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Acute and Late Toxicities of Hypofractionated Radiotherapy with Concurrent Cisplatin for Treatment of Stage II to IVA Head and Neck Cancer

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ABSTRACT
Objective to assess acute and late toxicities of hypofractionated radiotherapy with concurrent cisplatin for treatment of stage II to IVa head and neck cancer. The present prospective study was conducted in department of Radiotherapy, Pt. JNM medical college and Regional cancer center (RCC) of Dr. BRAM Hospital Raipur. In our study in 6 weeks - skin reaction are-46.3% cases of grade II and 36.5% cases of grade III. Mucositis are- 46.3% cases of grade II and 31.7% cases of grade III. salivary gland toxicity are-44 % cases of grade II and 31.7% cases of grade III. dysphagia are-48.7% cases of grade II and 31.7% cases of grade III. Maximum cases have grade 2 followed by grade 3 toxicities. It is due to low immunity in the last week of radiation, absorbed radiation dose is more than tolerance dose of mucosa it is associated with superadded infection we have found that most of the acute toxicities regressed over 3-4 months at 6th month there is development of late radiation fibrosis and xerostomia.

INTRODUCTION

Radiotherapy and Surgery are the only curative treatments for head and neck carcinomas. Although chemotherapy alone is not curative, it enhances the effects of radiotherapy and is routinely used as part of combined modality treatment in patients with stage III or IV disease in concurrent setting and neoadjuvent setting in some subsites.

Non Metastatic Head and Neck Cancers (Stages I–IVB)

- Goal of treatment is to achieve maximum cure rates with minimum morbidity
- Since head and neck cancers have implications for speech and swallowing, an attempt is made at organ preservation

Non surgical protocols showing similar cure rates as surgery.

Stage I/II (Early): Single Modality Treatment (Either Surgery or Radiotherapy)

- Surgery is preferred to radiotherapy as a single modality in
- Sites where surgery is not morbid (cosmetically and functionally), e.g. oral cancers
- Accessible lesions
- Lesions involving or close to bone to minimize radiotherapy related bone damage
- Young patients (to keep radiotherapy in reserve in case of a second primary)
- Radiotherapy is preferred over surgery as a single modality when
- There is impairment of function/cosmesis with surgery, e.g. base of tongue
- Surgery is technically difficult with high morbidity and poor results, e.g. nasopharynx
- There is a high risk for surgery
- Radiotherapy can be external, brachytherapy or combined external beam with brachytherapy

Stage III/IVA (Advanced): Multimodality Treatment

- Options
- Surgery followed by adjuvant post-operative radiotherapy (PORT) or postoperative chemo-radiotherapy (POCRT)
- Definitive radiotherapy (RT) or concurrent chemo-radiotherapy (CCRT) [ordinarily using platinum-based chemotoxic agent(s)]
- Radiotherapy with cetuximab in case CCRT is not feasible, followed by planned (when indicated) or salvage surgery (in case of relapse)
- Primary surgery is preferred in oral and paranasal sinuses due to involvement/proximity of bone
- Primary chemoradiotherapy (CRT) is preferred in lesions suitable for organ preservation in the laryngopharynx, oropharynx and nasopharynx

Stage IVB:

- Primary CRT when surgery is not possible[6].

Conventional fractionation-Multiple daily fractions of 1.8-2 Gy .In head and neck cancer 70Gy in 35 fractions 2 Gy per fraction daily for 5 days in a week in 7 weeks is most common used.

Hyper Fractionation: In head and neck cancer a hyperfractionated schedule of 80.5Gy in 70 fractions 1.15Gy twice daily in 7weeks is used.

Accelerated Treatment:

- Alternative to hyper fractionation
- Rationale–To reduce repopulation in rapidly proliferating tumors by reducing overall treatment time
- Pure accelerated treatment–same total dose delivered in half the overall time by giving 2 or more fractions per day
- Impure accelerated treatment–dose is reduced or rest period is interposed in the middle of treatment
- Comparison of head and neck cases accelerated regimen 72Gy in 45 fractions 1.6 Gy in 3 fractions daily in 5weeks with 70Gy in 35 fractions in 7 weeks

CHART (Continuous Hyperfractionated Accelerated Radiotherapy):

- With CHART treatments total dose of 54Gy can be delivered in 36 fractions in 12 consecutive days in 6hrs interval 3 times a day with dose of 1.5Gy per fraction

Hypo Fractionation:

- More than 2 Gy dose per fraction is delivered in shorter period of time
- Rationale-Treatment completed in a shorter period of time

Hence this study was conducted to assess acute and late toxicities of hypofractionated radiotherapy with concurrent cisplatin for treatment of stage II to IVa head and neck cancer.

