Early vs late tracheotomy for prevention of pneumonia in mechanically ventilated adult ICU patients: a randomized controlled trial

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(Article begins on next page)
EARLY VS. LATE TRACHEOTOMY FOR PREVENTION OF PNEUMONIA IN MECHANICALLY VENTILATED ADULT ICU PATIENTS: A RANDOMIZED CLINICAL TRIAL

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Abstract (word count: 266)

Context. Tracheotomy is used to replace endotracheal intubation in patients requiring prolonged ventilation. However, there is considerable variability in the time considered optimal for performing tracheotomy. This is of clinical importance because (a) timing is a key criterion for performing a tracheotomy; (b) patients who have a tracheotomy use a large amount of resources.

Objective. To determine the effectiveness of early tracheotomy (after 6-8 days of laryngeal intubation) compared to late tracheotomy (13-15 days of laryngeal intubation) in reducing the incidence of pneumonia and increasing the number of ventilator- and ICU-free days.

Design, setting, and patients. Randomized clinical trial performed in 12 Italian ICUs from June 2004 to June 2008 that included 600 adult patients without lung infection who had been ventilated for 24 hours and had a Simplified Acute Physiology Score II between 35 and 65, and a sequential organ failure assessment score ≥ 5.

Interventions. Patients who showed, 48 hours after inclusion: (a) worsening of respiratory conditions; (b) unchanged or worse sequential organ failure assessment score; and (c) no pneumonia were randomized to early (N=209) or late (N=210) tracheotomy. Patients that received a tracheotomy after randomization were 145 in the early and 119 in the late group.

Main Outcome Measures. Primary end-point was incidence of ventilator-acquired
pneumonia.

**Results.** Ventilator-acquired pneumonia in the early and late groups was observed in 30 (14%, 95% confidence interval 10 to 19%) and 44 (21%, 95% confidence interval 15 to 26%) patients, respectively (P=0.073).

**Conclusion.** Among mechanically ventilated adult ICU patients, early tracheotomy compared to late tracheotomy did not result in statistically significant improvement in incidence of ventilator-acquired pneumonia.

**Trial Registration:** ClinicalTrials.gov: NCT00262431
Introduction

Tracheotomy is a surgical procedure that is performed to replace endotracheal intubation in patients who are expected to require prolonged mechanical ventilation. Advantages of tracheotomy include prevention of ventilator-acquired pneumonia (VAP), earlier weaning from respiratory support, and reduction in sedative use. Although in recent years the use of tracheotomy has increased by nearly 200%, analysis of a large database showed considerable variation in the timing of tracheotomy and in the incidence of tracheotomy. This observation is of clinical importance because (a) timing is an important criterion for tracheotomy, as many clinicians perform a tracheotomy based on identification of a specific time window; (b) tracheotomy is associated with high resource use.

A consensus conference recommended performing tracheotomy after 3 weeks of endotracheal intubation. Although this time-scale for tracheotomy is widely used, observational studies have reported that earlier tracheotomy may be associated with quicker weaning from mechanical ventilation. However, randomized clinical trials have failed to confirm this observation. Rumbak and coworkers showed that tracheotomy within 2 days of admission reduced mortality rate, occurrence of pneumonia, and intensive care unit (ICU) length of stay compared to tracheotomy performed after 14-16 days of endotracheal intubation. Blot and coworkers showed...
that mortality, duration of mechanical ventilation and ICU stay, and incidence of infections did not differ between patients randomized to receive a tracheotomy within 4 days following onset of mechanical ventilation and those randomized to maintain endotracheal intubation for at least 14 days.\textsuperscript{16}

We examined the hypothesis that tracheotomy performed after 6-8 days of endotracheal intubation compared to tracheotomy performed after 13-15 days of endotracheal intubation would reduce incidence of VAP.
Methods

From June 2004 to June 2008, patients were recruited from 12 Italian ICUs. Review boards approved the protocol, and written consent was obtained from competent patients. In incompetent patients, consent was issued from the referring physician (not involved in the study) and the family.17

Patients were enrolled in the study if they: (a) were older than 18 years of age; (b) had been mechanically ventilated for acute respiratory failure for 24 hours; (c) had a Simplified Acute Physiology Score II (SAPS) between 35 and 65;18 (d) had a sequential organ failure assessment (SOFA) score equal to or greater than 5;19 (e) did not have pulmonary infection, as estimated by a Clinical Pulmonary Infection Score (CPIS) score less than 6.20, 21 Patients were not enrolled if they had: (a) chronic obstructive pulmonary disease; (b) anatomical deformity of the neck including thyromegaly and cervical tumors; (c) history of esophageal/tracheal or pulmonary cancer; (d) previous tracheotomy; (e) soft tissue infection of the neck; (d) hematological malignancy; (e) pregnancy.

