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Unplanned Interruption of Radiotherapy in Head and Neck Cancers: report from a Regional Cancer Centre

Authors
Najmi Arshad Manzoor, Shah Saqib Ahmad, Rasool Malik Tariq, Wani Shaq-ul-Qamar, Jan Yasmeen[1], Wani Shahid Bashir, Lone Mohammad Maqbool, Afroz Fir, Khan Nazir Ahmad
Department of Radiation Oncology, Sheri-kashmir Institute of Medical Sciences, Srinagar J&K India
[1]Department of Community Medicine, SKIMS Medical College Srinagar J&K India
Corresponding Author
Dr Arshad Manzoor Najmi
Email: *arshadmanzoor99@gmail.com*

ABSTRACT

Background and Objectives: *Any unplanned interruption in head and neck cancers can affect loco regional control rates. Treatment induced toxicities and radiotherapy equipment breakdown or maintenance are the commonest reasons for treatment interruption. We evaluated occurrence and causes of unplanned interruption of radiotherapy in patients of head and neck cancers receiving radical radiotherapy protocol.*

Material and Methods: *We conducted a retrospective study of 60 patients enrolled for radical Radiotherapy in our Regional Cancer Centre and recorded all relevant details like; patient characteristics, treatment received as well as details of treatment interruptions.*

Observations: *Most of the patients were in the age group 55-64 years with males comprising 63.3% of cases. Oral cavity was the commonest subsite involved (33.3%) followed by larynx (23.3%). 60% patients started their radiotherapy within 4 weeks of first visit to our OPD and in only 10% of cases waiting period contributed to delay of more than 4 weeks. The average radiotherapy dose received by patients was 65.4 Gy, and the average fraction number was 32.5. 38 patients (63.3%) received single agent cisplatin based concurrent chemotherapy. The average overall treatment time (OTT), including interruptions, was 50.1 days. Treatment interruption was seen in 46.6% cases, out of which treatment induced toxicity contributed to 71.4% and radiotherapy machine related issues lead to interruption in 28.5% patients. Mucositis was the commonest toxicity observed, in half the patients with interruptions. The treatment breaks were mainly compensated by increasing treatment time for all remaining fractions, as per the departmental protocol and/or by treating them on Saturday of last week also.*

Conclusion: *All efforts should be made to prevent and minimize the treatment interruptions in patients receiving radiotherapy of head and neck cancers in view of clonogenic repopulation affecting the control rates. At the same time, all interruptions should be properly compensated by a standard departmental protocol.*

Keywords: *Radiotherapy, Interruption, Head and Neck, Mucositis.*

INTRODUCTION

Radiation therapy is one of the main treatment modalities in non-cutaneous squamous cell carcinoma of head and neck, whether as definitive radiotherapy or as adjuvant radiotherapy. It's a well known fact that during the course of prolonged treatment schedule, repopulation of

tumor cells as well as normal cells occur. This accelerated tumor clonogen repopulation can lead to reduced tumor control. In the conventional fractioning for treatment of head and neck tumors, intervals of approximately one week are associated with a 10%–12% reduction in the local control of the disease.[(1)]

Studies have demonstrated that the minimum interruption interval which may significantly affect the treatment outcome is around two days. Any interruption resulting in prolongation of the overall treatment time is potentially hazardous; these interruptions occur in more than 30% of treatments.[(2)]

Head and neck cancer patients have invariably long radiotherapy protocols running for 6-7 weeks. Any delay or interruption in treatment results in extension of overall treatment time, which can affect the management of disease. The reasons for this prolongation in treatment time may be due to fault in radiotherapy machine or patient factors like treatment related toxicities and waiting time for start of radiotherapy. These toxicities especially oral mucositis are more pronounced in patients receiving concurrent chemoradiation.

Different institutions have their own ways of compensating for interruptions in the radiotherapy protocols, but there is no universal consensus for the method employed. Common ones being: treating on weekends or public holidays, increasing number of fractions (including twice daily fractions), increasing treatment time for remaining fractions or shifting patients to a different radiotherapy machine, wherever applicable.

The present study was aimed at finding out the overall treatment time as well as occurrence and causes of unplanned radiotherapy interruptions in patients of non-cutaneous squamous cell carcinoma of head and neck.

