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

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Author's response to reviews: see over
Reviewer: Mark Smithers

Comment 1: It is presumed that the trial was assessed by the institutional ethics committees in each hospital. This needs to be stated. (major compulsory revision)

Addition on page 6: “The study protocol was approved by the ethics committee of all participating institutions and written informed consent was obtained from all patients”

Comment 2: Was there central supervision for the conduct of the trial? (minor essential revision)

Addition on page 5: Central randomisation took place at the Erasmus University Medical Center in Rotterdam (by trial coordinator TCK).

Comment 3: 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)

See revision of discussion on page 14-18

Comment 4: The polymorphism section needs to be expanded or left out and reported separately (major compulsory revision)

We agree with the reviewer that the polymorphism section is of limited value and distracts the attention from the original results. Therefore, this section is left out the manuscript.

Comment 5: Make it clear whether or not CT scanning was performed on all patients entered into the trial

Addition on page 9: “Preoperative staging by CT of the chest and the upper abdomen was performed in 149 patients (88%); two patients (1%) died before the planned CT scan; six patients (4%) were staged by endoscopic ultrasound, external ultrasonography of the cervical and upper abdominal region and chest radiography. From twelve patients (7%) no additional information on preoperative staging was available.”

Comment 6: When was the CT scan done to assess response.

Addition on page 5: “Response evaluation was done three to four weeks after the last cycle of chemotherapy.”

Comment 7: There should be p values added to all the variables as a separate column in the tables.

See tables 1 to 4.
Comment 8: 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.

It is not clear what the reviewer is mentioning here. See page 10 for the section. We could not trace the number of 65 (43+32=75)

Comment 9: 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?

On page 10: “Two patients allocated to preoperative chemotherapy, were directly lost to follow-up after randomization. Tracing back the original patient’s files was impossible; therefore, it is not clear if these two patients truly received chemotherapy followed by surgery.”

Comment 10: 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.

Addition on page 11: “In the CS group, six patients did not receive an oesphagectomy because of tumor growth in adjacent structures (aorta or bronchial tree) and one had tumour positive celiac lymph nodes at laparotomy. In the S group, seven patients did not undergo surgical resection because of tumor encasement of the aorta or the bronchial tree and five due to tumor positive celiac lymph nodes at laparotomy.”

Comment 11 and 12: 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 i.e. 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.

Addition of table 4: Sites of first failure, survival status and cause of death in patients with R1 resection.”

On page 12: “Eight patients treated with preoperative chemotherapy developed a second primary tumor; five squamous cell carcinomas of head and neck, one pancreatic, one lung and one breast carcinoma. In contrast, four patients who underwent immediate surgical resection developed a second primary tumor, all squamous cell carcinomas of head and neck.”

Comment 13: Not all patients with a R1 resection die from disease so on page 16 it is better to use the term complete dissection rather than “curative”.

The term curative has been replaced by complete dissection.
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 their 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.

See revision of discussion on page 14-18
Reviewer: Trevor Leong

This paper is somewhat intriguing for several reasons. Firstly, I cannot understand why a study that completed recruitment in 1996 has taken so long to be reported. Secondly, this trial was conducted at approximately the same time period as the much larger US INT0113 and UK MRC OE2 trials, thereby allowing some comparisons to be made with these trials. The INT0113 trial showed no benefit for neoadjuvant chemotherapy while the OE2 trial demonstrated improved survival with neoadjuvant chemotherapy.

See page 14: “Why it took so long to report the design and results of this study is not completely understood. The main reason is change of personnel (the trial coordinator [TCK] moved to another hospital) and growing interest in other chemotherapeutic regimes (like the combination of oxaliplatin and paclitaxel) in patients with esophageal cancer.”

I have some comments and questions.

Minor comments/questions/revisions

Comment 1: Did this trial include standardization of preoperative staging? ie. were all patients staged with CT scans. Was there standardization of surgical technique? One of the caveats of the OE2 trial is that there was no standardization of preoperative staging or surgical technique. In contrast, all patients in INT0113 underwent CT staging, and surgery was conducted according to protocol guidelines at experienced centres. This may partly explain the difference in results between the two trials.

