Clinical Impact of Remnant Lymphatic Invasion on The Recurrence of Esophageal Squamous Cell Carcinoma After Esophagectomy with Neoadjuvant Chemotherapy: A Retrospective Study

Sho Okuda
Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University

Kenoki Ohuchida (kenoki@surg1.med.kyushu-u.ac.jp)
Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University

Koji Shindo
Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University

Taiki Moriyama
Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University

Jun Kawata
Department of Anatomic Pathology, Pathological Sciences, Graduate School of Medical Sciences, Kyushu University

Koji Tamura
Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University

Masafumi Sada
Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University

Kinuko Nagayoshi
Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University

Yusuke Mizuuchi
Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University

Naoki Ikenaga
Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University

Kohei Nakata
Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University

Yoshinao Oda
Department of Anatomic Pathology, Pathological Sciences, Graduate School of Medical Sciences, Kyushu University

Masafumi Nakamura
Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University

Research Article

Keywords: esophageal squamous cell carcinoma, neoadjuvant chemotherapy, recurrence factor, lymphatic invasion

Posted Date: February 22nd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1319782/v1

Abstract

Background: For stage II and III esophageal squamous cell carcinoma (ESCC), neoadjuvant chemotherapy (NAC) followed by esophagectomy is recommended in Japanese guidelines. However, recurrence of ESCC is common regardless of the NAC regimen and operation method, and the effect of NAC on recurrence is limited.

Methods: We retrospectively analyzed the outcomes of 54 patients who underwent esophagectomy for ESCC after NAC from 2010 to 2017. We selected 53 patients with ESCC without NAC followed by esophagectomy from 2001 to 2017 for comparison.

Results: Among patients who underwent NAC followed by surgery, lymphatic invasion (ly) (hazard ratio: 2.632; 95% CI: 1.04–6.68, $p = 0.042$) and microscopic residual tumor (R) (hazard ratio: 24.21, 95% CI: 1.92–305, $p = 0.014$) were independent factors significantly associated with 3-year recurrence-free survival in patients with esophagectomy after NAC in multivariate analysis. In patients without ly after NAC, the presence of lymph node metastasis in pathological diagnosis (pN) was not significantly related to recurrence ($p = 0.2401$). Recurrence was significantly related to ly (+) ($p = 0.0024$) in the group with pN after NAC. There were significantly fewer ly (+) patients in the NAC (+) group ($p = 0.0332$) than those in the NAC (-) group.

Conclusion: The presence of ly was an independent risk factor for recurrence of ESCC after esophagectomy following NAC. pN was not a significant recurrence factor for cases with esophagectomy following NAC in multivariate analysis. Adjuvant treatment after surgery may be required in cases with remnant ly after NAC.

Background

Esophageal cancer is the seventh most common cancer worldwide [1]. In Japan, more than 85% of esophageal cancers are esophageal squamous cell carcinoma (ESCC) [2]. Neoadjuvant therapy is recommended for advanced esophageal cancer to improve patient prognosis by downstaging tumors [3–6] and controlling local and distant micrometastasis [7,8]. Despite advances in neoadjuvant therapy, surgical technique and patient selection, the 5-year recurrence-free survival (RFS) rate after neoadjuvant therapy followed by esophagectomy is approximately 35%–55% [9,10]. In Japan, the Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus 2017 [11,12] recommend neoadjuvant chemotherapy (NAC), not neoadjuvant chemoradiotherapy (CRT), as preoperative therapy for advanced ESCC before esophagectomy. In addition, adjuvant therapy in cases with NAC is not recommended after surgery [9]. However, the impact of surgery after NAC on the recurrence in patients with ESCC is limited [9,13].

Several risk factors for recurrence have been identified in cases with neoadjuvant CRT [14–16]. In such analysis of ESCC patients who underwent neoadjuvant CRT and esophagectomy, lymphovascular invasion was indicated as an independent risk factor for recurrence [14–16]. Advanced stage indicators

including T and N in pathological diagnosis are also risk factors for recurrence of ESCC following curative resection with or without neoadjuvant therapy [17–21]. However, the risk factors for recurrence after esophagectomy with NAC alone for ESCC have not been clarified so far.

The present study aimed to identify the post-NAC specific recurrence factors for ESCC. We analyzed the clinicopathological factors focusing on patients treated with NAC alone followed by esophagectomy.

Methods

Patients

We retrospectively reviewed the records of 111 consecutive patients who underwent curative operation for ESCC at the Department of Surgery and Oncology, Kyushu University Hospital between April 2010 and July 2017 (Fig. 1). The tumor staging was classified according to the Japanese Classification of Esophageal Cancer, 11th Edition [22,23]. Demographic, clinical, surgical, pathological, postoperative, and survival data were collected from the prospectively entered clinical database of the department. Only patients identified as ESCC on record were included. Patients who did not receive NAC or patients with no record of residual tumor (R) and who had macroscopic R were excluded. After application of the criteria, 54 patients were extracted as the NAC (+) group. For comparison with the NAC (+) group, we established a NAC (-) group (Fig. 2). We retrospectively reviewed the records of 232 consecutive patients who underwent curative operation for ESCC between December 2001 and July 2017. Among the patients without NAC, pathological T0N0 or T1N0 cases were excluded to align the background of both groups. Patients with no R record and macroscopic R were also excluded. After application of the criteria, 53 patients were extracted as the NAC (-) group.

This study was approved by the institutional review board of the Kyushu University Hospital (2020-198) and written informed consent was obtained from all the patients.

Diagnosis and treatment

Clinical diagnosis was determined by barium swallow, esophagogastroduodenoscopy (EGD), endoscopic ultrasound, contrast-enhanced computed tomography (CT), and whole-body positron emission tomography. Clinical stage II and III patients underwent NAC followed by esophagectomy.

The NAC regimen consisted of 80 mg/m^2 of cisplatin administered intravenously on day 1 followed by continuous intravenous infusion of 800 mg/m^2 5-fluorouracil on days 1 through 5. Most patients were administered the medication for two cycles every 4 weeks. NAC was discontinued if the patient experienced any issues (for example, severe allergy or side effects). At approximately 4 weeks after the last round of NAC, the patients underwent the operation. To assess medical operability, cardiac and pulmonary functions were evaluated by electrocardiography, echocardiography, and pulmonary function tests. All patients had an American Society of Anesthesiologists physical status of I or II. The operation

for ESCC in this study was a subtotal esophagectomy with three-field regional lymph node dissection (3-FL) regardless of the use of thoracoscope and laparoscope.

