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Original Article

Impact of non-adherence to radiotherapy on 1-year survival in cancer patients in Catalonia, Spain

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ABSTRACT

Background: This study aims to assess the effects of non-adherence to external beam radiation therapy in cancer patients receiving treatment with a curative.
Methods: This retrospective cohort study collected health records data for all cancer patients treated with external beam radiotherapy with curative intent in 2016 in Catalonia, Spain. Adherence was defined as having received at least 90% of the total dose prescribed. A logistic regression model was used to assess factors related to non-adherence, and its association with one-year survival was evaluated using Cox regression.
Results: The final sample included 8721 patients (mean age 63.6 years): breast cancer was the most common tumour site (38.1%), followed by prostate and colon/rectum. Treatment interruptions prolonged the total duration of therapy in 70.7% of the patients, and 1.0% were non-adherent. Non-adherence was associated with advanced age, female gender, and some localization of primary tumour (head and neck, urinary bladder, and haematological cancers). The risk of death in non-adherent patients was higher than in adherent patients (hazard ratio [HR] 1.63, 95% confidence interval 0.97–2.74), after adjusting for the potential confounding effect of age, gender, tumour site and comorbidity.
Conclusion: Non-adherence to radiotherapy, as measured by the received dose, is very low in our setting, and it may have an impact on one-year survival.

Adherence to chemotherapy and hormone therapy has proven to be a relevant problem in cancer patients undergoing different treatment regimens [1–3]. Adherence is defined as the degree to which the patient's behaviour is consistent with the therapy prescribed by their doctor, and normally it is measured as the percentage of doses received relative to those indicated. The most typical cutoff to define adherence in these terms is 80% [4]. In patients with breast cancer, non-adherence is associated with a higher risk of recurrence and death [5,6]. One literature review estimated the proportion of patients with breast cancer who are adherent to hormone therapy during their first year of treatment at 79%, dropping to 56% in the fifth year [7].

Radiotherapy differs from oral endocrine therapy and chemotherapy in that it generally has a short duration (maximum 8 weeks) and entails regular medical and technical supervision over the course of treatment. This context is favourable to high adherence rates once the patient has agreed to undergo treatment. As a result, assessing adherence has not been considered very relevant in radiation oncology, and what research has been published is oriented toward assessing interruptions (missed appointments during the course of treatment) rather than evaluating adherence in terms of receiving the prescribed doses [8,9].

Since the 1990s, the public healthcare system in Catalonia (Spain) has maintained a registry of all patients receiving radiotherapy with public financing. This study makes use of these data,

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aiming to assess adherence to external radiotherapy measured by the percentage of the total dose received in all cancer patients treated with radiotherapy and the impact on one-year survival.

Material and methods

The initial cohort included all cancer patients indicated for treatment with radiotherapy in 2016, provided they had received at least one fraction of the prescribed treatment. We collected retrospective data from the register of patients treated with external beam radiotherapy in the 11 publicly funded radiation oncology services in Catalonia. This represents about 90% of all patients receiving radiation therapy in the region.

The variables included were: hospital, age, gender, tumour site targeted, treatment indication (curative versus palliative), total doses and sessions prescribed, final doses and sessions received, date of treatment initiation and finalization, and treatment interruptions and their causes. The causes of interruption considered included those related to the equipment (both unexpected breakdowns and planned maintenance); logistical challenges affecting patients (usually transport); public holidays; medical problems related to the patient (disease progression, intercurrent illness, and/or treatment change); and personal reasons. It was possible to consider more than one cause of treatment interruption in the analysis. The minimum basic discharge data set was the source of data to identify the comorbidity (Charlson Comorbidity Index) of patients before starting radiotherapy treatment. Vital status was ascertained from the Catalan Health Service database of insured persons, which is updated monthly with the official mortality statistics. For reasons of confidentiality, it was not possible to obtain data on the specific cause of death.

The analysis was restricted to the patients receiving treatment with a curative intent, defined from the standard prescribed sessions according to tumour site. This number of sessions was established for each tumour site; this definition allowed for some patients with metastasis to be included in the cohort, but these patients were excluded from the analysis. We also excluded from this analysis patients under the age of 18, those receiving only brachytherapy, patients with treatment interruptions for medical reasons (poor general condition due to treatment, disease progression, intercurrent illness, and/or treatment change), and those who died within the first month of finishing treatment. We considered these to be cases with an inappropriate indication for radiotherapy with a curative intent.

