ORIGINAL RESEARCH PAPER
Volume - 12 | Issue - 05 | May - 2023 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

# THE IMPACT OF SURGICAL SITE INFECTION IN HEAD AND NECK CANCER RECURRENCE (HNSCC).

Oncology

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| **Dr Mohd Aizaz Khan** | Senior Resident, Department Of Surgical Oncology, Vydehi Institute of Medical Sciences |
| **Dr Amritha G Prabha** | Assistant Professor, Department Of Surgical Oncology, Vydehi Institute of Medical Sciences |
| **Dr Uma Sharma** | Senior Resident, Department Of Surgical Oncology, Vydehi Institute of Medical Sciences |
| **Dr Giridhar CM** | Assistant Professor, Department Of Surgical Oncology, Vydehi Institute of Medical Sciences |
| **Dr MS Ganesh** | Professor and Head, Departemnt Of Surgical Oncology, Vydehi Institute of Medical Sciences |
| **Dr Jithin T Chand** | Senior Resident, Department Of Surgical Oncology, Vydehi Institute of Medical Sciences |

## ABSTRACT

**Background:** Surgical site infection (SSI) following head and neck oncological surgery is a well known complication and has been debated to be associated with cancer recurrence. Currently, there is no recent literature discussing association of SSI and HNSCC recurrence. The aim of this study was to evaluate the association between SSI and HNSCC. **Methods:** A retrospective review of 289 patients with HNSCC at our institution between 2018 and 2021. Patients were included if they underwent Primary resection for HNSCC. Data collected included age, sex, primary site, type of surgery and reconstruction, previous treatments, postoperative complications (SSI and reconstructive), Adjuvant treatment and Recurrence. **Results:** The mean age was 51 years (31-77). 63 patients(21.8%) developed SSI. Recurrent disease developed in 51 patients (17.6%). The recurrence rate in patients with SSI was 23.8% (15 patients) while patients without SSI had a recurrence rate of 15 .9 % (36 patients). **Conclusion:** There is association between SSI and adverse cancer outcome, but the cellular link between them remains elusive. SSI may also lead to delays in necessary post op radiation , which can result in an increased of cancer recurrence. A standardized prospective study with appropriate statistical power is justified.

## KEYWORDS

Surgical site infection, Recurrence, Head and Neck Cancer Surgery, Adjuvant treatment.

## INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) includes tumors of the oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx. Overall57.5% of global HNCs occur in Asia, especially in India where itaccounts for 30% of all cancers[1].With 1,19,992 new cases and 72,616 deaths due to oral cancers in 2018, India has the highest oral cavity cancer patients in the world[2]. A main source of perioperative morbidity after HNC surgery is surgical site infection (SSI), which has been consistently reported in over 20% of cases[3]. Post-operative SSI leads to substantial physical, psychosocial, and financial burdens on patients, providers, and hospital systems.[4] Importantly, SSI may also lead to delays in necessary post-operative radiation, which can result in an increased risk of cancer recurrence and decreased over- all survival.[5]While several clinical risk factors for SSI have been identified, many are largely immutable including extent of cancer resection, prior radiotherapy, age, and comorbidity.[6] Risk factors for SSIs have been analyzed in a number of studies and included higher American Society of Anesthesiologists (ASA) score, comorbidities, smoking, alcohol consumption, previous RT or CT, advanced tumor stage, longer duration of surgery, blood loss and/or anemia, hypoalbuminemia and/or malnutrition (weight loss), presence of tracheotomy, flap reconstruction, and clean-contaminated surgery Although different authors analyzed these risk factors, significant disagreements with heterogeneous results exist in the literature.

Despite the use of prophylactic antibiotics and the best pre- and post-operative care, HAIs incidence is still high due to the expanding microbial resistance.[7]

Surgical-site infection (SSI) following head and neck oncological surgery is a well known complication and has been debated to be associated with cancer recurrence. Currently, there is no recent literature discussing association of SSI and HNSCC recurrence. The aim of this study was to evaluate the association between SSI and HNSCC.

## MATERIALS AND METHODS

A retrospective review of 289 patients with HNSCC at our institution between 2019 and 2021. Patients were included if they underwent Primary resection for HNSCC. The subsites included in the study were oral cavity, oropharynx, hypopharynx, , and larynx Data collected included age, sex, primary site, type of surgery and reconstruction, previous treatments, postoperative complications (SSI and reconstructive), Adjuvant treatment and Recurrence. Patients were observed for atleast 1 year. Clinical data including age, sex, postoperative infection (local/regional or distant), site of lesion, tumor stage, adjunctive radiation therapy (preoperative and postoperative), pathologic findings (margins, cervical metastases, and extracapsular lymph node extension), recurrence, and survival were recorded. Primary lesions were staged according American Joint Committee on Cancer (AJCC) criteria. Wound infection(SSI) was defined as purulent discharge or mucocutaneous fistula formation or both during the post operative period.