MATERIAL & METHODS

We retrospectively studied 60 patients of histologically documented non-cutaneous squamous cell carcinoma of head and neck, who were registered at our regional cancer centre during the year 2014 and were enrolled in radical radiotherapy protocol. Metastatic patients were excluded. Patients' general characteristics like age, sex, ECOG performance status and subsite involved, were recorded. All data relating to patients was well maintained in the files at hospital-based cancer registry (HBCR). All operative and histopathological details were recorded. Date of registration in the department as well as date of start and completion of radiotherapy was recorded. Only patients who had ECOG performance score of less than or equal to 2 were included. Radiotherapy details like dose and fractionation, along with details of chemotherapy were documented. Radiotherapy was delivered by megavoltage telecobalt-60 unit by conventional fractionation i.e. one fraction/day; 5 fractions/week. Patients with concurrent protocols received cisplatin based chemotherapy infusion in daycare ward; either weekly @40mg/mt^2 or 3-weekly @ 100 mg/mt^2. The interruptions in treatment were expressed in terms of whole days and were defined as unplanned gap in between treatment; those apart from the routine weekend break on Saturdays and Sundays. These interruptions were recorded with regards to their durations and causes. All these events were recorded from patients on their follow up visits and telephone calls were made to few patients who were not on regular follow up to elicit all the details. The observations were analyzed in SPSS for Windows version 16 by using general descriptive statistics method, along with Chi-square and F-test.

RESULTS

At our Regional cancer centre (recently upgraded to state cancer institute) 3891 new cancer patients were registered in 2014, out of which 101 patients had non cutaneous squamous cell carcinoma of head and neck. 60 patients were eligible for the study.

[Table-1]

		N=60	%
Age (years)	<35	2	3.3
	35-44	10	16.6
	45-54	10	16.6
	55-64	22	36.6
	65-74	14	23.3
	>74	2	3.3
Sex	Males	38	63.3
	Females	22	36.6

Most of the patients were in the age group 55-64 years (36.6%) and there was preponderance in favor of males (63.3%) as compared to females.

[Table-2]

Subsite involved	N=60	%
Larynx	14	23.3
Oral cavity	20	33.3
Hypopharynx	12	20.0
Nasopharynx	10	16.6
Maxilla	4	6.6

Oral cavity was the commonest subsite involved with 33.3% of patients, followed by larynx with 23.3%.

[Table-3]

		N=60	%
ECOG P.S	0	10	16.6
	1	42	70.0
	2	8	13.3
	>2	0	0,0
T- stage	T1	8	13.3
	T2	10	16.6
	T3	32	53.3
	T4	10	16.6
N-stage	N0	14	23.3
	N1	32	53.3
	N2	14	23.3
	N3	0	0,0
M-stage	M	0	0,0

Majority of the patients included in the study had ECOG performance score of 1 (70%) followed by 0 (16.6), As far as TNM staging was concerned, T3 was the predominant tumor stage, observed in 53.3% while as N1 was the commonest nodal stage observed (53.3%). No patient enrolled had metastatic disease.

36 patients (60%) started their radiation within 4 weeks of being first seen in Oncology OPD, when they were registered. Of the remaining 40% (24 patients) in whom radiation was started after more than 4 weeks of registration, 14 patients (23.3%) had their radiation deferred because of upfront surgery. 4 patients(6.6%) chose to receive radiation late because of personal reasons and 6 patients(10%) received radiation later than 4 weeks due to waiting period in the department. The average waiting time period for starting radiotherapy after registration in the oncology OPD was 16.6 days (2.3 weeks).

[Table-4]

N=60			%
Radiotherapy	Average dose	65.4 (Gy)	
	Average fraction number	32.5	
Chemotherapy	Received	38	63.3
	Single drug	38	63.3
	3 weekly regime	22	36.6
	Weekly regime	16	26.6

The average radiotherapy dose received by patients was 65.4 Gy, (range=60-70Gy) and the average fraction number was 32.5 (range = 27-35). 38 patients (63.3%) received single agent cisplatin based concurrent chemotherapy on Monday. Out of those 11 patients (36.6%) received 3 weekly cisplatin; while as 8 patients (26.6%) received weekly cisplatin.

The average overall treatment time (OTT), including interruptions, was 50.1 days (range= 40-70 days).

[Table-5]

		N	%	p-value
Interruption seen N=28	Treatment toxicity	20	71.4	0.0014 Sig
	Machine related	8	28.5	
Chemo received N=38	Interruption seen	24	63.1	X^2 =9.58 P=0.004 Sig
	Not seen	14	36.8	
Chemo not received N=22	Interruption seen	4	18.1	
	Not seen	18	81.8	

The overall incidence of interruptions during radiotherapy was 46.6% (28/60) (range 3-21 days). Radiotherapy machine related issues contributed to 28.5% (8) interruptions and treatment induced toxicities were responsible for

71.4% (20) and the result was statistically significant. Out of these 20 cases multiple toxicities were seen in 12 and single toxicity in 8 patients.

Of the 38 patients who received chemotherapy, interruptions was seen in 24(63.1%) out of which 18 were due to toxicities and 6 due to radiotherapy machine related causes. On the other hand out of the 22 patients who didn't receive chemotherapy, interruptions were seen in only 4(18.1%). The reasons for interruptions in those 4 patients were radiation induced mucositis (2) and machine related issues (2).The results were statistically significant.

