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Review

Management of interruptions in radiotherapy treatments: Adaptive implementation in high workload sites

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ABSTRACT

Owing to predictable or unpredictable causes, interruptions may arise during therapy. On average, the extension of fractionated radiotherapy treatments is prone to be delayed by several weeks and interruptions can come up extending overall treatment time (OTT). Clonogenic cells of aggressive tumors might benefit from this situation, modifying local control (LC).

Preserving treatment quality in radiotherapy is an essential issue for the treatment outcome, and our institution is increasingly concerned about this line of work.

Establishing some objective criteria to schedule patients that have suffered interruptions along their treatments is of capital importance and not a trivial issue. Publications strongly encourage departments to minimize the effect of lag periods during treatments. Therefore, in July 2017, our facility implemented the so called 'Protocol to Manage Interruptions in Radiotherapy', based on a scoring system for patient categorization that considers not only histology but also associated comorbidity and sequence of the therapy.

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1. Background

Interruptions in radiotherapy treatments are always consequence of undesirable incidents that may jeopardize tumor control probability (TCP), especially in high proliferative tumor cells.[1–3]

Many authors have correlated a poor LC when OTT is extended, due to repopulation of clonogenic cells that contribute to improve cell survival and, hence, decrease the Biological Equivalent Dose to the tumor (BED_{10}).[2] Even more, Withers et al.[4] found a non-constant behavior in duplication time of clonogens linked to the shortening of the cell cycle time, a decrease in the cell loss factor and a rising growth fraction in oropharyingeal cancer triggered at 4 ± 1 weeks. This time dependent behavior was also observed in studies such as Tarnawski et al.[5] reporting a decreasing dose/time factor (κ) during treatment. It has also been reported that position and consecutive days of interruption seem not to be of significant importance at least if the lag period is moderate.[5–8]

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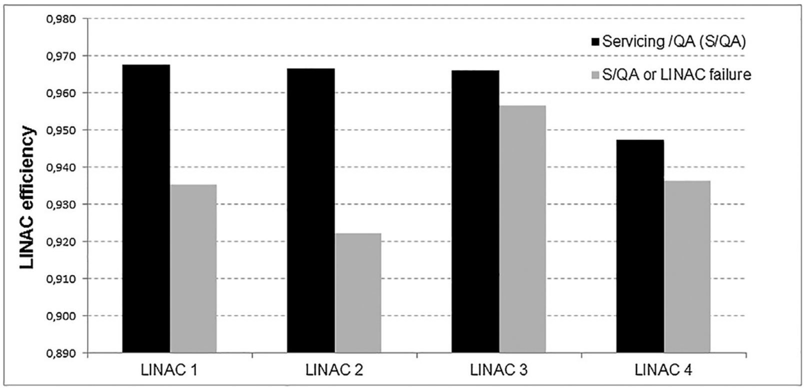

Fig. 1 – Uptime of our four linear accelerators. Black bars depict efficiency when only servicing and QA are considered. Values are below figures stated in Ref. 1 (range 0.95–0.98) when machine failure is added to statistics (grey bars), mainly associated with machine aging.

These effects have been widely analyzed in Head and Neck cancer and an exhaustive overview from the last forty years is summarized and discussed in Ref. 2, but main conclusions can be extended to many other locations treated with radiotherapy.

Based on clinical results, one can quantify the radiobiological effect of an interruption and evaluate statistical uncertainty using Monte Carlo methods, by tuning simulation parameters (selecting a cell growth model and statistics and survival model, i.e. LQ model, for TCP calculation) and fitting them to retrospective studies[9] (overall survival and local failure observed).

Both retrospective analysis and Monte Carlo simulations give us an approach of the time factor κ (Gy/d) that determines the rate of decrease of BED_{10} per day of treatment extension; therefore, compensation strategies[1,7,10,11] may lead us to balance the loss of LC and preserve the therapeutic index.

Development of radiomics and its application will offer promising prognostic factors linked to biomarkers[12–14] that might be used in a near future as supplementary information with regards to biological response, identifying tumor habitats of specific physiological behavior.[15]

2. Materials and methods

Since interruptions in radiotherapy affect all institutions, publications suggest the necessity of a compensation procedure at least in the most proliferative cases.

