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Clinical Impact of Upper Extremity Deep Vein Thrombosis in the Retrosternal Reconstruction After Esophagectomy

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25 **Abstract**

26 **Background**

27 Upper extremity deep vein thrombosis (UEDVT) is relatively rare but cannot be
28 negligible because it can cause fatal complications. Although it is reported that
29 the occurrence rate of UEDVT has increased due to central venous catheter
30 (CVC), cancer, and surgical invasion, there are still limited information for
31 esophagectomy. The aim of this study was to evaluate the clinical factors,
32 including CVC placement and thromboprophylaxis approach, as well as
33 retrosternal space's width as a predictive factor for UEDVT in patients receiving
34 esophagectomy.

35 **Methods**

36 This study included 66 patients who underwent esophagectomy with retrosternal
37 reconstruction using a gastric tube. All patients routinely underwent contrast-
38 enhanced computed tomography (CT) on the 4th postoperative day. Low-
39 molecular-weight-heparin (LMWH) was routinely administered by the 2nd
40 postoperative day. To evaluate retrosternal space's width, (a) The distance from
41 sternum to brachiocephalic artery and (b) the distance from sternum to vertebra
42 were measured by preoperative CT, and the ratio of (a) to (b) was defined as the
43 width of retrosternal space.

44 **Results**

45 Among all patients, 11(16.7%) suffered from UEDVT, and none was
46 preoperatively received CVC placement, while 7 were inserted in non-UEDVT
47 cases. Retrosternal space's width in patients with UEDVT was significantly
48 smaller than that in patients without UEDVT (0.17 vs. 0.26; $P < 0.0001$). A cutoff

49 value of the width was 0.21, which has high sensitivity (87%) and specificity (82%)
50 for UEDVT prediction, respectively.

51 **Conclusion**

52 The existence of CVC may not affect the development of UEDVT, but
53 preoperative evaluation of retrosternal ratio may predict the occurrence of UEDVT.

54

55 ■ **Keywords:**

56 Upper Extremity Deep Vein Thrombosis, Esophagectomy,

57 Retrosternal Reconstruction, Central Venous Catheter, Thromboprophylaxis

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59

60 ■ **Abbreviations and Symbols:**

61 *UEDVT; Upper extremity deep vein thrombosis*

62 *PE; pulmonary embolism*

63 *CVC; central venous catheter*

64 *LMWH; Low-molecular-weight-heparin*

65 *CT; computed tomography*

66 *PICCs; peripherally inserted central catheters*

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73 **Introduction**

74 Currently, neoadjuvant chemotherapy/chemoradiation followed by curative
75 esophagectomy is a standard therapy for stage II/III advanced esophageal
76 cancer (1). Since esophagectomy requires an invasive procedure regardless of
77 the open or thoracoscopic approach, it is well-known that esophagectomy
78 revealed a high incidence of postoperative complications with 40-50% of the
79 cases in Japanese NCD database (2). Complications after esophagectomy
80 include a wide range of events, such as anastomotic leakage, bleeding, conduit
81 ischemia, recurrent laryngeal nerve injury, surgical site infection, intrathoracic
82 abscess, and venous thromboembolism (VTE) (3) (4).

83 It is generally accepted that VTE is a concerning matter, which has been
84 reported to be 2.9 to 7.3% and could lead to pulmonary embolism (PE) and other
85 respiratory sequelae (5) (6). As well as lower extremity deep vein thrombosis
86 (LEDVT), upper extremity deep vein thrombosis (UEDVT), which occurs in the
87 subclavian, axillary, internal jugular, and/or brachial veins, cannot be negligible,
88 accounting for up to 10% of all documented DVTs (7). Its incidence has increased,
89 and the presence of central venous catheter (CVC) has been described as the
90 most significant risk factor of UEDVT, at least 50%, followed by cancer and major
91 surgery within 30days. Compared with patients with LEDVT, patients with UEDVT
92 tend to be younger and more common in cancer, and less likely to have acquired
93 or hereditary thrombophilia (7). The frequency of acute PE, a fatal complication
94 of UEDVT, is approximately 6-36% and 2-5% for recurrence at 12 months, which
95 should be identified in the early phase (7) (8) (9) (10). Therefore, early detection

96 by routine examination is crucial, and it is worth investigating the usefulness of
97 various diagnostic tools, including Computed Tomography (CT) (7).