MATERIALS AND METHODS

The present prospective study was conducted in department of Radiotherapy. JNM medical college and Regional cancer center (RCC) of Dr. BRAM Hospital Raipur. This thesis was approved by ethical and

scientific committee Pt. JNM medical college Raipur. Duration of study was during July 2018-September 2019.

Inclusion Criteria:

- Patients with head and neck carcinomas
- Biopsy proven case of head and neck carcinoma
- stage II to IVA
- Normal blood profile
- Karnofsky performance scale (KPS)>70%

Exclusion Criteria:

- Patients with co morbidities (heart disease, lung disease etc.)
- Patients with metastasis
- Total 41 patients of head and neck cancer (stage II to IVA) have been taken in this study
- Informed written consent have been taken from every patient
- Detail history was recorded from each patient pertaining to the onset and duration of present complaint
- Physical examination was done on all patients including general, local and systemic examination
- All the routine investigations including CBC, RFT, LFT, X-ray chest, CECT face and neck, ECG was done on all the cases
- Patients have been simulated with appropriate immobilisation then planned with IMRT and VMAT. We have evaluated the plan for dose to primary site and dose to organ at risk, better plan have been executed
- Treatment planning have been perform using VARIAN (eclipse V.S 13.6.23) treatment planning system
- Dose to PTV and OARs was calculated
- Treatment toxicities during course of radiation and after radiation have been compared using QUANTEC data and RTOG, CTC version 3.0 respectively
- Follow up was done for 6 month. Patients were evaluated for local response and toxicities

The comparison of the doses delivered to PTV and OARs was done using paired wilcoxon sign rank test.

RESULTS AND DISCUSSIONS

Maximum no of patients are age group between 41-50 year (34.14%). It is due to male patients are more prone to Head and Neck Carcinoma. They have consumption of tobacco related products for long period of time. According to our study most patients have left sided disease in 18 (44%). It may be due to most patient are right handed and they use to keep tobacco related products on left side in oral cavity. According to our study we observe that maximum number of patients are of oral cavity 36.59% followed by oropharynx 29.27%. It is due to people used to keep tobacco related products in mouth. According to our study most patients presented with locally advance disease of stage IVA 58.54% and with early stage II 12.2%. it is due to in Chhattisgarh state patients came with locally advanced stage. It is due to illiteracy, poverty, lack of awareness, lack of health facility.

In our study treatment should be completed within 1 week from estimated total duration (39 days) percentage are 41.4%, Rest of 58.6% patients delayed their treatment 39 days+2weeks. It mainly due to radiation-related toxicities other reasons are distance of the treatment facility from home, age of the patient, advance stage , illiteracy and particular disease sites.

In our study we observe response at 6 weeks, 3 months and 6 months. In 6 months- there is complete response in 36.6% of cases, partial response in 39 %, stable disease in 12.2% and progressive disease in 4.8 % cases. It is due to 58.4% cases have presented to us with stage IVA and they not response completely and tend to progress even after treatment. In our study in 6 weeks-skin reaction are-46.3% cases of grade II and 36.5% cases of grade III. Mucositis are-46.3% cases of grade II and 31.7% cases of grade III. salivary gland toxicity are-44 % cases of grade II and 31.7% cases of grade III. dysphagia are-48.7% cases of grade II and 31.7% cases of grade III. we have found that maximum cases have grade 2 followed by grade 3 toxicities. It is due to low immunity in the last week of radiation, absorbed radiation dose is more than tolerance dose of mucosa and it is associated with superadded infection. we have found that most of the acute toxicities regressed over 3-4 months and at 6th month there is development of late radiation fibrosis and xerostomia.