Excised specimens were confirmed by two or more pathologists, and the postoperative diagnosis was determined following the Japanese Classification [22,23]. Follow-up examinations were performed for 5 years after operation using tumor marker measurements every 3 months, contrast-enhanced CT every 6 months, and EGD every year.

Statistical analyses

Statistical analysis was performed using JMP® 15 (SAS Institute Inc., Cary, NC, USA). The 3-year RFS was calculated from the date of the operation to the date of recurrence, and patients without recurrence 3 years after operation were censored at that time. Patients who were lost to follow-up were also censored at the date of last contact. Univariate analysis for 3-year RFS was estimated with the Kaplan–Meier method, and 3-year RFS estimates were compared using the log-rank test. Multivariate analysis for 3-year RFS was performed using a Cox proportional hazards model. The variables with $p < 0.05$ in univariate analysis were included in the multivariate models. Student's t-test and ANOVA were used for the comparison of continuous variables. Pearson's χ^2 test was used to compare categorical variables. The threshold for significance was $p < 0.05$.

Results

Patient characteristics

A total of 54 patients were eligible for inclusion in the NAC (+) group (Fig. 1). Table 1 shows the detailed clinical and pathological characteristics of the included patients. Japanese guidelines indicate that NAC should be performed for only stage II and III patients [11,12]. However, post-NAC preoperative diagnosis included three (6%) stage I patients. Furthermore, two (4%) patients were stage 0, four (7%) patients were stage I, and three (6%) patients were stage IV in pathological diagnosis. Among the 54 total patients, 18 (33%) patients had lymphatic invasion (ly) and 3 (6%) patients had microscopic R.

Survival analysis in the NAC (+) group

Kaplan–Meier analysis showed that lymph node metastasis in pathological diagnosis (pN) ($p = 0.0211$), venous invasion (v) ($p = 0.0066$), ly ($p = 0.0006$), and R ($p < 0.0001$) were significantly associated with 3-year RFS in patients who underwent NAC (Table 2). The Kaplan–Meier curves according to postoperative diagnosis are shown in Fig. 3. In the multivariate analysis, the independent factors significantly associated with 3-year RFS in patients with esophagectomy after NAC were ly (hazard ratio: 2.632; 95% CI: 1.04–6.68, $p = 0.042$) and R (hazard ratio: 24.21, 95% CI: 1.92–305, $p = 0.014$) (Table 3). In the patients without ly (n = 36), there was no significant difference in 3-year RFS according to the presence and absence of pN ($p = 0.2401$) (Fig. 4a). However, in patients with pN, a significant increase in the

recurrence rate was observed in patients with ly compared with those without ly (p = 0.0024) (n = 41) (Fig. 4b).

Comparison of characteristics between NAC (-) and (+) groups

We established the NAC (-) group (n = 53) (Fig. 2) and compared the characteristics of patients in the NAC (-) and (+) groups (Table 4). The NAC (+) group included significantly more advanced cases in clinical T (p = 0.0337), N (p < 0.0001), and stage (p < 0.0001) than the NAC (-) group. In contrast, pathological results showed that there were significantly fewer ly (+) cases in the NAC (+) group than those in the NAC (-) group (p = 0.0332). No significant difference in pN was observed between patients with or without NAC (p = 0.0844).

Discussion

This study investigated the clinicopathological factors of patients treated with curative operation for ESCC after NAC, with the aim of identifying NAC-specific recurrence factors. The results showed that ly and R in pathological examination were significantly associated with recurrence. Previous studies showed that R is a well-known recurrence factor regardless of NAC [24–27], and thus we focused on ly in the analysis. Our results showed that ly was a significant recurrence factor among patients with pN, although the presence of pN was not significantly correlated with the recurrence rate among patients without ly.

Previous studies have shown that lymphovascular invasion is an independent risk factor for recurrence after preoperative CRT and esophagectomy in patients with ESCC [14–16]. Yoshida et al [28] reported that v was an independent risk factor for early recurrence within 6 months of resectable advanced ESCC following NAC, and Zhang et al [29] demonstrated that simultaneous ly and v were significantly correlated with postoperative recurrence for ESCC without neoadjuvant or adjuvant therapy. However, no report has examined the clinical significance of ly invasion as distinguished from v invasion in cases of NAC only rather than neoadjuvant CRT. This is the first study that has focused on ly, and our results show that ly is an independent recurrence factor in patients treated with esophagectomy after NAC alone.

Previous studies have shown that advanced stage indicators including T and N in pathological examination are risk factors for the recurrence of ESCC following curative resection [17–21]. Wang et al [18] reported that patients with pN had a much higher recurrence rate than patients without pN. However, in the present multivariate analysis, pN was not an independent risk factor for recurrence. Furthermore, the presence or absence of pN was not significantly related to recurrence among the patients without ly. In contrast, ly was significantly associated with the recurrence rate in patients with pN. The fact that pN was not a significant factor for recurrence in our study may be related to the surgical method specific to Japan. In Japan, 3-FL is the standard method for lymph node dissection in esophageal cancer operation, in line with the esophageal cancer practice guidelines of Japan [11,12]. The widespread use of 3-FL in Japan is due to the rapid increase in the number of laparoscopic esophagectomy for esophageal cancer in recent years [30]. Meta-analyses and studies comparing 3-FL and 2-FL reported a tendency for a better

prognosis of the 3-FL group [31–37]. Ye et al [34] reported that 3-FL provides a better 5-year survival rate than 2-FL for thoracic esophageal cancer with lymph node metastasis. In the present study, pN was not a risk factor in NAC cases, indicating that 3-FL possibly decreased the significance of lymph node metastasis in the risk of recurrence. Taken together, the present data suggests that remnant ly invasion, rather than remnant lymph node metastasis, is a critical risk factor for recurrence in patients who underwent esophagectomy with 3-FL after NAC.