98 In esophageal cancer patients who underwent esophagectomy followed by
99 gastric tube reconstruction, Takahashi et al. reported that the compression of the
100 left brachiocephalic vein by the narrowness of retrosternal space contributes to
101 the occurrence of UEDVT and referred to the significant difference in the
102 likelihood to generate UEDVT by retrosternal reconstruction compared with the
103 posterior mediastinal route. Also, the effectiveness of preoperative CT
104 examination for evaluating the width of retrosternal was revealed as a predictive
105 factor for UEDVT (11). However, in the previous study, all the participants
106 received CVC before esophagectomy, and it has not been described whether
107 CVC placement increases the UEDVT occurrence. In addition, the efficacy of
108 postoperative thromboprophylaxis, low-molecular-weight heparin (LMWH), has
109 not been estimated.

110 In the present study, we confirmed the effectiveness of retrosternal space
111 measurement by preoperative CT and evaluated the significance of CVC
112 placement and prophylactic anticoagulant therapy's efficacy for UEDVT in the
113 esophageal cancer patients with retrosternal reconstruction.

114

115 **Patients and Methods**

116 **Patients**

117 The present study enrolled 66 consecutive patients with thoracic esophageal
118 carcinoma who underwent either right transthoracic esophagectomy via
119 thoracotomy or thoracoscopic esophagectomy, all with gastric tube

120 reconstruction through a retrosternal route in the Gastrointestinal Tract Surgery,
121 Fukushima Medical University Hospital from January 2016 to November 2020.
122 CVC was not preoperatively placed in most patients, including peripherally
123 inserted central catheters (PICCs). An approximately 4-cm-wide gastric tube
124 preserving the greater omentum was created, and after pulling up the gastric tube,
125 cervical esophagogastrostomy was performed at the left side of the neck.
126 The level of oral side dissection is routinely at the upper thoracic esophagus,
127 which is at the level of the Aortic arch, and straightening of the gastric tube is
128 performed. The anastomosis site is generally at the cranial side of the left
129 brachiocephalic vein and visible from the cervical incision.

130 Retrosternal reconstruction was routinized in our institution and performed in all
131 66 cases. Preoperative and postoperative clinicopathological data were collected,
132 including the following information: demographics, type of treated diseases, type
133 of surgical procedure, and data from laboratory tests on the 4th postoperative
134 day. The clinical and pathological staging was based on the 8th edition of the
135 TNM classification (12).

136 All patients underwent subcutaneous injection of low molecular weight heparin
137 twice a day from the 2nd postoperative evening. Postoperative complications
138 were defined as any complication with Clavien grade ≥ 1 using the Clavien–Dindo
139 classification (13).

140 The study was approved by the ethics committee of Fukushima Medical
141 University. All patients provided written informed consent. All experiments were
142 carried out in accordance with the approved study plan and relevant guidelines.

143

144 **Diagnosis of postoperative UEDVT**

145 To find out any complications, all patients routinely underwent contrast-
146 enhanced computed tomography (CT) from the cervix to the pelvic floor on the
147 4th postoperative day. UEDVT was defined as an intraluminal filling defect in a
148 brachiocephalic, subclavian, axillary, brachial, internal jugular, or external jugular
149 vein (Fig.1).

150

151 **Measurement of the width of the retrosternal space using preoperative**
152 **contrast-enhanced computed tomography**

153 To assess the width of the retrosternal space, (a) the distance from the back of
154 the sternum to the ventral part of the brachiocephalic artery and (b) the distance
155 from the back of the sternum to the ventral part of the vertebra were measured
156 using a preoperative axial contrast-enhanced CT image in all the patients. The
157 ratio of (a) to (b) was calculated, and it was defined as the width of the retrosternal
158 space due to the consideration of the difference in individual body shape. The
159 area of the retrosternal space was measured at the level of the left
160 brachiocephalic vein using the preoperative axial contrast-enhanced CT image
161 (Fig. 2) (11).