In our facility, high workload and aging of radiotherapy units demand efficient organization and require a prioritization if at least urgent interruption cases are meant to be covered. Study of the efficiency of our four linear accelerators (uptime ranged between 0.92 and 0.96) confirms the necessity of improving effectiveness through specific prioritization criteria. As seen in Fig. 1, non-operative time due to Servicing/QA and LINAC failure involves not only treatment interruptions but also limits the possibility of transferring patients from one to a dosimetric equivalent LINAC.

The Record and Verify System (R&V System) used in our institution is ARIA Oncology Information System (Varian Medical Systems, Palo Alto, California). This system provides a streamlined workflow that, among other aspects within the course, has an input activity encoding that the medical oncologist can modify depending on patient priority.

Along a 13 months period, retrospective observations of 807 treatments where carried out in our site (Fig. 2). Data analyzed revealed that 73% of treatments were extended by at least 1 day with respect to original OTT. Grouping these interruptions into 5 days period bins, 76.7% had lengthened OTT from 1 to 5 days; 17.3% of patients, from 6 to 10 days and 6.0% that lengthened OTT in more than 10 days. Long interruption periods are often linked to medical problems, and our staff is trained for early radiotherapy reaction detection and preventive care. However, there is a small probability associated with intercurrent disease or acute reactions (Fig. 3).

Taking these observations into consideration, an Interruption Protocol is strongly recommended in order to establish some objective criteria for patient management based on histology, tumor extension and treatment intent since neither the method nor the urgency of compensation demanded in each case are the same.

In this document we present the steps followed and tools used to implement the protocol in July 2017, achieving two targets: (a) minimize the interruption sources in a prospective way and (b) address treatment interruptions according to human and material resources in our facility.

Overview of the whole process and steps followed during implementation are summarized below, highlighting the main aspects (Fig. 4):

Step 1. Review of the literature available at present time. The bulk of publications are centered in head and neck cancer, revealing a lack of information in other categories.
Step 2. Formative session to Radiation Oncology Department personnel. In this session, an overview is given underlining the importance of this protocol implementation, target patients that could benefit from that and resources and optimal methods to balance the potential lost LC.
Step 3. Create a Committee. Before implanting such a protocol, a consensus is needed to best fit patient categories to facility resources. For this propose, a Committee composed of a Medical Oncologist, a medical physicist and a

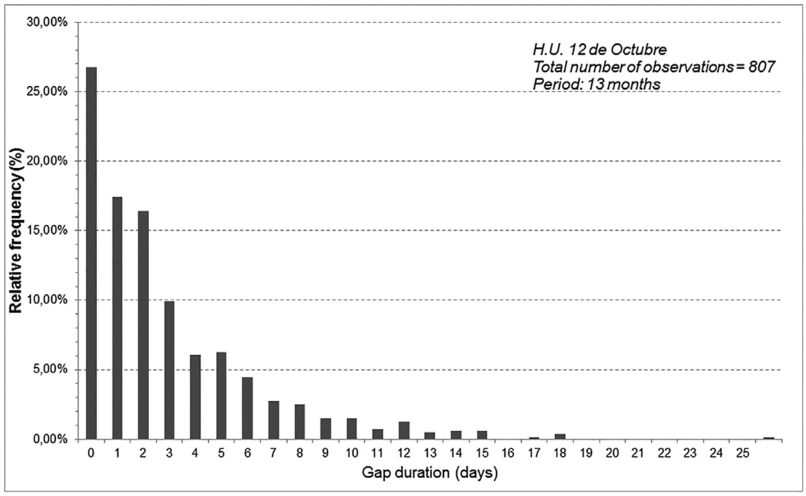

Fig. 2 – During 13 months, 73% of patients treated suffered at least 1 day interruption. This statistics consider public holidays as an interruption.

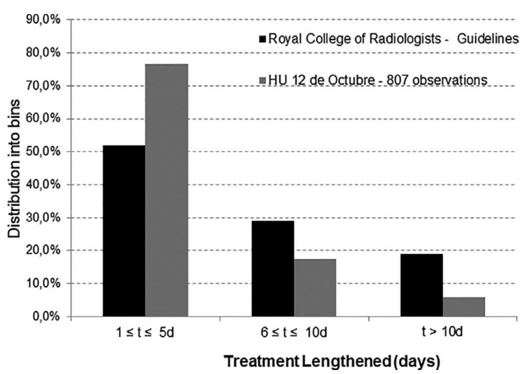

Fig. 3 – Distribution of lag periods in H.U. 12 de Octubre, coherent with benchmarks in publications.[1] Almost 20% of patients had lengthened OTT from 6 to 10 days.