On page 7: the use of standard surgical techniques for the different location of the tumors is outlined.

On page 9: “Preoperative staging by CT of the chest and the upper abdomen was performed in 149 patients (88%); two patients (1%) died before the planned CT scan; six patients (4%) were staged by endoscopic ultrasound, external ultrasonography of the cervical and upper abdominal region and chest radiography. From twelve patients (7%) no additional information on preoperative staging was available.”

Comment 2: It would be helpful to include the preoperative stage grouping of patients in Table 1. I note in Table 3 that 39% of patients in the surgery alone arm had nodal disease and 14% had celiac nodal disease. In other words, were these patients appropriately selected for surgery? The median survival in the surgery alone group was only 12mth, which is lower than in INT0113 (16.1mth) or OE2 (13.3mth).

Unfortunately, endoscopic ultrasound was not routinely performed. Therefore, we feel that addition of the preoperative TNM stage based on CT-scan only is not very useful. Furthermore, the MRC and Intergroup trial did not mention the preoperative TNM stage as well.

Indeed, controversy exists about the implications of tumor positive celiac lymph nodes. Some clinicians exclude these patients for curative treatment options, whereas others believe that these patients are still eligible for surgery. In our institution, patients with carcinoma of the
distal esophagus and suspected celiac lymph node involvement are considered eligible for primary surgery.

On page 17: “It appears that the S group in present trial had the worst survival outcome. This could be due to the fact that the Intergroup and the MRC trial included more OAC than OSCC patients. Subgroup analysis of the MRC trial, including only OSCC patients, showed a median survival time of 11 months for patients who underwent surgery alone [12].”

Comment 3 and 4: The chemotherapy regimen of cisplatin and etoposide is unusual and would not be a commonly used regimen for oesophageal cancer. The INT0113, OE2 and RTOG 85-01 trials were all using cisplatin and 5-FU at the time this trial was being conducted.

RTOG 85-01 was a randomized trial comparing chemoradiation to radiotherapy alone (not chemotherapy alone as stated in the discussion).

See revision of discussion on page 14-18. Indeed RTOG 85-01 was a randomized trial comparing chemoradiation to radiotherapy alone. However, in the revised discussion the trial is not mentioned anymore.

Comment 5: The authors claim that the T-variant allele of the ABCB1 gene polymorphism may be a predictive marker for response to preoperative chemotherapy. However, the design of the study does not really allow differentiation between a predictive marker or a prognostic marker. Would patients harboring the variant allele have had better survival regardless of whether or not they received preoperative chemotherapy? This was not tested in the surgery alone group

We agree with the reviewer that the polymorphism section is of limited value and distracts the attention from the original results. Therefore, this section is left out the manuscript.
Reviewer: Pierre G Thirion

Comment 1 Title:
Discretionary Revision: I would suggest adding the term “resectable” (oesophageal) should be added, to better define the patients group

We agree. See page 1: The title of the manuscript is replaced by: “Chemotherapy Followed by Surgery versus Surgery Alone in Patients with Resectable Oesophageal Squamous Cell Carcinoma: Long-term Results of a Randomized Controlled Trial”

Comment 2 Abstract:
Minor Essential Revision: In the material and method paragraph it should be clear that the primary end-point was OS, and the secondary end-points were DFS, pattern of failure and toxicity. The polymorphism study is an unplanned subgroup analysis.

We agree with the reviewer that the polymorphism study is an unplanned subgroup analysis. We feel with the other reviewers that this section is of limited value and distracts the attention from the original results. Therefore, this section is left out the manuscript.

On page 2: Additional sentence in the abstract: “The primary study endpoint was overall survival (OS), secondary endpoints were disease free survival (DFS) and pattern of failure.”

Comment 3 Abstract: Minor Essential Revision: In the results paragraph, the pattern of failure results should be mentioned (as the end-point is mention in material and methods).

We agree. On page 2: Additional sentence in the abstract: “No difference in failure pattern was observed between both treatment arms.”

Comment 4 Abstract: Minor Essential Revision: In the results paragraph, as the polymorphism profile is significant in multivariate analysis, the mention of the results of univariate analysis is not relevant. It should be clear that the polymorphism analysis was only conducted on the chemotherapy patients.