Forty-eight hours after enrollment, patients were randomized to receive a tracheotomy after 6-8 days of endotracheal intubation (early) or after 13-15 days of endotracheal intubation (late) if: a) the arterial oxygen pressure (PaO2) was less than or equal to 60 mmHg with a fraction of inspiratory oxygen (FiO2) of at least 0.5 and a
positive end-expiratory pressure (PEEP) of at least 8 cmH₂O; b) an attending clinician not involved in the study considered that the acute clinical condition requiring ventilatory support was still unresolved; and c) the SOFA score remained equal to or greater than 5. Patients were not randomized if there was: (a) improvement in respiratory conditions identified as a PaO₂ greater than 60 mmHg with a FiO₂ less than 50% and PEEP less than 8 cmH₂O and the attending clinician considered that the acute clinical condition requiring mechanical ventilation had resolved; (b) pulmonary infection as estimated by a Clinical Pulmonary Infection Score (CPIS) score greater than 6; (c) moribund state or death.

Tracheotomy was not performed if one of the following a priori defined conditions occurred: (a) improvement in oxygenation, identified as a PaO₂ greater than 60 mmHg with a FiO₂ less than 50% and PEEP less than 8 cmH₂O and the attending clinician considered that the acute clinical condition requiring mechanical ventilation had resolved; (b) moribund state or death; (c) intra-cranial pressure greater than 15 mmHg and/or cerebral perfusion pressure less than 60 mmHg; (d) platelet count less than or equal to 50,000/mm³, activated partial thromboplastin time or prothrombin time longer than 1.5 seconds, or bleeding time greater than twice normal in the 24 hour prior to the scheduled tracheotomy. Patients randomized to early or late that did not receive the planned tracheotomy were still included in the final analysis due to the intention-to-treat design.
Adverse events associated to tracheotomy were classified as “intra-operative” (minor bleeding i.e. bleeding that could be controlled by digital pressure, significant bleeding i.e. any bleeding event that required the administration of 1 unit of packed red cells, difficult tracheotomy tube placement, i.e. requiring more than 2 attempts at insertion during primary placement procedure, hypoxemia i.e. oxygen saturation of < 90% for > 90 seconds, arrhythmia, cardiac arrest) and “post-operative” (stoma inflammation, stoma infection, minor bleeding, major bleeding, pneumothorax, subcutaneous emphysema, tracheo-esophageal fistula, cannula displacement or need for cannula replacement) and their occurrence recorded during the 28-days study period.23

The presence of VAP was defined using the simplified Clinical Pulmonary Infection Score (CPIS) score.21 A score of 0, 1 or 2 is given for tracheal secretions, chest X-ray infiltrates, temperature, leukocyte count, and of 0 or 2 for PaO₂/FiO₂ (or evidence of acute respiratory distress syndrome: ARDS) and microbiology21. A CPIS greater than 6 was considered to indicate the presence of VAP.21, 24 The score was calculated on study entry, immediately before randomization, and every 72 hours till day 28 from randomization.19 The CPIS score was also evaluated before performing scheduled tracheotomy. A clinician blinded to patient allocation that looked at clinical charts remotely and not seeing the patient evaluated the non-objective components of the CPIS score (quality of secretions, chest X-ray, evidence of ARDS). The SOFA
score was calculated using the most abnormal value for each of the six organ systems and was calculated on admission and before randomization.

