Causes of unplanned interruption of radiotherapy*

Causas de interrupção não-programadas da radioterapia

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Abstract

OBJECTIVE: To evaluate the occurrence and causes of unplanned interruption of radiotherapy. **MATERIALS AND METHODS:** Retrospective study developed in the Division of Radiotherapy of Hospital Alemão Oswaldo Cruz in São Paulo, SP, Brazil, with data collected from 560 dossiers of patients submitted to radiotherapy in the period between January 1, 2005 and December 31, 2005. Chi-squared and Student *t* tests were utilized in the data analysis, and $p < 0.05$ was considered as statistically significant. **RESULTS:** Interruption of treatment was identified in 350 cases, corresponding to 62.5% of the patients. The reasons for treatment interruption were the following: preventive device maintenance (55%), patient's own private reasons (13%), adverse reactions to the treatment or to combined radiotherapy/chemotherapy (6%), clinical worsening (3%), two or more combined reasons (23%). The interruption time interval ranged between 1 and 24 days (mean 1.4 day). One-day interruption was mostly due to preventive device maintenance (84.4%); two–five-day interruption was due to combined reasons (48.28%). **CONCLUSION:** The most frequent cause of interruption was preventive device maintenance, with maximum two-day time interval.

Keywords: Radiotherapy; Cancer; Interruptions; Treatment.

Resumo

OBJETIVO: Avaliar a ocorrência e as causas de interrupção não-programadas da radioterapia. **MATERIAIS E MÉTODOS:** Estudo retrospectivo realizado no Serviço de Radioterapia do Hospital Alemão Oswaldo Cruz, na cidade de São Paulo, SP. Os dados foram obtidos dos prontuários dos 560 pacientes submetidos a radioterapia, de 1º de janeiro de 2005 a 31 de dezembro de 2005. Os dados foram analisados pelos testes qui-quadrado e *t* Student, e os valores de $p < 0,05$ foram considerados com significância estatística. **RESULTADOS:** Foram identificados 350 pacientes que interromperam seus tratamentos, o que representou 62,5% do total da amostra. Os motivos foram: manutenção do aparelho (55%), motivos particulares dos pacientes (13%), reações do tratamento ou da associação com quimioterapia (6%), piora clínica (3%), associação de motivos (23%). O intervalo de tempo de interrupção variou de 1 a 24 dias, com média geral de 1,4 dia. Na interrupção de um dia a maior incidência foi ocasionada pela manutenção (84,4%); de dois a cinco dias a interrupção foi causada pela associação de motivos (48,28%). **CONCLUSÃO:** A causa mais freqüente de interrupção encontrada foi a manutenção preventiva e seu intervalo máximo foi de dois dias.

Unitermos: Radioterapia; Câncer; Interrupções; Tratamento.

INTRODUCTION

The combination of early diagnosis and current therapeutic methods (radiotherapy, chemotherapy, surgery and bone marrow transplant) has allowed the achievement of increasing survival rates and better quality of life for patients considered as incurable[1].

Currently, radiotherapy is considered as the most effective curative treatment after surgery for cancer. About one third of the population will develop the disease, and will require this therapeutic modality, and 60% of the patients will be submitted to radiotherapy for curative purposes, often combined with surgery and chemotherapy[2].

Studies in the literature have evidenced the influence of the total duration of the treatment on the local management of the disease. Such studies suggest that this influence occurs not only in cases of patients receiving radical therapy (exclusively radiotherapy), but also in cases of patients receiving adjuvant radiotherapy or combined radiotherapy/brachytherapy[3,4]. The unplanned increase in the total radiotherapy duration may cause alteration in the local management of the disease reducing cure rates[5].

Most of times, conventional treatments with radiotherapy are delivered in five weekly fractions of 1.8 Gy to 2.0 Gy throughout an uninterrupted variable period of two-eight weeks, depending on the disease to be treated; however, alterations in the therapeutic scheme may occur, like in cases of accelerated fractioning (1.8 Gy to 2.0 Gy in two or three fractions/day, with the same total dose in half of time, hyperfractioning (1.1 Gy to 1.2 Gy in two or three fractions/day), hypofractioning (two or three fractions/week). The fractioning is

aimed at allowing the normal cells recovery after each fraction delivery[6].

