

The effect of neoadjuvant chemoradiotherapy on airway colonization and postoperative respiratory complications in patients undergoing oesophagectomy for oesophageal cancer[†]

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Abstract

Respiratory complication is one of the important postoperative complications of oesophageal cancer. The aim of this study was to evaluate whether neoadjuvant chemotherapy before surgery is effective for postoperative respiratory complications. In this study, patients with oesophageal cancer were divided into two groups: one with neoadjuvant therapy and the other without neoadjuvant therapy. Before surgery, they all underwent bronchoscopy and bronchoalveolar lavage. We evaluated respiratory complications and the effects of preoperative neoadjuvant therapy. Forty patients (M/F = 23/17 and mean age 61 years) were enrolled in this study. Twenty-two cases had cancer in the middle part and 18 in the lower part of the oesophagus. Significant correlation was observed between the number of positive micro-organisms and difficulty in weaning and receiving neoadjuvant therapy. But no significant correlation was found between neoadjuvant therapy and respiratory complications.

Keywords: Airway colonization • Neoadjuvant therapy • Oesophageal cancer • Pulmonary complications

INTRODUCTION

Oesophageal cancer is considered an invasive disease which usually appears in an advanced stage, as in half of the patients, the disease is advanced at the time of diagnosis and 30–40% has diagnosable distant metastasis [1]. Many studies have reported that the results of radiotherapy alone are not desirable either [2, 3]. The combination of radiotherapy with surgery does not increase the survival rate and its effect on the local control is not clear either. Chemoradiotherapy and then surgery have potential advantages such as decreasing the stage of disease, increasing the possibility of tumour resection with negative radial margin and removing of micrometastatic disease [4]. The most important complications that lead to death are pneumonia and adult respiratory distress syndrome (ARDS) [5]. On the other hand, some studies reported contradictory results and considered it as a safe preoperative method [6].

The aim of this study was to evaluate the role of neoadjuvant therapy in postoperative respiratory complications in patients who underwent oesophageal resection by the transthoracic or transhiatal method.

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MATERIALS AND METHODS

In this randomized clinical trial, 40 cases of oesophageal cancer (22 middle and 18 lower part), who were candidates for surgery, were referred to Mashhad University of Medical Sciences during 2008–2009. They were randomly divided into two groups. One group underwent neoadjuvant chemoradiotherapy which was based on the following protocol.

They received 4000-rad radiation during 4 weeks and at the same time received chemotherapy based on cisplatin and 5 FU, and then they were ready for surgery 6 weeks post-radiochemotherapy.

Patients in the second group were ready for surgery without receiving neoadjuvant therapy. Complete evaluation was pre-operatively performed.

Inclusion criteria were (i) oesophageal cancer of (1/3) middle and (1/3) lower parts of the oesophagus and (ii) presence of bronchoscopy and bronchoalveolar lavage (BAL) results before surgery. Exclusion criteria were (i) cervical oesophageal cancer, (ii) inability to sustain surgery, (iii) respiratory complications such as pneumonia before surgery and (iv) weight loss of more than 30%.

Bronchoscopy and BAL were performed 24 h before surgery and BAL samples were taken from all patients. The samples were

sent to the microbiology laboratory for determining the micro-organism.

Based on the surgeon's opinion, the patients underwent oesophagectomy (transthoracic or transhiatal). 30 min, before the surgery, patients received a dose of antibiotic (ceftriaxone 1 g) and after the surgery the antibiotic was continued for 7 days (in all of the patients). The anastomosis was in the neck in all patients and the stomach was used as a conduit. Patients usually were extubated in the operating room after the surgery, but in case of intolerance, they were extubated in the ICU. After toleration of the weaning we extubated with the use of T-tube. Nutritional jejunostomy was also performed for all patients. Enteral nutrition was performed by jejunostomy 24 h after surgery. The patients were controlled during hospitalization for respiratory complications, such as atelectasia, pneumonia, ARDS and difficult weaning (DW) (defined as the need for ventilator for more than 48 h) [5], and hospital mortality related to infectious complications. Data were analysed by SPSS software version 11.5 and Fisher's exact test was used for comparison between two groups. $P < 0.05$ was considered statistically significant.

RESULTS

Among 40 patients, 23 were males and 17 were females. The mean age of the cases who underwent neoadjuvant therapy was 60 years and of the patients who did not was 62 years. Table 1 shows patient characteristics. No organism was found in 9 cases (22.2%) and positive culture was found in 31 cases (77.8%). Significant correlation was observed between the number of positive micro-organisms and receiving neoadjuvant therapy (Table 2) ($P = 0.041$).