162

163 **Statistical analysis**

164 The data were analyzed using Prism version 9.0.0 (86) (GraphPad Software
165 LLC, San Diego, CA, USA). Continuous data were compared between the two
166 groups using the Mann–Whitney U test or Student's t test. Categorical data were

167 compared using the Chi-square test. To identify risk factors related to UEDVT,
168 univariate analyses were performed using the Chi-square test. Those variables
169 remaining in the logistics equation at the last step were considered as
170 independent risk factors. P value <0.05 was considered statistically significant.
171 The optimal cutoff point of the width of the retrosternal space for the prediction of
172 UEDVT was determined so that the Youden index (sensitivity + specificity - 1)
173 would be maximized using receiver operating characteristic (ROC) curve analysis.

174

175 **Results**

176 ***Incidence and clinical course of UEDVT after esophagectomy***

177 All the esophagectomies were conducted with retrosternal reconstruction.
178 UEDVT developed in 11 of the 66 patients (16.7%). A significant difference was
179 not observed between patients with and without UEDVT regarding
180 clinicopathological factors, including preoperative and operative factors and
181 postoperative complications (Table 1). Also, there was no significant difference
182 between 2-field and 3-field lymph node dissection($p=0.46$). Among the 11 UEDVT
183 patients (Table 2), 10 patients suffered UEDVTs in the left internal jugular vein
184 and one patient in the left subclavian vein, whereas no UEDVT occurred in the
185 right-side upper extremity deep vein. Small PE without any symptom was
186 detected by the image in 3 cases (27.3%) in the UEDVT patients, which did not
187 result in any severe condition, including respiratory failure or fatalities. For
188 UEDVT patients, prophylaxis LMWH subcutaneous injection was switched to

189 continuous intravenous heparin infusion in optimal dose following guideline (14),
190 and edoxaban was induced when the oral intake started. In all but one case,
191 contrast-enhanced CT was performed three months after esophagectomy. The
192 thrombus had disappeared in 8 of the 10 patients. In the other two cases,
193 contrast-enhanced CT revealed that the thrombus remained, but the
194 anticoagulant therapy was terminated as a chronic thrombosis (Table 2).

195 ***Width of retrosternal space as a preoperative risk factor for UEDVT after***
196 ***retrosternal reconstruction.***

197 To preoperatively estimate the risk of UEDVT in patients with retrosternal
198 reconstruction, we evaluated the width of the retrosternal space. The width of the
199 retrosternal space in patients with UEDVT was significantly smaller than that in
200 patients without UEDVT (0.17 vs. 0.26; $P < 0.0001$). A cutoff value of 0.21 was
201 established so that the Youden index (sensitivity + specificity-1) would be
202 maximized. Using this cutoff value, UEDVT was detected with a sensitivity of 87%
203 and a specificity of 82% (Table 3). This result indicated the importance of
204 evaluating the retrosternal space as a predictive risk factor before
205 esophagectomy.

206 ***Correlation between UEDVT and CVC after esophagectomy with***
207 ***retrosternal reconstruction.***

208 Among UEDVT cases, none was preoperatively received CVC placement,
209 while 7 were inserted in non-UEDVT cases (n=55), and there was no correlation
210 between UEDVT and CVC placement (Table 4, $P=0.21$). LMWH was routinely

211 administered twice a day on the 2nd postoperative day as postoperative
212 thromboprophylaxis in all the cases. Also, there was no significant difference in
213 inflammatory response and D-dimer between patients with and without UEDVT
214 (Table 4).

