Asian Pacific Journal of Cancer Care
Vol 7 No 1 (2022), 3-8
Original Research

Adherence to Radiotherapy in the Treatment of Cancer Patients: A Tertiary Care Institute Experience at Punjab

Karuna Singh Baba Farid University of Health Sciences, Faridkot, India
Eastpal Singh Baba Farid University of Health Sciences, Faridkot, India
Manjit Kaur Rana All India Institute of Medical Sciences, Bathinda, India.
Pardeep Sharma Baba Farid University of Health Sciences, Faridkot, India
Sheetal Sachdeva Baba Farid University of Health Sciences, Faridkot, India

Aim: The present study was carried out to analyse the incidence of non-adherence to the radiotherapy treatment and study the factors associated with non- adherence.
Patient and methods: The retrospective study was conducted at a tertiary cancer care institute, Punjab. All the patients treated during one year with curative intent with conventional fractionation were included. Incidence of non-adherence was driven and the various parameters like age, gender, site of tumor, stage of disease, intent of treatment, distance from the treating institute, financial constraints were analysed.
Results: A total of 660 patients were taken. 6 out of 660 did not come for treatment initiation, hence 654 patients were eligible to be studied. The cumulative incidence of non -adherence was 12.8% (84 out of 654). The majority of patients were of head and neck 31 (36.9%), Elderly >60 years 27 (32.1%), Stage IV 42 (50 %), patients residing in more than 50 km from the institute 47 (55.9%), concurrent chemotherapy 71 (84%), the a major proportion of patient had more than 1 week gap 54 (64%) with 25 (29%) having more than 2 weeks gap. The factors found to be associated with non- adherence was elderly age (p value 0.06), advanced stage (p value 0.003), use of concurrent chemotherapy (p value 0.001), distance from the institute (p value 0.03), treatment with radical intent (p value < 0.001), patients utilizing various government schemes (p value 0.004). No significant association was found between the gender and site of the tumor (p value 0.17 and 0.14 respectively) with the non -adherence.
Conclusions: The factors associated were stage of disease, elderly, concurrent chemotherapy, more distance travelled to reach the institute. Non adherence needs to be addressed by proper counselling of patients at the first visit to hospital itself. After the 3 week of radiotherapy treatment patient needs to be seen and followed more frequently when chances skipping treatment are high.

Introduction

Cancer treatment is a multimodality approach and radiotherapy plays a vital part, which utilizes ionizing radiation to treat various malignant tumors. It has been used to treat some benign disease and other disorders [1]. Soon after Roentgen's discovery of X -rays in 1895, ionizing radiation was applied to the treatment of cancer, with remarkable results. Radiation therapy is a time tested treatment modality since ages which has radiobiological principles as its backbone. Withers way back in 1975 define the basis of radiation effects in terms of four principles namely repair of DNA damage, redistribution of cells in the cell cycle, repopulation and reoxygenation of hypoxic tumor cells and later steel added one more factor of radiosensitivity in 1989 [2,3]. Carefully controlled doses of ionizing radiation induce damage to the DNA in cells, with preferential effects on cancer cells compared with normal tissues, providing treatment benefits in most types of cancer and saving lives. They also define the concept of fractionation. The most commonly prescribed

conventional fractionation uses 1.8–2.2 Gy per fraction for five fractions in a week for 5-7 consecutive weeks [2,3].

Over the period of time there are many modifications applied to the conventional radiation therapy schedule. In the current era we have different fractionation schedules which are time tested. Adherence to the cancer treatment is important in terms of outcome, locoregional control and survival. Many times, unplanned interruptions happen either due to technical breakdown of the machine or treatment-related toxicities, sometimes patients do not come for radiotherapy. These interruptions become an important issue and affects the chances of patient getting cured. Different reasons account for this, some of which are social taboos, religious customs, myths about radiotherapy, financial constraints, alternative medicine treatment, etc. This ultimately affects the local control and overall survival [4].

