Indian J Gastroenterol (May–June 2015) 34(3):240–244
DOI 10.1007/s12664-015-0571-6

ORIGINAL ARTICLE

Chylothorax after esophagectomy for esophageal cancer: Risk factors and management

Rahul Gupta[1] · **Harjeet Singh**[1] · **Saurabh Kalia**[1] · **Rajesh Gupta**[1] · **Rajinder Singh**[1] · **G. R. Verma**[1]

Received: 11 January 2015 / Accepted: 11 May 2015 / Published online: 2 June 2015

Abstract
Background Chylothorax is an uncommon complication of esophagectomy. It carries significant morbidity and mortality. The predisposing factors are ill-defined.
Methods We retrospectively evaluated the data of 45 patients of carcinoma esophagus who underwent esophagectomy after neoadjuvant chemoradiotherapy (NACRT) from January 2010 to July 2012 in our tertiary health care center.
Results Four patients (8.88 %) had chylothorax. On analysis of perioperative factors, it was found that patients with chylothorax had tumor in middle third of thoracic esophagus (100 %), shown partial response to neoadjuvant chemoradiation (NACRT) (100 %) and were associated with difficult mediastinal dissection (75 %) leading to higher blood loss requiring transfusion unlike those without chylothorax. There was no significant difference in the incidence of chylothorax following transhiatal, 3/35=8.57 % or transthoracic esophagectomy 1/10=10 % (p=0.898). Three patients were managed by transabdominal en masse ligation of tissue between aorta and azygos vein while one patient was managed conservatively. Patients were discharged after a mean hospital stay of 15.5 days. The 30-day mortality rates in the two groups were similar (0 % vs. 4.8 %).
Conclusion Difficult mediastinal dissection during esophagectomy in middle esophageal cancer may lead to thoracic duct injury. Complete response to NACRT may reduce the risk of chylothorax. Early transabdominal en masse ligation carries excellent results. Low output fistula following thoracic duct injury can be managed conservatively.

Keywords Chemoradiation · Neoadjuvant therapy · Thoracic duct · Transhiatal · Transthoracic

Introduction

Chyle leak after esophagectomy is an infrequent complication. The reported incidence of chylothorax in transhiatal esophagectomy ranges from 0.6 % to 10.5 % [1–3]. Due to this low incidence, there is very few evidence on its predisposing factors and its optimal treatment of choice. Occurrence of chylothorax in postoperative period is associated with increase in the incidence of major complications and in hospital mortality by several folds [4]. Also, since the introduction of neoadjuvant therapy in the multimodality treatment of esophageal cancer, its impact on incidence of postoperative chylothorax is not known.

Despite various attempts at developing criteria to facilitate decision making with regard to treatment of chylothorax, there are no guidelines as yet and many surgeons give trial of conservative medical management while others prefer early thoracic duct ligation [4, 5].

We aimed to identify the risk factors for postoperative chylothorax in our subgroup of patients and its optimal treatment.

Methods

We retrospectively evaluated the data of 45 patients of esophageal cancer (44 squamous cell carcinoma, 1 adenocarcinoma) who underwent esophagectomy after neoadjuvant

✉ G. R. Verma
grverma@gmail.com

[1] Surgical Gastroenterology Division, Department of General Surgery, Postgraduate Institute of Medical Education and Research, Chandigarh 160 012, India

therapy from January 2010 to July 2012 in our tertiary health care center. Patients with esophageal cancer were diagnosed by endoscopic biopsy and staged by computed tomography of neck, chest and abdomen (CT), or positron emission tomography (PET-CT). All patients had locally advanced disease (T3 or T4 or node positive) and hence received neoadjuvant chemoradiation. The response to neoadjuvant therapy was assessed by endoscopy, CT and/or PET-CT. After 5.4–10.3 weeks of neoadjuvant therapy, 35 patients underwent transhiatal esophagectomy (THE), 7 patients underwent minimally invasive esophagectomy, and 3 patients had transthoracic esophagectomy (TTE). Surgery was performed by senior consultants. Thoracic duct was not identified intraoperatively. Postoperatively, chylothorax was suspected in patients with high chest tube output (>500 mL/d) or if the color of the chest tube fluid turn milky white. Chylothorax was confirmed by "cream test" [5] or by high triglyceride levels (>110 mg/dL) in the chest and/or hiatal tubes. The management of chylothorax was based on the amount of drain output and the clinical condition of the patient. An effort was made to compare the patients with and without chylothorax after esophagectomy.

