Oncologic outcomes after resection of para-aortic lymph node metastasis in left-sided colon and rectal cancer

Junichi Sakamoto (Btaq1659@gmail.com)
Tochigi Cancer Center https://orcid.org/0000-0002-4316-0763

Heita Ozawa
Tochigi Cancer Center

Hiroki Nakanishi
Tochigi Cancer Center

Shin Fujita
Tochigi Cancer Center

Research

Keywords: colorectal cancer, para-aortic lymph node dissection, para-aortic lymph node metastasis

Posted Date: April 29th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-24720/v1

Abstract

Background The optimal surgical management strategy for para-aortic lymph node (PALN) metastasis has not attracted as much attention as surgery for liver or lung metastasis. The purpose of this retrospective study was to evaluate the oncologic outcomes after synchronous resection of PALN metastasis in left-sided colon and rectal cancer.

Methods Between January 1986 and August 2016, 29 patients with pathologically positive PALN metastasis who underwent curative resection at our hospital were retrospectively reviewed. We examined clinicopathological characteristics, long-term oncologic outcomes, and factors related to favorable prognosis in patients with PALN metastasis.

Results The 3-year overall survival and recurrence-free survival (RFS) rates were 50.5% and 17.2%, respectively. Six (20.7%) patients experienced no recurrence in the three years after surgery. Postoperative complications were seen in nine (31.0%) patients. The three-year RFS rate was significantly better in the pM1a group than in the pM1b/pM1c group (26.3% and 0.0%, respectively, $p = 0.032$).

Conclusions PALN dissection for left-sided colon or rectal cancer with synchronous PALN metastasis can be a feasible treatment option in selected patients.

Background

Para-aortic lymph node (PALN) metastasis occurs in less than 1.3% of colorectal cancer (CRC) patients.[1] PALN is associated with poor prognosis.[2]

While management of metastatic CRC has long been based on systemic chemotherapy, several studies have suggested that more aggressive surgical resection is a potentially curative treatment for liver and lung metastasis in selected patients with acceptable postoperative morbidity.[3–5] Recently, surgical resection has been established as the standard therapy for liver and lung metastasis.

However, the clinical significance of surgical management of synchronous PALN metastasis remains highly controversial because of the lack of definitive evidence regarding survival outcomes and the safety of surgical techniques.[6] There is insufficient data to guide the stratification of patients for aggressive treatment.

We aimed to clarify the oncologic outcomes after synchronous resection of PALN metastasis in left-sided colon and rectal cancer.

Materials And Methods

Patients

In this retrospective cohort study in a single institution, between January 1986 and August 2016, 574 patients with stage Ⅳ CRC underwent surgery, including noncurative surgery, at our cancer center. Of these, 43 underwent PALN dissection synchronously with primary CRC resection.

The selection criteria for PALN dissection were as follows: (1) pathological diagnosis of CRC; (2) suspected PALN metastasis on preoperative imaging, such as abdominal/pelvic computed tomography (CT) or positron emission tomography; and (3) judgment that curative resection was possible (i.e., no signs of upward PALN swelling extending above the renal vessels, or obvious invasion of PALN metastases to the great vessels). Curative resection was defined as complete tumor resection with all margins being negative. The indications for PALN dissection were thoroughly discussed and determined at our multidisciplinary team conferences with radiologists and hepatobiliary surgeons.

In total, 29 patients who were pathologically positive for PALN metastasis were included. We excluded patients with secondary malignancies and double cancer.

The study protocol was conducted in accordance with the Declaration of Helsinki. The need for written consent from study subjects was waived by the institutional review board. This retrospective study was approved by the Ethical Advisory Committee of Tochigi Cancer Center before study initiation.

Evaluation parameters

The classification system of the Union for International Cancer Control (8th edition) was used to determine pathological tumor depth and distant metastasis. The extent of regional lymph node metastasis was classified into three categories according to their location: (1) pericolic/perirectal lymph nodes were defined as lymph nodes close to the bowel wall; (2) intermediate lymph nodes were defined as lymph nodes along the feeding arteries; and (3) main lymph nodes were defined as lymph nodes related to the origin of the feeding artery. In addition, lateral pelvic nodes were defined as lymph nodes along the common internal and external iliac vessels and downward to the level of the obturator internus muscles. Postoperative complications were classified according to the Clavien and Dindo classification.

Surgery and follow-up

Curative surgery was performed following the standard principles of total mesorectal excision. After identification of the ureter and gonadal vessels, PALN dissection began from the aortic or bifurcation of the iliac artery. We removed all lymphovascular tissues in the area using the following boundaries: the lower border of the left renal vein, the right border of the inferior vena cava, and the right border of the left gonadal vessels (Fig. 1).

Patients underwent a standardized follow-up every three months for the first three years. At each follow-up, physical examination and laboratory test were performed. CT was performed every six months. Colonoscopy was performed one year after surgery, and repeated at least every two years.

Main outcome measures

The primary end points were three-year overall survival (OS) and recurrence-free survival (RFS) rates.

Statistical analysis

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R Commander designed to add statistical functions frequently used in biostatistics.

Differences in categorical and continuous variables were analyzed using the chi-square test (or Fisher's exact test) and Student's *t*-test. The Kaplan-Meier method was used to compare OS and RFS rates. Univariate and multivariate analyses of factors associated with oncologic outcomes were evaluated using the Kaplan-Meier method, and the Cox proportional hazards model was used to estimate hazard ratios. Survival curves were created using the log-rank test. From the receiver operating characteristic (ROC) curves, the threshold of PALN metastasis was set to four (area under the ROC curve, 0.741; 95% CI, 0.531–0.951). A probability level of $p<0.05$ was considered to indicate a statistical difference.