Incidence and type of microorganisms and their frequencies are shown in Table 3.

Seven patients had weaning difficulties of whom six were in the neoadjuvant therapy receiving group and one case in the group not receiving neoadjuvant therapy. The mean duration of intubation in all patients was 2.1 ± 0.7 days, but other patients

Table 1: Patients characteristics

Parameter	With neoadjuvant	Without neoadjuvant	P-value
Sex (M/F)	11/9	12/8	0.21
Mean age (years)	60	62	0.29
Mean body mass index	17.9 ± 8.2	18.1 ± 3.8	0.69
Positive history of smoking	11	10	0.827
Positive history of COPD	1	1	1.000
Tumour location	1/3 middle: 12 1/3 lower: 8	1/3 1/3	0.77
Technique of surgery	Transhiatal:10 Transthoracic:10	Transhiatal:10 Transthoracic:10	1.000
Pathology (stage)			
I	0	1	0.81
IIA	9	10	
IIB	3	2	
III	8	7	

were extubated in the operation room. Significant correlation was found between DW and the status of receiving neoadjuvant therapy before surgery (Table 4) ($P = 0.039$).

There was no significant correlation between length of stay in the ICU and hospitalization with receiving neoadjuvant therapy (Tables 5 and 6).

Two cases (5%) died in the third and seventh postoperative days of whom one case was in the neoadjuvant therapy receiving group and the other in the group not receiving neoadjuvant therapy. The cause of mortality in both patients was myocardial infarction and no case of mortality related to respiratory complications was reported.

Postoperative minor respiratory complications (atelectasis) were only observed in two cases (5%); one case was in the neoadjuvant therapy receiving group and another in the group not receiving neoadjuvant therapy. Two cases were improved by conservative treatment and no significant difference was found between the two groups. Major complications, including pneumonia, ARDS and second mortality, were not observed in the patients.

Table 2: Relationship between the number of positive organisms and history of neoadjuvant therapy (Fisher's exact test)

History of neoadjuvant therapy	Result of culture		P-value
	Negative culture (n = 9)	Positive culture (n = 31)	
Negative	7 (77.8%)	13 (41.9%)	0.041
Positive	2 (22.2%)	18 (58.1%)	

Table 3: Frequency of positive pathogens in 31 patients (more than 1 microbial organism was diagnosed for some patients)

Type of microbe	n (%)
<i>Streptococcus α haemolyticus</i>	23 (74.1)
<i>Pneumococcus</i>	7 (22.5)
<i>Pseudomonase aeruginosa</i>	4 (1.2)
<i>Staphylococcus aureus</i>	2 (0.6)
<i>Streptococcus pyogenes</i>	2 (0.6)
<i>Klebsiella</i>	2 (0.6)
<i>Staphylococcus epidermidis</i>	1 (0.3)
<i>Enterococcus</i>	1 (0.3)

Table 4: Relationship between the number of positive organisms and difficult weaning (Fisher's exact test)

DW	Result of culture		P-value
	Negative culture	Positive culture	
Negative (33)	8 (24.2%)	25 (75.8%)	0.039
Positive (7)	1 (14.3%)	6 (85.7%)	

Table 5: Comparison of two groups in terms of length of hospitalization in the ICU

Status of receiving neoadjuvant therapy	ICU hospitalization (mean \pm SD)	P-value
Received (n = 20)	1.9 \pm 1.16 days	0.077
Not received (n = 20)	2.9 \pm 2.3 days	

Table 6: Comparison of two groups in terms of length of hospitalization

Status of receiving neoadjuvant therapy	Hospitalization (mean \pm SD)	P-value
Received (n = 20)	11.63 \pm 2.56 days	0.061
Not received (n = 20)	13.23 \pm 2.16 days	

DISCUSSION

Oesophageal cancer has a specific geographical pattern, which may be more obvious than other tumours caused by intervention of environmental factors [7]. In the past, complete removal and whole body radiotherapy were the only choices of therapy. Developments in chemotherapy, radiotherapy and different endoscopic treatments have increased the treatment options. Accurate staging is always mandatory since the treatment is based on the stage of disease [8].

