Original Article

Do we need to spare central nervous system structures during head and neck cancer intensity modulated radiotherapy?

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ABSTRACT

Background: Fatigue has always been a distressing symptom for patients of head and neck cancer (HNC) on radiotherapy. Although modern technologies like intensity modulated radiotherapy (IMRT) have been instrumental in reducing many of the distressing side-effects but the recent observation of increased fatigue has been a concern. Recent publications though very few hinted at possible correlation with dosage to central nervous system (CNS) structures. The current resource review highlights a very preliminary example of a futuristic approach. **Materials and Methods:** This retrospective analysis comprising of 20 HNC patients receiving either postoperative or radical radiotherapy by IMRT were evaluated with CNS dosage. The main organs contoured in planning computed tomography (CT) scan were brainstem (BS) and posterior fossa (PF) excluding BS. The dose received to these organs was recorded. The literature reported CNS structure dosage, which can probably cause increased fatigue was assessed. **Results:** Among the 20 nonnasopharyngeal HNC, 13 received radical radiotherapy and 7 had postoperative radiotherapy. Six patients had treatment gap varying between 2 and 10 days, mostly due to hematological toxicities and oral mucositis. The median volumes of PF and BS were 263.5 and 25.1 cc. Dmax for BS and PF ranged between 4.8 and 44.76 Gy and 23.8–63.2 Gy and the median Dmean for PF was 8.89 Gy. **Conclusion:** Future prospective analysis with inclusion of modified brief fatigue inventory scale and dosimetric evaluation of CNS structures would probably answer the necessity of sparing CNS structures and spare patients from excessive fatigue and related consequences.

Key words: Central nervous system dosage, fatigue, head and neck cancer, intensity modulated radiotherapy

INTRODUCTION

Since last 10 years intensity modulated radiotherapy (IMRT) has become a standard of care in the management of head and neck cancer (HNC). The prospective randomized data are favoring better toxicity profile and in the long-term an improved quality of life (QOL) has been the biggest boon.[1]

Fatigue is a known occurrence among HNC patients and factors like younger age, advanced stage, associated depressive symptoms and re irradiation have all been implicated.[2] The patterns of symptomatology although differ between survivors and nonsurvivors of HNC. A recent article analyzed these issues and among the survivors there is improvement in different symptoms over time and European Organization for Research and Treatment of Cancer (EORTC) QOLQ-C30 and H and N35 were able to address these issues.[3,4] The dosimetric evaluation, especially related to radiotherapy technique has not been assessed in detail. Especially with IMRT newer organs at risk (OAR) and their acute and late effects have become paramount in deciding patients overall QOL. Though incidental, but an important finding from PARSPORT trial was excessive fatigue among IMRT patients. Gulliford *et al*. have analysed the dosimetric explanation in this group of patients.[5]

This preliminary resource review attempts at evaluating dosimetric parameters of the central nervous system (CNS) structures among 20 nonnasopharyngeal cancer patients undergoing IMRT.

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MATERIALS AND METHODS

Twenty patients of HNC receiving postoperative ($n = 7$) and radical radiotherapy ($n = 13$) with IMRT were retrospectively reviewed. There were 4 females and 16 male patients. The median age of the patients was 57.5 years. The primary disease sites were oral cavity,[6] oropharynx,[5] larynx[5] and hypopharynx.[1] The details of the diagnosis of these 20 patients are given in Table 1. The IMRT dose planned was between 60 and 70 Gy with conventional fractionation and concurrent chemotherapy as per high-risk features. The OAR concerned was delineated in radiotherapy planning scans. Standard contouring guideline was followed while contouring brainstem (BS) and posterior fossa (PF) excluding BS.

From the approved IMRT plans of these patients' volumes of BS and PF and maximum dose received to them as well as the mean dose received to PF were noted. The radiotherapy review charts for these patients and also the hospital electronic database were looked for to identify any treatment break, grade 3 or more mucositis and oral infection, hospitalization and other adverse events. The adverse events and treatment breaks were an indirect sign of excessive fatigue as has been reported by various literature.

RESULTS

Among the 20 nonnasopharyngeal HNC, 13 received radical radiotherapy, and 7 had postoperative radiotherapy. Fourteen patients received concurrent chemotherapy with 11 out of them received cisplatin. There were three patients who had neo-adjuvant chemotherapy as well. Six patients had treatment gap varying between 2 and 10 days, mostly due to hematological toxicities and oral mucositis. These details are elaborated in Table 2.

The median volumes of PF and BS were 263.5 (range: 157–350) and 25.1 (range: 21–40.2) cc respectively. Dmax for BS and PF ranged between 4.8 and 44.76 Gy and 23.8–63.2 Gy respectively. Similarly, the Dmean for PF ranged between 1.5 and 21.15 Gy and median of D mean was 8.89 Gy. The details of these are given in Table 3. There were 6 out of 20 patients who had treatment break varying between 2 and 10 days excluding Saturdays and Sundays (conventional fractionation was 5 fractions per week from Monday to Friday). The reasons for treatment interruption were excessive generalized weakness in all of them and it was secondary to either extensive mucositis more than grade 3 or low blood counts. In addition, three patients had hospitalization due to inadequate oral intake and repeated oral infections.

