using a univariate approach, we were able to identify 3 risk factors with the potential to discriminate between subjects with and without SSI. We found that ASA score $\geq 3$, duration of surgery $\geq 120$ minutes and nnIS risk $\geq 1$ were associated with a significant increase in SSI in patients with laryngeal carcinoma.

ASA score divides patients into 5 categories according to the American Society of Anesthesiologists classification. In our study, ASA score 3 (we did not have patients with ASA score 4 and 5) was a significant risk factor for SSI, which agrees with the findings reported by other authors\textsuperscript{22,31}.

Extended operative time has been associated with an increased risk of SSI. Operative time longer than 2 hours is recognized as an independent risk factor for SSI in cancer surgery\textsuperscript{31}. This is due to the more advanced stage of disease and possible concomitant diseases in the patient, greater tissue damage, blood loss, and damage to local blood vessels compromising intraoperative antibiotic tissue levels over time. By using univariate analysis we also found the patients with the duration of surgery longer than 120 minutes to be at a higher risk of SSI.

The nnIS basic SSI risk index is composed of the following criteria: American Society of Anesthesiologists score of 3, 4, or 5; wound class; and duration of surgery\textsuperscript{32}. The nnIS risk score is calculated from the following data: ASA score, wound class and duration of surgery. It was found to be positively correlated with the risk of SSI\textsuperscript{12,33}. In our study, univariate analysis revealed that nnIS index $\geq 1$ was related to a higher incidence of SSI. By univariate analysis, Petrosillo \textit{et al.} also found the nnIS score $>0$ to be significantly associated with SSI occurrence\textsuperscript{14}. Univariate analysis in a tertiary care hospital in Greece showed that the nnIS risk index of 2 or 3 was significantly associated with an increased risk of SSI\textsuperscript{35}.

Although nnIS score is a reliable, accurate and useful tool for identifying general surgical patients at risk of SSI, it does not incorporate factors specifically relevant to the cancer population. Cancer patients are a specific patient population with an increased risk of developing SSI. Malignant tumor is identified as an independent factor for SSI in head and neck surgery and in noncolorectal abdominal surgery\textsuperscript{10,36}.

The length of hospital stay prior to surgery greater than 48 hours is a previously recognized risk factor for SSI\textsuperscript{15,33,37}. The reason is patient colonization with intrahospital microbial flora. In contrast, in our study, longer preoperative stay in hospital (longer than 2 days) was not significantly associated with SSI on univariate analysis.

Regarding age, sex, BMI, history of smoking and underlying diabetes, there was no significant difference between the groups with and without SSI, similar to the results reported by Ogihara \textit{et al.}\textsuperscript{10} and Hirakawa \textit{et al.}\textsuperscript{24}.

The present study showed that the causative agents of SSIs were similar to the causative agents reported by the authors from Portugal and UK\textsuperscript{15,25}.

The overall rate of SSI was smaller than reported in other studies. Postoperative infection can be reduced with antibiotic prophylaxis\textsuperscript{38}. In order to prevent infection in laryngeal and pharyngeal cancer surgery, we use a combination of antibiotic agents covering aerobic, anaerobic and gram-negative bacteria intraoperatively, followed by their administration for 4 days more, considering it superior to single agents. Some authors report that prolonged and one-day antibiotic regimens for clean-contaminated procedures were similar in efficacy\textsuperscript{39-41}. In some countries, one-day course of antibiotic is a standard protocol after head and neck surgery, while prolonged antibiotic courses are still frequently used in common surgical practice in Japan, particularly in clean-contaminated procedures\textsuperscript{10}. Not all procedures need prophylaxis. Roumelaki \textit{et al.} observed the use of prophylactic antibiotics for 76\% of clean procedures, extended duration of prophylaxis and excessive use of antibiotic combinations at a tertiary hospital in Greece\textsuperscript{35}. Clean-contaminated procedures have a higher incidence of postoperative infections\textsuperscript{41}. Patients undergoing clean-contaminated surgical procedures in the upper aerodigestive tract may require antibiotic prophylaxis and close monitoring. This is
particularly important in patients with postoperative tracheostomy, as was the case in our study. Penel et al. report on a high occurrence of wound infection despite antibiotic prophylaxis. This study identified post-laryngectomy tracheostomy as a major risk factor for SSI and concluded that long-term curative anti-biotherapy must be evaluated in cancer head and neck surgery requiring post-laryngectomy tracheostomy. Lee et al. also found that SSI was significantly higher in patients with tracheostomy.

In contrast to the low incidence of infection, over-administration of antibiotics is a potential risk for antibiotic resistance, increased costs, adverse reactions and development of *Clostridium difficile* colitis. In our study, we had 2 cases of *Clostridium difficile* colitis, so shortest effective regimen should be used.

A clear limitation of this study was a small sample size of patients with SSI in the cohort, which reduced the statistical power achievable. Also, the sample size (N=18) of patients with SSI was too small to yield results that would be statistically significant on multivariate analysis of risk factors.

This study showed that the length of hospital stay was significantly higher in patients with SSI, which is consistent with other authors’ findings. Longer hospital stay may have great impact on health care costs, quality of life and final treatment outcome.

References

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Sažetak

ČIMBENICI RIZIKA ZA INFEKCIJU KIRURŠKOG MJESTA U OPERACIJAMA KARCINOMA GRKLJANA


Infekcije kirurškog mjesta (IKM) predstavljaju značajan čimbenik za obolijevanje i smrtnost u bolesnika operiranih zbog karcinoma grkljana. Cilj ove prospektivne studije koja je obuhvatila 227 bolesnika bio je odrediti incidenciju IKM te utvrditi čimbenike rizika za njezin nastanak. Studija je isključila bolesnike s prethodnom radio- i/ili kemoterapijom. Svi su bolesnici imali poslijeoperacijsku traheostomu, a primali su antibiotičku profilaksu koja je sadržavala cefalosporin, aminoglikozid i metronidazol. Uočeno je da je srednja incidencija IKM 6,5% (18 bolesnika), uz 4 (22,22%) slučaja s površinskom incizijskom infekcijom, 11 (66,22%) s dubokom incizijskom infekcijom i 3 (16,66%) s infekcijom organa ili prostora. Ostale infekcije su bile upala pluća (1 bolesnik) i kolitis prouzročen bakterijom Clostridium difficile (2 bolesnika). Srednje trajanje bolničkog liječenja u bolesnika kod kojih se razvila IKM bilo je dulje od onih bez IKM (33,5 dana prema 16 dana; \(p<0,001\)). Koristeći univarijatnu analizu nađeno je da su ASA skor ≥3 Američke udruge anestezio loga, kirurška intervencija dulja od 120 minuta i NNIS (Nacionalno praćenje nozokomijalnih infekcija) indeks rizika ≥1 značajno udruženi s pojavom IKM. Godine, spol, tjelesna masa, pušenje, dijabetes, duljina prijeoperacijskog boravka u bolnici nisu povezani s IKM. Najčešće izolirani mikroorganizam je bila Klebsiella spp.

Ključne riječi: Kirurška rana, infekcija; Glava i vrat, tumori – kirurgija; Glava i vrat, tumori – komplikacije; Laringealni tumori – epidemiologija; Rizični čimbenici