[Table-6]

		N	%
Toxicity Observed N=20	Single toxicity	8	40
	Multiple toxicities (>1)	12	60
Mucositis (grade >3)		14	50.0
Neutropenia (grade >3)		8	14.2
Renal failure		4	14.2
Fever		2	7.1
Shock		2	7.1
Skin reaction (grade >3)		2	7.1
Gastrointestinal toxicity(grade >3)		2	7.1
Death		2	7.1

The commonest toxicity observed was oral mucositis seen in 50% (14), Neutropenia and Cisplatin induced renal failure, each, were seen in 14.2% of patients (4). Two patients developed grade-4 mucositis and renal failure with shock and ultimately died. 4 patients had treatment interru-ptions twice and 2 patients had interruptions thrice during their course of treatment.

[Table-7]

		Total number N=60	Treatment Interruptions N (%)	p-value
Age(years)	<35	2	2(100)	0.42 NS
	35-44	10	0(0)	0.02 S
	45-54	10	4(40)	0.77 NS
	55-64	22	14(63.3)	0.23 NS
	65-74	14	8(57.1)	0.59 NS
	>74	2	0(0)	0.56 NS
Sex	Males	38	20(52.6)	0.61 NS
	Females	22	8(36.3)	
Subsite involved				
	Larynx	14	4(28.5)	0.32 NS
	oral cavity	20	8(40.0)	0.65 NS
	Hypopharynx	12	10(83.3)	0.11 NS
	Nasopharynx	10	6(60)	0.59 NS
	Maxilla	4	0(0)	0.16 NS

On analyzing the patients with treatment interruptions with regards to age, sex and subsite involved, we found no statistical significance.

[Table-8]

		N	Treatment Interruptions N(%)	p-value
ECOG P.S	0	10	4(40.0)	0.77 NS
	1	42	20(47.6)	0.89 NS
	2	8	4(50.0)	0.90 NS
T- stage	T1	8	4(50.0)	0.22 NS
	T2	10	2(20.0)	0.73 NS
	T3	32	16(50.0)	0.73 NS
	T4	10	6(60.0)	0.59 NS
N-stage	N0	14	2(14.2)	0.06 NS
	N1	32	18(56.2)	0.33 NS
	N2	14	8(57.1)	0.59 NS
M-stage	M	0	0(0)	-

Similarly the analysis of treatment interruption visa-vis ECOG performance status and TNM stage didn't reveal a statistically significant result. All the patients with treatment breaks were compensated by increasing treatment time for every remaining fraction as per the departmental protocol. Two patients were compensated by treating them on Saturday of last week also.

DISCUSSION

There is enough evidence to suggest that prolongation in overall treatment time due to uncompensated treatment interruptions in fast growing tumors like head and neck cancers increases the risk of local recurrences[3].

These effects are seen not only during primary curative radiotherapy but also during chemoradiotherapy, adjuvant post-operative radiotherapy. The reduction in local control rate varies with the duration of treatment gaps. It has been seen to be approximately 0.7–1.4% for a gap

of 1 day rising to 14–20% for a 7-day gap [4,5]. The majority of these reports relate to patients receiving treatment of 60–66 Gy over 6–6.5 weeks.

A study on Laryngeal Cancer revealed that even an unscheduled gap of one day during radiotherapy can result in absolute reduction of local control by 1.4%[6]. Hence it is imperative that treatment interruptions during the Radiotherapy protocol should be avoided or at least minimized as far as possible. In this regard many centres try to adopt the Mackillop ASARA Principle (As Short As Reasonably Achievable) [7] Tumor control is not affected in Head and Neck Cancers only but in other cancers also. Chen et al reported a 9% decrease in the rate of disease free survival in patients with non small cell lung cancer who had extended their overall treatment time for one week because of unplanned interruptions during radiotherapy[8]. Similarly Perez et al. reported that patients with stage T2 prostate cancer presented pelvic failures and poorer responses when the overall treatment time was more than 9 weeks, as compared with those who completed the treatment in less time [9].

Head and neck cancers are quite common in our centre and these patients often have compromised nutrition at diagnosis owing to involvement of oral cavity and throat. During the course of radiotherapy nutrition status deteriorates further due to onset of mucositis which contributes to treatment interruptions. Hence this study was conducted in head and neck cancers to evaluate the treatment interruptions during radiotherapy in our set-up.