The primary outcome variable was the 28-day cumulative incidence of VAP calculated from the date of randomization. Secondary outcome variables were: (a) number of ventilator-free days during the 28 days immediately after randomization, calculated from the date of randomization to the date of the first period of spontaneous breathing that lasted at least 48 consecutive hours; (b) number of ICU-free days during the 28 days immediately after randomization, calculated from the date of randomization to the date of an ICU discharge; (c) number of patients in each group who were alive during the 28 days immediately after randomization. Long-term outcome was evaluated in the two groups as hospital length of stay, and need after hospital discharge of long term care facility. Mortality at one year from randomization was evaluated trying to contact all study patients who had been discharged alive from hospitals.

To limit effects of management heterogeneity among centers on outcome variables, all patients were placed in the semi-recumbent position, and weaning from mechanical ventilation and use of sedatives and analgesics were constrained by protocols. The choice of technique and the location for tracheotomy (bedside versus operating room) were not protocol controlled.
Concealed randomization was conducted centrally using a computer-generated randomization schedule. Based on previous data, the predicted incidence of VAP was 30%. The trial was designed to enroll 320 patients in order to demonstrate a 35% relative reduction in VAP (from 30% to 20%) with an alpha of 0.05 and a power of 80% assuming that some of the subjects randomized to each group could not actually receive a tracheotomy. All analyses were conducted on an intention-to-treat basis. Values are reported as mean (standard deviation) or median (interquartile range). Comparisons between groups (early vs. late) and between different study times were conducted using chi-squared test, Fisher’s exact test, paired and unpaired two-tailed T-test and Wilcoxon’s test. Kaplan-Meier curves were compared by the log-rank test; cumulative incidence of VAP was compared by Gray’s test considering death as a competing event. Hazard ratios were calculated using Cox and Fine & Gray models; proportional hazards assumption for the use of these models was evaluated by graphic evaluation of scaled Schoenfeld-Type residuals. A probability of 0.05 on two-sided testing was regarded as significant (STATA 9.2; STATA Corp, Texas and R 2.5.0, package cmprsk; open source).
Results

Of the 600 enrolled patients, 419 patients were randomized to receive an early (N=209) or a late (N=210) tracheotomy. The remaining 181 patients were not randomized because of improvement in respiratory conditions (N=92), occurrence of pulmonary infection (N=24), and moribund state or death (N=65). Of the 209 patients randomized to the early group, 145 patients received a tracheotomy after 7 (1) days of endotracheal intubation. Of the 210 patients randomized to the late group, 119 patients received a tracheotomy after 14 (1) days of endotracheal intubation (Figure 1). Analyses were conducted on the intention-to-treat population of 419 patients.

Baseline characteristics at admission or before randomization did not differ between the two groups. At randomization, type of admission was medical (40 vs. 36 %), for scheduled surgery (8 vs. 10 %) and unscheduled surgery (41 vs. 45 %), and trauma (11 vs. 9 %) in the early and late group, respectively. At randomization, the SOFA score increased and oxygenation parameters significantly worsened in both groups (Table 1).

All tracheotomy were performed at the bedside using percutaneous techniques33 (“Griggs” technique34 in the 72% of early and 73% of late and “percutwist” technique35 in the 25% of early and 22% of late). Adverse events associated to tracheotomy are indicated in Table 2. Thirty-nine % of the patients in both group (57 patients in early and 46 patients in late group) experienced an adverse effect.
**Figure 2** shows the Kaplan-Meier curves for cumulative incidence of VAP according to whether patients were randomized to early or late tracheotomy. VAP was observed in 30 patients in the early group (14%, 95% confidence interval 10 to 19%) and in 44 patients in the late group (21%, 95% confidence interval 15 to 26%) \((P=0.073)\).

The numbers of ventilator- and ICU-free days and the incidence of successful weaning and of ICU discharge were significantly greater in patients randomized to early tracheotomy than in patients randomized to late tracheotomy; there were no differences between the groups in survival at 28 days (Table 3). Hazard ratio and 95% confidence interval of developing VAP, of remaining connected to the ventilator, of remaining in the ICU and of dying were 0.66 (0.42 to 1.04), 0.70 (0.56 to 0.87), 0.73 (0.55 to 0.97), 0.80 (0.56 to 1.15), respectively.

