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Incidence of aspiration pneumonia (AP) and associated risk factors among patients of head and neck squamous cell cancer undergoing chemoradiotherapy

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Abstract
Background: Aspiration pneumonia (AP) is one of most important and underreported complication of chemoradiotherapy in head and neck cancer. Most patients with head and neck cancer develop mucositis & dysphagia during chemoradiation that in turn cause increased risk of aspiration and subsequent pneumonia, which can leads to prolonged hospitalization, treatment interruption or delay, morbidity and mortality. This study designed to find cause -specific incidence of AP, patient and treatment related clinical risk factors and management of AP acquired during chemoradiotherapy.
Material and Methods: It is a prospective study including 84 patients of biopsy proven unresectable head and neck squamous cell carcinoma diagnosed from May 2019 to October 2020 in Tertiary care center of western India. All patients treated with curative intended chemoradiotherapy. Pneumonia acquired during chemoradiotherapy was defined as occurrence of Pneumonia within 90 days of commencement of chemoradiation. CTCAE V3.0 scale for aspiration pneumonia grading was taken.
Result: Among the 84 Patients, 9 (10.71%) patients developed AP during and after treatment. Out of these 9 patients, 7 patients were hospitalized with a median length of stay 7 days. Early diagnosis and prompt use of antibiotics made possible decrease mortality in all hospitalized AP patients and rest two patients with AP developed sepsis which managed in ICU.
Conclusion: Incidence of AP in HNC patients receiving radiotherapy was approximately 10.71%. Significant risk factors associated with increased risk of AP included namely age>55 years, site of tumor like laryngeal and hypopharyngeal, grade 3 dysphagia, poor oral hygiene and habitual alcohol dinking.

Keywords: head and neck cancer, chemoradiation, aspiration pneumonia

Introduction

Background

It is estimated that there are more than half a million new cases of head and neck cancer diagnosed annually worldwide [1]. HNC patients generally treated with surgery and radiotherapy or concomitant chemoradiation. Radiotherapy or concurrent chemoradiotherapy has become standard of care for HNC patients as definitive or adjuvant treatment [2]. Management of locally advanced head and neck cancer remains a challenge because of high recurrence rate. As alternative to surgery with or without adjuvant RT, concomitant chemoradiation alone showed promising results on Locoregional control with survival benefit for all head and neck cancer patients with advantage of organ preservation and better cosmetic outcome. However it also poses risk of significant acute and late toxicities that can have profound impact on survivorship and quality of life among survivors. In RTOG 91-11 clinical trial [3], non-cancer related death were more common among patients treated with chemoradiation than with radiation alone in further follow-up, despite better organ preservation. This suggests patients cured by CRT need appropriate management against the late toxicities.

AP acquired during radiotherapy defined as pneumonia secondary to inhalation of food particles, saliva, contents of gastric regurgitation and other foreign substances within 3 months of commencement of chemoradiotherapy in HNC patients. HNC patients who have undergone definitive chemoradiotherapy tend to have moderate to severe swallowing difficulty, poor oral intake due to mucositis & pretreatment malnourished status during CRT or due to radiation induced fibrosis of pharyngeal musculature after completion of treatment [4]. Patients who have swallowing difficulty may aspirate when trying to eat or drink. Its combination with neutropenia may lead to aspiration pneumonia during CRT. Chemotherapy induced neutropenia, vomiting and weakened immune system usually contribute to increased susceptibility of respiratory infections lead to aspiration pneumonia, sepsis and mortality due to respiratory failure.

Incidence of aspiration rate following CRT for HNC is as high as 68% [5, 9]. It is important for clinicians to assess the risk of aspiration pneumonia In CRT receiving patients and efforts should be done for prevention and early treatment to prevent morbidity and mortality.

This is a prospective study to estimate incidence of AP acquired during CRT and to evaluate its clinical risk factors in HNC patients.

Material and Methods

Between May 2019 to October 2020, 84 patients with locally advanced unresectable head and neck cancer (Stage III & IV) patients received definitive concurrent chemoradiation with and without induction chemotherapy at a tertiary care center of western India. Patients were selected if they had Biopsy proven squamous cell carcinoma, Stage

III & IV, ECOG performance status 0-1, normal hematological profile and normal kidney and liver function. Patients with double malignancy, uncontrolled intercurrent comorbidity, distant metastasis and history of previous treatment with surgery or RT or chemotherapy for any malignancies were excluded. All patients had been signed an informed written consent.