Some authors believed that combination of radiotherapy and neoadjuvant chemotherapy led to increased respiratory complications, increased time on the ventilator and DW [5, 9]. Previous study showed that receiving neoadjuvant therapy was not considered an important factor for increased length of hospitalization in the ICU [10, 11].

Avendano *et al.* [5] defined DW as intubation more than 48 h after surgery and he reported that preoperative neoadjuvant therapy was effective in alleviating DW. Hagry *et al.* [6] showed that the mean time of intubation was 7 days.

After developed techniques of surgery and postoperative care, in some centres have decreased the rate of mortality and morbidity after oesophagectomy, the mortality rate in many centres performing oesophageal surgery is still high (around 12%) [12]. In the study of Urschel and Vasan [13], some factors after neoadjuvant therapy were considered important in increasing postoperative complications: bone marrow suppression, mucositis, odinophagy and anorexia, which lead to disturbances in the immune and nutrition systems, infectious complications and disorder in injury repair.

Hagry *et al.* [6] reported that neoadjuvant therapy and then surgery had acceptable complications, and it was effective in decreasing the stage of M1, T4 and T3 tumours with a higher chance of resection. Another study performed by Ruol *et al.* [14] showed that neoadjuvant chemoradiotherapy did not increase the main complications and the mortality rate, and it was safe even in older age. Riedel *et al.* [15] reported that there was no

case of mortality related to respiratory complications and even preoperative radiotherapy did not cause pneumonitis or changes in ventilatory tests after surgery.

CONCLUSION

Since the use of preoperative chemoradiotherapy neoadjuvant therapy is increasing for oesophageal cancer and because it is not related to the presentation of major negative complications not does it result in mortality, this method can be used safely in patients.

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APPENDIX. CONFERENCE DISCUSSION

Dr M. Mulligan (Seattle, Washington, USA): I have a couple of questions. Was there any difference in the distribution of surgical approach between the two groups? Was there a disproportionate presence of transhiatal or transthoracic approaches in the neoadjuvant or non-neoadjuvant groups?

Dr Bagheri: There's no difference between the two groups. It's the surgeon's opinion.

Dr Mulligan: I'm not aware of any literature that says that clinical outcomes are driven by airway colonization. This has been extensively studied in the ICU population wherein colonization is merely an epiphenomenon. I don't know if you're aware of that literature, but I've never seen that correlate. My question to you is, do you think you're looking at the right morbidities? You see a correlation with difficulty in weaning and you don't see a correlation between the incidence of respiratory complications. However, if you look at the things that would tend to migrate intuitively with difficulty in weaning, it would be failure to ambulate. So perhaps you could look at disposition status, malnutrition, prolonged ileus, DVT, and PE. These are the kinds of things that I would think would cluster together in a population that has been sort of rendered a little less functional by several weeks of chemotherapy. Do you have any data on those other sorts of complications?

Dr Bagheri: I considered this situation only for weight. The patients with a decrease in weight, weight loss of more than 30%, were excluded from the study. In our patients, the history of DVT isn't considered. In my country the prevalence of DVT is different from America and Europe: a much lower incidence of DVT is seen before the neoadjuvant therapy and after surgery. It is an important issue that this incidence is so low. But in this study I considered only the weight of the patients for these criteria that you mention.

Dr M. Schweigert (Nuremberg, Germany): I have a couple of questions. You said you had randomly designed that 20 people received neoadjuvant chemotherapy or chemoradiation therapy and 20 not. Were there any clinical data? What were your indications for the neoadjuvant therapy? I have seen one slide where it said stage I, for example, you would see stage I disease in the neoadjuvant therapy group.

The other question is, did you have any drop-offs? In our experience, when people receive neoadjuvant induction therapy, not everyone progresses to surgery because of side complications of the neoadjuvant therapy. Did you manage to get all 20 of your patients from the induction therapy to surgery, or did you have to fit in more than 20 patients in order to have 20 patients for your comparison?

Dr Bagheri: In my university we have an accepted protocol for performing neoadjuvant therapy in oesophageal cancer, not the impression for decrease of tumour size or resectability, but just the impression for the control of micrometastasis, and the stage I group is in this situation. I don't understand your second question.

Dr Schweigert: All 20 patients who received induction therapy, were they all fit for surgery afterwards, or did you have any complications during your induction therapy?

Dr Bagheri: Complications other than pulmonary?

Dr Schweigert: Yes, so they were not fit for the operation.

Dr Bagheri: I haven't any other complication that results in some difference within this group.