215

216 **Discussion**

217 VTE is an emerging complication requiring continuous attention as well as
218 other surgical complications, especially in highly invasive surgery like
219 esophagectomy. In VTE, LEDVT tends to attract attention in general, but the
220 frequency of UEDVT is not negligible due to the characteristic of esophagectomy,
221 which conducts cervical manipulation and reconstructs through a narrow
222 retrosternal pathway (11). According to the American College of Surgeons
223 National Surgical Quality Improvement Program Participant Use Data File (ACS-
224 NSQIP PUF), the incidence of DVT is about 7%, and UEDVT comprises 57% of
225 all DVTs in the analysis of more than 460000 cases of general surgery, except
226 esophagectomy (15). It is reported that primary UEDVT is only about 20%, and
227 its leading causes are venous thoracic outlet syndrome, Paget-Schroetter
228 syndrome, and idiopathic, while secondary UEDVT accounts for 80% (16). The
229 predominant cause of secondary UEDVT is a CVC placement, which occupies at
230 least two-thirds, followed by cancer and major surgery within 30days (7).
231 Malignancy has been reported to increase the risk of UEDVT in 18-fold (17), and
232 the presence of CVC scored with an odds ratio of 9.7(CI=7.8 to 12.2) (18). In our

233 present study, the incidence of UEDVT was 16.7% in 66 consecutive patients
234 who underwent esophagectomy with retrosternal gastric tube reconstruction,
235 which is less frequent than the previous report that the incidence of UEDVT was
236 25.5% in retrosternal gastric tube reconstruction (11). All the UEDVTs in our
237 cases occurred postoperatively in the proximal left-side veins, while there was no
238 primary UEDVT case detected preoperatively.

239

240 Several reports mentioned the disadvantages of the retrosternal route, such as
241 cardiac compression and reconstructed organs' necrosis, when the retrosternal
242 space is narrow (19) (20). Retrosternal reconstruction has been reported as an
243 independent risk factor for UEDVT after esophagectomy, and its ratio of UEDVT
244 is 25.5%, significantly higher than 4.9% of posterior mediastinal reconstruction
245 (11). Retrosternally shifted gastric tube may contribute to the left brachiocephalic
246 vein's compression and form UEDVT in the proximal left-side veins (Fig.3). In the
247 present study, all UEDVT occurred in the proximal left-side veins. Anastomotic
248 leakage, inflammatory response, and other factors did not show any significant
249 differences in generating UEDVT. Therefore, it is likely that mechanical
250 compression for the left brachiocephalic vein is closely related to develop UEDVT.
251 Among several factors in the reconstructive route, the width of retrosternal space
252 has been mentioned as an important factor affecting compression strength. The
253 previous report mentioned there is a significant difference in the width of
254 retrosternal space, and the ratio of thinner space tends to be higher to generate
255 thrombosis (11). Following the definition of the retrosternal space ratio, our cutoff
256 value (0.21) shows high sensitivity of 87% and specificity of 82%, which is similar

257 to the previous report. Therefore, the compression by gastric tube and the narrow
258 width of retrosternal space might have much more influence on UEDVT.
259 Only considering the incidence of UEDVT, posterior mediastinal reconstruction
260 should be preferable if the retrosternal width is less than 0.21. But when it comes
261 to other complications, such as anastomotic leakage, especially in the high-risk
262 group (patients with dialysis, diabetes, poor nutritional condition, etc.),
263 retrosternal reconstruction might be better. Depending on each case background,
264 we should consider the reconstruction route individually. When the retrosternal
265 reconstruction route was chosen, we should predict the incidence of UEDVT and
266 prepare early intervention if the retrosternal width is less than 0.21.

267 It has been widely believed that CVC placement is the most frequent reason
268 for generating UEDVT in various disease and gastrointestinal cancer patients,
269 but no study has described the relationship between CVC and UEDVT in
270 esophagectomy cases. Our present study revealed no significant difference to
271 cause UEDVT whether CVC exists or not. The frequency of UEDVT without
272 CVC cases was 18.6% and is comparable to the previous report (11). Since this
273 case series consisted of a minor population of patients receiving CVC insertion,
274 it is difficult to draw a solid conclusion regarding if the CVC insertion could
275 increase the incidence of UEDVT in esophagectomy patients. Further study will
276 be required in patients with more big cohorts or prospective patients receiving
277 CVC insertion routinely. This is a unique report to describe whether the
278 presence of CVC affects the UEDVT's formation in patients who underwent
279 esophagectomy with retrosternal reconstruction in the current clinical practice.