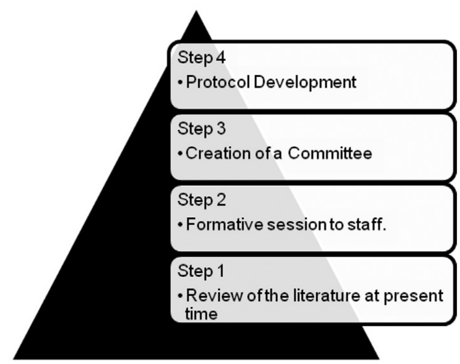

Fig. 4 – Implementation of the protocol and steps followed.

Radiographer was created. Further on, this Committee will follow the application of the protocol periodically.

Based on the guidelines proposed by the Royal College of Radiology,[1] the aim of this Committee before the launch was, on the one hand, to discuss and adapt this document not only to pathologies treated but also to material and human resources and, on the other hand, to analyze the causes of interruptions and how to detect and avoid them when possible.

Preventive measures adopted to minimize triggering events can be sorted into the following:

LINAC availability. There is one LINAC with an intentionally lower workload that can occasionally assume the transfer of patients (also avoiding to schedule treatment quality plan evaluations), especially on Fridays when twice-daily treatment is an option as long as weekend provides time to repair normal tissue.[8–11,16–19]

Servicing and Quality Assurance (QA). All servicing and QA are programmed on Tuesday to Thursday so even if OTT is extended, an extra day is not added to the weekend gap.[2] In a near future, the commissioning of a dosimetric equivalent LINAC will offer the chance to transfer target patients.

Treatment onset. For achieving an optimal biological response, the initial fraction of radical intent treatments is always scheduled on Monday to Thursday.[19]

Patient care. Medical and Nursing care support[1,19] is a key preventive measure that cooperates so that the toxicity impact and radiation reactions can be diminished. There are protocols available in our facility depending on tumor location.

Step 4. Protocol development. As described below, the strategy of compensation has to be selected based on a hierarchy classification.

Patient Categorization. In Table 1, parameters 1–5 (higher to lower weight) are considered to obtain a patient categorization that has to be encoded in the ARIA R&V System as a care path is created.

Most common characteristics evaluated in our facility for tumor growth rate classification encompass histology, degree of differentiation, tumor vascularity and Ki-67 Proliferative Index. Dose compensation takes this parameter into account through κ factor.

Table 1 – Parameters considered in H.U. 12 de Octubre to categorize patients.

1. Treatment Intent	Comprises radical and palliative intention, giving priority to radical intent due to inherent TCP.
2. Time sequence and fractionation	Radiotherapy time sequence in comparison to surgery also contributes to scoring, giving more weight to exclusive high proliferative tumors and neoadjuvant rather than adjuvant treatments. Similar priority is given when scoring hypofractionated against conventional treatments.[16]
3. Histology 4. Extension of the tumor	Histology and extension of the tumor may be part of decision criteria as the growth rate and LC are closely related to them.[1,6,8,10]
5. Comorbidity	Charlson Comorbidity Index (CI) prognoses risk of mortality[17,18] under comorbid conditions and can help in some cases to discriminate treatments with a priori better outcome. Age is considered as a split component and comorbidity scoring from CI = 0.1 (no comorbidity), to CI ≥ 3 (high comorbidity).