The main purpose of neoadjuvant therapy is to downstage the primary tumor to facilitate complete resection [3–6] and to reduce micrometastasis that cause local or systemic recurrence [7,8]. Pathological tumor regression and the number of involved lymph nodes have been reported to be significantly associated with the prognosis of the patients who have received neoadjuvant CRT for esophageal cancer [6,38–43]. However, the prognostic impact of pathological ly status in patients with esophageal cancer who have undergone NAC has not been fully investigated. In our study, we found that patients with NAC have significantly less ly invasion than patients without NAC, suggesting that NAC contributes to regulate ly invasion, which is a type of micrometastasis. These data may suggest that remnant ly invasion after NAC reflects the limited control of micrometastasis in patients with NAC.

This study has several limitations. First, it was a retrospective study of a small number of patients that was conducted at a single institution. Selection bias was also present in the extraction of the NAC (-) group. Moreover, we did not establish criteria for NAC dosage reduction during the study period. The administration and dosage of NAC were ultimately decided by the attending physicians depending on the patient's condition and/or willingness, and thus the NAC (+) group in our study included patients with both full-dose and lowered-dose NAC. Therefore, further prospective multi-institutional studies with larger populations are required to assess the true impact of remnant ly invasion for ESCC patients with NAC following esophagectomy.

Conclusion

We found that the presence of ly in pathological examination was an independent risk factor for recurrence of ESCC after esophagectomy with 3-FL following NAC. pN was not a significant recurrence factor in the present multivariate analysis of cases treated with 3-FL and NAC. The present data also showed that ly was a significant risk factor for recurrence regardless of pN and that patients with NAC have significantly less ly than those without NAC although the NAC group included more advanced cases in clinical diagnosis than the non-NAC group. These data suggest that the remnant ly invasion after NAC reflects the insufficient control of micrometastasis. Therefore, adjuvant treatment after surgery may be desirable in cases with remnant ly invasion after NAC.

Abbreviations

ESCC, esophageal squamous cell carcinoma; **RFS**, recurrence-free survival; **NAC**, neoadjuvant chemotherapy; **CRT**, chemoradiotherapy; **R**, residual tumor; **EGD**, esophagogastroduodenoscopy; **CT**,

contrast-enhanced computed tomography; **3-FL**, three-field regional lymph node dissection; **ly**, lymphatic invasion; **pN**, lymph node metastasis in pathological diagnosis; **v**, venous invasion.

Declarations

Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. Approval for this study was obtained from the institutional review board of the Kyushu University Hospital (No. 2020-198). Informed consent to participate was obtained from all individual participants included in the study.

Consent for publication

Informed consent for publication was obtained from all individual participants included in the study.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was funded by JSPS KAKENHI (Grant Number JP19H03732, JP20K17621, and JP21K19530).

Authors' contributions

SO, KO, and MN contributed to the conception and design of work. JK and YO contributed to the pathological examination. All authors contributed to the data analysis and interpretation, approved of the final version to be published, agreed to be accountable for all aspects of the work, and ensured that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Acknowledgements

This work was supported by JSPS KAKENHI Grant Numbers JP19H03732, JP20K17621, and JP21K19530.

We thank Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2018;68:394–424.

2. Watanabe M, Tachimori Y, Oyama T, Toh Y, Matsubara H, Ueno M, et al. Comprehensive registry of esophageal cancer in Japan, 2013. Esophagus. Springer Singapore; 2021;18:1–24.

3. Blackham AU, Yue B, Almhanna K, Saeed N, Fontaine JP, Hoffe S, et al. The prognostic value of residual nodal disease following neoadjuvant chemoradiation for esophageal cancer in patients with complete primary tumor response. Journal of Surgical Oncology. 2015;112:597–602.

4. Kamarajah SK, Navidi M, Wahed S, Immanuel A, Hayes N, Griffin SM, et al. Significance of Neoadjuvant Downstaging in Carcinoma of Esophagus and Gastroesophageal Junction. Annals of Surgical Oncology. Springer International Publishing; 2020;27:3182–92.

5. Bollschweiler E, Hölscher AH, Metzger R, Besch S, Mönig SP, Baldus SE, et al. Prognostic significance of a new grading system of lymph node morphology after neoadjuvant radiochemotherapy for esophageal cancer. Annals of Thoracic Surgery. Elsevier Inc.; 2011;92:2020–7.

6. Berger AC, Farma J, Scott WJ, Freedman G, Weiner L, Cheng JD, et al. Complete response to neoadjuvant chemoradiotherapy in esophageal carcinoma is associated with significantly improved survival. Journal of Clinical Oncology. 2005;23:4330–7.

7. Matsuyama J, Doki Y, Yasuda T, Miyata H, Fujiwara Y, Takiguchi S, et al. The effect of neoadjuvant chemotherapy on lymph node micrometastases in squamous cell carcinomas of the thoracic esophagus. Surgery. 2007;141:570–80.

8. Hiraki Y, Kimura Y, Imano M, Kato H, Iwama M, Shiraishi O, et al. Controlling lymph node micrometastases by neoadjuvant chemotherapy affects the prognosis in advanced esophageal squamous cell carcinoma. Surgery Today. Springer Singapore; 2021;51:118–26.

9. Ando N, Kato H, Igaki H, Shinoda M, Ozawa S, Shimizu H, et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). Annals of Surgical Oncology. 2012;19:68–74.

10. Mariette C, Dahan L, Mornex F, Maillard E, Thomas PA, Meunier B, et al. Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: Final analysis of randomized controlled phase III trial FFCD 9901. Journal of Clinical Oncology. 2014;32:2416–22.

11. Kitagawa Y, Uno T, Oyama T, Kato K, Kato H, Kawakubo H, et al. Esophageal cancer practice guidelines 2017 edited by the Japan Esophageal Society: part 1. Esophagus. 2019;16:1–24.

12. Kitagawa Y, Uno T, Oyama T, Kato K, Kato H, Kawakubo H, et al. Esophageal cancer practice guidelines 2017 edited by the Japan Esophageal Society: part 2. Esophagus. 2019;16:25–43.

13. Yamasaki M, Yasuda T, Yano M, Hirao M, Kobayashi K, Fujitani K, et al. Multicenter randomized phase II study of cisplatin and fluorouracil plus docetaxel (DCF) compared with cisplatin and fluorouracil plus Adriamycin (ACF) as preoperative chemotherapy for resectable esophageal squamous cell carcinoma (OGSG1003). Annals of Oncology. Elsevier Masson SAS; 2017;28:116–20.