All other variables age, gender, primary tumor site, body mass index, TNM staging defined by AJCC 8th edition, tumor histology, cigarette smoking, alcohol consumption and oral hygiene were noted.

All the patients had a staging CT scan of head and neck, chest X ray, FOL (oropharynx, pharynx, larynx) and tumor biopsy. Following enrolment, patients received cisplatin 30mg/m^2 weekly along with radiation. External beam radiotherapy 66 Gray was delivered (200cGy per fraction per day, fraction given 5 days per week) by a Telecobalt machine using two opposed parallel lateral fields. Patient were evaluated weekly during treatment or more frequently if clinically indicated. Treatment efficacy was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [12]. Toxicities such as mucositis, dysphagia were evaluated by Common Terminology Criteria for Adverse Events version 3.0.

Aspiration pneumonia

Different definitions of aspiration pneumonia were used in previous studies [13, 15]. In this study, symptomatic aspiration pneumonia during CTRT was defined as a clinical condition meeting all of following criteria (1) patients had both symptoms & signs suggesting pneumonia. The subjective symptoms included wet cough, sputum and fever. The objective signs included presence of coarse crackles in the chest or infiltration on chest x-ray or consolidation on chest CT or aspiration observed in modified barium swallow, (2) Clinically suspected AP (delayed swallowing or choking) or by endoscopic or video-fluorographic examination (3) Sputum culture showing no evidence of microorganism causing atypical pneumonia such as Legionella or mycoplasma. CTCAE V3.0 scale for aspiration pneumonia grading was taken (Table 1). Most of patients were having G3 (7 patients) and G2 (2 patients).

Table 1

Aspiration grading (CTCAE v3.0)			
G1	G2	G3	G4
Asymptomatic ("silent aspiration"); endoscopy or radiographic (e.g., barium swallow) findings	Symptomatic (e.g., altered eating habits, coughing or choking episodes consistent with aspiration); medical intervention indicated (e.g., antibiotics, suction or oxygen)	Clinical or radiographic signs of pneumonia or pneumonitis; unable to aliment orally	Life-threatening (e.g., aspiration pneumonia or pneumonitis)
Consider Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L)			

Patients with head and neck cancer often developed aspiration pneumonitis frequently caused by organism colonizing oropharynx and upper airways. Most common microbiological species isolated in sputum specimen Klebsiella pneumonie, Pseudomonas aeruginosa, Haemophilus influenza, Streptococcus pneumoniae, staphylococcus aureus and Beta haemolytic streptococci.

Statistical analysis

The primary endpoints of study were cumulative incidence proportion and incidence of AP during and after treatment with curative chemoradiotherapy for HNC. Mortality rate due to aspiration pneumonia in HNC patients cannot be investigated due to shorter follow-up span of study and initiation of corona pandemic.

Patients taken in account for AP were either spot diagnosis of primary AP or recurrent pneumonia due to dysphagia. Incidence duration was calculated from date of first chemoradiotherapy to next 3 months. Incidence rate, cumulative incidence proportion was calculated as well as corresponding 95% confidence intervals. To study association between demographic, patient's characteristics, treatment characteristics and risk of contingency tables were performed, analyzed and compared using χ^2test. A p-value$\leq$ 0.05 was considered significant.

Results

Data pertaining to patient's baseline and treatment related characteristics are summarized in Table 2.

Table 2: Patient's baseline characteristics

Patients characteristics	Number of patients (%)
Age at diagnosis	
<55 years	47 (58%)
>55 years	37 (42%)
Gender	
Male	70 (83.3%)
Female	14 (16.7%)
ECOG PS	
0	45 (53.6%)
1	34 (40.5%)
2	5 (5.9%)
Primary site	
Oral cavity	18 (21.4%)
Oropharynx	31(36.9%)
Hypopharynx	15 (17.9%)
Larynx	20 (23.8%)
T-stage	
T1	0
T2	9 (10.7%)
T3	40 (47.6%)
T4	35 (41.7%)
N-stage	
N0	5 (5.9%)
N1	32 (38.1%)
N2	44 (52.4%)
N3	3 (3.6%)
Clinical stage	
III	26 (31%)
IVA	55 (65.5%)
IVB	3 (3.5%)

Median age of patients was 52.70years (range 27-70). All 84 patients received chemoradiotherapy along with weekly cisplatin. Dysphagia grade 3 occurred in 21 (25%) patients on at least one time point during 90 days of starting of treatment. Among 84 patients, 9 (10.71%) developed aspiration pneumonia within 90 days of commencement of chemoradiotherapy. Median time from starting of treatment to aspiration pneumonia events occurring was 39 days.). All patients were followed as per study protocol weekly during CRT and monthly after completion of CRT till 90 days. Out of 84, 21 patients developed severe dysphagia (Table 3).