280

281 For the prevention of DVT, the guideline recommends a variety of approach as
282 prophylaxis, such as Low Molecular Weight Heparin (LMWH) and compression
283 stockings, but there are few references with regard to UEDVT; thus, it is generally
284 recommended to take the same approach as for LEDVT (21) (22). In all our cases,
285 LMWH was administered subcutaneously as postoperative thromboprophylaxis,
286 but the frequency of UEDVT was almost the same as previously reported.

287 Although the preventive effect for UEDVT has not been clarified, the effectiveness
288 of low-molecular-weight-heparin has been reported for lower extremity deep vein
289 thrombosis, and it seems to be worthwhile to keep administering it.

290 Moreover, according to the Antithrombotic Therapy and Prevention of
291 Thrombosis, 9th edition Guideline, 3 months of continuation of anticoagulant
292 therapy with LMWH, vitamin K antagonists and factor Xa inhibitor for the cases
293 of UEDVT is recommended. In our cases, we prescribed edoxaban, a factor Xa
294 inhibitor and their UEDVTs were disappeared in all but two cases (23). As
295 previous studies have reported that the mortality was significantly higher in the
296 group of UEDVT without anticoagulants, it might be preferable to continue oral
297 anticoagulant therapy if the risk of bleeding is low (24) (25).

298

299 The definition of UEDVT was confirmed by routine CT scan at postoperative
300 4th day (POD) in our study. CT scan has high sensitivity and specificity with 91%
301 and 93%, respectively (26). Based on that, we conducted our present study,
302 whereas it is worthwhile to evaluate the effectiveness of compression ultrasound
303 (US), clinical symptom score and D-dimer as a diagnostic tool. Ultrasonography

304 is often preferred as a less expensive and readily available alternative, which has
305 high sensitivity (97%) and specificity (96%) (26). However, the usefulness of
306 Ultrasonography is still controversial regarding clinical probability and objectivity,
307 and although there is a clinical decision score such as the Constans score for
308 UEDVT, the diagnostic accuracy is not high enough to justify using this score as
309 a standalone tool (27). D-dimer's sensitivity and specificity at the cutoff value of
310 500 µg/L were 92-100% and 14-60%, respectively. It indicates that the sensitivity
311 of D-dimer testing as high as in patients with suspected LEDVT, whereas the
312 accuracy of specificity remains to be discussed (10) (28). In the present study,
313 D-dimer's elevation was confirmed with almost all the cases receiving
314 esophagectomy, and it was not useful as a specificity marker by itself. Taken
315 together, we believed that CT scan in the early period after esophagectomy might
316 be superior to the other diagnostic tools.

317

318 Limitations of this study are the retrospective data nature, the small number of
319 patients at a single institute. Comparison of usefulness for prevention with or
320 without anticoagulation was not validated. However, since this is the first study to
321 describe the evaluation of UEDVT with or without CVC placement and
322 postoperative thromboprophylaxis after esophagectomy, we believe that the
323 present study will provide useful information to clinicians, and further
324 accumulation of retrospective and prospective studies is required.

325

326 In conclusion, the incidence of UEDVT detected by routine POD4 CT was
327 16.7% in patients who underwent esophagectomy with retrosternal gastric tube

328 reconstruction. All UEDVT occurred in the proximal left-side veins. The existence
329 of CVC may not affect the generation of UEDVT, but preoperative evaluation of
330 retrosternal ratio may predict the occurrence of UEDVT.

331

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333 Not applicable

334 **Competing financial information**

335 The authors declare no competing interests.

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446 **Figure legends**

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448 **Fig.1**

449 Upper extremity deep vein thrombosis in the left internal jugular vein after
450 esophagectomy with retrosternal reconstruction. Contrast-enhanced CT on the
451 fourth postoperative day and the open arrows indicate an intraluminal filling defect
452 in the left internal jugular vein.