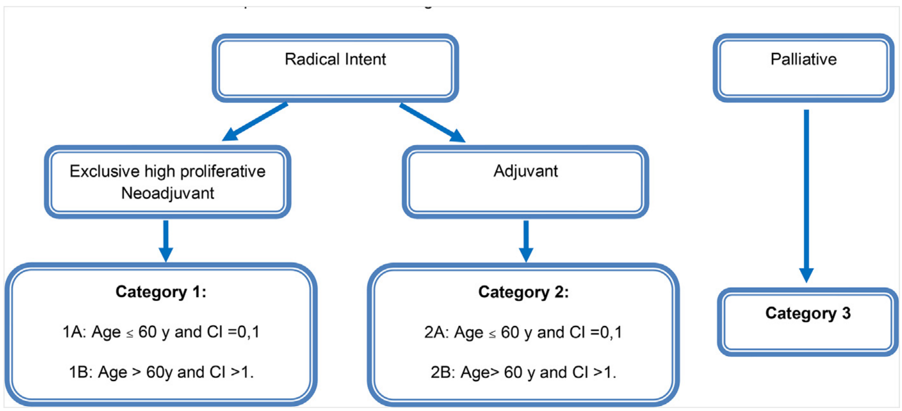

Fig. 5 – Decision algorithm for patient prioritization employed in our facility.

Patient encoding. A decision algorithm has been created according to parameters 1–5 for obtaining patient categories. Proposed categories 1, 2 and 3 in Ref. [1] are maintained, but split into subcategories: 1A, 1B, 2A, 2B and 3. Once defined, medical oncologists are required to enter codification in patient's care path. A consulting process can be executed through an application with Visual Basic 6.0 developed in our department,[20] exporting the desired period to an excel file. This process is executed by medical physicists and a ranked list is then reported to medical oncologists (Fig. 5).

Compensation method. The Committee will review the priority list and settle the compensation method in each case. These methods are well known and pros and cons widely discussed in the literature.[1,7,10,11,16,19,21,22]

Depending on human and material resources, this item may vary and had to be reviewed and adapted as long as new equipment might be installed (i.e. dosimetricaly equivalent LINACs) or just for staff availability reasons (i.e. treating over the weekend).

Dose compensation considers histology dependent κ factor (Gy/d)[3,7,23] and a trigger time T_K[1,4] for accelerated cell repopulation of 28 days. As described in the literature, κ factor represent the loss of BED per day in relation to intended outcome as OTT is extended over fast tumor repopulation threshold and can reach a value as high as 0.9 Gy/d for squamous cell carcinoma of the head and neck region.[1]

3. Results and discussion

Main causes of treatment interruptions are well known. Although some of them can be avoided or minimized by putting into practice preventive measures, almost 70% of interruptions have to do with public holidays, servicing or LINAC failure. Owing to this, discontinuation affects all radiotherapy centers and development of such a protocol is thus strongly recommended, focusing on how to compensate missed fractions and to whom, based on international consensus recommendations.[1] Otherwise, lag periods will induce deleterious effects in the presence of aggressive tumors.

In addition, there is an opportunity of increasing treatment quality by counteracting causes as long as most of them can be pre-planned.

Correlation between prolonged OTT and loss of LC is widely confirmed with regards to head and neck cancer,[2] but can be extended to many other pathologies, especially relevant in cases of a high tumoral growth rate.[7,10,11]

Facilities with moderate to high intensive workload represent a demanding situation and require even more staff commitment to best adapt the protocol to existing resources.

With reference to compensation methods, other hospitals that employ similar protocols are able to apply weekend compensations[19] (need of additional resources implicit), transfer patients to dosimetricaly equivalent LINACs during servicing or duplicate daily fractions.[3] Weekend treatments, maybe the ideal measure (except at the end of a treatment), is not an affordable method in our hospital due to the lack of additional resources in spite of its positive cost-effectiveness and quality of care improvement.[19]

Nor transferring patients to other machine is an available method so far, but this has been taken into consideration for further machines in a close future as adaptability is of key importance if OTT extension has to be minimized.

Occasionally, fractions can be duplicated on Fridays with a separation interval of 8 h[10,7] once the toxicity to organs at risk has been previously evaluated.[24]

Unluckily, in the majority of cases an extension of OTT is assumed and extra fractions are calculated based on Biological Equivalent Dose to organs at risk (BED_3) and to the tumor (BED_{10}). An averaged scenario is admitted, assuming a T_K of 28 days[1,4] despite other references[6,8,25] and α/β and κ specific for each pathology are used to approach realistic compensation.[3,7,11,23,26]

From our view point, these constrains limit the methods to be used and make remarkable the necessity of encoding patients into split categories as proposed (1A, 1B, 2A, 2B and 3) so prioritization is easier and well defined. This arrangement has been deeply discussed, yielding an agreement that scores not only histological characteristics but also comorbidity index, age of patients and sequence of radiotherapy treatment as we believe that the urgency of compensation has to consider the tumor growth rate as much as prognostic parameters or neoadjuvant therapies.