Adherence was calculated as the percentage of doses received relative to those prescribed. The cut-off was set at 90%, in agreement with clinicians and taking into account the type of treatment under study (short duration) and its therapeutic importance. In our care context, the radiation oncology services have protocols in place to calculate the necessary doses according to the service-related, logistical, or schedule-related interruptions experienced, and to extend the length of treatment in order to ensure that patients receive at least the total doses prescribed. Patients who did not receive 90% of the total dose due to non-medical reasons, including patient-related ones, were considered non-adherent.

We performed a descriptive statistical analysis of the variables and a multivariable logistic regression, using adherence as the outcome variable and adjusting for hospital, age, gender, comorbidity and tumour site. Results are expressed as odds ratios (OR) with their 95% confidence intervals (CI). For the survival analysis, we constructed a Kaplan-Meier curve and fit a Cox proportional hazards model, adjusting for age, sex, hospital, comorbidity and the diagnosis motivating the radiotherapy indication. All analyses were undertaken using SPSS software (version 21).

Results

Fig. 1 presents the patient selection flowchart. Of the 15,501 patients treated, 371 were excluded because they did not meet the inclusion criteria, 5133 because they received radiotherapy with a palliative intent, 728 because the patients stopped treatment for medical reasons, 446 because they had metastasis and

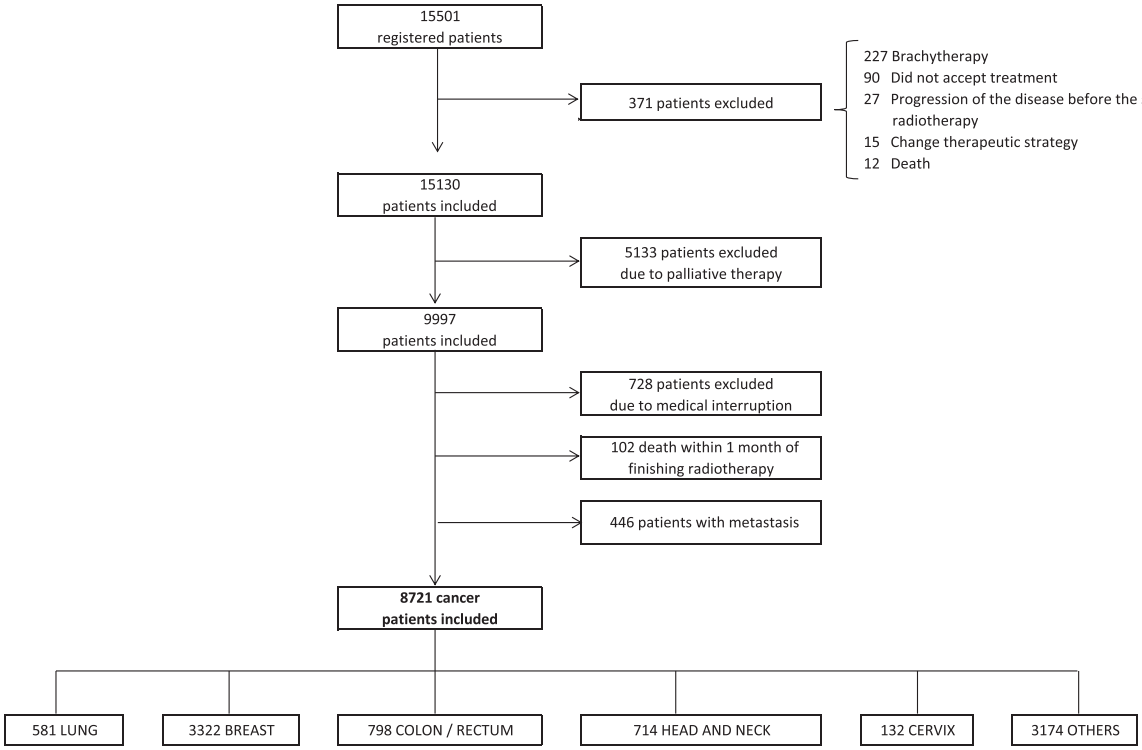


Fig. 1. Flow chart of patients.

102 who died within a month of finalizing treatment. The final cohort was 8721 patients: 38.1% had breast cancer; 16.5%, prostate cancer; and 9.2%, colorectal cancer. Smaller proportions had cancers of the head and neck, the lung, and other types.