This association between interruptions and treatment outcome has been consistent for several disease sites such as head and neck cancers, lung cancer, cervical cancers, breast cancer and other sites [5]. Delay or prolongation of treatment is associated with relative risk of local recurrence by upto 2% per day for specific malignancies [6]. The previous two decades have experienced remarkable changes in the technology of delivering radiation. The technology has moved from conventional two-dimensional radiotherapy to particle beam therapy [7].

Non adherence to treatment issue has often been ignored and consequences of non compliance never been addressed. A clinical audit performed to provide key information associated with radiotherapy process. Some of the key factors that have been assessed compliance to radiotherapy, waiting time to radiation therapy, intention of treatment, effect on overall treatment time, and integration with allied treatment modalities [8]. Non compliance to the planned treatment course is one of the major reasons for the treatment failure. In this study we tried to analyse the factors and reasons behind not following the treatment recommended for their treatment.

Materials and Methods

We retrospectively evaluated the radiotherapy records of those patients who were treated in the radiotherapy department at the Institute. A total of 660 patients were found eligible. 6 out of 660 patients did not came for treatment even when their plans were ready to execute. Hence 654 patients were eligible for the study. Their records were analysed for compliance to the treatment protocol. Compliance was defined as completion of prescribed dose of radiation during the prescribed time frame. Noncompliance was defined as the premature termination of the planned treatment by the patient without consultation or recommendation from the treating clinician. Majority of the patients were of head and neck, gynaecologic, breast and oesophagus diagnosis. The usual dose prescription was 66–70 Gy @2 Gy per fraction for head-and-neck cancer, 50 Gy @2Gy per fraction for breast cancer, 50 Gy @2Gy per fraction of external beam radiation for cervical cancer, 50.4Gy @1.8Gy per fraction for GI tumors. Dose was delivered with 2 Gy per fraction for five fractions in a week over a period of 6-7 weeks. Compliance was found to be associated with various factors such as age, gender, site of primary disease, distance patients had to travel to receive treatment, administration of concurrent chemotherapy, and financial expenses of the treatment.

Results

The characteristics of the patients included in the study has been given in Table 1.

Parameter	Total number n (654) (%)	Adherence 570 (%)	Non adherence 84 (%)
Gender			
Male	315 (48.1)	273 (47.8)	42 (13.3)
female	339 (51.8)	297 (52.1)	42 (12.3)

Age			
<20 years	3 (0.4)	3 (0.52)	0
21-30 yrs	16 (2.4)	12 (2.1)	4 (4.7)
31-40 yrs	77 (11.7)	70 (12.2)	7 (8.3)
41-50 yrs	157 (24)	140 (24.5)	17 (20.2)
51-60 yrs	192 (29)	167 (29.2)	25 (29.7)
61-70 yrs	154 (23)	127 (47)	27 (32.1)
71-80 yrs	43 (6.5)	42 (7.3)	1 (1.1)
>80 yrs	12 (1.8)	9 (1.5)	3 (29.7)
Site of tumor			
Head and neck	172 (26.2)	141 (24.7)	31 (36.9)
Breast	118 (18)	110 (19.2)	8 (9.5)
Gynec	135 (20.6)	119 (20.8)	16 (19)
Thoracic	25 (3.8)	24 (4.2)	1 (1.19)
CNS	23 (3.5)	19 (3.3)	4 (4.7)
GI	89 (13)	71 (12.4)	18 (21.4)
GU	50 (7.6)	45 (7.8)	5 (5.9)
Bone and soft tissue	6 (0.9)	5 (0.8)	1 (1.19)
other	36 (5.5)	36 (6.3)	0
Intent			
Radical	622 (95)	538 (94.3)	84 (100)
palliative	32 (4)	32 (5.)	0
Chemotherapy			
Yes	441 (67)	379 (66.4)	62 (73.8)
no	213 (32)	191 (33.5)	22 (26.1)
Stage of tumor			
Stage I/II	76 (11.6)	67 (11.1)	3 (3.5)
Stage III	403 (61.2)	357 (62.6)	39 (46.4)
Stage IV	175 (26.7)	146 (25.6)	42 (50)

Table 1. Characteristics of Patients.