Due to a high workload, compensation of the whole numbers of cessations is not affordable and 3 categories may drive to ambiguous criteria in some cases. We consider it extremely useful to split categorization into 5 lines as it enables a better adaptivity to the whole process.

The development of a homemade application[20] to obtain a ranked list periodically will not only help to filter out treatments affected but to generate statistics to be analyzed in the long term.

Some authors address the possibility of identifying quantitative CT image markers as prognostic parameters[13] of cancer recurrence. This analysis modality could offer additional information for patient prioritization. Besides, our facility will be equipped in the near future with an MRI scanner aimed to provide multimodal image registration and patient monitoring. This opportunity allows the extension of its potential use for radiomics purposes, connecting images features with tumor parameters commonly obtained with inmunohistochemistry analysis.

Furthermore, diffusion-weighted or dynamic contrast-enhanced sequences could be used as non-invasive techniques to evaluate tumor necrotic fraction[27] before radiotherapy and at the time of discontinuation, yielding to a biological response prediction and, consequently, cooperating to warrant a more accurate categorization.

Our institution treats more than 2300 cancer patients per year with external radiotherapy (VMAT, IMRT, SRS, SBRT and 3DCRT) and high (HDR) and low (LDR) dose rate braquitherapy. To face this challenging workload, we use four linear accelerators (LINAC), a HDR afterloading platform and a dedicated operating theater.

High intensive workload is prone to hazard treatment quality, but we believe that retaining prescribed dose and fractionation schedule must be a key priority within any quality program. According to legality,[28] protocols endorsed by international societies and publications have to lay down the entire basis for a radiotherapy process. However, no specific mention is made in legislative decrees[28] despite the adverse consequences of extended OTT.

Scheduled and unscheduled interruptions need to be considered as frequent events (Fig. 2) and some quality parameters can be defined to quantify measures proposed (such as duration of interruptions, dose corrections executed or distribution of main interruption causes) and benchmarked to assess the efficacy of the protocol[16,19] and improvement of outcomes should be re-evaluated as new technology is integrated in the foreseeable future.

4. Conclusions

High workload and aging of our radiotherapy units demand efficient organization so as to preserve treatment quality.

Statistics show that 73% of the patients treated in our institution suffer at least 1 day interruption. Within this group, 76.6% had lengthened OTT from 1 to 5 days; 17.3% from 6 to 10 days and 6.0%, more than 10 days (Fig. 2). Beside the interruptions due to public holidays and servicing/QA, aging of our linear accelerators represents a factor that might contribute to OTT extension as seen in Fig. 1.

We believe that the development of a protocol to manage interruptions is strongly recommended since treatment interruptions are present in 3/4 of treatments and may jeopardize the therapy outcome, especially in proliferative tumors.

Based on existing publications, the protocol identifies the main causes of interruptions in our hospital and establishes recommendations to prevent avoidable cessations. Additionally, a criteria categorization based on 5 parameters has been proposed to encode patient priority and, adapted to available resources, selection of the most effective method of compensation. The 5-parameter scoring is a helpful unbiased tool that will allow an appropriate selection of patients.

Another key point to optimize the protocol path is the filtering of patients. A home-made application has been developed in our department for the consulting process to create a ranked priority list, thus making easier and faster any decision-making process.

According to continuous quality improvement, and assuming that human and material resources might change in a close future, a follow up – committee will periodically review and adapt the methods of compensation in our hospital as well as analyze in the long term quality parameters with reference to this protocol. Also an approach to radiomics applied to CT and MRI images will be taken into consideration for further protocol revisions.

To summarize, publications are mostly focused on Head and Neck tumors, but similar consequences of interruptions can be extended to other pathologies, especially in high proliferative tumor cells. This publication not only presents a protocol implementation but a way to emphasize the preservation of treatment quality as no specific regulatory compliance exists with regard to OTT extension.

Conflict of interest

None declared.

Financial disclosure

None declared.

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