Table 3: Analysis of potential risk factors for aspiration pneumonia

Analysis of potential risk factors Variables	Aspiration Pneumonia N (%)	No aspiration pneumonia N (%)	P-value (χ^2)
Gender			
Male	7 (77.8)	63 (84)	P=0.636 NS
Female	2(22.2)	12 (16)	
Age in years			
≤55	2(22.2)	45 (60)	P<0..030 S
>55	7 (77.8)	30 (40)	
Site			
Oral cavity	0	18 (24)	
Oropharynx	1(11.1)	30 (40)	P<0.008 S
Larynx	4 (44.45)	11 (14.7)	
Hypopharynx	4 (44.45)	16 (21.3)	
Clinical stage			
III	1 (11.1)	25 (33.3)	P=0.173 NS
IV	8 (88.9)	50 (66.7)	
Response to treatment			
Complete	7 (77.8)	40 (53.3)	P=0.163 NS
Incomplete	2 (22.2)	35 (46.7)	
Tube feeding			
Yes	1 (11.1)	22 (29.3)	P<0.247 NS
No	8 (88.9)	53 (70.7)	
Dysphagia ≥ 3			
Yes	8 (88.9)	13 (17.3)	P<0.0000 1 S
No	1 (11.1)	62 (82.7)	
Smoking			
Yes	8 (88.9)	51 (68)	P=0.195 NS
No	1 (11.1)	24 (32)	
Drinking habit			
Yes	7 (77.8)	25 (33.3)	P<0.009 S
No	2 (22.2)	50 (66.7)	

Total 9 (10.71%) patients developed aspiration pneumonia (7 patients Grade 3 & 2 patients Grade 2). In these 9 patients, 8 were having severe dysphagia and 1 was having moderate dysphagia. This was statistically significant (p-value <0.00001). Eight patients had aspiration based on chest x-ray alone or combined with modified barium swallow (MBS) in rest one patient. MBS was requested for one patients because of strong suspicion of aspiration pneumonia but having normal chest x-ray, later aspiration was demonstrated on MBS.

All 9 patients received Broad spectrum antibiotics and supportive care. Out of 9, 7 patients were admitted to cancer ward and in those admitted, and rest two patients had undergone sepsis admitted in ICU. In these two septic patients with aspiration, vigorous treatment initiated including IV fluids, broad spectrum antibiotics covering pseudomonas infection like piperacillin/tazobactem IV 4.5gm 8hrly along with levofloxacin 500mg/100ml IV OD and fluconazole 200mg/100ml, steroids, antiemetic and analgesics. They were able to recover in average 15 days duration. Rest seven patients received inj. ceftriaxone 1gm IV BD along with amikacin 500mg BD for five days followed by oral antibiotics levoflox 500mg OD next 5 days.

Significant risk factors for AP included advanced age>55 years (p-value 0.030), laryngeal & hypopharyngeal tumor (p-value 0.008), severe dysphagia (p-value <0.00001), habitual drinking (p-value<0.009) and poor oral hygiene. Other associated risk factors were gender, advanced clinical stage and smoking but not significant (Table II).

Incidence rate of AP 10.71% (9cases) within 3 months of starting CRT. Cumulative incidence proportions of developing AP 8.33% (7 cases) during CRT.