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 management of the disease[7]. Treatment delay, planned or unplanned radiotherapy gap, resulting in extension of the total treatment duration, represent relevant factors affecting the management of the disease[8].

Variations in the indication for treatment, as adjuvant, radical or palliative radiotherapy, also define different variables in the influence exerted by the above-mentioned factors. Failures in the sequence of five weekly fractions are defined as interruptions, provided they are not planned by the radiotherapist, while weekends are considered as part of the five-weekly-fraction scheme with a two-day interval, not being considered as interruptions[9].

The effects from radiotherapy interruption on the treatment outcomes in head and neck tumors are widely known[8]. Studies in the literature[3,4] report the negative effects from radiotherapy interruption.

Adverse effects from the extension of the total treatment duration as a result of radiotherapy interruption also have been observed in cases of postoperative radiotherapy where intervals of > 10 days resulted in a 10% to 20% decrease in the five-year survival rate[7].

Videtic et al.[10] have analyzed the radiotherapy interruption effect on patients with small cell lung cancer treated with combined radiotherapy/chemotherapy, and concluded that this gap, even if utilized to minimize adverse side effects, affected the local management of the disease and reduced the survival of these patients.

Chen et al.[11] have found results indicating 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.

Perez et al.[12] have reported that patients with stage T2 prostate cancer presented pelvic failures and poorer responses when the overall treatment time was > 9 weeks, as compared with those who completed the treatment in less time; however,

worsening of the response has not been evidenced in patients treated with doses > 72 Gy.

Maciejewski & Majewski[13] have evaluated patients with invasive bladder cancer, reporting that the prolongation of the overall treatment time from 40 to 55 days reduces the rate of local management from 50% to 5%.

According to the "Guidelines for the management of a radical unscheduled interruption or prolongation of a radical course of radiotherapy"[14], studies demonstrate that the minimum interruption interval which may significantly affect the treatment outcome is around two days; although these guidelines also mention that any interruption resulting in prolongation of the overall treatment time is potentially hazardous; these studies also report that interruptions occur in more than 30% of treatments.

According to the mentioned Guidelines[14], the causes of treatment interruptions may be considered as follows: a) the foreseeable causes, i.e., those scheduled or previously known — preventive equipment maintenance, local and national public holidays, specific treatment schemes with only two or three weekly fractions, and non-overlapping treatment in cases of combined teletherapy/brachytherapy; b) the unforeseeable ones, i.e., those unscheduled — occurring because of the treatment toxicity (acute effects of the treatment), especially in cases of combined radiotherapy/chemotherapy, clinical intercurrences, equipment breakdown, and also patients´ private reasons.

At the level of institutions, the most frequent interruptions occur because of planned preventive equipment maintenance, equipment breakdown and public holidays.

Studies[3,4,7,14] approach the methods utilized to counterbalance the interruptions effects, however, a consensus on this issue is still to be reached.

According to Dale et al.[3], interrupted treatments should be individually analyzed, considering the absence of an universal method to solve all the resulting problems. Once the interruption has occurred, it is necessary to determine the number of missed fractions, and try to complete the treatment within the previously determined

period (treating the patient twice a day or, alternatively, continuing the treatment over a weekend). Another alternative is to introduce an altered fractionation schedule to compensate the interruptions. The quadratic-linear model currently prevails in the field of radiobiology[15], but this topic is not under the scope of the present study.

The present study was aimed at evaluating the occurrence and causes of unplanned radiotherapy interruptions, and analyzing the reasons and interruption time intervals.

MATERIALS AND METHODS

The present retrospective study was developed in the Department of Radiotherapy at Hospital Alemão Oswaldo Cruz, in the city of São Paulo, SP, Brazil. Data were collected from the dossiers of 560 patients submitted to radiotherapy in the period between January 1st and December 31st, 2005. This center assists private/health insurance patients (public health system patients excluded) in the hospital/hospital-day and in other institutions. All of the patients underwent treatment in a 6 MV Varian (Clinac) linear accelerator. The moments of the interruptions along the treatments were not analyzed in the present study.

Weekends and public holidays were excluded from the analysis, and were not considered as interruptions for the purposes of the present study. However, in cases of public holydays falling near a weekend, with a working day between them, this working day without treatment was considered as an interruption.