Table 1 shows the patient characteristics. Over half were women, and their mean age was 63.6 years. One per cent were non-adherent. Treatment interruptions for any reason affected 70.7% of the patients with at least one missed appointment. Most of the interruptions were related to equipment failures/maintenance and public holidays. Just 4.8% of the treatments were interrupted for personal reasons, while 13.0% of the interruptions were for other reasons. Interruptions extended treatment duration by more than two days in 69.1% of the cases (6020/8712). Also, 45.6% of de patients had no comorbidities.

Table 2 presents the factors related to non-adherence (less than 90% of the prescribed doses received). Women showed similar adherence than men (OR 1.19 95% CI 0.63–2.24). Advanced age appeared to confer a higher risk of non-adherence; however, neither the results for gender nor age were statistically significant. Some diagnoses did show a significant association with non-adherence, including tumours of the head and neck (OR 2.64 95% CI 1.01–6.91). Patients with haematological cancers (OR 2.80 95% CI 0.290–8.76) and cervical cancer (OR 2.08 95% CI 0.47–9.09) also tended to be less adherent. On the other hand, patients with breast and prostate cancers showed high levels of adherence. Non adherence increased with number of comorbid pathologies, although this association was not statistically significant.

Table 3 presents the results of the Cox model. After adjusting for age, gender, hospital, comorbidity and diagnosis, there was a not statistically significant difference in survival between patients who did and did not receive at least 90% of the planned treatments. Non-adherent patients had a higher risk of death at one year compared to adherent ones (OR 1.63 95% CI 0.97–2.74). Fig. 2 shows the survival curve according to adherence, as defined by percentage of the dose received (excluding patients who stopped treatment for medical reasons). When the analysis focused on patients who dropped out for exclusively personal reasons, the risk of mortality was also double, although given the low volume of cases (only 291 patient dropped out exclusively for patient-related reasons) the results did not reach statistical significance after adjusting for age, gender, tumour site and comorbidity (OR 1.88 95% CI 0.41–8.61).

Discussion

The proportion of patients who did not adhere to radiotherapy (as measured by those not receiving a sufficient percentage of their prescribed doses) was very low compared to that observed in patients receiving other oncological treatments, like oral chemotherapy or hormone therapy. Just 1.0% of all 8721 included patients receiving radiotherapy with curative intent in 2016 in Catalonia suspended their course of treatment before reaching 90% of the total doses prescribed. When non-adherence was attributable to non-medical reasons (progression of the disease, intercurrent disease and/or change of therapy), it was associated with lower one-year survival. This result clearly indicates that radiotherapy is associated with high rates of adherence in our setting, thanks in part to its short duration and the strict medical supervision involved. Classically, shorter treatments are associated with a lower risk of non-adherence [10].

This result implies two relevant corollaries: first, non-adherence to radiotherapy is associated with an increased risk of death in cancer patients receiving this therapy, and second, there are some factors that can slightly increase the risk of non-adherence, including advanced age and diagnosis of some tumour types.

Adherence is probably of special importance for tumour sites such as the head and neck, bladder and cervix, as well as haematological cancers, which in our setting were all associated with a higher risk of non-adherence. It is possible that these patients dropped out of treatment for reasons that are not contemplated in our study, for example socioeconomic determinants [11]. In studies performed in populations with low socioeconomic status, tumours of the cervix and the head and neck were also associated with a greater risk of missed appointments in multivariable analysis [8]. Elsewhere, too, head and neck cancers were associated with a greater risk of missed appointments, as reported by Rangarajan in India [12].

In radiation oncology, a large and consistent body of evidence shows that treatment interruptions for any reason worsen the patient's prognosis [11,13–17]. This knowledge underpins the notable efforts made to compensate interruptions with additional fractions in order to administer at least the prescribed doses by treatment end. The number of interruptions due to weekday public holidays is very high in our country. This factor and others mean

Table 1
Description of patient characteristics (N = 8721*).