Comment 5 Abstract: Minor Essential Revision: In the conclusion paragraph, given that the polymorphism analysis is an unplanned subgroup analysis, the conclusion should be more careful, e.g. Polymorphism profile could be associated with better clinical outcome.

Regarding comment 4 and 5: The polymorphism section is left out the manuscript.

Main text:
Introduction:
Comment 6: Discretionary Revision: Authors should give a comprehensive list of the potential rational of pre-operative chemotherapy: tumour shrinkage, increase R0 resection.

See additional sentence on page 4: “The potential benefits of preoperative chemotherapy include increasing the likelihood of curative resection by downstaging the tumor and rapidly improving tumor-related symptoms. It is also been thought that systemic chemotherapy could contribute to the eradication of micrometastases and circulating tumor cells.”
Comment 7: Major Compulsory Revision: Authors should provide evidences supporting the rational and reliability of polymorphism study on post-chemotherapy pathology

The polymorphism section is left out the manuscript

3-2 Results
Comment 8: Minor Essential Revision: Clarify the resectability criteria

Additional sentence on page 5: “Patients were deemed resectable if the disease was clinically limited to the locoregional area (tumor stage 1, 2 or 3; any nodal stage and no metastases). Patients with carcinoma of the distal esophagus and suspected celiac lymph nodes involvement (M1a) were also considered eligible for surgery.”

Comment 9: Major Compulsory Revision: In the statistical method paragraph: the authors need to explain why with a sample size of 160, more than 160 patients were included

Additional sentence on page 9:”An additional number of nine patients were included to adjust for study drop-outs.”

Comment 10: Discretionary Revision: The landmark method is used because of the difference in overall treatment duration

Additional sentence on page 8:”Disease-free survival was calculated from a landmark time of 6 months after date of randomisation to allow for the difference in timing of surgery between the two treatment groups [7].”

Comment 11: Minor Essential Revision: Table 1: age description should use median, min and max (not mean)

We agree. See adjustment in table 1.

Comment 12: Major Compulsory Revision: Table 1: No comment in the text on the fact that 1 patient had a cervical tumour location (= not eligible)

Additional sentence on page 9:”One patient, allocated to preoperative chemotherapy, had a tumor located in the cervical part of the esophagus (the reason why this patient was included and randomised remains unclear, even after retrospective analysis of the patient’s record).”

Comment 13: Minor Essential Revision: pCR rate is 7% (in chemo group) and not 3%.

We agree. See adjustment on page 11.

Comment 14: Minor Essential Revision: Clarification is needed regarding postoperative morbidity figures. As I understand the table the number of patients experiencing at least one post-operative morbidity event is the same in the 2 groups, but lung toxicity was a more frequent event with preoperative chemotherapy. If so it should be clear if the number or percents mentioned are patients or events.

Additional sentence on page 11:”Data on postoperative complications was available of 67/76 (88%) of patients in the CS group and 75/82 (91%) patient in the S group. The frequency of nonfatal postoperative events was closely similar in both groups (table 2).”
Comment 15: Minor Essential Revision: Resection status. Is there a difference in R2 resection rate?

Additional sentence on page 11: “Of the 69 patients in the CS group who underwent surgical resection, 71% had R0 resections, 25% had R1 resections, and 4% had R2 resections. Of the 70 patients in the S group who underwent surgical resection, 57% had R0 resections, 29% had R1 resections, and 14% had R2 resections.”

3-3 Discussion
The authors clearly identify the limitation of the study

Comment 16: Minor Essential Revision: The authors should compare their results with other major preoperative chemotherapy trials (EO2 and Kelsen), both on the similarity and difference. Several aspects should be looked at:
1- Compliance (low in chemo arm) and toxicity
2- Postoperative morbidity and mortality
3- The clinical and pathological response rate
4- OS and DFS benefit
5- Pattern of relapse

Comment 17: Discretionary Revision: The authors should make better use of the data on the pattern of relapse in R0 resection patients. The latter results of the present study is one of its strength, and is hypothesis generating to explain the effect of preoperative chemotherapy (no effect on metastatic disease) and is in keeping with the UK experience

Comment 18: Major Compulsory Revision: the comments on chemo-radiation should be removed as they are not in keeping with the subject of the study and not supported by the present results

Regarding comment 16 to 18, see the total revision of discussion on page 14-18.
Reviewer: Val Gebski

Major Compulsory

Comment 1: A CONSORT flow diagram of patient screening & progression through the various stages of treatment etc should be provided – e.g. how many patients received the opposite treatment, how many did not proceed to surgery etc

We agree. See the revised Figure 1.