Acute Toxicities: In our study ACUTE TOXICITIES in 6 weeks skin reaction are 36.5% cases of grade III and 4.9% are grade IV. Study by Gopa ghosh *et al* They reported as grade I skin toxicity is 100%, grade II 92.5%, grade III 7.5% and grade IV 0%[1] . In our study Mucositis are 31.7% cases of grade III, 12.2 % are grade IV. we have found that maximum cases have grade 2 followed by grade 3 toxicities. It is due to low immunity in the last week of radiation, absorbed radiation dose is more than tolerance dose of mucosa and it is associated with superadded infection. According to Dean *et al*. Yahyaet al An explanation for the results in this study is that the G3 mucosities was most commonly observed[2]. This explanation is supported by the work of Dean *et al,* who found that the volume of mucosa receiving more than 2.2 Gy per fraction had the strongest association with the incidence of severe mucositis. Study by Rosario Mazzola et al Acute mucositis was recorded as follow: grade 0 (G0) in 4% of patients, G1 in 26%, G2 in 50%, G3 in 20%[3] . In our study Dysphagia are 31.7% cases of grade III and 7.3% are grade IV. Study by Bhide *et al* It was shown a significant correlation between length of

Table 1: Skin toxicities

Skin(N=41)	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
1ST Week	41(100%)	0	0	0	0
2ND Week	24(58.5%)	17(41.5%)	0	0	0
3RD Week	3(7.3%)	32(78%)	6(14.7%)	0	0
4TH Week	0	24(58.5%)	15(36.6%)	2(4.9%)	0
5TH Week	0	14(34.2%)	19(46.3%)	6(14.6%)	2(4.9%)
6TH Week	0	5(12.2%)	19(46.3%)	15(36.5%)	2(4.9%)

Table 2: Mucositis

Mucositis (N=41)	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
1ST Week	41(100%)	0	0	0	0
2ND Week	28(68.3%)	13(31.7%)	0	0	0
3RD Week	9(22%)	24(58.5%)	8(19.5%)	0	0
4TH Week	0	21(51.2%)	20(48.8%)	0	0
5TH Week	0	15(36.6%)	20(48.8%)	4(9.8%)	2(4.9%)
6TH Week	0	4(9.8%)	19(46.3%)	13(31.7%)	5(12.2%)

Table 3: Salivary gland

Salivary Gland (N=41)	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
1ST Week	41(100%)	0	0	0	0
2ND Week	26(63.4%)	15(36.6%)	0	0	0
3RD Week	8(19.5%)	25(61%)	8(19.5%)	0	0
4TH Week	0	13(31.7%)	26(63.4%)	2(4.9%)	0
5TH Week	0	10(24.4%)	23(56.1%)	6(14.6%)	2(4.9%)
6TH Week	0	7(17%)	18(44%)	13(31.7%)	3(7.3%)

Table 4: Dysphagia

Dysphagia (N=41)	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
1ST WEEK	41(100%)	0	0	0	0
2ND WEEK	30(73.2%)	11(26.8%)	0	0	0
3RD WEEK	5(12.2%)	32(78%)	4(9.8%)	0	0
4TH WEEK	0	29(70.7%)	12(29.3%)	0	0
5TH WEEK	0	12(29.3%)	22(53.6%)	5(12.2%)	2(4.9%)
6TH WEEK	0	5(12.2%)	20(48.7%)	13(31.7%)	3(7.3%)

Table 5: In 6 weeks

6 weeks	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Skin	0	5(12.2%)	19(46.3%)	15(36.5%)	2(4.9%)
Mucositis	0	4(9.8%)	19(46.3%)	13(31.7%)	5(12.2%)
Salivary gland	0	7(17%)	18(44%)	13(31.7%)	3(7.3%)
Dysphagia	0	5(12.2%)	20(48.7%)	13(31.7%)	3(7.3%)

Late Toxicities

Table 6: Skin

Skin (N=41)	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
1ST MONTH	4(9.7%)	15(36.6%)	19(46.3%)	2(4.9%)	1(2.4%)
2ND MONTH	4(9.7%)	15(36.6%)	19(46.3%)	2(4.9%)	1(2.4%)
3RD MONTH	12(29.2%)	14(34.2%)	15(36.6%)	0	0
4TH MONTH	13(31.7%)	22(53.6%)	6(14.6%)	0	0
5TH MONTH	17(41.5%)	18(44%)	6(14.6%)	0	0
6TH MONTH	22(53.6%)	15(36.6%)	4(9.7%)	0	0

Table 7: Mucositis

Mucositis (N=41)	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
1ST MONTH	3(7.3%)	15(36.6%)	20(48.7%)	2(4.9%)	1(2.4%)
2ND MONTH	5(12.2%)	15(36.6%)	20(48.7%)	1(2.4%)	0
3RD MONTH	11(26.8%)	14(34.2%)	16(39%)	0	0
4TH MONTH	12(29.3%)	22(53.6%)	7(17%)	0	0
5TH MONTH	16(39%)	18(44%)	7(17%)	0	0
6TH MONTH	21(51.2%)	15(36.6%)	5(12.2%)	0	0