	n	%
Gender		
Men	3955	45.4
Women	4766	54.6
Age (mean 63.6 ± 13.5 years)		
≤49 years	1298	14.9
50–59 years	1843	21.1
60–69 years	2368	27.2
70–79 years	2250	25.8
≥80 years	962	11.0
Tumour site		
Head and neck	714	8.2
Colorectal	798	9.2
Trachea, bronchus, lung	581	6.7
Skin	132	1.5
Breast	3322	38.1
Bones and connective tissues	129	1.5
Uterus	178	2.0
Prostate	1436	16.5
Urinary bladder	80	0.9
Central nervous system	303	3.5
Haematological	305	3.5
Cervix	132	1.5
Other digestive	326	3.7
Other	385	3.3
Concomitant chemotherapy		
Yes	2202	25.2
No	6218	71.3
Unknown	301	3.5
Comorbidities		
Non	3978	45.6
1–2	1771	20.3
3+	432	5.0
Unknown	2540	29.1
Death at one year	824	9.8
Non-adherent	87	1.0
Total treatment interruptions due to:	6170	70.7
Equipment	3884	62.9
Personal reasons	297	4.8
Logistical reasons	805	13.0
Public holidays	5191	84.1
Days of treatment prolongation		
≤2 days	2692	30.9
3–4 days	2509	28.8
5–7 days	2051	23.5
8–9 days	613	7.0
≥10 days	847	9.7

* Total number of cases *N* = 8721. The difference relative to the total N corresponds to missing values.

Table 2
Prognostic and therapeutics factors associated with non-adherence.

		Non-adherence			
		N	(% Non-adherent)	ORa (95% CI)	*p*
Adherent		8595	1.0		
Gender	Men	3890	1.1	1	
	Women	4705	0.9	1.19 (0.63–2.24)	0.589
Age group	≤49 years	1285	1.1	1	
	50–59 years	1820	1.0	1.05 (0.51–2.16)	0.898
	60–69 years	2327	0.6	0.61 (0.28–1.33)	0.212
	70–79 years	2218	1.1	1.12 (0.54–2.36)	0.759
	≥80 years	945	1.6	1.37 (0.61–3.07)	0.448
Tumour site	Colorectal	784	0.8	1	
	Head and neck	695	2.3	2.64 (1.01–6.91)	0.048*
	Trachea, bronchus, lung	570	1.1	1.35 (0.43–4.29)	0.609
	Skin	130	2.3	2.42 (0.58–10.12)	0.225
	Breast	3283	0.7	0.77 (0.28–2.09)	0.608
	Bones & connective tissues	129	2.3	2.56 (0.60–10.86)	0.203
	Uterus	172	1.2	1.13 (0.21–5.99)	0.888
	Prostate	1418	0.8	1.10 (0.39–3.07)	0.863
	Urinary bladder	79	3.8	4.69 (1.08–20.24)	0.039*
	Central nervous system	293	0.7	0.70 (0.14–3.60)	0.671
	Haematological	305	2.3	2.80 (0.90–8.76)	0.077
	Cervix	132	2.3	2.08 (0.47–9.09)	0.333
	Other digestive	324	0.0	-	0.994
	Other	281	0.7	0.83 (0.16–4.22)	0.818
Comorbidities	0	3913	0.8	1	
	1–2	1733	1.2	1.30 (0.72–2.36)	0.380
	3+	424	1.7	1.71 (0.72–4.07)	0.224
	Missing	2525	1.1	1.34 (0.80–2.25)	0.268
Interruptions	No	2542	1.3	1	
	Yes	6053	0.9	1.32 (0.76–2.29)	0.323
Causes of interruption					
Equipment	No	2278	1.4	1	
	Yes	3775	0.6	0.58 (0.32–1.07)	0.081
Personal reasons	No	5756	0.5	1	
	Yes	297	9.4	19.65 (10.19–37.87)	<0.001*
Logistical reasons	No	5248	0.9	1	
	Yes	805	1.1	1.79 (0.71–4.55)	0.219
Public holidays	No	950	2.9	1	
	Yes	5103	0.5	0.19 (0.11–0.35)	<0.001*
Death at one year	No	7493	0.9	1	
	Yes	806	1.9	1.82 (0.96–3.44)	0.066

n (%): number of cases (% non-adherence); The difference relative to the total N corresponds to missing values.
ORa: odds ratio adjusted for centre, age group, gender, diagnosis, Comorbidities; CI: confidence interval.
* Statistical significance, $P < 0.05$.

that only about a third of the treatments in our setting finish by the expected date, necessitating a substantial effort in clinical management to complete the prescribed doses on time. The success of these efforts is evidenced by the low number of patients who do not receive their full dose once treatment has started. Thus, even the patients whose treatment duration is extended by more than two days have a high probability of finally receiving the totality of the prescribed dose, with the subsequent benefits on their prognosis. There is another option to cope with this problem, namely, adding a second fraction on some treatment days, which was the option chosen in 12.1% of the cases in our cohort. Another option would be to work on Saturdays, as in other countries, which would solve both problems (doses and overall treatment time), but this option is not easily applicable in our health system due to management criteria for organizing of delivery of radiation oncology.

