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Late toxicities among laryngopharyngeal cancers patients treated with different schedules of concurrent chemoradiation at a rural tertiary cancer care center

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Abstract

Background: Concurrent chemoradiation is the treatment of choice for laryngeal-pharyngeal cancers. Apart from survival organ preservation remains major aims of the treatment. Advanced radiation techniques like VMAT have shown to reduce morbidity. The purpose of our study is to assess the late toxicities in patients treated with concurrent chemoradiation and its association with dose to organs at risk. **Aims:** Assessment of late toxicities following concurrent chemoradiation in patients with laryngopharyngeal cancers. **Materials and Methods:** Retrospective study at a tertiary cancer centre on patients with laryngeal and pharyngeal cancers treated with concurrent chemoradiation with VMAT upto a total dose of 69.3 -70 Gy in 33-35 fractions and concurrent chemotherapy with Cisplatin was done. Severe late toxicities and its association with demographic and clinical parameters and dose to OAR were studied. Data was analysed using EpiData analysis v2.2.2.182. **Results:** Of the 93 patients studied majority were males above 55 years. Oropharynx was the commonest site (58%) with T3 and N2 in majority. Late dysphagia and odynophagia was seen in 18(21%) and 23(27%) patients respectively. 16 (17%) had tube dependence and nine (9.6%) had aspiration pneumonia. D60,V50 and V60 along with site , node positivity and weight loss were found to be significantly associated with severe late toxicity. **Conclusion:** Oropharyngeal cancers, node positivity and weight loss were found to have significant grade III and above toxicities including tube dependency. Dose to larynx showed association with severe late toxicities, though dose to constrictors could not.

Key words: Chemoradiation, cisplatin, toxicities, tube dependency

Introduction

Laryngopharyngeal cancers comprise 1%–2% of all cancers worldwide. Pharyngeal cancers (excluding nasopharynx) account for 6.6% and laryngeal cancers 4.8% of all cancers in men and 0.5% and 1% in women, respectively.[1] In India, head-and-neck cancers are one of the most common cancers among males. As per the cancer registry reports, the incidence of the hypopharynx and laryngeal cancers are age-standardized rates-2.1–6.1 among males and 0.3–1.8 among females and 3.5–9.7 among men and 0–1.3 among women, respectively.[2]

Concurrent chemoradiation (CT-RT) is currently the standard of care in laryngopharyngeal carcinomas.[3] CT-RT has been shown to be better than sequential radiotherapy (following induction chemotherapy) and radiotherapy alone regarding preservation of larynx.[3,4]

CT-RT schedule using cisplatin (CDDP) 100 mg/m^2 3 weekly, is commonly used.[4-7] The addition of chemotherapy to external beam radiotherapy is often associated with increased toxicity and affects patient compliance. Unlike acute toxicities which can be managed symptomatically, late toxicities are often underestimated and ill-managed. During CT-RT for laryngeal and pharyngeal cancers, structures involved in deglutition receive higher radiation doses. This can cause dysphagia, stenosis/strictures or recurrent episodes of aspiration and patient becomes dependent on feeding tube.[5,6] CT-RT causes laryngeal edema, stridor, or cartilage necrosis and this necessitates tracheostomy or laryngectomy.[7]

Due to poor tolerance observed with the CDDP 100 mg/m^2, some institutions administer weekly CDDP of 30 mg/m^2 or 40 mg/m^2.[8,9] Various radiotherapy schedules (conventional fractionation, hyperfractionation, simultaneous integrated boost, concomitant boost technique, etc.) are used in the treatment of laryngopharyngeal cancers. However, studies showing inter-comparison between different chemo-radiation schedules and the associated toxicities are few.[8]

In this retrospective study, we have assessed the acute and late toxicities of CT-RT on laryngopharyngeal cancer patients and tried to analyze the factors associated with late toxicities in particular. The dose received by constrictors and larynx and their association with late toxicities also were also analyzed.

Methodology

In this retrospective cohort study, laryngopharyngeal cancer patients treated with CT-RT using volumetric modulated arc therapy technique (VMAT) were studied from January 2012 to December 2015. The study was conducted during June 2016–November 2016. The study was approved by the Institutional Review Board-Ethics Committee (IRB no 1616/IRB-SRC/13/MCC/11–06–16/6.). Approval was obtained from the Union Ethics Advisory Group, Paris, France also.

