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Review

Effect of radiotherapy delay in overall treatment time on local control and survival in head and neck cancer: Review of the literature

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ABSTRACT

Treatment delays in completing radiotherapy (RT) for many neoplasms are a major problem affecting treatment outcome, as increasingly shown in the literature. Overall treatment time (OTT) could be a critical predictor of local tumor control and/or survival. In an attempt to establish a protocol for managing delays during RT, especially for heavily overloaded units, we have extensively reviewed the available literature on head and neck cancer. We confirmed a large deleterious effect of prolonged OTT on both local control and survival of these patients.

1. Introduction

The time factor is a key element in radiation oncology.[1] Furthermore, the importance of delays during a course of radiotherapy (RT) has been emphasized in recent decades, and different recommendations on the delay-compensation options have been published.[2–5] Fast tumor cell repopulation has been suggested as the main reason why prolonging overall treatment time (OTT) negatively affects local control (LC) and overall survival (OS) in many human tumors.[6] However, there is still a considerable lack of high-level evidence supporting this observation.

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The aim of the present review is both to provide an insight into the problem and to establish an evidence-based protocol to practically address delays in OTT in RT, especially in centers with a considerable workload. To do so, first, we conducted an extensive bibliographic search for articles with the highest level of evidence available. Next, we developed a protocol focusing on different tumor sites and histological groups depending on the observed level of evidence. By summarizing the available evidence, we tried to identify which tumors and situations need to be prioritized for further compensation, so that RT units with excessive workload can at least compensate in the most urgent cases.

The present work focuses exclusively on head and neck cancer (H&NC), by far the most extensively studied tumor site.

2. Materials and methods

An extensive bibliographic search was undertaken focusing on the possible relationship between prolongation of OTT and loco-regional control (LRC) or overall survival (OS) in H&NC. In this sense, we consider '*Significant*' any study showing a significant adverse relationship between prolongation of OTT and LRC and/or OS, even if the relationship is for LC only, but not for regional control or vice versa, or if it includes survival types other than OS. If no significant adverse relationship is seen, the report is considered '*Non-significant*' (NS).

We searched several databases, including MEDLINE, using free terms/MESH terms in the Title/Abstract which included "tumoral repopulation", "radiotherapy delays", "treatment interruptions", "overall treatment time", "time factor", "compensation maneuvers", and "time relationship". After identifying original, full-text articles, we also searched their reference lists. In an attempt to avoid time period bias (e.g., old techniques such as orthovoltage, inadequate doses, and pre-CT era of treatment planning), we arbitrarily chose 1980 as the earliest valid date. We included, however, only one article addressing orthovoltage,[7] since it was one of the most cited works in the search.

Assuming that most of the information included was retrospective, we paid special attention to the quality of the reported data by carefully dividing the articles into those based on univariate analysis (UN-An) or multivariate (MV-An) analysis. Thus, we categorized each article as MV-An when this was explicitly stated by the authors or determined unequivocally from the data. Any other situation was categorized as UN-An. When only the abstract was available, we generally considered these cases as UN-An.

Anatomical subsites were considered 'mixed' when they included at least two predominant subsites. Stage was classed as stage I–II, III–IV, or mixed. However, in a series where a subsite or stage was clearly marginal with respect to sample size, we included it in the most representative group.

Some authors have calculated the loss of LRC in terms of a percentage lost per day or week, often indicating the median or mean/average ± the range. To simplify the matter, we considered only the median or mean/average values. In addition, Fowler et al.[8] calculated the percentage LCR lost per day or week when the authors of original papers had not done so, and recalculated it from authors that had done so. We included both calculated and recalculated values, the latter indicated as the original author with the added term "as in Fowler '92".

Some authors estimated the required daily dose increase to offset the loss of LRC resulting from delays in RT (again, with a median or mean/average value ± range), although the approaches used were very heterogeneous, as follows:

1. The raw 'γ/α' factor, applicable when using very small fractions.
2. D_{prolif}, the tradeoff dose per day when a fraction size of 2 Gy (or other) is used.
3. The most heterogeneous group, including different definitions of the previous two, as 'dose lost', 'extra dose', 'significant repopulation more than…', 'mean time factor', 'proliferation rate', and many others (for simplicity, grouped under the term '*k* factor')

Undoubtedly, since the third form refers to one of the first two, without specifying exactly which one, we preferred to group them together, even at the risk of overlap.

Similarly, Withers et al.[9] calculated the average '*k* factor' from data sets when the original studies had not provided it and recalculated it from studies which had previously calculated it. Again, we included all the available calculated values, and, as above, indicated the author of the original paper with the added term "as in Withers '88".

While investigating whether prolonged OTT negatively affected both LRC and OS in patients receiving RT for H&NC, we partially set aside those reports that show what happens when OTT is *shortened*, since this was not envisaged as the main objective of this study. Therefore, articles about accelerated fractionation (AC-Fx) schemes were not included in the present work, unless when within the previously mentioned search strategy limits. Such articles were taken into account for comparison purposes and to 'complete the picture' in Section 4.

3. Results

Of sixty-five articles considered eligible for this study, 58 contained original data and 4 were pooled-data analyses of previously published series. The other three articles comprised an editorial, a commentary, and a literature review. Therefore, our study is based on 62 studies with a median of 465 patients per article (range, 42–4668). The larynx was the most frequently reported anatomical site (26/62, 41.9%), followed by mixed sites (e.g. two or more different sites; 24/62, 38.7%).

While most reports are from retrospective series, 12 reports included data from prospective studies. Except for two AC-Fx reports, all of them are *Significant*. The 4 pooled-data reports are also *Significant*.

Table 1 shows the main results of the review. Practically all the subgroups are *Significant*, both in terms of LRC and OS. However, reports of AC-Fx seem to worsen the results. In terms of LRC, the worsening is only about 2%, but the difference in OS exceeds 20%, because five out of six OS-NS reports correspond to AC-Fx schemes.