

# **Split-Course Radiotherapy for Bladder Cancer in the Elderly : Nonsense or Commonsense? A Report of 76 patients.**

**Phillips H.A and Howard G.C.W**

*Clinical Oncology 1996 8:35-38.*

## **AIM:**

The abstract does not clearly identify the aim of the study. The authors state in the abstract that the policy in their department has been split-course radiation treatment for elderly patients when their ability to tolerate a radical course of radiation treatment is in doubt, but they do not state what usual radical treatment in their department is. The objectives are reported in the methods section to be 1)to assess the patient population characteristics who were chosen for the treatment 2)to assess the efficacy tolerability and toxicity of treatment and 3)to analyse whether the gap was used to stop treatment. The endpoints are stated in the methods section to be cystoscopic response a 6 months as a primary index of survival, although survival was also recorded. Toxicity of treatment was also documented.

The typical patient with bladder cancer is a long term smoker with significant cardiopulmonary dysfunction and often elderly, and as such is a poor candidate for both radical surgery and radical radiotherapy. Practically a number of these patients will need to be hospitalised during treatment for intercurrent illness and toxicity. It is important to document both treatment outcome and toxicity in this group of patients. What is not clear is the reasons for choosing the split course schedule i.e. whether this was an attempt to treat more elderly patients radically, and to identify a subset of patients who would benefit and tolerate higher dose radiation, or whether the aim was to compare this schedule with radical radiation. What is missing in this study is a control arm either the gold standard treatment arm or comparisons with palliative treatment.

There are no clearly stated hypotheses here.

## **TRIAL SUMMARY:**

This is a retrospective case review of 76 patients treated in a single institution in Edinburgh, Scotland. Patients were included on an intention to treat basis and were followed up by review of the case notes.

## **TRIAL DESIGN:**

Patient accrual is by review of case notes of patients treated between 1987 and 1992. Patients were identified from the department database on intention to treat basis. It is important to include the patients who did not complete or start treatment in this group as co-morbidity and disease toxicity are a major factor in non-completion and non-starters. No mention of the eligibility and exclusion criteria is made, or of the criteria for radical treatment or lower dose palliative treatment. In short we have no idea why these patients were treated with this regimen, compared with the other regimens commonly used in this department, or whether these patients were purely those deemed not fit for surgery. As mentioned above there are no controls or case matching with other regimens. No mention is made of prognostic factors other than staging. It is implied but not stated that all patients were node negative.

### **Treatment Description:**

The treatment description is inadequate. There is no definition of the target volume other than to say that the volume included the bladder and the prostatic urethra with a margin (size not stated). The authors say that they used a cystogram to plan the volume but do not comment whether this was the sole modality used to determine the treatment volume. The authors do state that pelvic nodes were not intended to be in the target volume, and that typical field sizes were 1000cm<sup>3</sup>. While this is helpful; it would be better to give mean and standard deviations of the field volumes achieved, as this relates to toxicity. The prescription point is not stated. The fractionation is described accurately except that the criteria to determine whether a patient was fit to proceed with the second phase of radiotherapy is not clear. Adjunctive treatments are not described.

### **Followup:**

The major endpoint was cystoscopic response at six months. Survival data was also collected as a secondary endpoint to response. The authors also state an aim to assess efficacy, tolerability and toxicity of the treatment in addition whether the gap was used to stop treatment. The toxicity was assessed using RTOG scoring scale for acute and late radiation reactions. It is not stated how efficacy is tested as this implies comparison with a standard treatment. Likewise, the authors have no measure of tolerability, which implies not just measuring patient toxicity, but the patient reactions to such toxicity. It may have been more useful to measure functional status weekly during treatment as an indicator in the how the

treatment impacted on patients. It is not stated by whom the followup was performed and what formal assessments were made at that time to determine side effects, disease progression, and health status.

#### **Statistical Tests.**

There is no comment in the methods section of the statistical methods used. Actuarial survival using the Kaplan-Meier method is presented. This is an appropriate measure of survival, and appropriately for the disease the authors use 1 and 2 year survivals. The authors do not state what statistical test was used to analyse the difference between the two survival curves. Survival is also presented in tabular form. It is not clear if this is censored data. If this is not censored data, then it means very little, especially in this age group.