Results

Out of 45 patients, four patients (8.88 %) developed chylothorax. The perioperative details of these four patients have been summarized in Table 1. Diagnosis of chylothorax was made after 1 to 4 days (mean 2.7 days) of surgery. Tumor was located in middle 1/3rd in all four patients of chylothorax whereas in patients without chylothorax, tumor in 75.6 % of them was located in lower 1/3rd esophagus. None of the patient with chylothorax showed complete clinical response to NACRT while 26.8 % of patients without chylothorax showed complete clinical response. Dissection was considered difficult by the operating surgeons in 75 % cases of chylothorax requiring multiple transfusions in two of them. No difficulty in dissection was experienced in 91.25 % cases without chylothorax. There was no significant difference in the incidence of chylothorax following transhiatal (3/35=8.57 %) or transthoracic esophagectomy (1/10=10 %). One patient of chylothorax who was converted from transhiatal approach to transthoracic approach, due to difficulty in separating the tumor from the mediastinal structures (Table 1) has been included in THE as we believe that thoracic duct injury had occurred during transhiatal mediastinal dissection. Transabdominal en masse ligation of tissue between aorta and azygos vein was done in three patients. Fourth patient with low output was successfully managed conservatively. Patients were discharged after a mean hospital stay of 15.5 days. Three patients are alive after median follow up of 10 months, and one patient succumbed from pneumonia after 50 days of surgery.

Discussion

Chylothorax is a potentially lethal complication of esophagectomy [4]. Most often it occurs due to thoracic duct injury during mediastinal dissection. The usual site of injury to the thoracic duct is in the mid-thorax, where the duct curves from right to left [2, 5].

In this study, we have made an attempt to identify the factors predisposing to development of thoracic duct injury (TDI) in our subgroup of patients suffering from squamous cell carcinoma of esophagus.

We found that all our patients with TDI had tumors in the middle third of thoracic esophagus. Similar finding has been reported by in a study by Rao et al. where the incidence of chylothorax in middle third lesions was 5.85 %, and for lower-third lesions, it was 0.80 % (p=0.0018) [5]. The explanation of this finding lies in the fact that thoracic duct is present in close approximation to the middle third of thoracic esophagus at the level of T4/T5 vertebrae where it crosses midline from right to left lying behind the esophagus and anterior to vertebrae [6].

All the patients in our study received NACRT. A study by Merritt et al. [7] reported higher incidence of chylothorax in neoadjuvant therapy group (7.4 %) compared to esophagectomy alone group (0 %). Neoadjuvant radiotherapy leads to tissue injury, tumor necrosis, and fibrosis. Radiation activates various cellular signaling pathways that lead to expression and activation of proinflammatory and profibrotic cytokines as well as vascular injury [8]. Damage to the vasculature and release of vasoactive cytokines enables fibrin to leak into the tissues, which promotes collagen deposition [9]. The risk, severity, and nature of radiation induced reactions in a patient depend upon factors like the total dose, the dose per fraction, and schedule of treatment (i.e. one vs. two or three treatments per day) [10]. Apart from radiation itself, the presence of the tumor may change the surrounding normal tissue and predispose it to injury [10]. They physically distort normal tissue architecture [11] and cause defects that can add to damage produced by radiation [12]. Tumor vessels leak fibrinogen, which is converted to fibrin, resulting in deposition of collagen and fibrosis [13]. This leads to difficult mediastinal dissection i.e. difficulty in separating esophagus and its tumor from the surrounding mediastinal structures and possibly increased risk of postoperative chylothorax as found in our study.

We noted that all the patients with chylothorax had partial response to NACRT. These patients also had difficult mediastinal dissection because of fibrosis and bulky tumor with significant intraoperative blood loss. The incidence of these findings was higher than in patients without chylothorax. This observation suggests that response to neoadjuvant therapy may have impact on the risk of postoperative chylothorax

Table 1 Demographics, clinical and pathological factors of the 4 cases

	Patient 1	Patient 2	Patient 3	Patient 4
Age	50	55	60	60
Sex	M	M	F	M
Grade of dysphagia	II	II	III	V
Location	Middle 1/3	Middle 1/3	Middle 1/3	Middle 1/3
Type	SCC	SCC	SCC, basaloid type	SCC
cTNM	T3N0M0	T3N1M0	T4N0M0	T4N1M0
Timing after NACRT to surgery (weeks)	6	7.5	9	8
Surgery	THE	THE	TTE	THE converted to TTE
Operative time (hours)	3.5	3.5	4	5
Blood loss (mL)	1000	300	500	1500
pTNM	pT2N0M0	pT3N1M0	pT3N0M0	pT3N0M0
Postop drainage (mL)				
POD0	1000	200	1000	1500
POD1	1400	150	1000	2000
POD2	2000	130	2000	2000
POD3	2500	200	2000	2000
POD4	1500	250		
Color turned milky	POD3	POD4	POD3	POD1
FJ feed (elemental feed)	POD1	POD1	POD1	POD1
Cream feed test	POD3	Not given	POD3	POD1
Triglyceride (mg %)	40	200	58	252
Re exploration	POD5	No	POD3	POD3
Other complications	Hypotension, Metabolic acidosis, Cervical leak, Pneumonitis	Nil	Nil	Atrial fibrillation, Postoperative ventilator support
Chyle leak stopped	rPOD 20	POD5	rPOD4	rPOD30
Discharge	POD25	POD8	POD11	POD18

SCC squamous cell carcinoma, *NACRT* neoadjuvant chemoradiotherapy, *THE* transhiatal esophagectomy, *TTE* transthoracic esophagectomy, *POD* postoperative day, *rPOD* postoperative day after reoperation

which needs to be evaluated in future studies with larger sample size.

