

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Weekday of oesophageal cancer surgery in relation to early postoperative outcomes in a nationwide Swedish cohort study
<b>AUTHORS</b>	Lagergren, Jesper; Mattsson, Fredrik; Lagergren, Pernilla

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Tom Wiggins Imperial College London, UK
<b>REVIEW RETURNED</b>	05-Feb-2016

<b>GENERAL COMMENTS</b>	<p>Very interesting and well written paper. The findings that weekday of surgery does not appear to influence short term outcomes is very interesting in the context of the author's previous results demonstrating worse long-term outcomes with later weekday of surgery.</p> <p>The work of this paper to establish that short-term outcomes are not affected by weekday of surgery is important to begin to contextualise the wider issues responsible for these long term affects such as likelihood of tumour recurrence as the authors have described within the discussion.</p>
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<b>REVIEWER</b>	Sjoerd M Lagarde Erasmus MC, Rotterdam, The Netherlands
<b>REVIEW RETURNED</b>	16-Feb-2016

<b>GENERAL COMMENTS</b>	<p>The present study tries to explain the major findings of a recently published study in the Annals of Surgery. It tries to give in-depth analyses in the present manuscript. It is all based on the fact that the earlier the weekday, the fresher the surgeon and the team and the better the long term outcomes. The main hypothesis of the study in the Annals was that the surgical precision might to some extent deteriorate later in the week due to the workload of the surgeons and the surgical team. The present study tries to look for an explanation, but only focuses on the occurrence of early and severe postoperative complications requiring reoperation, since earlier work of the group showed that patients who require reoperation within 30 days, have a worse long term outcome. Although an interesting hypotheses this is also puzzling. Personally, I think that most severe complications happen on day 4-6 (anastomotic leak, pneumonia etc etc,) meaning if patients have been operated early during the week, this will happen during the weekend and it is more likely that a delay in recognition will occur in the weekend.</p> <p>However, the present study showed that comparison of surgery later</p>
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	<p>in the week (Wednesday-Friday) with earlier in the week (Monday-Tuesday) showed no increased risk of death or reoperation within 30 days of surgery. The manuscript is rather limited in the results section and although the abstract suggests that the study looks at early and severe postoperative complications, we only have information about the combined endpoint (30day reoperations and mortality). No results are given about the severity of complications and no separate numbers are given about reoperation rate and mortality rates. This is especially important since I suspect that there will be a bias in year of operation and reoperation rate since the use of radiologic guided drains in the more recent years. If possible I would like the authors to add more in depth information about the above mentioned things. Although I realize the problem with these large population based studies.</p> <p>Back to the Annals paper than, their main hypothesis was that the surgical precision might to some extent deteriorate later in the week, leading to worse long term survival. However this is not reflected in more reoperations or more early deaths. So what then will be the reason? The only reason I can think of , is that the tired surgeon performs less adequate resections, causing worse long term survival Is there less extensive surgery later in the week, are there more irradical resections later in the week?, is the lymph node harvest lower later in the week?. The inclusion of also this hypotheses and results would give the manuscript far more body and relevance.</p>
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<b>REVIEWER</b>	Michael Schweigert Department of General and Thoracic Surgery Städtisches Klinikum Dresden Dresden, Germany
<b>REVIEW RETURNED</b>	08-Mar-2016

<b>GENERAL COMMENTS</b>	<p>Lagergren and colleagues conducted a population based study following their publication in the Annals of Surgery 2015. Both study population and period are identical. In their previous work the authors had recognized an association between weekday of oesophagectomy and 5-year-survival . They had postulated that surgery later in the week deteriorates the 5-year-survival rate.</p> <p>Now the authors analyzed the relation between weekday of surgery and short term operative complications (reoperation) and 30-day-mortality. In contrast to the previous study they found no association.</p> <p>In general, the paper is well written and interesting. The size of the study population is impressive. In accordance with the authors I am convinced that the interpretation of the data is not marred by possible confounders as year of operation, neoadjuvant therapy, and operative procedure.</p> <p>The discussion section of the manuscript has several shortcomings. The authors only discuss the possible confounders (see above). The conflicting results of the two studies are not discussed. The authors provide no possible explanation for the fact that weekday of surgery affects the 5-year-mortality but not the 30-day-mortality. Some speculation on the possible reasons would stimulate the discussion section. The authors should also outline whether their database is sufficient to identify further possible reasons besides reoperation to explain the long term differences or whether not.</p>
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	<p>The authors should also look into the possibility that the results of the previous study are marred by thus far not identified shortcomings/confounders. If one looks at a 5 year period many interfering factors have to be taken into consideration. This should be discussed, too.</p> <p>What is the authors recommendation based on their findings? Should we avoid oesophagectomy on Fridays?</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1, Tom Wiggins, Imperial College London, UK

Very interesting and well written paper. The findings that weekday of surgery does not appear to influence short term outcomes is very interesting in the context of the author's previous results demonstrating worse long-term outcomes with later weekday of surgery.

The work of this paper to establish that short-term outcomes are not affected by weekday of surgery is important to begin to contextualise the wider issues responsible for these long term affects such as likelihood of tumour recurrence as the authors have described within the discussion.

Reply: Thank you for these positive remarks.

Reviewer: 2, Sjoerd M Lagarde, Erasmus MC, Rotterdam, The Netherlands

The present study tries to explain the major findings of a recently published study in the Annals of Surgery. It tries to give in-depth analyses in the present manuscript. It is all based on the fact that the earlier the weekday, the fresher the surgeon and the team and the better the long term outcomes. The main hypothesis of the study in the Annals was that the surgical precision might to some extent deteriorate later in the week due to the workload of the surgeons and the surgical team. The present study tries to look for an explanation, but only focuses on the occurrence of early and severe postoperative complications requiring reoperation, since earlier work of the group showed that patients who require reoperation within 30 days, have a worse long term outcome. Although an interesting hypotheses this is also puzzling. Personally, I think that most severe complications happen on day 4-6 (anastomotic leak, pneumonia etc etc,) meaning if patients have been operated early during the week, this will happen during the weekend and it is more likely that a delay in recognition will occur in the weekend.