453 **Fig.2**

454 The width of retrosternal space was defined by the ratio of (a) to (b).

455 (a); the back of the sternum to the ventral part of the brachiocephalic artery.

456 (b); the back of the sternum to the ventral part of the vertebra.

457 To evaluate the retrosternal space, Contrast-enhanced CT was conducted
458 preoperatively within three months.

459 **Fig.3**

460 Non-UEDVT case after esophagectomy with gastric tube through the retrosternal
461 reconstruction route. Open arrows indicate the compression of the left
462 brachiocephalic vein by gastric tube and brachiocephalic artery.

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Figures



Figure 1

Upper extremity deep vein thrombosis in the left internal jugular vein after esophagectomy with retrosternal reconstruction. Contrast-enhanced CT on the fourth postoperative day and the open arrows indicate an intraluminal filling defect in the left internal jugular vein.

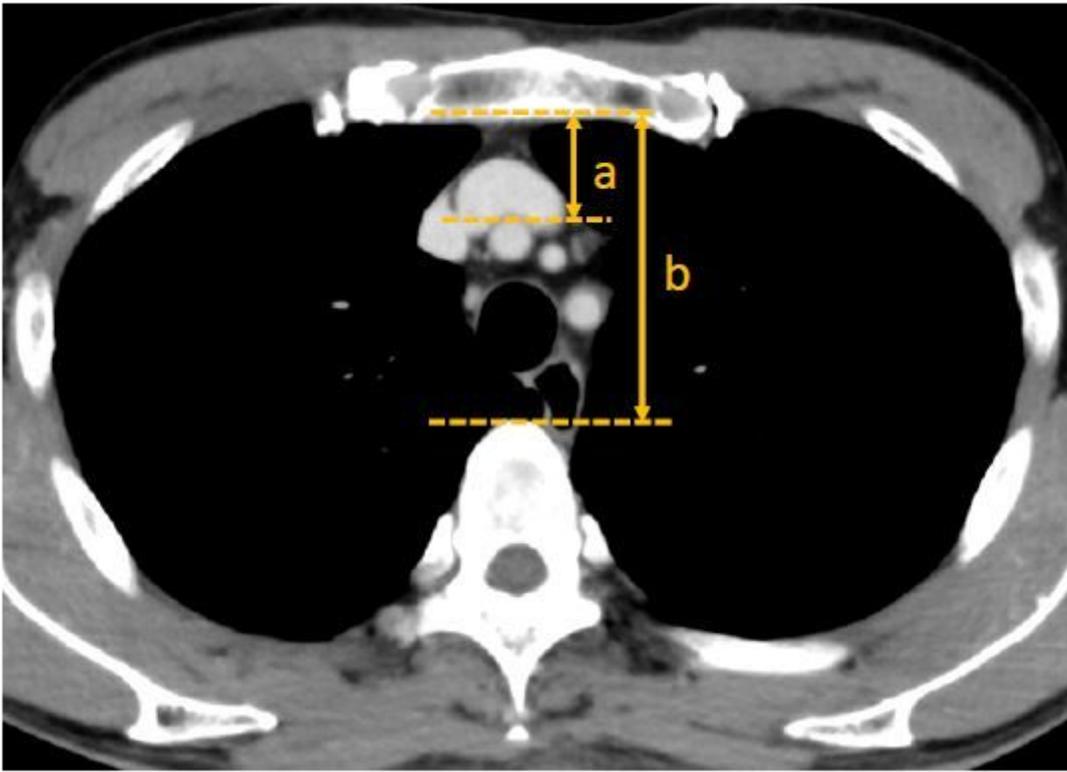


Figure 2

The width of retrosternal space was defined by the ratio of (a) to (b). (a); the back of the sternum to the ventral part of the brachiocephalic artery. (b); the back of the sternum to the ventral part of the vertebra. To evaluate the retrosternal space, Contrast-enhanced CT was conducted preoperatively within three months.



Figure 3

Non-UEDVT case after esophagectomy with gastric tube through the retrosternal reconstruction route. Open arrows indicate the compression of the left brachiocephalic vein by gastric tube and brachiocephalic artery.

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