Median and interquartile range of the hospital length of stay was 31 (17-49) and 32 (18-59) days in early and late, respectively. Data on mortality at one year and need of long-term care facility were obtained in 292 of the patients that left the hospital alive (144 in the early group and 148 patients in the late group). Survival at one year was 50% (72 patients; confidence interval: 41 to 61%) in the early group and 43% (63 patients; confidence interval: 34 to 52%) in the late group \((P=0.248)\). Admission to long-term care facility was required by the 39% (56 patients) in the early and in the 36% (53 patients) in the late \((P=0.915)\).
Discussion

The present study shows that tracheotomy performed after 6-8 days of endotracheal intubation did not result in a reduced incidence of VAP compared with tracheotomy performed after 13-15 days of endotracheal intubation.

Prolonged endotracheal intubation is known to be associated with airway tissue trauma, infection, patient discomfort, and need for high doses of sedation.\textsuperscript{36,37} Tracheotomy, the procedure that creates temporary or persistent access to the trachea, is commonly performed to replace endotracheal intubation in ICU patients who are expected to require prolonged mechanical ventilation\textsuperscript{3,4} since provides an access to the airway that is more stable and better tolerated than endotracheal intubation and that facilitates toilet of pulmonary secretions, oral feeding, and patient communication.\textsuperscript{3,4,38} The National Association of Medical Directors of Respiratory Care recommended that tracheotomy should replace endotracheal intubation in patients who still require mechanical ventilation 3 weeks after admission and noted that identification of the optimal time for a tracheotomy to be performed is one of the most important criteria when deciding to perform a tracheotomy.\textsuperscript{10} Introduction of percutaneous tracheotomy techniques into clinical practice\textsuperscript{39} has made tracheotomy possible at the bedside without need for surgeons or operating room\textsuperscript{23} and increased use of tracheotomy in the ICU by nearly 200\%\textsuperscript{6}. 
Analysis of the US National Trauma Databank showed that the rates and timing of tracheotomy varied significantly across ICUs. A preconceived notion of efficacy in the absence of any evidence to support an optimal time for a tracheotomy has been advocated to explain this discrepancy between the wide use of tracheotomy on the one hand and its inconsistent and non-homogenous clinical use on the other. This may be of particular clinical importance since patients receiving a tracheotomy represent a cohort which is among the most resource intensive to provide care for.

A prospective randomized trial that included 120 patients reported that performing tracheotomy within 2 days of admission was associated with a halving of 30-day mortality rate, a reduced occurrence of pneumonia, and a shortened ICU length of stay compared to performing tracheotomy within 14-16 days of admission. A later meta-analysis noted that performing a tracheotomy up to 7 days after initiation of endotracheal intubation shortened the duration of mechanical ventilation and length of stay in intensive care but did not affect outcome compared to later tracheotomy. A more recent clinical trial that included 123 patients showed that mortality, duration of mechanical ventilation, duration of ICU stay, and incidence of infections did not differ between patients randomized to receive a tracheotomy within 4 days following onset of mechanical ventilation and those in whom endotracheal intubation was maintained for at least 14 days.

The present study estimated the need for prolonged ventilation by (a) severity of
illness and (b) need for ventilatory support required to obtain pre-defined oxygenation criteria. These criteria selected patients who at study enrollment had a SAPS II score of 50.8 (8.2) and at randomization had an increase in SOFA score and a worsening in respiratory parameters. Ferreira recently demonstrated that mortality in patients matching these criteria ranged between 35 and 40%.\textsuperscript{19} Under these circumstances and in contrast to previous trials,\textsuperscript{15,16,41} almost two thirds of the screened patients were randomized and underwent the scheduled tracheotomy. Patients who, although randomized did not actually receive a tracheotomy, were included in the final analysis because of the intention-to-treat design.

We chose the 28-day cumulative incidence of VAP as the primary outcome variable. Occurrence of VAP was evaluated with a score that combines objective (temperature, and PaO2/FiO2 values, leukocyte count, and microbiology findings) and non-objective (quality of secretions, chest X-ray interpretation, evidence of ARDS) components\textsuperscript{20,21,24}. To minimize the potential bias of the latter on evaluation of the primary outcome variable we had the non-objective components of the score evaluated by clinicians blinded to patient allocation and that looked at the clinical charts remotely and not seeing the patient.