### Inclusion Criteria

1) Primary Head and Neck SCC
2) Patients treated with curative intent.
3) Patient with purulent discharge or Mucocutaneous fistula or both during post op period
4) No Previous history of cancer in past

### Exclusion Criteria

1) Patient with ulcerative /fungating mass over skin .
2) Non Squamous Cell Carcinoma histology
3) Patients without clear surgical margins

### Statistical Analysis

Data were entered in Microsoft Excel and the categorical data were analyzed by a chi-square test using SPSS (version 16). The association of Surgical Site infection and recurrence of cancer was reviewed and compared. A p-value of $P < 0.05$ was accepted to be statistically significant.

## RESULTS

The mean age was 51 years (31-77 years). Wound infection was present in 63 patients (21.8%). Patient-related characteristics are shown in Table 1. We observed that the frequency of wound infection was higher in male compared to female patients, and this result was statistically significant. The odds ratio 3.52 (95% CI: 1.75–7.07) showed that male patients have more than 3 times higher chances of acquiring an infection than female patients. The age of patients did not

affect the incidence of wound infection.

**Table 1- Distribution Of Patients With And Without Ssi By Different Variable**

| Variable | No of cases with SSI(%) | No of cases without SSI(%) | P value (X2 test ) |
|---|---|---|---|
| Mean age | 63 | 59 | |
| Male | 45 | 162 | |
| Female | 18 | 64 | |
| Stage | | | |
| I | 3(4.8) | 16(7) | 0.46 |
| II | 9(14.3) | 47(20.8) | |
| III | 13(20.6) | 72(31.9) | |
| IV | 38(60.3) | 91(40.3) | |
| | 63 | 226 | |
| Adjuvant Radiotherapy | | | |
| No | 12 | 63 | 75 |
| Yes | 51 | 163 | 214 |
| | 63 | 226 | 289 |

Sixty three patients (21.8%) had developed surgical site infection. This group was comparable to the group of patients without infection regarding age, stage of tumor and adjuvant treatment. Advanced T stage of tumor (T3/T4) with SSI were present in 42 (66.67%) patients .Patients with no cervical lymphadenopathy developed SSI in 38 (60.3%) whereas N1,N2 and N3 disease were 13(20.6%), 8(12.7%) and 4(6.3% ) respectively.

**Table 2- Distribution Of Patients With And Without SSI By Different Variable**

| Variable | No of cases with SSI(%) | No of cases without SSI(%) | P value (X2 test ) |
|---|---|---|---|
| T stage | | | |
| T1 | 5(7.9) | 21(9.3) | 0.44 |
| T2 | 16(25.4) | 55(24.3) | |
| T3 | 15(23.8) | 63(27.9) | |
| T4 | 27(42.9) | 87(38.5) | |
| Total | 63 | 226 | |
| N stage | | | |
| N0 | 38(60.3) | 112(49.5) | 0.32 |
| N1 | 13(20.6) | 59(26.1) | |
| N2 | 8(12.7) | 41(18.1) | |
| N3 | 4(6.3) | 14(6.2) | |
| Total | 63 | 226 | |

Recurrent disease developed in 51 patients (17.6%). The recurrent rates by stage are shown in table 3. The data show an increase in recurrence rates with increase in disease stage that was statistically significant (p=0.032).

**Table 3- Recurrence By Tumour Stage**

| Stage | No of cases(%) | No of recurrences(%) | P value |
|---|---|---|---|
| I | 2(3.9) | 17(7.1) | 0.032 |
| II | 14(27.5) | 42(17.6) | |
| III | 10(19.6) | 75(31.5) | |
| IV | 25(49.0) | 104(43.7) | |
| | 51 | 238 | |

The recurrence rate in patients with SSI was 23.8% (15 patients) while patients without SSI had a recurrence rate of 15 .9 % (36 patients). which also reached statistical significance (p=0.043).The recurrence rates with and without by tumor stage are shown in table 4. The recurrence rates were higher in patients in whom SSI developed irrespective of the disease stage .The advanced stage disease (stage III-IV) was associated with an increased risk of SSI (80.9%) and recurrence 66.7%).