Variables evaluated were the following: sex, age, International Disease Code (IDC), combined radiotherapy/chemotherapy, presence of absence of treatment interruption in consecutive days or not, and, in case of presence of interruption, classification into 1–5-day intervals, 6–15-day intervals or more-than-16-day intervals. Reasons for these interruptions also were taken into consideration.

The reasons for treatment interruption were classified into treatment effects, clinical worsening as a result of the disease and not of the treatment, patients' private reasons, preventive equipment maintenance,

equipment breakdown, and also a combination of reasons, when two or more of the previously mentioned reasons caused treatment interruption.

Data were tabulated and entered into an Excel worksheet, and statistically analyzed by means of chi-squared and t-Student tests, with values corresponding to $p < 0.05$ being considered as statistically significant.

RESULTS

In a sample of 560 patients included in the present study, 261 were men, and 299, women, with ages ranging from 5 to 94 years (mean = 58 years, standard deviation = 9); statistical differentiation of sex was not taken into consideration. In the analysis of ages, patients with > 40 years represented 86.5% of the whole sample.

The IDC was redistributed according to tumors localization, independently from their staging: breast, 201 patients (36%); abdomen and pelvis, 112 patients (20%); prostate, 106 patients (19%); chest, 79 patients (14%); and other types (11%), which will not be described because of their low incidence; breast and prostate tumors were separately analyzed, considering their higher incidence as compared with the others.

As regards radiotherapy interruption, 350 patients who interrupted their treatment were identified in the present study, representing 62.5% of the sample. The reasons for interruptions were classified into five different types according to the recommendations included in to previously mentioned Guidelines[14] (Table 1).

The patients presenting combined reasons for treatment interruption were reclassified as to determining the types of reasons for such interruptions. Seventy-one of these patients, corresponding to 89.9%, had their radiotherapy interrupted because of preventive equipment maintenance.

As regards interruption time interval, the patients were divided into three groups — one-day interruption, two–five-day interruption and six or more days of interruption — with the respective reasons for these interruptions (Table 2).

Most frequently, one-day-interruptions were caused by preventive equipment maintenance (84.41%); on the other hand, none of the six-day interruptions (0%) was caused by preventive equipment maintenance.

The interruption time interval ranged from one to 24 days (mean = 1.4, standard deviation = 9.5) Table 3).

The low average of days (1.2 days) without treatment because of preventive equipment maintenance is the evidence of

an appropriate quality control, avoiding extended periods without treatment caused by equipment breakdown.

Two groups of patients who has presented treatment interruptions were statistically analyzed by means of the chi-squared test: the first group included all the patients who had their treatment interrupted because of equipment maintenance, and the second one, for other reasons, demonstrating statistical significance ($p = 0.000000010$).

The result of the statistical analysis of the interruption time interval, also demonstrated statistical significance in the comparison between these same groups [equipment maintenance (1.73) versus other reasons (3.85)], i.e., the patients remained without treatment for longer periods because of other reasons than for equipment maintenance (t Student average of maintenance days versus other reasons: $p = 0.0000000063$).

Statistical significance also was found as a result of the comparison between the mean interruption time interval because of clinical worsening (8.42 days) versus patients' private reasons: $p = 0.014680042$.

The analysis of the mean interruption time interval related to reactions to the treatment (5.8) versus patients' private reasons (1.8) also demonstrated statistical

Table 1 Classification of reasons for treatment interruption.

Interruption reasons	n	%
Preventive equipment maintenance	193	55%
Patients' private reasons	46	13%
Reactions to the treatment itself or association with chemotherapy	20	6%
Clinical worsening as a result of the disease	12	3%
Combined reasons (two or more reasons have caused the interruption)	79	23%

n, number of patients.

Table 2 Interruption reasons and time interval.

	Interruption					
	One day		2–5 days		6 or more days	
Reasons	n	%	n	%	n	%
Preventive equipment maintenance	157	84.41	36	24.82	0	0.00
Patients' private reasons	26	13.98	19	13.10	1	5.26
Reactions to the treatment itself or association with chemotherapy	2	1.08	1	6.89	8	42.11
Clinical worsening as a result of the disease	1	0.54	7	4.83	4	21.05
Combined reasons (two or more reasons have caused the interruption)	0	0.00	73	50.34	6	31.58

n, number of patients.