14. Hsu PK, Chien LI, Wang LC, Chou TY. Lymphovascular invasion and extracapsular invasion are risk factors for distant recurrence after preoperative chemoradiotherapy and oesophagectomy in patients with oesophageal squamous cell carcinoma. European Journal of Cardio-thoracic Surgery. 2017;51:1188–94.

15. Tu CC, Hsu PK, Chien LI, Liu WC, Huang CS, Hsieh CC, et al. Prognostic histological factors in patients with esophageal squamous cell carcinoma after preoperative chemoradiation followed by surgery. BMC Cancer. BMC Cancer; 2017;17:1–9.

16. Lagarde SM, Phillips AW, Navidi M, Disep B, Immanuel A, Griffin SM. The presence of lymphovascular and perineural infiltration after neoadjuvant therapy and oesophagectomy identifies patients at high risk for recurrence. British Journal of Cancer. Nature Publishing Group; 2015;113:1427–33.

17. Lee PC, Mirza FM, Port JL, Stiles BM, Paul S, Christos P, et al. Predictors of recurrence and disease-free survival in patients with completely resected esophageal carcinoma. Journal of Thoracic and Cardiovascular Surgery. The American Association for Thoracic Surgery; 2011;141:1196–206.

18. Wang N, Jia Y, Wang J, Wang X, Bao C, Song Q, et al. Prognostic significance of lymph node ratio in esophageal cancer. Tumor Biology. 2015;36:2335–41.

19. Moon DH, Jeon JH, Yang HC, Kim Y Il, Lee JY, Kim MS, et al. Intramural Metastasis as a Risk Factor for Recurrence in Esophageal Squamous Cell Carcinoma. Annals of Thoracic Surgery. The Society of Thoracic Surgeons; 2018;106:249–56.

20. Khan M, Urooj N, Syed AA, Khattak S, Kazmi A, Ashraf MI, et al. Prognostic Factors for Recurrence in Esophageal Cancer Patients Treated With Neoadjuvant Therapy and Surgery: A Single-institution Analysis. Cureus. 2020;12.

21. Kang CH, Hwang Y, Lee HJ, Park IK, Kim YT. Risk Factors for Local Recurrence and Optimal Length of Esophagectomy in Esophageal Squamous Cell Carcinoma. Annals of Thoracic Surgery. The Society of Thoracic Surgeons; 2016;102:1074–80.

22. Japan Esophageal Society. Japanese Classification of Esophageal Cancer, 11th Edition: part I. Esophagus : official journal of the Japan Esophageal Society. NLM (Medline); 2017;14:1–36.

23. Japan Esophageal Society. Japanese Classification of Esophageal Cancer, 11th Edition: part II and III. Esophagus : official journal of the Japan Esophageal Society. 2017;14:37–65.

24. Markar SR, Gronnier C, Duhamel A, Pasquer A, Thereaux J, Du Rieu MC, et al. Significance of microscopically incomplete resection margin after esophagectomy for esophageal cancer. Annals of Surgery. 2016;263:712–8.

25. Hulshoff JB, Faiz Z, Karrenbeld A, Kats-Ugurlu G, Burgerhof JGM, Smit JK, et al. Prognostic Value of the Circumferential Resection Margin in Esophageal Cancer Patients After Neoadjuvant Chemoradiotherapy. Annals of Surgical Oncology. 2015;22:1301–9.

26. Gilbert S, Martel AB, Seely AJ, Maziak DE, Shamji FM, Sundaresan SR, et al. Prognostic significance of a positive radial margin after esophageal cancer resection. Journal of Thoracic and Cardiovascular Surgery. Elsevier Inc.; 2015;149:548–55.

27. Jo Schlick CR, Khorfan R, Odell DD, Merkow RP, Bentrem DJ. Margin Positivity in Resectable Esophageal Cancer: Are there Modifiable Risk Factors? Annals of Surgical Oncology [Internet]. 2020 [cited 2021 Aug 27];27:1496–507. Available from: https://doi.org/10.1245/s10434-019-08176-z

28. Yoshida N, Baba Y, Shigaki H, Harada K, Iwatsuki M, Sakamoto Y, et al. Risk factors of early recurrence within 6 months after esophagectomy following neoadjuvant chemotherapy for resectable advanced esophageal squamous cell carcinoma. International Journal of Clinical Oncology. Springer Japan; 2016;21:1071–8.

29. Zhang H, Chen X, Wang S, Fan J, Lu L. Poorer prognosis associated with simultaneous lymphatic and vascular invasion in patients with squamous carcinoma of the thoracic oesophagus. European Journal of Cardio-thoracic Surgery. 2017;52:378–84.

30. Inomata M, Shiroshita H, Uchida H, Bandoh T, Akira S, Yamaguchi S, et al. Current status of endoscopic surgery in Japan: The 14th National Survey of Endoscopic Surgery by the Japan Society for Endoscopic Surgery. Asian journal of endoscopic surgery. 2020;13:7–18.

31. Udagawa H. Past, present, and future of three-field lymphadenectomy for thoracic esophageal cancer. Annals of Gastroenterological Surgery. 2020;4:324–30.

32. Matsuda S, Takeuchi H, Kawakubo H, Kitagawa Y. Three-field lymph node dissection in esophageal cancer surgery. Journal of Thoracic Disease. 2017;9:S731–40.

33. Shang QX, Chen LQ, Hu WP, Deng HY, Yuan Y, Cai J. Three-field lymph node dissection in treating the esophageal cancer. Journal of Thoracic Disease. 2016;8:E1136–49.

34. Ye T, Sun Y, Zhang Y, Zhang Y, Chen H. Three-field or two-field resection for thoracic esophageal cancer: A meta-analysis. Annals of Thoracic Surgery. Elsevier Inc; 2013;96:1933–41.

35. Ma GW, Situ DR, Ma QL, Long H, Zhang LJ, Lin P, et al. Three-field vs two-field lymph node dissection for esophageal cancer: A meta-analysis. World Journal of Gastroenterology. 2014;20:18022–30.

36. Altorki N, Kent M, Ferrara C, Port J. Three-field lymph node dissection for squamous cell and adenocarcinoma of the esophagus. Annals of Surgery. 2002;236:177–83.

37. Lerut T, Nafteux P, Moons J, Coosemans W, Decker G, De Leyn P, et al. Three-field lymphadenectomy for carcinoma of the esophagus and gastroesophageal junction in 174 R0 resections: Impact on staging, disease-free survival, and outcome: A plea for adaptation of TNM classification in upper-half esophageal carcinoma. Annals of Surgery. 2004;240:962–74.