Another factor which may affect the risk of TDI is the type of surgical approach. In this study, the incidence of TDI was not affected by the surgical approach (Table 2). A meta-analysis by Rindani et al. included 44 studies showed that in the incidence of chylothorax was 2.1 % after transhiatal and 3.4 % after TTE [14]. A multicentric randomized trial from the Netherlands showed no major difference in morbidity after transthoracic or transhiatal approach [15]. However, Bolger et al. reported a higher incidence of chylothorax with transhiatal esophagectomy. In their series of 95 transhiatal resections, the incidence of chylothorax was 10.5 % and the incidence following 442 transthoracic procedures was 0.2 % ($p<0.001$) [3].

Thoracic duct is not identified during THE or TTE. The mediastinal dissection of esophagus during TTE is under vision while it is performed blindly in THE. That increases the likelihood of inadvertent injury to thoracic duct during THE. Prophylactic thoracic duct ligation has been recommended by some to prevent this complication in postoperative period and its morbidity [16]. But the evidence supporting routine use of this policy in all patients is conflicting [17]. Based on our limited observation, we suggest that prophylactic thoracic duct ligation may be beneficial in patients undergoing transhiatal or TTE for middle third esophageal tumor who partially respond to NACRT.

There is controversy concerning the management of chylothorax. Some authors prefer nonoperative approach [18], while others advocate early reoperation [19]. The reported mortality rate with nonoperative management is as high as 50 % in some reports. Nonoperative management may be suitable for low output chyle leak as seen in one of our patient [18]. There are no controlled studies to define the best timing for the operation. Thoracic duct ligation can be done by transthoracic or transabdominal approach. Mason et al. reported

Table 2 Comparison of various clinic pathological factors between patients with and without chylothorax

Clinical variables	Chylothorax (n=4)	No chylothorax (n=41)
Age	56.25 (50–60 years)	51.8 (42–64 years)
Sex (M:F)	3:1	1.2:1
Location of tumor		
• Middle 1/3	4 (100)	10 (24.3)
• Lower 1/3	0	31 (75.6)
Histopathology		
• SCC	4 (100)	40(97.5)
• Adenocarcinoma	0	1 (2.5)
cT3	2 (50)	27 (65.85)
cT4	2 (50)	14 (34.14)
cNx	0	2 (4.87)
cN0	2 (50)	14 (34.14)
cN1	2 (50)	17 (41.46)
cN2	0	8 (19.51)
cM0	4 (100)	41 (100)
NACRT	4 (100)	41 (100)
Response of NACRT		
• Partial	4 (100)	30 (73.1)
• Complete	0	11 (26.8)
Mean interval between NACRT and surgery	7.6±1.2 (6–9 weeks)	8.6±4.5 (5.4–10.3 weeks)
Type of esophagectomy		
• THE	3 (75)	32 (78)
• TTE (open)	1 (25)	2 (4.8)
• TTE (MIE)	0	7 (17)
Intraoperative difficulty	3 (75)	4 (9.75)
Morbidity	4 (100)	21 (51.2)
30 days mortality	0	2 (4.8)

Values are *n* (%)

SCC squamous cell carcinoma, *NACRT* neoadjuvant chemoradiotherapy, *THE* transhiatal esophagectomy, *TTE* transthoracic esophagectomy, *MIE* minimally invasive esophagectomy

that transabdominal ligation of thoracic duct is useful alternative for thoracic duct leaks in thoracic surgeries [20]. Many other series have reported good results of transabdominal ligation of thoracic duct [1, 2]. The advantages of transabdominal approach are avoidance of thoracotomy with its associated pulmonary complications, lack of thoracic duct duplications near the origin from cisterna chyli leading to successful ligation at the hiatus and no need of localizing the exact site of leak before ligation [1]. We found out that thoracic duct even if ligated securely after identification at the hiatus does not necessarily reduce chyle output probably due to alternate lymphatic pathways which may open after chemoradiotherapy to the mediastinum. Identification of the duct separately is not necessary if all structures to the right of the aorta and anterior to the thoracic vertebra are included. It is suggested that including the fibrofatty tissue in the ligature may prevent the delicate thoracic duct from getting injured by the ligature itself [1]. We have used similar technique transabdominally at the hiatus with the gastric conduit retracted laterally. With the increasing experience in video assisted thoracoscopic surgery (VATS), surgeons are also performing thoracoscopic guided mass ligation of tissue between the aorta and azygos vein at the hiatus [21].