Table 3 Mean number of days without treatment.

Reasons	Number of days (mean)
Preventive equipment maintenance	1.2
Patients' private reasons	1.8
Reactions to the treatment itself or association with chemotherapy	5.8
Clinical worsening as a result of the disease	8.42
Combined reasons (two or more reasons have caused the interruption)	3.25
Overall	1.4

significance, corroborating the relevance of treatment side effects when the patients' adherence to the treatment is considered (t Student average reaction to the treatment days *versus* patients' private reasons: $p = 0.000982904$).

No statistical significance was found in the sample of the present study in the comparison between the groups of patients with reactions to the treatment (5.8 days) and clinical worsening (8.42 days), probably because of the low number of patients included in these groups (t Student test – mean number of days – reaction to treatment versus clinical worsening: $p = 0.310165484$).

DISCUSSION

This is the first Brazilian study evaluating the causes of unplanned interruption of radiotherapy.

James et al.[16], in a national audit study about head & neck cancer developed in the United Kingdom, have evaluated the management of treatment interruptions in 55 radiotherapy centers, and have found a rate of interruption of 55% corresponding to 1,506 of 2,553 patients who have interrupted their treatments; however, when extended treatment period (one additional day) was taken into consideration, the mean interruption rate increased to 73%.

Duncan et al.[17] have reported 68.9% of cases of treatment interruption in their study with 383 patients with larynx cancer.

Erridge et al.[18] have found 425 patients (66%) who had interrupted their treatment with external and intracavitary radiotherapy for uterine cervix cancer.

The "Guidelines for the management of a radical unscheduled interruption or prolongation of a radical course of radiotherapy"[14] reported 66% of treatment interrup-

tion in cases of patients with laryngeal tumors.

Bese et al.[9], in the first study evaluating the effects from treatment interruptions in 853 patients with breast cancer have found 87% of them who had interrupted their treatment.

González San Segundo et al.[8] remark the scarcity of studies evaluating treatment interruptions incidence.

In the present study concerning the occurrence of treatment interruption, 350 patients (62.5%) had their treatment interrupted for at least one day.

No other similar study evaluating a whole sample of patients was found in the literature, but interruption rates similar to other studies were found, corroborating the correctness of the methodology utilized in the present study.

In the present study, the reasons for treatment interruption were classified according the above mentioned Guidelines[14] (preventive equipment maintenance, representing 61% of reasons for treatment interruption, followed by unexpected equipment breakdown with 19%, reactions to treatment with 14%, and finally, patient's private reason with 6%).

In addition, in the present study, equipment maintenance (55%) represented the main reason for treatment interruption, followed by patient's private reasons (13%) and reactions to the treatment itself or to combined radiotherapy/chemotherapy (6%). The interruption rate for reasons of clinical worsening was the lowest (3%).

In the present study, combined reasons (two or more reasons causing the interruption) presented a 23% incidence, but correlate studies were not found among those reviewed.

The results of the present analysis were statistically significant, demonstrating the

impact of the preventive equipment maintenance on the incidence of treatment interruptions.

The interruption time interval ranged between one and 24 days (mean = 1.4 day).

Studies reviewed[5,17,19,20] on cases of head and neck cancer suggest that an unscheduled one-day interruption may result in 1.4% absolute decrease in the local management of the disease; on the other hand, about seven days of interruption in the treatment may cause a decrease in the local management of the disease ranging between 3% and 25%, adversely affecting the response to the therapy. However, these studies have shown to be inconclusive as for the phase of the treatment where the interruptions occurred (e.g., early, middle or later phases)[5,14].

Most frequently (84.4%), one-day interruptions occurred because of equipment maintenance, followed by patients' private reasons (13.9%); 48.28% of 2–5-day interruptions occurred because of combined reasons, and in 89.9% of these cases, one of the reasons was equipment maintenance; 42.11% of 6-or-more-day interruptions were caused by reactions to the treatment and none (0%) by equipment maintenance, demonstrating an appropriate quality control, avoiding extended periods without treatment because of equipment breakdown.