38. Reynolds JV, Muldoon C, Hollywood D, Ravi N, Rowley S, O'Byrne K, et al. Long-term outcomes following neoadjuvant chemoradiotherapy for esophageal cancer. Annals of Surgery. 2007;245:707–16.

39. Mariette C, Piessen G, Briez N, Triboulet JP. The number of metastatic lymph nodes and the ratio between metastatic and examined lymph nodes are independent prognostic factors in esophageal cancer regardless of neoadjuvant chemoradiation or lymphadenectomy extent. Annals of Surgery. 2008;247:365–71.

40. Talsma AK, Shapiro J, Looman CWN, Van Hagen P, Steyerberg EW, Van Der Gaast A, et al. Lymph node retrieval during esophagectomy with and without neoadjuvant chemoradiotherapy : Prognostic and therapeutic impact on survival. Annals of Surgery. 2014;260:786–93.

41. Chirieac LR, Swisher SG, Ajani JA, Komaki RR, Correa AM, Morris JS, et al. Posttherapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemoradiation. Cancer. 2005;103:1347–55.

42. Schneider PM, Baldus SE, Metzger R, Kocher M, Bongartz R, Bollschweiler E, et al. Histomorphologic tumor regression and lymph node metastases determine prognosis following neoadjuvant radiochemotherapy for esophageal cancer: Implications for response classification. Annals of Surgery. 2005;242:684–92.

43. Miyata H, Tanaka K, Makino T, Yamasaki M, Miyazaki Y, Takahashi T, et al. The Impact of Pathological Tumor Regression and Nodal Status on Survival and Systemic Disease in Patients Undergoing Neoadjuvant Chemotherapy for Esophageal Squamous Cell Carcinoma. Annals of Surgical Oncology. Springer International Publishing; 2018;25:2409–17.

Tables

Table 1. Characteristics of patients in the NAC (+) group (n = 54)

Age, years	
Median (range)	64 (44 - 79)
Sex [n (%)]	
Male / Female	44 (81) / 10 (19)
Location [n (%)]	
Ce / Ut / Mt / Lt / Ae	2 (4) / 2 (4) / 32 (59) / 16 (30) / 2 (4)
Post-NAC diagnosis [n (%)]	
T	
1a / 1b / 2 / 3	1 (2) / 15 (28) / 15 (28) / 23 (43)
N	
0 / 1 / 2 / 3	15 (28) / 14 (26) / 16 (30) / 9 (17)
Stage	
I / II / III	3 (6) / 25 (46) / 26 (48)
Operative Time, min	
Median (range)	607 (340 - 935)
Blood loss, g	
Median (range)	100 (21 - 524)
Pathological diagnosis [n (%)]	
T	
0 / 1a / 1b / 2 / 3 / 4a	1 (2) / 4 (7) / 15 (28) / 10 (19) / 23 (43) / 1 (2)
N	
0 / 1 / 2 / 3 / 4	13 (24) / 8 (15) / 26 (48) / 5 (9) / 2 (4)
Stage	
0 / I / II / III / IV	2 (4) / 4 (7) / 20 (37) / 25 (46) / 3 (6)
v	
(-) / (+)	42 (79) / 11 (21)
ly	
(-) / (+)	36 (67) / 18 (33)
R	

0 / 1	51 (94) / 3 (6)

NAC, neoadjuvant chemotherapy; **Ce**, cervical esophagus; **Ut**, upper thoracic esophagus; **Mt**, middle thoracic esophagus; **Lt**, lower thoracic esophagus; **Ae**, abdominal esophagus; **T**, depth of tumor invasion; **N**, grading of lymph node metastasis; **v**, venous invasion; **ly**, lymphatic invasion; **R**, residual tumor

Table 2. Univariate analysis for 3-year RFS of NAC (+) group (n = 54)

	n (%)	Mean RFS [months]	3-year RFS rate [%]	*p*
Characteristic	54 (100)	17	46	
Age, years				0.9282
≤ 64	28 (52)	18	42	
> 64	26 (48)	10	51	
Sex				0.3678
Male	44 (81)	18	48	
Female	10 (19)	12	38	
Location				0.5223
Ce, Ut, Mt	36 (67)	17	40	
Lt, Ae	18 (33)	13	57	
Post-NAC diagnosis				
T				0.1507
T1	16 (30)	21	57	
T2, 3	38 (70)	14	41	
N				0.8802
N0	15 (28)	16	42	
N1 - 3	39 (72)	17	48	
Operative time, min				0.3781
≤ 600	26 (48)	10	59	
> 600	28 (52)	18	36	
Blood loss, g				0.1503
≤ 100	30 (56)	16	37	
> 100	24 (44)	19	59	
Pathological diagnosis				
T				0.3843
T0, 1	21 (39)	20	50	
T2 - 4	33 (61)	15	44	
N				0.0211

N0	13 (24)	22	81	
N1 - 4	41 (76)	16	37	
v				0.0066
(-)	42 (78)	19	54	
(+)	11 (20)	12	12	
ly				0.0006
(-)	36 (67)	19	61	
(+)	18 (33)	13	14	
R				<0.0001
R0	51 (94)	18	48	
R1	3 (6)	3	33	

RSF, recurrence-free survival; **NAC**, neoadjuvant chemotherapy; **Ce**, cervical esophagus; **Ut**, upper thoracic esophagus; **Mt**, middle thoracic esophagus; **Lt**, lower thoracic esophagus; **Ae**, abdominal esophagus; **T**, depth of tumor invasion; **N**, grading of lymph node metastasis; **v**, venous invasion; **ly**, lymphatic invasion; **R**, residual tumor

Table 3. Multivariate analysis for 3-year RFS of the NAC (+) group

	Hazard ratio	95% CI	*p*
pN (pN1-4 vs. pN0)	3.433	0.778 - 15.2	0.104
v (v (+) vs. v (-))	1.137	0.397 - 3.26	0.811
ly (ly (+) vs. ly (-))	2.632	1.04 - 6.68	0.042
R (R (+) vs. R (-))	24.21	1.92 - 305	0.014

RSF, recurrence-free survival; **NAC**, neoadjuvant chemotherapy; **pN**, pathological grading of lymph node metastasis; **v**, venous invasion; **ly**, lymphatic invasion; **R**, residual tumor