Table 8: Salivary Gland

Salivary Gland (N=41)	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
1ST Month	2(4.9%)	18(44%)	19(46.2%)	2(4.9%)	0
2ND Month	11(26.8%)	13(31.7%)	15(36.6%)	2(4.9%)	0
3RD Month	18(44%)	11(26.8%)	10(24.4%)	2(4.9%)	0
4TH Month	24(58.5%)	8(19.5%)	8(19.5%)	1(2.4%)	0
5TH Month	31(75.6%)	1(2.4%)	7(17%)	2(4.9%)	0
6TH Month	39(95.1%)	0	0	2(4.9%)	0

Table 9: DYSPHAGIA

Dysphagia (N=41)	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
1ST Month	10(24.4%)	16(39%)	12(29.3%)	2(4.9%)	1(2.4%)
2ND Month	14(34.2%)	13(31.7%)	12(29.3%)	2(4.9%)	0
3RD Month	18(44%)	13(31.7%)	10(24.4%)	0	0
4TH Month	22(53.6%)	11(26.8%)	8(19.5%)	0	0
5TH Month	30(73.2%)	7(17%)	4(9.8%)	0	0
6TH Month	31(75.6%)	6(14.6%)	4(9.8%)	0	0

Table 10: In 6 months toxicities

6 months	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Skin	22(53.6%)	15(36.6%)	4(9.7%)	0	0
Mucositis	21(51.2%)	15(36.6%)	5(12.2%)	0	0
Salivary gland	39(95.1%)	0	0	2(4.9%)	0
Dysphagia	31(75.6%)	6(14.6%)	4(9.8%)	0	0

pharyngeal mucosa treated to 50 Gy and 60 Gy and the incidence of grade 3 dysphagia[4]. According to Rosario Mazzola *et al* Acute dysphagia was recorded as follow: G0 in 24% (n = 12), G1 in 32% (n = 16), G2 in 38% (n = 19), G3 in 6% (n = 3). No case of G4 toxicity was registered[5]. In our study salivary gland toxicity are 31.7% cases of grade III and 7.3 % are grade IV. Study by Gopa ghosh *et al* They reported acute xerostomia grade I contributed to 40% and grade II 18% of cases[6]. In our study in LATE TOXICITY we reported that there was regression of acute toxicity over 3-4 months and at the 6th month follow up there is grade I radiation fibrosis present in 61% of patients and grade I xerostomia in 24.4% of patients. Other late toxicity like mandibular osteoradionecrosis, hoarsness and spinal myelopathy and TM joint fibrosis is not seen in any of the case. we have found that most of the acute toxicities regressed over 3-4 months and at 6th month there is development of late radiation fibrosis and xerostomia.

According to Mutlay Sayan *et al* Combined late toxicities were reported in 38% of patients. 3.9% of the patients had Osteo-Radio Necrosis of the mandible[7]. Study by Shao-Hui Huang et al severe muscular fibrosis rate was 5% and severe xerostomia was 22%. Spontaneous Osteoradionecrosis is dose dependent and related to the volume of mandible receiving radiotherapy beyond 50-60 Gy[8] . According to Gopa ghosh *et al.* They reported grade I radiation fibrosis in 7.5% cases, grade I dysphagia in 7.5%, grade I xerostomia in 27.55, grade II xerostomia in 5% of the patients[9]. study by L.M. Chen *et al*. in 6 months resulting in a 18% Cases of Grade 3 xerostomia[10]. According to Santa Cruz O *et al* The overall incidence of grade ≥3 toxicities were mucositis 32%, xerostomia 7%, dysphagia 53% and osteonecrosis 1%. Other Late grade ≥3 toxicities were fibrosis 6%, fistula 1% and skin necrosis 1%[11]. According to Shao-Hui Huang *et al.* severe muscular fibrosis rate was 10% and severe xerostomia was 22%, Spontaneous Osteoradionecrosis is dose-dependent and related to the volume of mandible receiving radiotherapy beyond 50-60 Gy[12].

CONCLUSION

we have found that most of the acute toxicities regressed over 3-4 months and at 6th month there is development of late radiation fibrosis and xerostomia

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