Out of 660 patients, 6 patients did not come to start their treatment, hence the evaluable patients were 654.

Among the 654 patients, 315 (48.1%) were males and 339 (51.8%) were females. Head and neck (26%), breast (18%), gynaecologic (20.6%) accounts for the major proportion of malignancies. The cumulative incidence of non-adherence was 12.8% (84 out of 654 patients). Various factors associated with non-adherence is given in Table 2.

Factors	Non adherence (%)
Distance from the institute	
<50 km	47 (55.9)
50-100km	25 (29.7)
>100 km	12 (14.2)
Chemotherapy	
Yes	71 (84)
No	13 (15)
Intent of treatment	
Radical	84 (100)
Palliative	none
Financial support	
Govt Scheme	71 (84.5)

Paid	13 (15)
Stage of disease	
Stage I/II	3 (3.5)
StageIII	39 (46)
StageIV	42 (50)
Time gap	
1 week	30 (35)
1-2 week	29 (34)
>2 week	25 (29)
Age	
21-30 yrs	4 (4.7)
31-40 yrs	7 (8.3)
41-50 yrs	17 (20.2)
51-60 yrs	25 (29.7)
61-70 yrs	27 (32.1)
71-80 yrs	1 (1.1)
>80 yrs	3 (29.7)

Table 2. Factors Affecting Compliance.

The most common cause of non-adherence is the development of radiation induced toxicities. These side effects generally develop in the second week of treatment with varying degree of severity. The head and neck patients develop dysphagia as result of mucositis and desquamation of skin in the irradiated areas. Chemotherapy given concurrently increases the side effects. Patients receiving pelvic radiation develop GI toxicities in form of diarrhoea and patients with breast conservation surgery followed by radiotherapy develop skin reactions in the inframammary region. Among the non-adherence patients, 47 (55.9%) used to come from a distance within 50 km from the institute. Majority of them were receiving concurrent chemotherapy 71 (84%) and all were treated with radical intent. 71 (84%) patients in the non-adherence group were getting some financial aids from the various government schemes. A major proportion of them were in stage IV cancers 42 (50%). A comparable number of patients took gap of 1 week and between 1-2 week (35%).

Discussion

Radiation treatment is a time tested modality in multimodality approach to cancer especially solid tumors. Radiation therapy is used to cure cancers that are localized; it can also provide local control in form of complete response with no evidence of recurrence in the treated area (curative) or symptom relief in cancers that are locally advanced or disseminated (palliative). It is frequently used in combination with surgery, either preoperatively or postoperatively, as well as in combination with systemic chemotherapy before, during, or subsequent to the course of Radiotherapy. Conventional fractionation was defined as delivering 1.8-2 Gy over 5 days a week over 6-7 weeks. It was proposed to achieve an acceptable therapeutic ratio- defined as probability of tumor control versus the probability of unacceptable toxicity. These radiobiology concepts have been thoroughly inspected and with the help of advanced and sophisticated equipments, altered fractionations schedules were explored to keep the overall treatment time short, like in continuous hyper fractionated accelerated radiotherapy for lung cancer and stereotactic body radiotherapy for tumors of central nervous system and lung [9]. This lesson we have learned in recent and ongoing COVID -19 era, during which it is worthwhile to keep the hospital visits to minimal.

Compliance to the treatment is unresolving issue in oncology management. The extended time gap intervals alter the aim of cure. Sub curative doses accelerates repopulation of tumor cells and makes the re treatment challenging. Different studies have suggested altered fractionation in head-and-neck cancer patients.

