

Effect of treatment interruptions in prostate cancer

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A recent study has shown that treatment interruptions during a fractionated external-beam radiotherapy course for localised prostate cancers may have a negative effect on patient outcome. Limiting or modifying the overall elapsed time between treatments is necessary.

Treatment interruptions during fractionated radiotherapy are clearly undesirable in the management of any cancer. Radiation damage must be accumulated within the shortest period of time possible, rendering cancer cells incapable of repair. The clinical effect of treatment interruptions has been clearly documented for head and neck squamous-cell carcinomas, with a decrease in local control rates.^{1,2} There has been no convincing evidence, however, that treatment interruptions have a similar effect on tumour control for localised prostate cancers treated in the modern era.^{3,4} The study by D'Ambrosio et al. is one of the few that demonstrates a detrimental effect of radiotherapy and treatment inter-

ruptions on biochemical failure rates in patients with localised prostate cancer, albeit only in low-risk patients.⁵

Although these observations are important and clinically relevant, this particular study has some pitfalls, which reflect the difficulty of assessing the effect of treatment interruptions. The data from D'Ambrosio et al. indicate worse outcomes in some patients with localised prostate cancer who have experienced treatment interruptions. The study reported biochemical failure rates in 1,796 patients with localised prostate cancer treated with external-beam radiotherapy between 1989 and 2004 at the Fox Chase Cancer Center. Treatment interruptions were correlated with biochemical failure rates: when the ratio of

no-treatment days to the total number of days elapsed exceeded 33%, the biochemical failure rates were significantly higher than when this ratio was less than 33%.

Although the authors do not specify the exact number of patients who experienced treatment interruptions, judging from the graphs, about 20%–25% of the patients had four or more interrupted days. Furthermore, no explanation for the interruptions was provided, or what their magnitude was. An assumption can be made that the longer the treatment interruptions, the worse the outcome for tumour control. The authors, however, failed to analyse treatment interruptions on a continuous scale, and instead used an arbitrary ratio

of no-treatment days to total elapsed number of days of 33% (corresponding to about four missed days). Finally, there is no information on how these interruptions were managed: were they ignored, were twice-daily treatments instituted to make up for lost days, or were the remaining fraction sizes increased to keep the overall treatment duration constant? The assumption is that no correction was made and treatments were continued without consideration to the interruptions.

The most striking finding in this particular study is that the effect of treatment interruptions was limited to low-risk patients. Treatment interruptions had no effect on biochemical failure rates in patients at intermediate or high risk. The interpretation of the authors is that the observed impact of interruptions on local therapy would have an effect on low-risk patients. This is somewhat counterintuitive since the effect of dose escalation, for example, has been most notably documented in high-risk, rather than low-risk patients. Moreover, the number of events in low-risk patients contributing to the divergence in the Kaplan–Meier curves was relatively small, perhaps around 10 in the cohort with a no-treatment to elapsed number of days ratio that exceeded 33%. This finding prompts the question about the causes of interruptions in the first place, and if there was a less strict policy of allowing treatment interruptions in low-risk versus high-risk patients. A repetition of the multivariate analysis with treatment interruptions as a continuous variable would be useful, in order to see whether the trend for worse outcome with longer interruption periods would be demonstrated.

Assuming that patients at the Fox Chase Cancer Center are representative

of patients with localised prostate cancer in general, a quarter of patients would then have interruptions that are considered 'significant' (that is, around four days). From this cohort, a significant difference in biochemical control rates was detected only in low-risk patients, who constituted around 40% of the entire cohort; therefore, treatment interruptions would have affected about 10% of all patients with prostate cancer treated with definitive radiotherapy. In these cases, however, the difference in biochemical control rates was large (82% vs 57% at 10 years). Regardless of any other factors that might have contributed to this variation, the difference between patients with and without interruptions is so large that it cannot be ignored. Despite the shortcomings and issues of this particular study, the impact of treatment interruptions should be taken into account and correction strategies should be explored, on the basis of this large difference.

The study by D'Ambrosio et al. does not suggest correction strategies in the event of treatment interruptions.⁵ The overall effect of treatment interruptions was limited to low-risk patients and is not as striking as the impact seen in head and neck cancers. This study, therefore, ultimately makes the case for what we all know intuitively: treatment interruptions should not be welcomed. Completing treatments within a certain chronological time is certainly desirable. Although the no-treatment day ratio of 33% was somewhat arbitrary, it provides a rough threshold of four missed days beyond which treatment interruptions should not be ignored. Instead of simply adding the missed fractions at the end of the treatment course, perhaps more attention should be paid to implementing alternatives

that will allow the initially planned overall treatment period to be maintained. The two alternatives would be to increase fraction sizes slightly to complete the treatments within the same overall time period, or to add a full fraction twice-daily during the week when an individual treatment is missed. The literature indicates hypofractionation as a reasonable approach for conventionally fractionated schedules in the treatment of prostate cancers.⁶ However, this is not practical if repeated interruptions occur. The other alternative, implementing occasional twice-daily treatments, would be practical for administrative and radiobiologic purposes, although inconvenient for the patients themselves.

Treatment interruptions during a fractionated external-beam radiotherapy course for the treatment of localised prostate cancers are undesirable, with evidence that they might affect tumour control rates in some patients. Although the overall effect of interruptions might be relatively small and difficult to document, the study by D'Ambrosio et al. suggests that interruptions of more than four treatment days are detrimental.⁵ If significant interruptions are encountered, correction strategies should be implemented to keep the overall elapsed treatment time reasonably short.

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Practice point

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