The patients with nasopharyngeal carcinoma, patients treated with techniques other than VMAT, patients who were on feeding tubes and those who had to undergo tracheostomy before the start of RT were excluded.

Locally advanced laryngopharyngeal cancers (T3, T4 [excluding cartilage invasion] and node positive) were treated with CT-RT. Radiotherapy was delivered by VMAT using conventional fractionation or simultaneous integrated boost technique. Patients with the Eastern Cooperative Oncology Group performance Status I were selected for CT-RT. Patients

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were treated up to a total dose of 70 Gy in 35 fractions or 69.3 Gy in 33 fractions, with cisplatin 40 mg/m^2 weekly or 100 mg/m^2 3 weekly.

After diagnosis and staging workup, treatment plan was concurred in the multispecialty board. All patients were seen by dietician and speech and swallowing therapist and cardiology, pulmonology, dental and ear-nose-throat (with audiogram) consultations were done before starting treatment. Immobilization with thermoplastic mold on an all in one board was done, and contrast-enhanced computed tomography (CT) scan was done with a slice thickness of 2.5 mm on CT simulator (GE Optima). Organs at risk (OAR) and target volume delineation are done as per the radiation therapy oncology group (RTOG) contouring guidelines. Radiation planning was done with VMAT on treatment planning system (TPS), Eclipse Version 10. After plan approval and patient-specific quality assurance tests, treatment plan was transferred to the linear accelerator (Varian ClinaciX) and treatment was executed.

During CT-RT, patients were reviewed by oncologists weekly with blood investigations. Weight and acute toxicities were documented in the radiation records. They were also reviewed by speech and swallowing therapist and dietician once a week. After completion of chemoradiation, patients were followed up at regular intervals by oncologists, speech, and swallowing therapist and dietician. Videofluoroscopy and fiberoptic endoscopic evaluation of swallowing test were done to assess the swallowing function. First follow-up after 2 weeks and the second review at 6 weeks of completion of radiation therapy was done. At 6 weeks direct laryngoscopy and pharyngoscopy was done followed by once in 6 months or early if symptomatic. Patients are followed up two monthly till 6 months, three monthly till 3 years, six monthly from 3 to 5 years and yearly thereafter. The toxicities are recorded as per Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03, June 14, 2010. US Department of Health and Human Services. National Institutes of Health National Cancer Institute.

Demographic (age, sex, co-morbidities) and clinical (tumor, node, metastasis staging, treatment schedules, weight loss, doses delivered to larynx, constrictors, acute and severe late toxicities, and dose to OAR) variables were collected from patient case records, radiation charts and TPS without the name or any other personal identifiers.

Data entry and analysis

Double data entry and validation were done in EpiData entry version 3.1. Any discrepancy in data entry was resolved by referring to the original data abstraction form. The final validated dataset was imported into EpiData analysis v2.2.2.182 (EpiData Association, Odense, Denmark) for analysis. Descriptive statistics such as proportions were used to summarize incidence of toxicities. Inferential statistics such as Chi-square and *t*-test were used to investigate factors associated with severe late toxicities.

Results

A total of 93 patients with laryngopharyngeal cancers treated with CT-RT were included in the study. Among them, 71 (87%) were aged 55 and above, majority were males. Oropharynx was found to be the common site (58%). The majority had T3 tumors (52%) and N2 disease (39%). About one-third (37%) of the patients received a chemotherapy schedule of 40 mg/m^2 weekly, whereas 31% received 100 mg/m^2 thrice weekly. More than two-third of the patients received 69.3 Gy/33 fractions with simultaneously integrated boost schedule as shown in Table 1.

Overall, tube dependence was seen in 16 (17%) patients. Around 35% of the patients had acute Grade III dysphagia and odynophagia. Late dysphagia and odynophagia were seen in 15 (16%) and 21 (23%) patients, respectively. Aspiration pneumonia was witnessed in 20 (21%) patients. However, Grade III late dysphagia and tube dependency did not show any significant association with dose to constrictors (Mean dose, D60, D50, V60, and V30).