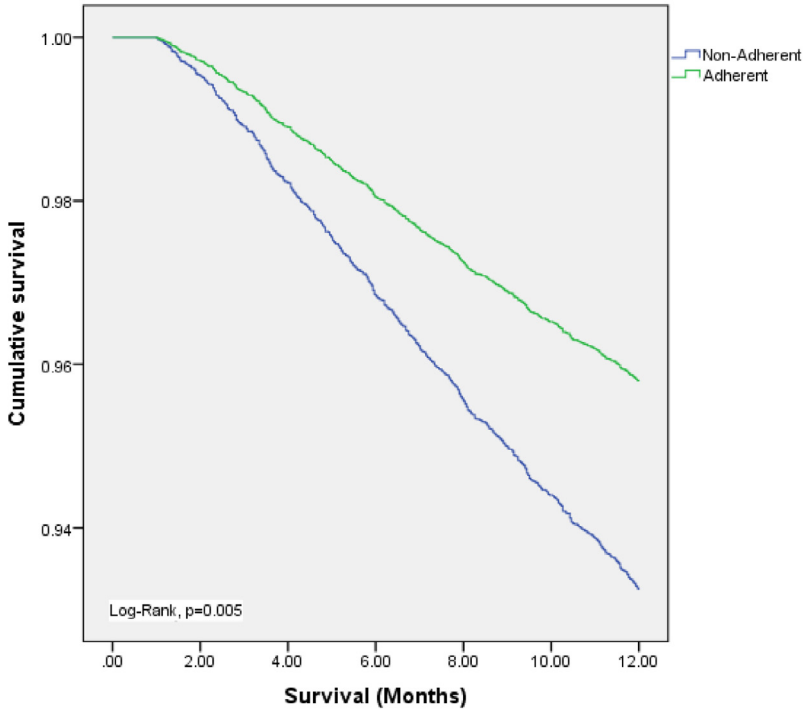
These results also pose a problem related to measuring adherence in radiation oncology, as practically all the published literature uses missed appointments, classified with criteria similar to ours, to study this endpoint. In fact, even in a clinical trial performed in patients with high-risk tumours, like those of the head and neck, the probability of missed appointments was very high, affecting up to 70% of the included patients. In an estimated 12.7% of the cases, this kept patients from receiving their full dose, and a quarter saw their treatment duration extended by more than five days [18]. Thus, adherence can be conceived in two ways: as missed appointments and as the proportion of doses received relative to those prescribed. With some exceptions [18], researchers have focused on the former, analysing the dose received only in a complementary way. In contrast, our study sheds light on the impact of doses on the patient's prognosis, which should be analysed independently from the prolongation of the treatment duration, even though its quantitative impact is limited. In that sense, our proposal builds on Khalil's work studying the impact of the total dose lost as a necessary measure to complement the data on missed appointments. Indeed, the effectiveness of the treatment is a function of both the total doses administered and the treatment time and fractioning.

Another aspect to highlight is that in this project, we made a considerable effort to specify the causes of the treatment interruption. In some cases, treatments were interrupted for more than one reason, and in our analysis, we excluded the patients whose treatment was interrupted for medical reasons upon careful review by the attending clinicians. We considered only patients who were non-adherent for other reasons, and this decision could explain

Table 3
Cox regression for one-year survival.