Patient education through interactive programmes can enhance the overall awareness about radiotherapy [10]. In addition to educational and counselling sessions, understanding and responding to patient's emotional issues is imperative to reduce the anxiety and increased preparedness to radiotherapy treatment [11].

Hansen et al. have shown that prolongation of the overall treatment time only leads to reduced locoregional control in well-to-moderately differentiated SCC of the head and neck [12]. Overgaard et al. have shown the importance of overall treatment time for the response to radiotherapy in patients with SCC of the head and neck [13, 14]. They concluded that the locoregional control rate, the disease-specific survival, and overall survival have significant dependency on the overall treatment time. The most beneficial results are achieved when this is short.

Various trials are going on to analyse the effects of hypo fractionated radiotherapy in cancers of different sites like breast, prostate, brain, and head and neck, cervix. With such short course of treatment, it has also been noticed that the compliance rate of patients to the radiotherapy has increased [15,16]. Squamous cell carcinoma (SCC) of the head and neck is a locoregional disease with comparatively less prone to develop metastasis, Radiotherapy and surgery are thus the treatment of choice depending on the anatomical site of tumor; surgery is preferred for early-stage carcinomas of oral cavity and maxillary sinus whereas Concurrent chemoradiotherapy is preferred for tumors located in nasopharynx, oropharynx, and hypopharynx.

Mohanti et al. analysed 2,167 head-and-neck cancer patients and found that only 56% of patients complied with the prescribed treatment; compliance was maximum with patients treated with curative intent [17]. Sharma et al. studied compliance in 47 elderly head-and-neck cancer patients and found 62% patients compliant to the prescribed treatment [18]. They found that compliance to therapy was not significantly associated with advanced stage, poor general condition, intent of treatment, or presence of comorbidity. Majority of the elderly patients showed mid-course treatment noncompliance. Radiation induced toxicities generally commence after 2 weeks of the initiation of treatment and thus patient experience acute toxicities during mid-course of treatment. hence they are more likely to default for further treatment.

Pandey et al. studied 324 patients of head-and-neck cancer treated with radical radiotherapy and found 76 patients to have discontinued treatment [19]. There was no predilection for treatment noncompliance with regard to patient age, educational status, religion, site of the disease, and use of neoadjuvant or concurrent chemotherapy. There tended to be a higher association of treatment noncompliance among patients residing >100 km away from the treatment centre, patients without the below poverty line card, unemployed patients, and patients with stage IV-A/B disease.

Badakhshi et al. have studied compliance in 1903 breast cancer patients and found significant correlation between noncompliance and patient's age, adjuvant hormonal therapy (97.0%), and adjuvant chemotherapy (96.8%) [20]. Noncompliant patients had suffered a 5.02- fold increased risk of local recurrence than compliant patients that was significant.

Yerushalmi and Gelmon retrospectively compared clinic- pathological features and outcomes of breast cancer patients who were adherent to suggested treatment of radiation, chemotherapy, and hormonal therapies to those who were noncompliant [21].

They found that noncompliance rates for chemotherapy, radiation, and hormonal treatment were 7%, 4%, and 37%, respectively. Elderly patients did not complied to chemotherapy and radiation, but younger women were more often noncompliant to hormonal treatment. Also, noncompliance with chemotherapy or radiation did not significantly affect 5-year local and distant disease-free survival rates whereas noncompliance with hormonal therapy was associated with decreased 5-year local and distant disease-free survivals ($P < 0.001$).

In a study by palwe V etal, 105 (6.7%)/1,548 patients were defaulters. They analysed that elderly

patients, head and neck cancers sites (52%), advanced stage and patients receiving concurrent chemotherapy are more likely defaulters. Patients receiving intensity modulated radiotherapy had low rates of nonadherence. Only 5% of defaulters had planned IMRT which causes less toxicities and thus increases chances of adherence. Distance from residence to hospital strongly influence the adherence of planned treatment due to logistic issues. Patients with Good socioeconomic background are more likely to complete their treatment. Non – adherence to planned treatment plan is common among patients who are referred for radiotherapy only from other institutes. This emphasis the fact that all treatment modalities should be made available at a single centre [22].