Table 4. Comparison of characteristics between the NAC (-) and (+) groups

	NAC (-) (n = 53)	NAC (+) (n = 54)	*p*
Age, years			
Median (range)	69 (34 - 83)	64 (44 - 79)	0.2659
Sex			
Male / Female	47 / 6	44 / 10	0.2965
Location			
Ce / Ut / Mt / Lt / Ae	2 / 6 / 29 / 12 / 3	2 / 2 / 32 / 16 / 2	0.5777
Clinical or post-NAC diagnosis			
T			
1a / 1b / 2 / 3	1 / 24 / 17 / 8	1 / 15 / 15 / 23	0.0253
1 / 2, 3	25 / 25	16 / 38	0.0337
N			
0 / 1 / 2 / 3	38 / 7 / 5 / 0	15 / 14 / 16 / 9	<0.0001
0 / 1 - 3	38 / 12	15 / 39	<0.0001
Stage			
I / II / III	22 / 20 / 8	3 / 25 / 26	<0.0001
Operative Time, min			
Median (range)	584 (293 - 984)	612 (340 - 941)	0.8550
Blood loss, g			
Median (range)	238.5 (60 - 1370)	100 (21 - 524)	<0.0001
Pathological diagnosis			
T			
0 / 1a / 1b / 2 / 3 / 4a	0 / 6 / 18 / 10 / 19 / 0	1 / 4 / 15 / 10 / 23 / 1	0.6931
0, 1 / 2 - 4	24 / 29	21 / 33	0.5029
N			
0 / 1 / 2 / 3 / 4	6 / 21 / 20 / 5 / 1	13 / 8 / 26 / 5 / 2	0.0495
0 / 1 - 4	6 / 47	13 / 41	0.0844
Stage			
O / I / II / III / IV	0 / 1 / 29 / 22 / 1	1 / 3 / 16 / 32 / 2	0.0941

v			
(-) / (+)	40 / 13	42 / 11	0.6425
ly			
(-) / (+)	24 / 28	36 / 18	0.0332
R			
0 / 1	52 / 1	51 / 3	0.3172

NAC, neoadjuvant chemotherapy; **Clinical or post-NAC diagnosis**, in NAC (+) group, post-NAC diagnosis is shown; **Ce**, cervical esophagus; **Ut**, upper thoracic esophagus; **Mt**, middle thoracic esophagus; **Lt**, lower thoracic esophagus; **Ae**, abdominal esophagus; **T**, depth of tumor invasion; **N**, grading of lymph node metastasis; **v**, venous invasion; **ly**, lymphatic invasion; **R**, residual tumor.

Figures

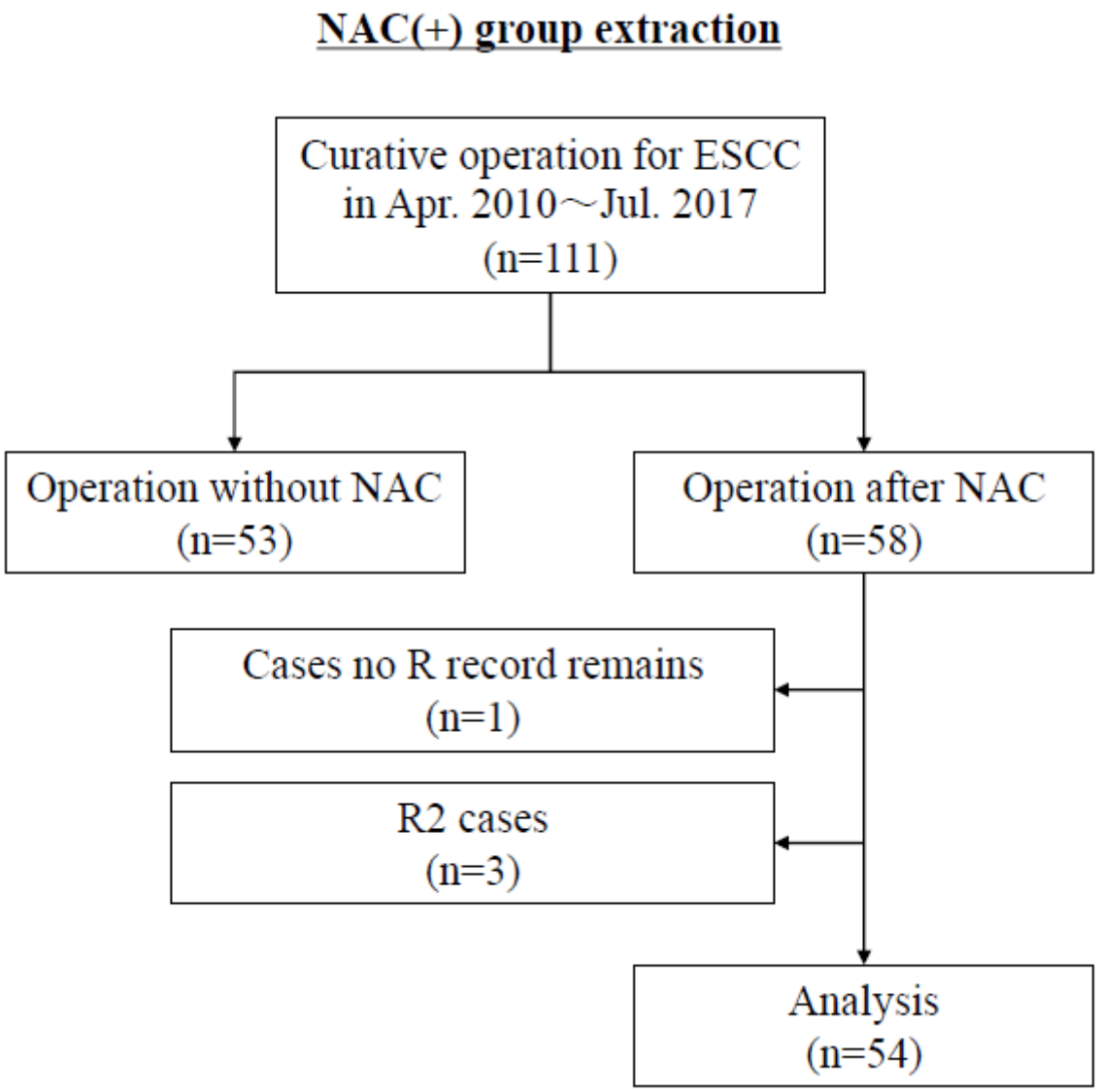

Figure 1

Diagram of case selection.