Reply: We tested the hypothesis that reoperations might contribute to explain our recent study showing worse long-term oncological outcomes following oesophagectomy conducted weekdays later in the working week since we had previously found a worse long-term outcomes following early postoperative reoperations. The hypothesis of this reviewer is interesting, but ii could not explain the worse survival with surgery late in the week.

However, the present study showed that comparison of surgery later in the week (Wednesday-Friday) with earlier in the week (Monday-Tuesday) showed no increased risk of death or reoperation within 30 days of surgery. The manuscript is rather limited in the results section and although the abstract suggests that the study looks at early and severe postoperative complications, we only have information about the combined endpoint (30day reoperations and mortality). No results are given about the severity of complications and no separate numbers are given about reoperation rate and mortality rates. This is especially important since I suspect that there will be a bias in year of operation and reoperation rate since the use of radiologic guided drains in the more recent years. If possible I would like the authors to add more in depth information about the above mentioned things. Although I

realize the problem with these large population based studies.

Reply: Thank you for these thoughtful comments. We did not have data to accurately state the severity of complications, but we did analyse some of the reoperations separately, e.g. reoperation for anastomotic leak. The total rate of reoperation and mortality were 10.9% and 5.3%, respectively. These data were added in the revised Results section (page 8).

Back to the Annals paper than, their main hypothesis was that the surgical precision might to some extent deteriorate later in the week, leading to worse long term survival. However this is not reflected in more reoperations or more early deaths. So what then will be the reason? The only reason I can think of, is that the tired surgeon performs less adequate resections, causing worse long term survival. Is there less extensive surgery later in the week, are there more irradical resections later in the week?, is the lymph node harvest lower later in the week?. The inclusion of also this hypotheses and results would give the manuscript far more body and relevance.

Reply: These hypotheses are interesting. However, in a separate paper from the same cohort, we have found no prognostic role of lymph node harvest during surgery for oesophageal cancer (van der Schaaf M, Johar A, Wijnhoven B, Lagergren P, Lagergren J. Extent of lymph node removal during esophageal cancer surgery and survival. *J Natl Cancer Inst* 2015;107(5)) Thus, that factor should not be a mechanism. The potential role of non-radical resection in relation to weekday of surgery would fit better is a study where long-term survival is the study outcome. We added a discussion about these issues in the revised Discussion section (page 11).

Reviewer: 3, Michael Schweigert, Department of General and Thoracic Surgery, Städtisches Klinikum Dresden

Lagergren and colleagues conducted a population based study following their publication in the Annals of Surgery 2015. Both study population and period are identical. In their previous work the authors had recognized an association between weekday of oesophagectomy and 5-year-survival. They had postulated that surgery later in the week deteriorates the 5-year-survival rate.

Now the authors analyzed the relation between weekday of surgery and short term operative complications (reoperation) and 30-day-mortality. In contrast to the previous study they found no association.

In general, the paper is well written and interesting. The size of the study population is impressive. In accordance with the authors I am convinced that the interpretation of the data is not marred by possible confounders as year of operation, neoadjuvant therapy, and operative procedure.

Reply: Thank you for these positive remarks.

The discussion section of the manuscript has several shortcomings. The authors only discuss the possible confounders (see above). The conflicting results of the two studies are not discussed. The authors provide no possible explanation for the fact that weekday of surgery affects the 5-year-mortality but not the 30-day-mortality. Some speculation on the possible reasons would stimulate the discussion section. The authors should also outline whether their database is sufficient to identify further possible reasons besides reoperation to explain the long term differences or whether not.

Reply: The studies are not in any direct conflict. It is possible that details during the tumour dissection are negatively influenced by surgeon fatigue, while any such factor does not influence the short-term outcomes. As suggested by reviewer 2, other hypotheses are that there is less extensive surgery later in the week, reflected by more irradical resections or a lower lymph node harvest later in the week. However, in a separate paper from the same cohort, we have found no prognostic role of lymph node harvest during surgery for oesophageal cancer (van der Schaaf M, Johar A, Wijnhoven B, Lagergren P, Lagergren J. Extent of lymph node removal during esophageal cancer surgery and survival. *J Natl Cancer Inst* 2015;107(5)) Thus, that factor should not be a mechanism. The potential role of non-

radical resection in relation to weekday of surgery would fit better is a study where long-term survival is the study outcome. We have added a discussion about these comments in the revised manuscript (page 11).

The authors should also look into the possibility that the results of the previous study are marred by thus far not identified shortcomings/confounders. If one looks at a 5 year period many interfering factors have to be taken into consideration. This should be discussed, too.

Reply: We believe that the limitations of the previous paper were thoroughly discussed in that paper, and are better placed there, while the shortcomings of the present study are focused on in this paper.

What is the authors recommendation based on their findings? Should we avoid oesophagectomy on Fridays?

Reply: There is a need for more research before any clinical recommendations can be given.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Tom Wiggins Imperial College London, UK
<b>REVIEW RETURNED</b>	06-Apr-2016

<b>GENERAL COMMENTS</b>	The authors have added to the discussion of the manuscript and have addressed the comments raised by the other reviewers.
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<b>REVIEWER</b>	Sjoerd Lagarde Erasmus MC
<b>REVIEW RETURNED</b>	15-Apr-2016

<b>GENERAL COMMENTS</b>	The revisions of the paper are adequate
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