#### **TRIAL CONDUCT:**

Quality control is the main issue here. There is no comment on whether the actual data entry, the treatment and field sizes were checked. There is no comment on the variation in the treatment delivery, and the number of protocol violations in terms of fields and fractionation variation. Of those who completed treatment 16 (30%) did not have a followup cystoscopy. Of the 16 half of them were not cystoscoped because they were deceased and a further 2 were lost to followup. The remainder were not cystoscoped because of general frailty or because of metastatic disease. The latter is not reason not to investigate the control of the primary and it may be that these patients were frail as well. In a study such as this where it is to be expected that there will be a certain proportion in which the extent of local control cannot be assessed because of humane reasons, it may have also been useful to assess the quality of local symptom control in the group and use this data as an indicator for palliation.

#### **RESULTS ANALYSIS:**

The criteria for the assessment of the efficacy and tolerability of the treatment were not adequately met. The study assessed response rates, and toxicity in terms of RTOG criteria, but falls down on assessing the impact of these outcomes on the functional status of this group of patients. This is particularly important in the group of patients who are often frail, and in whom the tolerability of even minor changes in health status can often mean the difference between independent living and hospitalisation.

There is no mention in the study of protocol variations, alteration in the treatment times, the adequacy of planning and dose prescription .

All patients are accounted for in the final analysis, including 2 patients lost to followup. It is not known at what stage these patients were lost to followup. The reasons for not completing treatment are poorly defined and in the largest group of patients were defined as "frailty" and "poor condition."

Reduction in Karnofsky status may be more informative than listing this generally as frailty. In addition, Table 4 also cites a significant number (10) patients as not completing treatment due to grade 2 and 3 bladder and bowel toxicity. While this is important to know these rates, it would be more applicable to the clinician to state this as reduction in functional state as, for example Grade 2 bladder toxicity in a younger population would not result in any person discontinuing treatment.

In those in whom the tumour recurred, 10% (9/18) were fit for radical surgery, resulting in overall documented complete response rates of 21/76 or 28%. It is not stated why these patients were not considered for surgery in the first instance. One could reason that if they were fit enough for radical surgery, then they would be fit enough for radical conventional radiation.

The authors go on to present Kaplan-Meier curves for actuarial survival for the patient group overall with the patients grouped as completers and non-completers of treatment. The results show a poorer survival in the non-completers of treatment , but the authors do not show any statistical analysis of the two curves. Along the x axis there is presented the figures for 1 to 4 year survivals so the yearly survival data can easily be read along the x axis of the curves. This is duplicated in a table where the data is presented as 1 and 2 year survivals and a confidence interval, and also in the text where median survivals are presented. This is not an appropriate measure of the middle number as survival data is most likely skewed. In this case the geometric mean or the mode is more representative of the whole sample (1).

The presentation of survival data as response rates based on separately 1) the whole cohort, 2) those completing treatment , 3) those with followup cystoscopy is good. It confirms that no patient who did not complete treatment had a complete cystoscopic response, and this is echoed in the survival data for the two groups. There is little information on those who did not complete treatment however other than that they had a poorer survival. In this group where symptoms are common and distressing it would be also useful to know if completing half of the treatment was useful in terms of symptom control and toxicity.

The authors state 7% of patients had greater than or equal to RTOG Grade 3 toxicity, four of whom only completed the first half of the treatment. The authors state that two late bladder complications were noted but do not state the treatment group these patients came from, the type and severity of toxicity , and what further treatment was required. In addition

they note that no severe or acute bowel toxicity occurred.

While it is valid to make these comments, the reader needs to know that the majority of late effects will occur after the time period of the study. No note of this is made in the discussion. The authors should have documented fully the toxicity of the 2 patients with severe bladder toxicity so that the readers could decide whether they find the toxicity acceptable. RTOG grade 3-5 toxicity includes a range of toxicity from severe discomfort to death, and which one of these occurred may influence the acceptability of the regimen!