When the individual six patients with treatment break were reviewed, four of them had PF Dmean more than 10 Gy and BS Dmax over 40 Gy. The same has been found in the recent Gulliford *et al*. article from patients of PARSPORT trial.[5]

DISCUSSION

Gulliford *et al*. in their retrospective analysis of PARSPORT data have concluded "the excess fatigue reported in the IMRT arm of the trial may, at least in part, be attributed to the dose distribution to the PF, cerebellum and BS."[1,5] This aspect of cancer related fatigue is definitely a new observation.

Cancer related fatigue although has been reported in several literature. Age, concurrent chemotherapy, low hemoglobin percentage and comorbidities have all been documented to be instrumental in causation. In 1998 Smets *et al*. have indicated that baseline pain and disease related disability can cause long-term fatigue among cancer patients.[6] The depression and fatigue symptoms increase during radiotherapy and about 50% patients of HNC experience them.[7,8]

The prospective documentation of fatigue among HNC patients have already been validated with modified brief fatigue inventory (MBFI) scale.[9] The scale actually analyses various aspects of cancer-related fatigue with common questionnaires in Likert pattern. It is easy to administer and can record fatigue objectively. Compared to fatigue specific scale, QOL scales like EORTC QLQ-C30 and QLQ-H and N35 questionnaires also reports about improvement in fatigue over time.[4,5,10] Different scales have also identified concurrent chemoradiation to be responsible for increased fatigue among HNC patients.[11] A recent Indian study also supported EORTC QLQ-C15-PAL questionnaire and reported median score of 50 for fatigue.[8]

Table 1: Details of the diagnosis

Patient number	Diagnosis
1	Ca Right PFS cT4N2
2	Ca BOT cT4N3
3	Ca Tongue cT4N1
4	Ca BOT cT3N1
5	Ca Supraglottic larynx cT3N1
6	Ca Larynx pT4N0
7	Ca Tongue pT1N1
8	Ca BOT cT3N2c
9	Ca Larynx cT3N1
10	Ca Tongue rcT2N2c
11	Ca lip pT1N1
12	Ca Tongue rpT1N0
13	Ca Larynx cT1N0
14	Ca Supraglottic larynx pT4N1
15	Ca Tongue rpT2N0
16	Ca BOT cT4N1
17	Ca Tongue pT2N0
18	Ca Left BM pT1N2
19	Ca Left tonsil cT4N2c
20	Ca Right BM

PFS: Pyriform sinus, BOT: Base of tongue, BM: Buccal muosa

Table 2: Demographic profiles of the patients

Patient/disease characteristics	Value
Diagnosis	Oral cavity Lip: 1 Buccal mucosa: 2 Tongue: 6 Oropharynx BOT: 4 Tonsil: 1 Larynx Glottic: 3 Supra-glottic: 2 Hypopharynx PFS-1
Age	Range: 32–77 years Median: 57.5 years
Gender	Male: 16 (80) Female: 4 (20)
Stage	Early stage: 3 (15) Locally advanced: 17 (85)
Radiotherapy intent	Radical: 13 (65) Postoperative: 7 (35)
Radiotherapy dose	70 Gy/35 fractions: 13 (65) 64 Gy/32 fractions: 3 (15) 60 Gy/30 fractions: 4 (20)
Chemotherapy	Concurrent chemotherapy: 14 (70) Cisplatin: 11 Carboplatin: 3 Neo-adjuvant chemotherapy: 3
Treatment gap	Yes: 6 No: 14 Reasons for treatment gap Haematological toxicity: 3 Mucositis: 3

BOT: Base of tongue, PFS: Pyriform sinus

Table 3: Dosimetric characteristics

Characteristics	Value
PF dose max (Dmax) (in Gy)	Range: 23.8–63.2 Median: 46.72
PF mean dose (Dmean) (in Gy)	Range: 1.5–21.15 Median: 8.89
PF volume (in cc)	Range: 157–350 Median: 263.5
BS Dmax (in Gy)	Range: 4.8–44.76 Median: 37.41
BS volume (in cc)	Range: 21–40.2 Median: 25.15

PF: Posterior fossa, BS: Brainstem

The uniqueness of Gulliford *et al*. study was the dosimetric explanation of excessive fatigue among HNC IMRT patients. Recently, Powell *et al*. also analyzed the fatigue and dosimetric correlation among nasopharyngeal patients and basal ganglia, pituitary and cerebellum were additional OAR with significance to grade 2 fatigue been established.[12] We believe that our short and preliminary report among 20 Indian HNC patients and dosimetric data of BS and PF was encouraging in view of its uniqueness and international similarity to published literature. The challenge would be to a prospectively document fatigue with validated MBFI and correlate them with a dose received to CNS structures. The meticulous target delineation of the CNS OAR and their effective sparing, if attempted can reduce cancer related fatigue among HNC patients. This might help in reducing untoward side effects of the treatment and will result in compliance and better outcome.

CONCLUSION

Fatigue and dosimetric explanation of the same among HNC patients is an ideal option for future IMRT planning. The validation with MBFI would rather answer many patient felt needs and probability of them can be identified at baseline. Prospective studies with large sample size and serial MBFI measurement and dosimetry of CNS structures is the need of the hour.

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