Grade III Laryngeal edema was seen in 11 (12%) patients. Posttreatment tracheostomy was done in 10 (11%) patients. On dosimetric analysis, the dose to 60% volume of the larynx (D60), Volume of larynx receiving 50 Gy (V50) and 60 Gy (V60) were found to be significantly associated with severe late toxicity. Necrosis of cartilage and laryngectomy occurred in 2 (2%). Stricture at the level of cricopharynx to esophagus was found in 6 (7%) patients. More than 10% weight loss was seen in one-third (34.4%) of patients. Other factors found to be significantly associated with severe

Table 1: Demographic and clinical characteristics of patients with laryngopharyngeal cancers treated with concurrent chemo-radiation at a tertiary cancer care center in Northern Kerala, India during 2012-16

Characteristics	*n* (%)
Total	93 (100)
Age group	
35-44	6 (6)
45-54	16 (17)
55-64	46 (50)
65 and above	25 (27)
Gender	
Males	89 (96)
Females	4 (4)
Cancer site	
Larynx	19 (20)
Hypopharynx	20 (22)
Oropharynx	54 (58)
Stage of primary tumor	
T1	6 (6)
T2	27 (29)
T3	48 (52)
T4	12 (13)
Nodal stage	
N0	26 (28)
N1	29 (31)
N2a	36 (38)
N3	2 (2)
Dose of chemotherapy	
40 mg/m^2 weekly	34 (37)
100 mg/m^2 weekly	29 (31)
Carboplatin	30 (32)
Type of radiotherapy	
69.3 Gy/33 fractions	63 (68)
70 Gy/35 fractions	29 (32)

[#]Fractions of radiotherapy. CDDP=Cisplatin

Table 2: Factors associated with severe late toxicities in patients with laryngopharyngeal cancers treated with concurrent chemo-radiation at a tertiary cancer care center in Northern Kerala, India during 2012-16

Characteristics	Severe late toxicity, *n* (%)	*P*
Age group		
<55	6 (6)	0.6
55-64	16 (17)	
65 and above	10 (11)	
Sex		
Male	28 (30)	0.7
Female	1 (1)	
Site		
Oropharynx	16 (17)	0.02
Larynx	8 (9)	
Hypopharynx	10 (11)	
T stage		
T1 and T2	7 (8)	0.29
T3	18 (19)	
T4	4 (4)	
N stage		
Node negative	4 (4)	0.04
Node positive	25 (27)	
Chemotherapy		
40 mg/m^2	11 (12)	0.8
100 mg/m^2	10 (11)	
Radiation dose		
69.3/33$^{\#}$ (SIB)	21 (23)	0.6
70 Gy/35$^{\#}$ (sequential)	8 (9)	
Weight loss		
Grade II weight loss	10 (11)	0.02
Grade III weight loss	16 (17)	
Dose to larynx		
Mean dose to larynx	72 (54-73)	0.4
Dose to 30% volume of larynx	72 (54-73)	0.1
Dose to 60% of volume of larynx	71 (46-72)	0.02
Volume of larynx receiving 50 Gy	100 (74-100)	0.03
Volume of larynx receiving 60 Gy	99 (56-100)	0.01
Dose to constrictors		
Mean dose to constrictor	65 (61-71)	0.32
Dose to 30% constrictor	72 (71-74)	0.28
Dose to 60% of volume of constrictor	70 (61-71)	0.38
Volume of constrictor receiving 50 Gy	94 (81-100)	0.2
Volume of constrictor receiving 60 Gy	76 (65-98)	0.4

$^{\#}P<0.05$. SIB=Simultaneous integrated boost

late toxicity were site, node positivity, and weight loss as shown in Table 2. Twenty-six percent of patients on CDDP (40 mg/m^2 dose) completed six cycles, whereas 60% completed at least five such cycles of chemotherapy. Only one patient could complete all three cycles of cisplatin at a dose of 100 mg/m^2, and three-fourth could complete two such cycles.

About 84% of patients receiving 69.3 Gy/33# completed treatment without any break. Only 2 (3%) patients had break longer than 7 days. Among patients receiving 70 Gy/35#, 72% completed without any break and none had a break more than 7 days.