The incidence of VAP was 14% in the early group (30 patients; 95% confidence interval 10 to 19%) and 21% in the late group (44 patients; 95% confidence interval 15 to 26%) (\(P=0.073\)). This 33% risk reduction was therefore smaller than planned and
did not reach statistical significance because the observed incidence of VAP in the control group was less than that predicted. Moreover, only 69% of the patients randomized to early and 57% of the patients randomized to late did receive the planned tracheotomy.

Other possible explanation is that there is really no improvement from earlier tracheotomy. Results of the present study show that while anticipating tracheotomy of one week decreased the need of ventilatory support and of ICU admission, planning an earlier tracheotomy actually (a) increased the number of patients that received a tracheotomy (69% of the patients randomized to early received a tracheotomy while 57% of the patients randomized to late received a tracheotomy); (b) did not decrease the incidence of VAP; (c) did not influence hospital length of stay, mortality at one year and need of long-term health care facility; but (c) increased the number of patients potentially exposed to the adverse effects related to the tracheotomy.

In conclusion our data show that, in intubated and mechanically ventilated adult ICU patients with a high mortality rate, tracheotomy performed after 6-8 days of endotracheal intubation did not result in a significant reduction in incidence of VAP compared to tracheotomy performed after 13-15 days of endotracheal intubation. Although the number of ICU and ventilator free days was higher in the former than in the latter, long-term outcome did not differ. Considering that anticipation of tracheotomy of one week increased the number of patients that received a tracheotomy
and that more than one third of the patients experienced adverse effect related to the tracheotomy, these data suggest that tracheotomy should not be performed earlier than after 13-15 days of endotracheal intubation.
Figure Legends

FIGURE 1. Flow chart of the study protocol

FIGURE 2. Kaplan-Meier curves of development of VAP according to whether patients received an early or a late tracheotomy.
Acknowledgment

Participating members of the Early vs. Late tracheotomy study group (ELT)
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Access to data
The corresponding author (VMR) confirms he had full access the data and takes complete responsibility for the integrity of the data, and the accuracy of data analysis.

Conflict of Interest
All authors (PIER PAOLO TERRAGNI, MASSIMO ANTONELLI, ROBERTO FUMAGALLI, CHIARA FAGGIANO, MAURIZIO BERARDINO, FRANCO BOBBO PALLAVICINI, ANTONIO MILETTO, SALVATORE MANGIONE, ANGELO U. SINARDI, MAURO PASTORELLI, NICOLETTA VIVALDI, ALBERTO PASETTO, GIORGIO DELLA ROCCA, ROSARIO URBINO, CLAUDIA FILIPPINI, EVA PAGANO, ANDREA EVANGELISTA, GIANNI CICcone, LUCIANA MASCIA, AND V. MARCO RANIERI) do not have any relevant financial interests and relationships or financial conflicts within the past 5 years and for the foreseeable future relevant to the topic of this study.
Author contribution

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Acquisition of data: Pier Paolo Terragni, Massimo Antonelli, Roberto Fumagalli, Chiara Faggiano, Maurizio Berardino, Franco Bobbio Pallavicini, Antonio Mileto, Salvatore Mangione, Angelo U. Sinardi, Mauro Pastorelli, Nicoletta Vivaldi, Alberto Pasetto, Giorgio Della Rocca, Rosario Urbino, Luciana Mascia, V. Marco Ranieri

Analysis and interpretation of data: Pier Paolo Terragni, Massimo Antonelli, Roberto Fumagalli, Luciana Mascia, Claudia Filippini, Eva Pagano, Andrea Evangelista, Gianni Ciccone, V. Marco Ranieri

Drafting the manuscript: Pier Paolo Terragni, Massimo Antonelli, Roberto Fumagalli, Gianni Ciccone, Luciana Mascia, V. Marco Ranieri

Critical revision of the manuscript for important intellectual content: Chiara Faggiano, Maurizio Berardino, Franco Bobbio Pallavicini, Antonio Mileto, Salvatore Mangione, Angelo U. Sinardi, Mauro Pastorelli, Nicoletta Vivaldi, Alberto Pasetto, Giorgio Della Rocca, Rosario Urbino, Claudia Filippini, Eva Pagano, Andrea Evangelista
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Supervision: V. Marco Ranieri
References


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Table 1. Characteristics of the study population at enrollment and at randomization