Discussion

Important goal of treatment in patients with head and neck cancer is not only cure but also preservation of quality of life after treatment. Usually locally advanced HNC carries poor prognosis due to high rate of loco-regional recurrences [16]. Chemoradiation improved loco-regional control & survival because of additive or synergistic effects in expense of increased acute toxicities and late complications caused by chemotherapy due to radio sensitization effect chemotherapy during CRT [17, 18]. There are many factors which play a role in developing of aspiration pneumonia during chemoradiation. Critical structures necessary of deglutition such as tongue, laryngeal and pharyngeal muscles may develop fibrosis due to high radiation dose which may be responsible for abnormal mobility of deglutition muscles, nerve impairment and muscular injury causing generalized weakness, uncoordinated swallowing and may lead to aspiration, dysphagia and stenosis observed following head and neck chemoradiation [19]. Lack of adequate passage of food bolus, poor hypopharyngeal transit, pharyngeal stasis, loss of supraglottic sensation for food clearing and inadequate closure of glottis also play a role [20]. Many other factors which may explain why aspiration during CRT may lead to pneumonia [5, 10, 11, 13]. Radiation induced xerostomia [21, 22] reduces salivary flow and allows proliferation of gram negative bacteria which are normally cleared with swallowing. Weakened immunity [23], diminished swallowing reflex [24] either age related or radiation induced, multiple comorbidities, mucositis and neutropenia increases chances of developing florid aspiration pneumonia and sepsis. Patients who develop fever with neutropenia during CRT for HNC should be treated for aspiration pneumonia even if chest x ray was normal because of possible delayed radiographic appearance [25, 26]. Broad spectrum antibiotics should be used for aspiration pneumonia [27, 28]. Most of patients diagnosed having aspiration pneumonia based on chest X ray alone, some of them having no findings on chest x ray, undergone MBS (2 patients) [29, 31].

The current study revealed incidence of AP 8.33% during

chemoradiation. In previous studies reported incidence of AP ranges from 5% to 25% [6, 8, 11, 32]. Eisbruch *et al* [5] performed video fluoroscopic swallow studies following CRT in HNC and reported 23% of their 29 patients treated with CRT (radiation concurrent with gemcitabine weekly) develop aspiration pneumonia within 14 months of completing their treatment. Pauloski *et al* [20] performed video fluoroscopic swallow studies. Patients having dysphagia during radiation had larger residue and higher rate of aspiration (22%) during swallowing study compared to ones with no dysphagia (3%).

Nguyen *et al* [6] reported that dysphagia and aspiration more often develop in patients who undergo CRT compare to RT alone. According to Mortensen HR *et al* [13] study, severe dysphagia occurred in 32% of 324 patients included in study and 5.3% of 324 patients developed AP within first year after RT with or without concurrent weekly cisplatin. Chin Nan Chu *et al* [9] reported incidence of AP in HNC patients during RT was approximate 5%. A larger Taiwanese retrospective study [32] of 15894 HNC patients reported only 5% incidence of pneumonia, most commonly associated with aspiration within three months of treatment. A recent population based study of 93,663 patients who underwent surgery for HNC found only 2% rate of AP [33]. Hunter *et al* [34] reported 15% of their 72 patients with locally advanced oropharyngeal cancer treated with IMRT concurrent weekly paclitaxel/carboplatin developed AP within 24 months of treatment.

Beibei Xu *et al* [35] retrospective study reported 1 and 5 year cumulative incidence of aspiration pneumonia was 15.8% and 23.8%. This study concluded significant risk factors (p<0.05) for AP was male gender, older age, associated comorbidities, hypopharyngeal tumors, no surgery prior to RT.

Sadayuki Kawai [36] *et al* study reported 21% two year cause specific cumulative incidence by CRT along with five independent risk factors namely habitual alcohol intake, use of sleeping pills, poor oral hygiene and co-existant other malignancies. Latest retrospective study by Hiromichi Shirasu *et al* [13] reported 95 patients (25.4%) developed Aspiration pneumonia among 374 patients during CRT in HNC patients and identified four independent risk factors namely poor oral hygiene, high N-classification, hypoalbuminemia and inpatient treatment.

In our study, we identified five independent risk factors for AP advanced age (>55year), poor oral hygiene, tumors involving larynx and hypopharynx, dysphagia grade3 or more and alcohol consumption similar to other studies.

Previous studies indicated that alcohol suppressed cough reflex, reduced consciousness and increased gastro-esop hageal reflex therefore habitual alcohol consumption may be involved in occurrence of AP [37]. Early initiation of swallowing exercises, speech therapy and better conformal radiation technique may prevent incidence of aspiration pneumonia.

Our study has several limitations such as retrospective study with limited number of patients, sometimes it is difficult to differentiate aspiration pneumonia during CRT from other types of pneumonia like due to immunocompromised status based on clinical manifestations or radiological patterns and definitions of AP varied among previous reports, shorter duration of follow up and conventional radiation rather than conformal lead to more fibrosis of pharyngeal musculature [38, 39]. Our predictive model may be more useful in identifying patients at high risk for AP so that preventive measures can be taken at early phase.

Conclusions

We investigated incidence and identified risk factors for aspiration pneumonia within 3 months of commencement of CRT in head and neck cancer patients. Estimated incidence was 8.33% during CRT. Prediction of aspiration pneumonia may extend life expectancy and quality of life in HNC patients.

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