		Survival at one year of treatment end			
		n	(% died)	HRa (95% CI)	*p*
Death at one year of treatment end		8299	9.7		
Adherence	Adherent	8216	9.6	1	
	Non-adherent	83	18.1	1.63 (0.97–2.74)	0.066
Gender	Male	3808	14.2	1	
	Female	4608	6.2	0.93 (0.78–1.11)	0.416
Age group	≤49 years	1243	6.3	1	
	50–59 years	1775	7.0	1.06 (0.79–1.43)	0.690
	60–69 years	2286	9.5	1.40 (1.06–1.85)	0.017*
	70–79 years	2185	10.7	1.80 (1.36–2.38)	<0.001*
	≥80 years	927	18.6	2.64 (1.96–3.56)	<0.001*
Tumour site	Colorectal	765	6.5	1	
	Head and neck	681	18.9	3.40 (2.43–4.77)	<0.001*
	Trachea, bronchus, lung	561	32.3	5.44 (3.94–7.52)	<0.001*
	Skin	129	24.0	2.69 (1.69–4.28)	<0.001*
	Breast	3223	1.7	0.31 (0.20–0.47)	<0.001*
	Bones and connective tissues	124	14.5	2.59 (1.47–4.56)	<0.001*
	Uterus	170	5.9	0.79 (0.37–1.70)	0.551
	Prostate	1397	1.3	0.17 (0.09–0.29)	<0.001*
	Urinary bladder	79	44.3	5.63 (3.59–8.82)	<0.001*
	Central nervous system	291	35.1	7.98(5.56–11.43)	<0.001*
	Haematological	286	8.7	1.50 (0.92–2.45)	0.104
	Cervix	127	15.7	3.07 (1.79–5.27)	<0.001*
	Other digestive	311	33.4	6.25 (4.42–8.86)	<0.001*
	Other	272	16.5	2.70 (1.77–4.10)	<0.001*
Comorbidities	0	3953	7.8	1	
	1–2	1763	14.7	1.15 (0.96–1.36)	0.128
	3+	431	21.3	1.35 (1.05–1.72)	0.017*
	Missing	2269	7.3	0.90 (0.74–1.09)	0.273

n (%): number of cases (% of death patients at one year of treatment end).
The difference relative to the total N corresponds missing values.
HRa: hazard ratio adjusted for centre, age group, gender, diagnosis, comorbidities; CI: confidence interval.
*Statistical significance, $P < 0.05$.



	N at Risk	at 1 year
Non adherent	83	68
Adherent	8204	7425

Fig. 2. Overall survival by adherence.

why our results showed a much lower proportion of non-adherents (1.0%) than other studies, for example, Khalil's [18], who reported that 12.7% of patients with head and neck cancer were non-adherent.

Some limitations of this study should be mentioned. First, due to reasons of confidentiality, it was not possible to ascertain the cause of death, precluding an analysis of cause-specific survival, which would have been more appropriate. Second, in 3.5% of the cases it was not possible to ascertain the vital status at one year after treatment. Third, although we adjusted for comorbidity, in 29.1% of the cases it was not possible to determine this information prior to the radiation oncology treatment, so we opted to include the patients with missing information for this variable as a category in the multivariate analysis. Fourth, no data were available on stage, either at diagnosis or before treatment initiation. Lastly, we were not able to analyse some other variables of interest, such as socioeconomic status or place of residence, which may be important explanations for non-adherence.

One strength of this study is the fact that it is population-based rather than limited to patients involved in a clinical trial for specific diagnoses. This approach minimized the selection bias, although we did not included the estimated 10% of patients receiving treatment in private facilities. The definition of the study population as cases treated with a curative intent, and the detailed definition of the causes of treatment interruption, are other relevant aspects, as is the review of dubious cases by clinicians. Also, the small percentage of cases with metastasis at the start of treatment were excluded, even though treatment intent was defined as curative, to minimize bias. Palliative indications could likewise have influenced non-adherence, possibly reducing it further due to shorter treatments [19], although these patients have limited survival time, which would have made it very difficult to pool these patients in an analysis of those treated with curative intent due to the different aims of the therapy.

Radiation oncology is a basic pillar of multidisciplinary cancer treatment, and it contributes independently to local disease control and overall survival [20]. It is necessary to measure non-adherence based on total doses received relative to prescribed doses, not just based on missed appointments. The percentage of non-adherent patients is very low (1.0%) according to the dose received, whereas 70.7% of the treatments had interruptions due to weekday public holidays, machine malfunctions, equipment maintenance, and personal reasons. Considering the quantity of interruptions due to public holidays, expanding services to Saturdays should be considered, as this could minimize the impact on the patient and allow compensation for total doses and treatment time. Overall, non-adherence may have a relevant impact on the prognosis of oncological diseases, and professionals should monitor it during the course of treatment.

Conflicts of interest

None.

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