In case of cervical cancer, the American Brachytherapy Society recommends keeping the total treatment duration to < 8 weeks i.e 56 days [23]. Chumworathayi et al. have found 100% completion of chemotherapy but with delay in 30.3% cycles in the 3 weekly group and 12.9% cycles delay in the weekly group, which was not significant [24] .

Palwe etal in their study cited certain interventions to improve the adherence to radiation therapy treatment. Since elderly patients are more prone to default, they should be given priority. Patients should be counselled regarding various aspects like nature of treatment, possible toxicities. Intervention should be made as early as possible to limit the side effects with close monitoring. Patients should be assessed nutrition and nasogastric tube / feeding gastrostomy should be done as and when required. Accommodation facility should be provided to the patients travelling long distance. Radiation oncologist along with psycho-oncologists or counsellors should understand the their fear and remove the misconceptions. Waiting time in the radiotherapy department should be kept minimal. Patients should be seen more frequently after the third week of radiotherapy treatment [22].

In conclusions, interruptions in the radiotherapy treatment adversely affects the outcome of disease. Non adherence to treatment is a major concern. The various parameters have been studied which can affect the treatment gaps. The factors suggested are age, gender, distance from the treating centre, financial constraints, toxicities of radiotherapy, advanced stage of disease. Counselling and addressing the various emotional issues and fear associated with radiation treatment can increase the chances of adherence to the treatment. The retrospective nature and limited number of patients are the limitations of the study.

References

References

1. Withers HR, Peters LJ. Biological aspects of radiation therapy. In: Fletcher GH, editor. Textbook of Radiotherapy. 3rd ed. Philadelphia: Lea & Febiger. 1980;103-180.
2. Withers HR. The four R’s of radiotherapy. In: Lett JT, Alder H, editors. Advances in Radiation Biology. New York: Academic Press; 1975; 5:241-274.
3. Steel G. Gordon, McMillan T.J., Peacock J.H.. The 5Rs of Radiobiology. *International Journal of Radiation Biology.* 1989; 56(6)DOI
4. Mackillop W.J., Bates J.H.T., O'Sullivan B., Withers H.R.. The effect of delay in treatment on local control by radiotherapy. *International Journal of Radiation Oncology*Biology*Physics.* 1996; 34(1)DOI
5. Rudat Volker, Nour Alaa, Hammoud Mohamed, Abou Ghaida Salam. Better compliance with hypofractionation vs. conventional fractionation in adjuvant breast cancer radiotherapy. *Strahlentherapie und Onkologie.* 2017; 193(5)DOI
6. Bese Nuran Senel, Hendry Jolyon, Jeremic Branislav. Effects of Prolongation of Overall Treatment Time Due To Unplanned Interruptions During Radiotherapy of Different Tumor Sites and Practical Methods for Compensation. *International Journal of Radiation*