**Table 4- Recurrence By Stage In Patients With And Without SSI**

| Stage | SSI(%) | No SSI(%) | P value |
|---|---|---|---|
| I | 1(6.7) | 1(2.7) | 0.043 |
| II | 4(26.7) | 10(27.8) | |
| III | 3(20) | 7(19.4) | |
| IV | 79(16.7) | 18(50) | |
| | 15(23.8) | 36(15.9) | |

## DISCUSSION

Upfront surgery remains an essential component in the management of HNC. For many patients with advanced oral cavity or laryngeal/hypo pharyngeal cancers, open resection with vascularized flap reconstruction continues to maximize oncologic control. Infection superimposed on surgical trauma and inflammation can also increase the risk of tumor recurrence. Infection results in a greater inflammatory response. Animal models have shown that post-operative infection increases angiogenesis and tumor recurrence[8] . This corresponds to an increase in serum VEGF. Surgical complications are also associated with an increased IL-6 response . Evidence also suggests that bacterial cell-wall components, such as lipopolysaccharide play a role in perioperative tumor growth [9] . Therefore, when infection occurs in the post- operative period, an inflammatory insult is added to the surgical injury. Many studies have been done to show the effect of post operative wound infection on tumor recurrence.

Murthy et al. [10]first described the association of delayed wound healing and systemic breast cancer recurrence. They found that patients had an increased rate of distant metastases, without influence on loco-regional recurrence .Anastomotic leak and intra-abdominal infection is a feared adverse event after surgery for colorectal cancer. Apart from the immediate risk of morbidity and mortality after surgery, it may also have prognostic implications. A meta-analysis has shown that in colorectal cancer, anastomotic leakage and peritoneal infection has a negative impact on tumor recurrence. [11] Infectious complications may also be a risk factor for gastric cancer recurrence .[12]The severity of the complication may also be correlated to the timing of recurrence .

Major infectious complications can occur after lung cancer re- section. These include empyema, pneumonia and mediastinitis. Complications such as these have been shown to be a strongly negative predictor of long-term survival in lung cancer patients [13].Previous reports on patients with SCCHN also have been conflicting. Improved survival was noted in patients who had wound infections after total laryngectomy and radical neck dissection for stage III laryngeal carcinoma by Schantz et al.[14] However, no survival advantage was found for other stages of laryngeal carcinoma. Similarly, in 75 patients with laryngeal cancer, Ramadan and Wetmore [15] demonstrated a favorable effect on the local recurrence rate in patients who had wound infection after total laryngectomy (which was statistically significant)

**Table 5: Association Between Infection And Head And Neck Cancer Recurrence**

| Study | Year | Country | Type Of study | Sample (N) | Recurrence (%) | Infection (N) | Infection &recurrence (N) | Follow up (Months) | Statistical association found |
|---|---|---|---|---|---|---|---|---|---|
| Jackson Rm et a[8] | 1989 | USA | retrospective | 100 | 39(39) | 14(14) | 8(57) | 60 | No |
| Grandis [9] | 1992 | USA | Retrospective | 134 | 68(51) | 29(22) | 14(20.6) | 34 | Yes |
| Rodrigo et al[10] | 1998 | Spain | Retrospective | 158 | 47(29.7) | 14(8.8) | 8(57) | 36 | Yes |
| Ishikawa et al[11] | 2013 | Japan | Retrospective | 108 | 35(32.4) | 24(22) | 11(31.4) | 24 | yes |
| Our study | 2023 | India | Retrospective | 289 | 51(17.6) | 63(21.8) | 15(23.8) | 12 | yes |

Jackson and Rice [16] found an overall higher incidence of tumor recurrence in those in whom postoperative wound infection developed (although not statistically significant), except in stage IV disease, in

which the rates were similar. Similarly, this adverse prognostic effect after excision of supra glottic squamous cell carcinoma has also been documented [17] in 158 patients operated on for supraglottic cancer. All patients had 3,year follow-up. Wound infection developed in 14 patients (8.8%). The overall recurrence rate was 29.7%. For those in whom a wound infec- tion developed the recurrence rate was 57%, compared with 27% for those in whom no such infection developed (p = 0.041)

Moreover, in the larger report to the date (134 patients with SCCHN from all sites), Grandis et al.(18 )found that postoperative wound infection was independently associated with increased recurrence rates and decreased survival, suggesting a possible relationship between local/regional immune function and postoperative infection. Twenty-nine (22%) had local or regional bacterial infections develop postoperatively. Re- currence rates were increased ( P = 0.008) in patients with postoperative wound infections compared with patients who had distant infections, e.g., pneumonia or urinary tract infection, or no infection. Disease-free survival also was adversely affected (P = 0.04)in this group. Both advanced tumor stage and postoperative wound infections were independently associated with decreased survival, with odds ratios of 2:3and 2:4,respectively. Ishikawa et al. [20] found that oral cancer patients who underwent resection and free-flap reconstruction had an increased rate of tumor recurrence and metastasis if they developed a surgical site infection.

## CONCLUSION

There is association between SSI and adverse cancer outcome, but the cellular link between them remains elusive. SSI may also lead to delays in necessary post op radiation , which can result in an increased of cancer recurrence. A standardized prospective study with appropriate statistical power is justified.

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