ESCC, esophageal squamous cell carcinoma; **NAC**, neoadjuvant chemotherapy; **R**, residual tumor. Diagnosis was based on the Japanese Classification of Esophageal Cancer (11th Edition) edited by the Japan Esophageal Society.

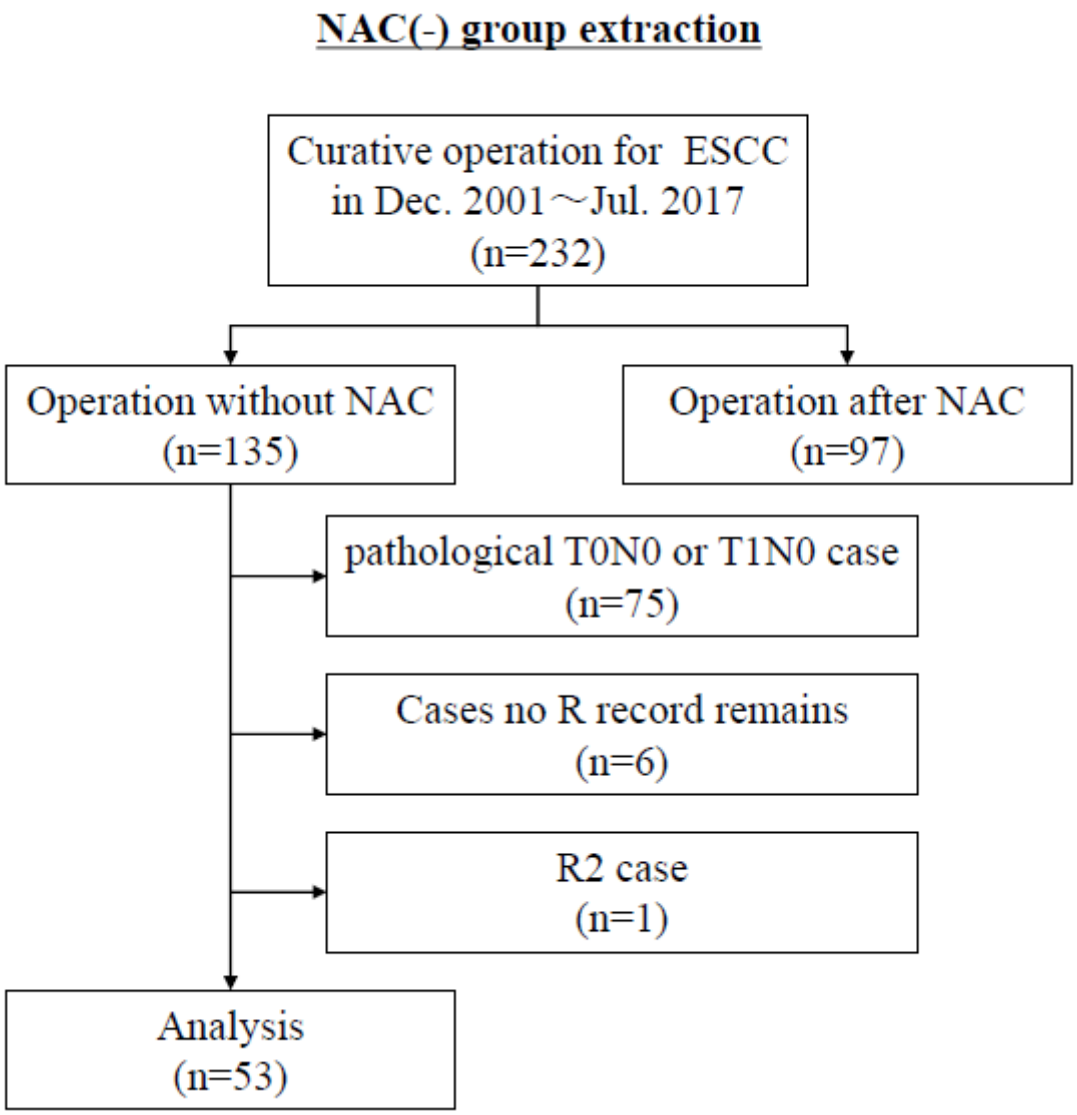

Figure 2

Diagram of case selection for the NAC (-) group.

ESCC, esophageal squamous cell carcinoma; **NAC**, neoadjuvant chemotherapy; **T**, depth of tumor invasion; **N**, grading of lymph node metastasis; **R**, residual tumor. Diagnosis was based on the Japanese Classification of Esophageal Cancer (11th Edition) edited by the Japan Esophageal Society.