### **CONCLUSIONS:**

The authors conclude that split radical fractionation merits consideration in the elderly or frail with potentially curable bladder disease, but who may not be fit for radical conventional radiation.

They comment that their results are as good as other studies of split radical radiotherapy in a nonselected group of patients and better than those achieved with conventional radiotherapy in elderly patients.

The authors fail to comment on their stated aims which were:

1. to assess the patient population characteristics in a group of patients treated with split course radical radiotherapy for bladder cancer. There is no comment of the population characteristics in the patients treated in this study.
2. to assess the efficacy, toxicity and tolerability of the treatment. The efficacy is assessed, but no mention of the standard treatment which would be offered to this group of patients in this institution is made. The toxicity is not adequately addressed. The tolerability is not assessed at all except in the context of whether patients were able to complete the treatment.
3. To assess whether the gap was used to stop treatment. I am unsure what exactly the authors meant when they say "used". The data implies that all those patients who did not complete treatment stopped at the end of phase I but does not state this outright. The authors do not state whether it was physician decision or patient decision to stop treatment. If the patients were being followed throughout the treatment on a regular basis (which would be regarded standard practise in most radiation oncology departments) theoretically this decision could be made at any time.

### **PRESENTATION:**

The argument for the rationale of the study is well presented. The aims are not explicitly stated in the abstract and the reader has to look into the text of the method section to find them. The presentation of the RTOG scoring system is good. This is better than giving a journal reference only. The Kaplan-Meier survival curves give no indication of the censored data which is wrong. They do give numbers of surviving patients along the x axis and this is good practise. The discussion is poorly written and does not tie together the ideas presented in the introduction and the results of the study.

### **ETHICS:**

I think this study is an ethical study to do, as toxicity is a major reason for the premature cessation of treatment in this group, and any regimens with equal survival and better toxicity will prove useful in this age group. Prior data has shown that this treatment is at least equivalent in bladder cancer patients and so it is reasonable to use this fractionation in a preliminary study. It would be better however to design this prospectively to compare the survival data and response rates of this regimen and the standard treatment in this department, as we have no ballpark to compare the usual response rates and toxicities in this institution with elsewhere.

### **RECOMENDATIONS:**

I would recommend that this study be published. The content is of general interest to most oncologists.

I would recommend that the following alterations be made:

1. Abstract to clearly state the aim of the trial
2. Authors to state the gold-standard treatment in the department, or what treatment these patients would otherwise have received.
3. Study to document what information was collected at the break in treatment and what criteria was used to determine if the patient stopped treatment
4. More information on the characteristics of the patient group treated to fulfil aim (1)
5. Authors to define tolerability and how they intended to measure this - if unable should be dropped from aims of study
6. Dose prescription points to be included in the methods section.
7. Target volume should be better defined.
8. Actual field size achieved should be presented as mean field size and standard deviation.
9. Adjunctive treatments should be described.
10. Table 6 can be deleted from the results section

11. Kaplan-Meier curves to show censored data
12. Some idea of the response rates of younger patients in the department with similar disease would be helpful, or if not available because the majority are treated surgically, the response rates of the surgical patients would be a good comparison.
13. More detail should be given on the followup assessments, what parameters were measured, whether this was in standard form, what criteria were used to measure or document disease progression, other than cystoscopy.

**SUMMARY:**

This is a retrospective review of the elderly patients with bladder cancer treated in a single institution with a split course radiotherapy. These patients would otherwise be thought not able to tolerate radical radiotherapy. This showed comparable response rates in those patients who finished treatment compared with other series of nonselected patients treated in this way, and also with elderly patients treated with conventional radiotherapy. The study is marred by lack of the patient group definition, and inadequate information of toxicity, which makes it difficult to extrapolate the results into a one's own practise population. This study is topical and of interest to the oncology readers. On the basis of this study I would look for more information on the points raised in this review, and if these were satisfied then I would consider changing my practise to include this technique.

**BIBLIOGRAPHY:**

1. Daly L.E, Bourke G.J, Mc Gilvray J. Interpretation and Uses of Medical Statistics. 4th Edn 1991, Blackwell Science Ltd.