The limitations of this study are the small sample size and retrospective analysis of prospective database.

In summary, post NACRT patients of squamous cell carcinoma of middle third of thoracic esophagus have difficult mediastinal dissection and high chances of developing postoperative chylothorax. Prophylactic thoracic duct ligation may be a better alternative in these patients [16].

Conclusion

Difficult mediastinal dissection during esophagectomy, in middle 1/3rd esophageal cancer after partial response to

chemoradiotherapy, may lead to thoracic duct injury. En mass transabdominal ligation of thoracic duct is rewarding.

Conflict of interest RG, HS, SK, RG, RS, and GRV declare that they have no conflict of interest.

Ethics statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study.

References

1. Schumacher G, Weidemann H, Langrehr JM, et al. Transabdominal ligation of the thoracic duct as treatment of choice for postoperative chylothorax after esophagectomy. Dis Esophagus. 2007;20:19–23.
2. Mishra PK, Saluja SS, Ramaswamy D, Bains SS, Haque PD. Thoracic duct injury following esophagectomy in carcinoma of the esophagus: ligation by the abdominal approach. World J Surg. 2013;37:141–6.
3. Bolger C, Walsh TN, Tanner WA, Keeling P, Hennessy TP. Chylothorax after oesophagectomy. Br J Surg. 1991;78:587–8.
4. Shah RD, Luketich JD, Schuchert MJ, et al. Postesophagectomy chylothorax: incidence, risk factors, and outcomes. Ann Thorac Surg. 2012;93:897–904.
5. Rao DV, Chava SP, Sahni P, Chattopadhyay TK. Thoracic duct injury during esophagectomy: 20 years experience at a tertiary care center in a developing country. Dis Esophagus. 2004;17:141–5.
6. Wirth W, Frommhold H. Der ductusthoracicus und seine variationen. Lymphographische studie. Fortschr Geb Rontgenstr Nuklearmed. 1970;112:450–9.
7. Merritt RE, Whyte RI, D'Arcy NT, Hoang CD, Shrager JB. Morbidity and mortality after esophagectomy following neoadjuvant chemoradiation. Ann Thorac Surg. 2011;92:2034–40.
8. Dent P, Yacoub A, Contessa J, et al. Stress and radiation-induced activation of multiple intracellular signaling pathways. Radiat Res. 2003;159:283–300.
9. Chen Y, Williams J, Ding I, et al. Radiation pneumonitis and early circulatory cytokine markers. Semin Radiat Oncol. 2002;12 1 Suppl 1:26–33.
10. Stone HB, Coleman CN, Anscher MS, McBride WH. Effects of radiation on normal tissue: consequences and mechanisms. Lancet Oncol. 2003;4:529–36.
11. Laug WE, DeClerck YA, Jones PA. Degradation of the subendothelial matrix by tumor cells. Cancer Res. 1983;43:1827–34.
12. Stone HB, Milas L. Enhancement of radiation-induced normal tissue damage by a fibrosarcoma. Int J Radiat Oncol Biol Phys. 1987;13:1721–4.
13. Dvorak HF. Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing. N Engl J Med. 1986;315:1650–9.
14. Rindani R, Martin CJ, Cox MR. Transhiatal versus Ivor-Lewis oesophagectomy: is there a difference? Aust N Z J Surg. 1999;69:187–94.
15. Hulscher JB, van Sandick JW, de Boer AG, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med. 2002;347:1662–9.
16. Lai FC, Chen L, Tu YR, Lin M, Li X. Prevention of chylothorax complicating extensive esophageal resection by mass ligation of thoracic duct: a random control study. Ann Thorac Surg. 2011;91:1770–4.
17. Hou X, Fu JH, Wang X, et al. Prophylactic thoracic duct ligation has unfavorable impact on overall survival in patients with resectable oesophageal cancer. Eur J Surg Oncol. 2014;40:1756–62.
18. Johnstone DW, Feins RH. Chylothorax. Chest Surg Clin North Am. 1994;4:617–28.
19. Merigliano S, Molena D, Ruol A, et al. Chylothorax complicating esophagectomy for cancer: a plea for early thoracic duct ligation. J Thorac Cardiovasc Surg. 2000;119:453–7.
20. Mason PF, Ragoowansi RH, Thorpe JA. Post-thoracotomychylothorax—a cure in the abdomen? Eur J Cardiothorac Surg. 1997;11:567–70.
21. Kumar S, Kumar A, Pawar DK. Thoracoscopic management of thoracic duct injury: is there a place for conservatism? J Postgrad Med. 2004;50:57–9.