*Oncology*Biology*Physics.* 2007; 68(3)DOI
7. Bucci M. K., Bevan A., Roach M.. Advances in Radiation Therapy: Conventional to 3D, to IMRT, to 4D, and Beyond. *CA: A Cancer Journal for Clinicians.* 2005; 55(2)DOI
8. Kaur Jaspreet, Mohanti Bidhu Kalyan, Muzumder Sandeep. Clinical Audit in Radiation Oncology: Results from One Academic Centre in Delhi, India. *Asian Pacific Journal of Cancer Prevention.* 2013; 14(5)DOI
9. Rastogi Kartick, Gupta Shivani, Bhatnagar AseemRai, Singh Daleep, Gupta Kampra, Choudhary AjaySingh. Compliance to radiotherapy: A tertiary care center experience. *Indian Journal of Cancer.* 2018; 55(2)DOI
10. Matsuyama Robin K., Lyckholm Laurie J., Molisani Anthony, Moghanaki Drew. The Value of an Educational Video Before Consultation with a Radiation Oncologist. *Journal of Cancer Education.* 2013; 28(2)DOI
11. Halkett Georgia, O'Connor Moira. What is the best way to support patients undergoing radiation therapy?. *Journal of Medical Radiation Sciences.* 2015; 62(1)DOI
12. Hansen Olfred, Overgaard Jens, Hansen Hanne Sand, Overgaard Marie, Høyer Morten, Jørgensen Karsten E., Bastholt Lars, Berthelsen Anne. Importance of overall treatment time for the outcome of radiotherapy of advanced head and neck carcinoma: dependency on tumor differentiation. *Radiotherapy and Oncology.* 1997; 43(1)DOI
13. Overgaard J, Alsner J, Eriksen J, Horsman MR, Grau C. Importance of overall treatment time for the response to radiotherapy in patients with squamous cell carcinoma of the head and neck. *Rays.* 2000; 25:313-319.
14. Thames H.D., Bentzen S.M., Turesson I., Overgaard M., Van den Bogaert W.. Time-dose factors in radiotherapy: a review of the human data. *Radiotherapy and Oncology.* 1990; 19(3)DOI
15. Bernier Jacques, Horiot Jean-Claude. Altered-fractionated radiotherapy in locally advanced head and neck cancer. *Current Opinion in Oncology.* 2012; 24(3)DOI
16. Barendsen G.W. Dose fractionation, dose rate and iso-effect relationships for normal tissue responses. *International Journal of Radiation Oncology*Biology*Physics.* 1982; 8(11)DOI
17. Mohanti B K, Nachiappan P, Pandey R M, Sharma A, Bahadur S, Thakar A. Analysis of 2167 head and neck cancer patients' management, treatment compliance and outcomes from a regional cancer centre, Delhi, India. *The Journal of Laryngology & Otology.* 2006; 121(1)DOI
18. Sharma Aman, Madan Renu, Kumar Rajeev, Sagar Prem, Kamal Vineet K., Thakar Alok, Sharma Atul, Mohanti Bidhu K.. Compliance to Therapy—Elderly Head and Neck Carcinoma Patients. *Canadian Geriatrics Journal.* 2014; 17(3)DOI
19. Revannasiddaiah Swaroop, Pant NirdoshKumar, Pandey KailashChandra. Evaluation of factors in relation with the non-compliance to curative intent radiotherapy among patients of head and neck carcinoma: A study from the Kumaon region of India. *Indian Journal of Palliative Care.* 2015; 21(1)DOI
20. Badakhshi Harun, Gruen Arne, Sehouli Jalid, Budach Volker, Boehmer Dirk. The impact of patient compliance with adjuvant radiotherapy: a comprehensive cohort study. *Cancer Medicine.* 2013; 2(5)DOI
21. Yerushalmi R, Gelmon KA. Noncompliance with adjuvant radiation, chemotherapy, or hormonal therapy in breast cancer patients. *Breast Dis.* 2009; 20:197-198.
22. Palwe Vijay, Patil Roshankumar, Pandit Prakash, Nagarkar Rajnish. Factors influencing non-adherence to radiotherapy: a retrospective audit of 1,548 patients from a tertiary cancer centre. *Journal of Radiotherapy in Practice.* 2019; 19(4)DOI
23. Nag Subir, Erickson Beth, Thomadsen Bruce, Orton Colin, Demanes Jeffrey D, Petereit Daniel. The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the cervix. *International Journal of Radiation Oncology*Biology*Physics.* 2000; 48(1)DOI
24. Chumworathayi B, Supraser P, Charoenkwan K, Srisomboon J, Phongnarisorn C, Siriaree S, et al. Weekly versus three-weekly cisplatin as an adjunct to radiation therapy in high-risk stage I-IIA cervical cancer after surgery: A randomized comparison of treatment compliance. *J Med Assoc Thai.* 2005; 88:1483-1492.