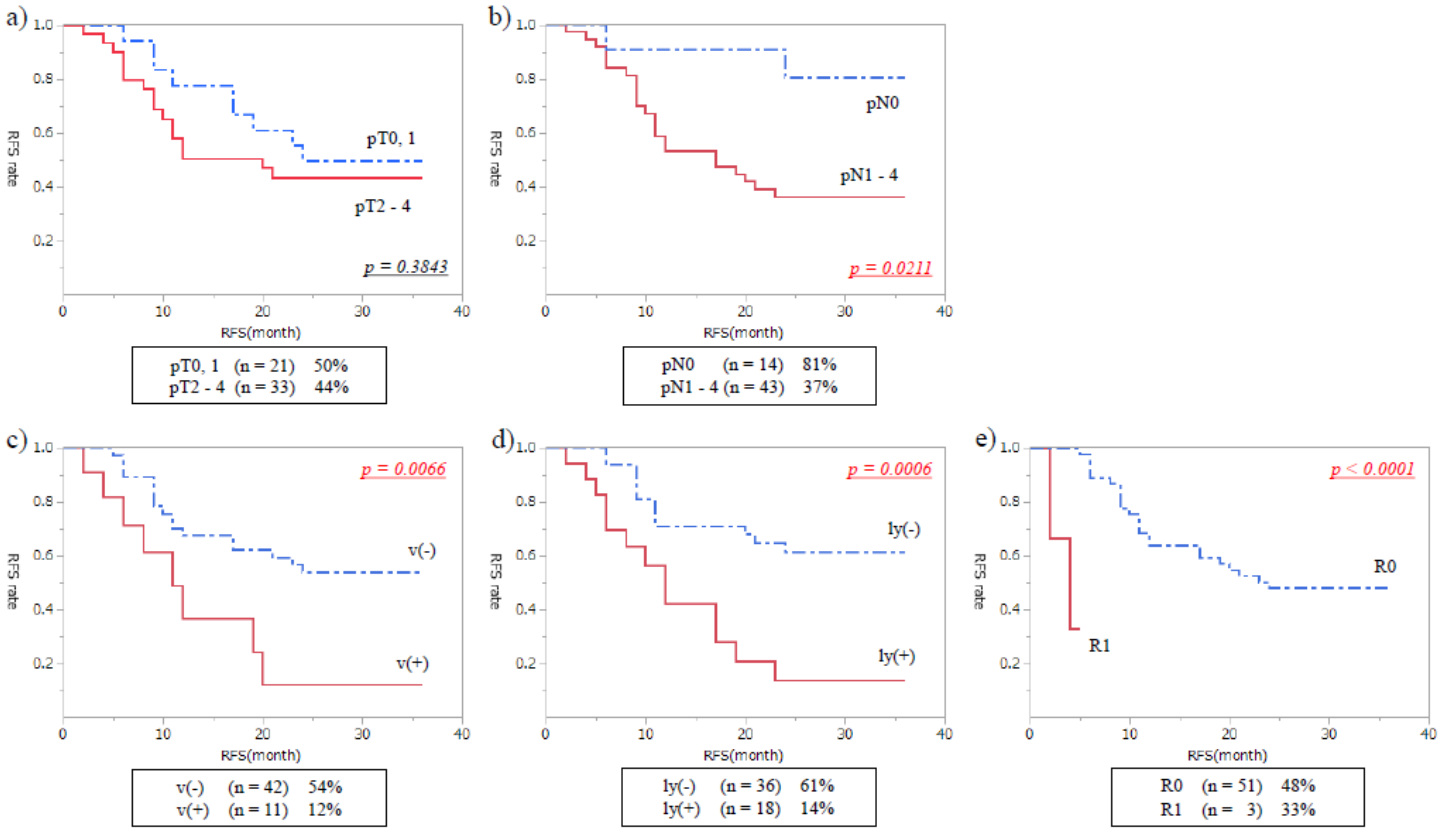

Figure 3

Kaplan–Meier estimates of 3-year RFS in NAC (+) patients in a) pT0, 1 and pT2-4 subgroups, b) pN0 and pN1-4 subgroups, and according to the presence of c) v, d) ly, and e) R.

RFS, recurrence-free survival; **NAC**, neoadjuvant chemotherapy; **pT**, depth of tumor invasion; **pN**, grading of lymph node metastasis; **v**, venous invasion; **ly**, lymphatic invasion; **R**, residual tumor. All factors were diagnosis based on the Japanese Classification of Esophageal Cancer (11th Edition) edited by the Japan Esophageal Society.

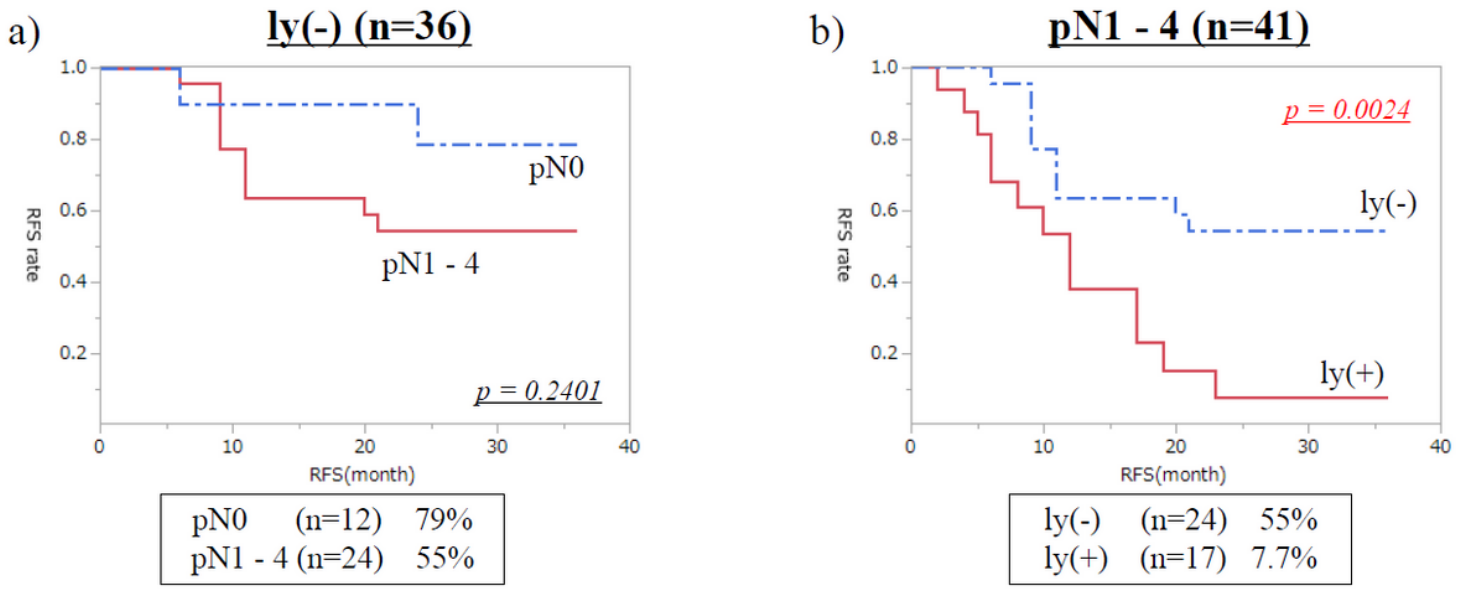

Figure 4

Kaplan–Meier estimates of 3-year RFS in NAC (+) patients.

a) RFS of ly (-) cases with and without pN.

b) RFS of pN (+) cases with and without ly.

RFS, recurrence-free survival; **NAC**, neoadjuvant chemotherapy; **pN**, grading of lymph node metastasis; **ly**, lymphatic invasion. All factors were diagnosed based on the Japanese Classification of Esophageal Cancer (11th Edition) edited by the Japan Esophageal Society.