Reviewer's report

Title: Chemotherapy Followed by Surgery versus Surgery Alone in Patients with Oesophageal Squamous Cell Carcinoma: Long-term Results of a Randomized Controlled Trial

Version: 1 Date: 1 October 2010

Reviewer: Mark Smithers

Reviewer's report:

General Comments:
The authors have presented a manuscript outlining the results of a RCT of preoperative chemotherapy vs surgery alone for SCC of the oesophagus. The original results were published in abstract form in 1997. Despite a number of the authors of the abstract being authors of this manuscript the reason for the delay to publication is not outlined. It is stated that there was no documentation as to whether two patients in the chemotherapy / surgery arm actually received chemotherapy or not. This makes one question the way the trial was conducted and as such a few issues need to be addressed in the methods. It is presumed that the trial was assessed by the institutional ethics committees in each hospital. This needs to be stated. (major compulsory revision) Was there central supervision for the conduct of the trial? (minor essential revision)

This was an important trial at the time and the outcomes are still important despite the time delay. The added value to the literature that this study provides is that etoposide was used instead of the usual 5FU and that response to therapy was used to define whether patients should have further preoperative therapy. The latter was not used in any of the previous neoadjuvant chemotherapy trials of that time (Subsequently, Bedenne et al used response to define whether surgery should be used or not). In recent times response to therapy is being more formally assessed in the management of patients with oesophageal cancer having neoadjuvant therapy making this aspect novel at that time the trial was conducted and relevant to recent therapy. This should be stressed in the discussion (discretionary revision)

The discussion needs to focus more on the context and time in when the trial was run and then outline how things have changed.(major compulsory revision)

The analysis of the polymorphisms in four genes is a study within a study and as such the methodology is poorly described and the results are presented as if all readers will understand the terminology which is not defined well in the manuscript. The results are reported from the group who had chemotherapy and then surgery and not the surgery alone group.

Whether the group being tested had chemotherapy preoperatively or surgery alone would not appear to be relevant to the results as presented. Given that the
authors had assessed response to chemotherapy it would have been more relevant to have assessed the outcomes in responders compared with nonresponders when assessing the relevance of the changes in this group studied.

Thus this aspect of the manuscript needs to be expanded or left out and reported separately (major compulsory revision)

Specific questions to be addressed:
Methods: (major / minor compulsory revisions)
Make it clear whether or not CT scanning was performed on all patients entered into the trial.

Given a response to therapy is an important part of this study the authors need to summarise what they mean by response and how it was measured. As well define response - complete / partial etc. A reference to WHO criteria is not enough.

When was the CT scan done to assess response.

The authors should not place R1 and R2 resections together. Patients with R1 resections may survive long term whereas R2 implies known gross disease was left insitu.

It is not clear how the authors are able to justify measuring disease free survival from 6 months after randomisation. They measure (correctly, I believe) disease free survival time from randomisation. DFS should be measured on an intention to treat basis from randomisation accepting that there will be those with disease ie not operated or R2 resection at time zero. To use the potential delay to resection in the treated arm as the reason to move the time point is flawed in a RCT such as this.

Table 1 relating to the polymorphism analysis was not available for assessment. The other tables are not correctly numbered.

Results:
There should be p values added to all the variables as a separate column in the tables.

In the “chemotherapy” group it is reported that 75 pts had two or more cycles but only 65 are reported in the next paragraph. Please outline what happened to the other 10 pts. The toxicity data is inadequate given that the chemotherapy regimen is not typical for this disease. Were there other toxicities eg gastroenterological etc. It is difficult to understand that the authors cannot establish whether two patients did or did not have chemotherapy in this arm of a randomised trial. Have the records been lost?

In the surgery group, 14 patients did not have a resection. Two patients died before resection. It is presumed that 12 patients had an operation but were not resected. The reasons for this need to be outlined. A nonresection rate of 17% in the surgery alone arm is very high and may be a contributor to the outcome of
the study.

The patterns of failure analysis should include patients with R1 resection. There will be a group of patients in each arm who did not have their disease resected (includes R2 resection) then there will be the reported sites of recurrence after resection. As well, in the table a 14% incidence of second primary is noted. This is very unusual and not mentioned in the text or discussed. If this is real it needs to be discussed ie the site of recurrence – residual oesophagus, head and neck or do the authors mean a cancer at a different site? This is not really a site of “failure” of the studied therapies and should be mentioned separate to what is outlined in the table.

Discussion

Not all patients with a R1 resection die from disease so on page 16 it is better to use the term complete dissection rather that “curative”.

In the discussion the authors use the “dismal” median survival to justify the use of chemoradiation therapy for this disease. In the context of when this trial was performed the median survival of the treated arm is similar to that reported in other chemo trials (MRC – positive trial, Kelsen) and chemoradiation trials (Walsh – positive trial, Urba). Thus the authors are not providing evidence from there study to justify “their opinion”.

As well the Stahl trial assessing definitive chemoradiation compared with preop CRT is quoted to support the addition of radiation. This trial was restricted to patients with T3,4 SCC of the upper third of the oesophagus. The discussion provided is thus not directly relevant to the presented study and if median survivals are to be used as comparators the outcomes of the authors report is equivalent to the Stahl study so that one might take the opposite tact and advocate the author’s regimen over the intensive toxic regimen used by Stahl.

Similarly way the authors have used the Bedenne trial as a reference in the discussion is questionable in the context of this trial. It would make more sense to reference the use of response to drive therapy as was performed by the authors and as was done by Bedenne et al.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have n competing interests