Reasons for RT break and chemotherapy break were aspiration pneumonia (14%), poor compliance (8%), Grade III vomiting (2%), deranged RFT (8%). Less than 5% of patients had Grade III and above hyponatremia, Grade III skin reaction and febrile neutropenia. Association of compliance to treatment with age was also analyzed**.** Treatment compliance was found to be better in patients with age <65 years. One patient with age <45 years had break for >10 days.

Discussion

Concurrent chemo-radiation is a globally accepted organ preservation protocol in laryngopharyngeal cancer treatment.[3] The concern over early and late toxicities of this protocol has been a subject of long-standing debates and discussion. The factors contributing to the toxicities need to be identified so that precautions can be taken to reduce the morbidity. The demographic and clinical characteristics, dosimetric data, schedule of concurrent chemotherapy, and its association with toxicities have been analyzed.

This study to assess the treatment-related toxicities in laryngeal and pharyngeal cancers treated with CT-RT using VMAT is one of the few reported in the Indian population. In this study, overall 31% of patients had severe late toxicity. Compared to other sites oropharyngeal primaries had statistically significant association with late toxicities. The probable reason may be that oropharyngeal cancers had higher T and N stage compared to the other two sites. In laryngeal and hypopharyngeal cancers, patients with T4 disease were treated with surgery as per the Institutional protocol.

Dose to larynx D60, V50, and V60 showed a statistically significant association with severe late toxicities. This may be due to large volume tumors at presentation leading to the larger target volume.

In our study, the incidence of severe late dysphagia was 16% and the tube dependence for more than 6 months was 17%. However, dose to constrictors (mean dose, D60, D50, V60, and V30) is not related significantly. Various studies on morbidity analysis of concurrent CT-RT in locally advanced head-and-neck cancers have shown that the incidence of tube dependence for 6 months and 12 months as 36% and 17%–30%[10-13] However, the dosimetric correlation with tube dependency has not been described so far.

Aspiration pneumonia was witnessed in 20 (21%) patients. More than 10% weight loss was seen in 16 (17%) of patients. Many studies have reported median weight loss during treatment as a percentage of initial weight and it was reported to be 10%–12%.[14-16] The possible relation of weight loss and aspiration pneumonia has been hypothesized by Nguyen *et al*.[5]

In this series, for the weekly schedule of chemotherapy, 60% of patients completed five cycles. For the 3 weekly schedules, only one patient could complete all three cycles of chemotherapy and three-fourth could complete at least two such cycles. This is in contrast to the data available from the RTOG 0129 trial.[17] Failure to complete the planned number of chemotherapy cycles were due to the presence of poorer prognostic factors. In our series, most patients had high volume disease that warranted irradiation of larger volume of tissues. In addition, poor nutritional status when compared to the western population may also be a factor. Optimization of nutritional status and aggressive nutritional therapy may be required to improve the CT-RT completion rates and reduction in morbidity rates.[18]

84% and 72% of patients receiving 69.3 Gy/33# and 70 Gy/35# completed the schedule without any break. Only 2 (03%) patients had a break longer than 7 days. The causes of treatment interruptions were aspiration pneumonia, poor compliance, and Grade III acute toxicities of vomiting and hyponatremia. Tejpal *et al*. have reported a study using low weekly dose of cisplatin in concurrent chemoradiation in advanced head and neck cancers in the Indian scenario.[18] In this study, an interruption rate of 15% was reported. Hospitalization for supportive care was required in 7.5% of patients. Only 2% of patients dropped out of the treatment and these were unrelated to treatment.

Being a retrospective analysis, the inherent biases and shortfalls are well kept in consideration. First, it is likely that many factors which significantly predicted the morbidity could have been missed out. Second, missing entries on various morbidities with their grades have led to ineligibility for inclusion in the analysis.

Conclusion

In concurrent chemoradiation for organ preservation protocols of laryngeal and pharyngeal cancers though VMAT as radiotherapy technique can be incorporated with an attempt to reduces the morbidity, nutritional management, and prevention of weight loss along with early diagnosis may also be helpful in the prevention of significant toxicity. The major drawback is that GTV was not considered separately for its influence on the toxicity apart regular drawbacks of retrospective analysis. The study may guide for future prospective studies on dosimetric analysis with respect to morbidity.

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Conflicts of interest

There are no conflicts of interest.

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