An audit was carried out twice in many radiotherapy centres in U.K to formulate the practice guidelines for management of treatment interruptions during radical radiotherapy and subsequently to assess the effect of those guidelines [10]. Their second audit found that the median time to start radiotherapy after being registered in the Oncology clinic was 3.9 weeks compared to 2.3 weeks in our study. We found that 60% of our patients started their radiotherapy within 4 weeks of their first visit to the OPD, which is comparable to 52% observed in the above mentioned audit. In fact of the remaining 40% whose treatment started more than 4 weeks of first visit in the department, only 10% (6 cases) had radiation delayed because of waiting time in the department. It's worth mentioning that the waiting time in our department had markedly reduced after acquisition of second Tele-cobalt unit. This has clinical importance as significant tumor progression has been seen in head and neck cancer patients within average period of 4 weeks [11].

The incidence of treatment interruptions was 55% and 63% in the above mentioned two audits. In our study the overall incidence of interruptions was 46.6%. Another study from Brazil reported a 62.5% incidence of interruption for patients undergoing Radiotherapy [12]. Duncan et al reported treatment interruption in 68.9% patients in their study with 383 patients of larynx cancer[13].

The reasons for interruptions can generally be classified into treatment related toxicities, patient's personal reasons, progression of primary disease during treatment and equipment related causes. Equipment related issues may be breakdown in machine or maintenance of machine. At times, there may be a combination of above mentioned reasons responsible for interruptions.

On dividing the duration of treatment gaps into two groups; one more than 7 days gap and the other less than or equal to 7 days, we found that 16 of 28 (57.1%) patients had treatment interruptions lasting for more than 1 week. In all these 16 patients the reason for interruption was treatment related toxicity. On the other hand in the remaining 12 patients, 8 had treatment break because of machine related issues (28.5%) and 4 had treatment induced complications. This is in contrast to the national audit study by James et al in the United Kingdom [10]. They found that the machine service and breakdown resulted in interruptions to 44% of patients. 39% of interruptions in their study were due to public holidays.

At our centre, other than the routine weekend gap, patients are treated on all public holidays. Hence we don't encounter interruptions due to public holidays which are commonly seen across centers

in western world. Moreover all the planned equipment maintenance at our centre is carried out on Saturdays so that patients aren't affected. This is in comparison to the study from Brazil in which equipment maintenance (55%) represented the main reason for treatment interruption [12]. In their study they also reported that clinical progression of primary disease and treatment toxicities lead to interruptions for longest period. This was comparable to our study where all the interruptions lasting more than one week were caused by treatment related toxicities.

Patient related factors leading to interruptions in our study were primarily acute toxicities which were culmination of both radiation therapy as well as chemotherapy. Treatment induced Mucositis was the commonest toxicity leading to treatment interruption seen in as many as 14/28 patients. In fact ulcerative mucositis has been said to be a major limitation to continuous, uninterrupted chemo radiotherapy in the management of head and neck cancers [14].

In view of the established detrimental effect of interruptions on loco regional control in head and neck cancers, there should be immediate and aggressive management whenever treatment is interrupted. This has been adequately described in the "Guidelines for the management of a radical unscheduled interruption or prolongation of a radical course of radiotherapy" recommending transference of the patient to another equipment in case of equipment maintenance or breakdown, if possible. Else patients should be compensated for the interruption by any of measures like; treating at the weekend and/or public holidays , treating twice a day each 6 hours apart (hyperfractio-nation), use of biologically equivalent dose (BED) calculations to derive an alternative schedule to modify number of treatment Fractions[15]

Worldwide there is no consensus on the compensation methods for the interruption effects. In view of this Dale et al recommended that interrupted treatments should be individually analyzed, considering the absence of a universal method to solve all the resulting problems [16]. At our centre we generally compensate the treatment break by using BED calculations thereby increasing the treatment time for all remaining fractions. Sometimes we treat patients on Saturday also, especially in the last week of protocol.

Efforts should be made at institutional level to prevent or minimize the incidence of treatment interruptions during radiotherapy. Radiotherapy centers should accomplish periodical preventive equipment maintenance at least every three months, which could help in avoiding frequent equipment breakdowns and subsequent treatment interruptions.

Vigorous and prompt management of treatment induced toxicities should be undertaken to reduce risk of prolonged treatment intervals. Chen et al, studying the causes of radiotherapy interruption in patients with nasopharyngeal carcinoma, reported that the patients who underwent pretreatment nursing consultation presented lower rates of treatment interruption because they could better withstand the side effects [17]. Moreover the increased use of 3-D conformal radiotherapy and IMRT is expected to result in better sparing of normal tissues leading to decreased toxicities.

CONCLUSION

Interruptions during radiotherapy protocol has a detrimental effect on the loco-regional control rate in head and neck cancers. Equipment related issues and treatment induced toxicities are the commonest reasons for interruptions in treatment. Every radiotherapy department should make efforts to prevent treatment interruptions by periodic maintenance of equipment and aggressive management of treatment induced toxicities so that overall treatment time is not prolonged. A universally accepted method to compensate for the interruption in radiation therapy is the need of the hour.

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