<table>
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<tr>
<th></th>
<th>early tracheotomy</th>
<th>late tracheotomy</th>
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<tr>
<td></td>
<td>(n =209 )</td>
<td>(n =210 )</td>
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<tr>
<td><strong>AT ENROLLMENT</strong></td>
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<td></td>
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<tr>
<td>Age, yrs</td>
<td>61.8 (17.4)</td>
<td>61.3 (16.8)</td>
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<td>Male, % [number]</td>
<td>66.0 [138]</td>
<td>67.6 [142]</td>
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<td>51.1 (8.7)</td>
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<td>SOFA score</td>
<td>7.9 (2.6)</td>
<td>7.6 (2.9)</td>
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<tr>
<td>PaO2, mmHg</td>
<td>123 (50)</td>
<td>123 (54)</td>
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<tr>
<td>FiO2</td>
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<td>9.8 (1.5)$^#$</td>
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<td>PEEP (cm H2O)</td>
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<td>9.3 (1.1)$^\circ$</td>
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</tbody>
</table>

Values are means (standard deviation). SAPS II represents simplified acute physiological score (range 0 and 163) and is an index of the severity of illness; higher values indicate greater severity. SOFA represents sequential organ failure assessment score, and is an index of the extent of organ (respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems) failure (range 0-24); higher values indicate greater severity of organ failure. PaO2 is arterial oxygen. FiO2 is inspiratory oxygen fraction ratio. PEEP is positive end expiratory pressure. $^\circ$ P=0.04; $^*$ P=0.03; $^\#$ P=0.02 “AT RANDOMIZATION” vs. “AT ENROLLMENT” (paired two-tailed T- test or Wilcoxon’s test); all comparisons between early and late were not significant (chi-squared test, unpaired two-tailed T- test or Wilcoxon’s test). All P values are two-tailed.
Table 2. Potential adverse events associated to tracheotomy in the early and late groups

<table>
<thead>
<tr>
<th></th>
<th>early tracheotomy (n = 145)</th>
<th>late tracheotomy (n = 119)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INTRA-OPERATIVE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor bleeding, n</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Significant bleeding, n</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tube dislocation, n</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>hypoxemia, n</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>arrhythmia, n</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>cardiac arrest, n</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>POST-OPERATIVE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>stoma inflammation, n</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td>stoma infection, n</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>minor bleeding, n</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>major bleeding, n</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>pneumothorax, n</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>subcutaneous emphysema, n</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>tracheo-esophageal fistula, n</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>cannula displacement or need for cannula replacement, n</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>TOTAL, n (%)</strong></td>
<td>57 (39)</td>
<td>46 (39)</td>
</tr>
</tbody>
</table>

All differences between early vs. late were not statistically significant (chi-squared test or Fisher’s exact test).
Table 3. Secondary end-points in the early and late tracheotomy groups

<table>
<thead>
<tr>
<th></th>
<th>early tracheotomy (n =209 )</th>
<th>late tracheotomy (n =210 )</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilator-free days at 28 days</td>
<td>11 (0-21)</td>
<td>6 (0-17)</td>
<td>0.016</td>
</tr>
<tr>
<td>ICU-free days at 28 days</td>
<td>0 (0-13)</td>
<td>0 (0-8)</td>
<td>0.015</td>
</tr>
<tr>
<td>Successful weaning, n (%)</td>
<td>161 (77) CI: 0.71 to 0.82</td>
<td>142 (68) CI: 0.61 to 0.74</td>
<td>0.002</td>
</tr>
<tr>
<td>ICU discharge, n (%)</td>
<td>101 (48) CI: 0.42 to 0.55</td>
<td>82 (39) CI: 0.32 to 0.46</td>
<td>0.029</td>
</tr>
<tr>
<td>Survival at 28 days, n (%)</td>
<td>154 (74) CI: 68 to 80</td>
<td>144 (68) CI: 63 to 75</td>
<td>0.248</td>
</tr>
</tbody>
</table>

Data of ventilator-free days and ICU-free days are median and interquartile range; all P values are 2-tailed (Wilcoxon’s test, log-rank test and Gray’s test). ICU stands for intensive care unit. CI stands for 95% confidence interval.