Suwinski et al.[5] reports that intervals of less than five days do not affect the incidence of disease recidivation, and recommends that, in cases where interruptions cannot be avoided, it should at least have its time interval reduced.

Bese et al.[9], in a study evaluating the effect of the treatment interruption in cases of breast cancer, report that they have not found adverse effects resulting from less-than-seven-day interruptions; on the other hand, in cases where the interruption duration was longer, they have found about 5% decrease in the local management of the disease.

Considering the different characteristics of the present study, the effects from treatment interruptions were not evaluated, but it is important to note that the average number of interruptions was relatively low.

Radiotherapy centers should accomplish periodical preventive equipment maintenance at least every three months, in

order to guarantee good quality assistance to patients, avoiding frequent equipment breakdowns that would contribute for more frequent and longer interruptions.

González San Segundo et al.[8] highlight the unquestionable necessity of quality control programs in radiotherapy centers, including dosimetric controls and preventive equipment maintenance with an appropriate periodicity to avoid that patients are submitted to treatment interruptions without any scientific grounds or evidence of effectiveness and safety.

According to Calcina et al.[21], radiotherapy centers should schedule fundamental and essential quality control tests for all of their equipment as necessary and according to their availability, assuring an appropriate treatment to the patients. Steps towards the management of treatment interruptions or extensions are described in the "Guidelines for the management of a radical unscheduled interruption or prolongation of a radical course of radiotherapy"[14] recommending an appropriate provision of human and physical resources (infrastructure), as well as the transference of the patient to another equipment in case of equipment maintenance or breakdown.

The following considerations should be taken into account:

– How many Brazilian radiotherapy centers could count on two radiotherapy apparatuses?

– If any, not always these apparatuses are technically similar, i.e. with different energies.

– How could the patients be transferred during equipment maintenance?

– Would it be actually feasible, considering that frequently there is a waiting time for treatment as a result from resources (equipment) scarcity?

– Would it be worthwhile to schedule equipment maintenance on weekends?

In Brazil, the monthly cost for preventive equipment maintenance on working days reaches US$ 2,500. In case of equipment maintenance on weekends, this cost increases to about US$ 3,500.

An study developed by Giessen et al.[22] reports annual values of about US$ 3,000 to US$ 91,740 (mean = US$ 41,390) for maintenance of linear accelerators (including spare parts).

The daily income generated by a linear accelerator is US$ 1,800 corresponding to: the cost per field (R$ 0.27) according to the AMB Table (Brazilian Medical Association), for 60 patients/day (12 equipment-hours/day × five patients/hour) with 2.5 fields per patient, on average. As a result, preventive equipment maintenance on weekends, is financially unfeasible.

Treatment interruptions occurring as a result of holidays, equipment breakdowns, or for social reasons used to be more easily accepted in the past as a function of the unawareness of tumors treatment methods and radiobiology[8], when the concepts of cumulative effects and standard dose were widely disseminated as mechanisms for counterbalancing treatment interruptions. Presently, new methods corroborate the effective biological effects as the best methods for counterbalancing interruptions, especially those with longer intervals[3,7,16,18].

The mentioned Guidelines[14] also recommend avoiding extended treatment interruptions.

In Brazil, some centers close for four to five consecutive days because of bridged holidays. Unfortunately, this practice is extremely frequent, especially when a holiday falling on a Wednesday causes the center to remain closed up to the next Monday, and these bridged days are not paid.

Additionally, efforts should be undertaken to improve the management of the reactions to the treatment and, consequently, reduce the risk for long treatment intervals.

For this purpose, patients should receive multiprofessional assistance not only from the radiotherapist but also from specialized nurses, nutritionists, dentists and others to minimize possible reactions to the treatment. Early in the treatment, guidance manuals should be given by nurses to the patients[23], facilitating the patients' adherence to the treatment.

Chen et al.[24], 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.

Considering the complexity of this theme, further, deeper studies in other radiotherapy centers are required to validate the methodology utilized, allowing the implementation in Brazil of guidelines regarding the management of treatment interruptions.

No other similar study if found in the literature evaluating a whole sample of patients, however similar rates of interruption were found in other studies, corroborating the correctness of the methodology utilized in the present study.

In conclusion, the most frequent cause of interruption is preventive device maintenance, with maximum two-day time interval.

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