Comment 2: Comparisons of outcomes by key subgroups should be provided (e.g. in a forest plot) together with tests for interaction. I would suspect that these would include the strata levels, tumour location, gender, and some of key variables in table 3. In fact table 3 is of limited value as it does not provide the reader of how these impact on outcome

On page 9 and in table 1: “Random assignment was stratified by age (<50; 51-60; >60), gender (male; female), weight loss (kg) in the past four months (0-5; 6-10; >10) and length of the tumor (cm) as measured by oesophago-gastroscopy (1-3; 4-6; 7-10; >10).”

Addition of figure 3 (forest plot): Survival by characteristics at randomisation and post-treatment.

Table 3 is left out the manuscript.

Comment 3: P7 strata levels for tumour length, weight, age etc, and randomisation details should be provided in this section.

On page 9 and in table 1: “Random assignment was stratified by age (<50; 51-60; >60), gender (male; female), weight loss (kg) in the past four months (0-5; 6-10; >10) and length of the tumor (cm) as measured by oesophago-gastroscopy (1-3; 4-6; 7-10; >10).”

Comment 4: P10 2nd paragraph, use power and significance instead of beta & alfa (which is confusing). Also indicate whether comparisons were one or two-sided

On page 8: “With these numbers of patients the statistical power should be sufficient (power = 0.8; significance 0.05) to detect an increase of the median survival from 10 to 18 months.”

On page 8: “All statistical comparisons were made with two-tailed tests and \( P \) values <0.05 were reported as significant.”

Comment 5: P11 Please provide median follow-up time. Also, A table of toxicities (including surgical) needs to be included – the description in the text is inadequate

On page 12: “At the time of analysis, the median follow-up was 15 months in the CS group and 14 months in the S group.”

See table 2 for surgical complications.

On page 10: “Detailed data on chemotherapy related toxicity is not available. In the prior phase II trial a high rate of grade III and IV nausea (38%) and vomiting (20%) was observed, probably due to the fact that 5-HT3 receptor blockers were rarely given throughout the study
period [8]. All patients in the current trial received prophylactic anti-nausea treatment with 5-HT3 receptor antagonists during chemotherapy. No grade III or IV nausea and vomiting were observed. The major non-hematological toxicity (grade III) was alopecia. Hematological toxicity grade III was observed in 23 patients (one renal, twenty-two hematological). Eight patients had grade IV hematological toxicity.”

Comment 6: P12 under patterns of failure – you mean 30 days post surgery?

Yes, we do.

Comment 7: P13. Omit the p-value for the PH test – this was only performed to obtain an estimate of the HR. Comparisons were made by the logrank test. Given other studies have provided 2-yr survival these should also be given (maybe in lieu of the 12 month rates)

See the revision on page 12: “Overall survival was better in the CS group than in the S group (P=0.03, by the log-rank test; hazard ratio [HR] 0.71; 95% CI 0.51-0.98; Figure 2A).”

See the revision on page 13: “In the CS group, there is prolonged disease-free survival compared with the surgical resection alone group (P=0.02, by the log-rank test; HR 0.72; 95% CI 0.52-1.0).”

Comment 8: P13 A multivariate analysis of key factors should be provided (in a table) with appropriate commentary. This also should include a statement of all the variables which were originally considered.

We feel with the other reviewers that this section is of limited value and distracts the attention from the original results. Therefore, this section is left out the manuscript.

Comment 9: P14 – were age, weight loss etc all significant in the multivariate analysis? If so the complete MVA results should be reported & if not why were these specifically selected (some data dredging seems to be going on here)

We feel with the other reviewers that this section is of limited value and distracts the attention from the original results. Therefore, this section is left out the manuscript.