Results

Clinicopathological characteristics are shown in Table 1. The median age of patients was 60 years (range: 35–74 years), and 15 (51.7%) were men. In 15 (51.7%) patients, the tumors were located in the rectum. Eighteen (62.1%) patients received adjuvant treatment. The most common histological type was moderately differentiated adenocarcinoma (n=19, 65.5%). Five (17.2%) patients had pT4b tumors, and 14 (48.3%) had no metastases to the main lymph nodes. In terms of other organ metastases, 19 (65.5%) patients were in the pM1a group. The median number of total harvested and metastatic PALNs was 12 (1–81) and four (1–71), respectively.

Table 1. Clinicopathological characteristics

*Data are presented as median (range), unless otherwise stated.

PALN, para-aortic lymph node

Operative and postoperative results are shown in Table 2. Only one (3.4%) patient was operated on using a laparoscopic approach. The median operating time was 248 (110–645) minutes and the median estimated blood loss was 628 (20–4900) g. The median hospital stay was 40 (8–106) days. Postoperative morbidity occurred in nine (31.0%) patients. There was no 30-day mortality, and no patients had grade Ⅲ and Ⅳ complications. The most common morbidity was surgical site infection (n=3, 10.3%). Postoperative recurrences occurred in 23 (79.3%) patients, and the most common site of recurrence was distant lymph nodes (n=9, 31%).

Table 2. Operative and postoperative results

*Data are presented as median (range), unless otherwise stated.

SSI, surgical site infection

The median follow-up was 30.0 months (range: 1.5–210.7 months). Of the total 29 patients, the three-year OS rate was 50.5% (Fig. 2a), and the three-year RFS rate was 17.2% (Fig. 2b). The three-year OS rate in the pM1a group was significantly better than in the pM1b and pM1c group (63.2 and 24.0%, respectively; hazard ratio [HR], 3.01; 95% confidence interval [CI], 1.19–7.65; p=0.015) (Fig. 3a). In addition, the three-year RFS rate was significantly different in the pM1a group and the pM1b and pM1c group (26.3 and 0.0%, respectively; HR, 2.49; 95% CI, 1.05–5.90; p=0.032) (Fig. 3b). There was no statistically significant difference in clinicopathological characteristics between patients with pM1a and pM1b and pM1c (Table 3).

Table 3. Comparison of clinicopathological characteristics between the pM1a and pM1b/c

*Data are presented as median (range), unless otherwise stated.

LN, mph node;

PALN, para-aortic lymph node

In the multivariate analysis (Table 4), the pM1a group was an independent prognostic factor for OS (HR, 5.15; 95% CI, 1.52–17.5; p=0.0084) and RFS (HR, 2.49; 95% CI, 1.05–5.90; p=0.038). The number of PALN metastases did not differ significantly based on OS or RFS.

Table 4. Univariate and multivariate analyses of overall survival and recurrence-free survival

HR, hazard ratio; CI, confidence interval; OS, overall survival; RFS, recurrence-free survival; PALN, para-aortic lymph node

Discussion

The present study demonstrated that PALN dissection for left-sided colon and rectal cancer with synchronous PALN metastasis without other organ metastases was associated with a favorable prognosis. This is one of a few characteristic studies that has shown the clinical significance of PALN dissection.

Similar to liver and lung metastasis, synchronous PALN metastasis from a CRC is categorized as Stage □ disease. Liver and lung metastasis resection are widely accepted as standard treatments and five-year survival rates are over 50% following surgery.[7]

PALN dissection was first described in 1950 by Dr. Deddish as a modification of the Miles abdominoperineal resection to reduce local recurrence in rectal cancer.[8] However, routine PALN dissection has since been abandoned in view of the increased surgical morbidity, such as urinary and sexual dysfunction, without corresponding improvements in recurrence rates and overall survival.[9] On the other hand, recent studies have reported that prolonged survival can be obtained following resection of PALN metastasis.[10–14] Each of these studies was a retrospective cohort study, and so significance of the PALN dissection remains unconfirmed and highly controversial.

We think that curative resection, using PALN dissection, is a prerequisite for a favorable prognosis. Past studies have shown that low curative resection rates lead to low survival rates.[12] Therefore, we did not perform PALN dissection on patients in whom it was established that curative resection was not possible based on preoperative imaging diagnosis.

Our PALN dissection area was similar to that of past studies. It is necessary to perform PALN dissection for right-sided colon cancer while maintaining the great vessels, such as the superior mesenteric artery or celiac artery. Because of this, in right-sided colon cancer, systematic PALN dissection is anatomically impossible and the dissection effect is not to be obtained as it is with left-sided colon and rectal cancers. For this reason, we limited the indication for PALN dissection to left-sided colon and rectal cancer.

The 3-year OS rate and the three-year RFS rate were significantly better in the pM1a group than in the pM1b/pM1c group, which was similar to the results of Yamada et al.[11] In our study, there were no significant differences in clinicopathological characteristics, such as tumor location and histology, the number of metastatic regional lymph nodes, and the number of metastatic PALNs in the pM1a group and pM1b/pM1c group (Table 3). These results suggest that other organ metastases without PALN are the

most important prognosticators. In our study, there was no distant lymph node recurrence in the pM1b/pM1c group, and all recurrences occurred in other organs. Consequently, patients with PALN metastasis with other organ metastases should be excluded from the indication for PALN dissection.

Song et al. reported that patients without disease recurrence had three or fewer PALN metastases.[14] Several other studies reported that fewer metastases may be a good indication for PALN dissection.[2, 15] Speaking of lateral lymph nodes in lower rectal cancer, Fujita reported that the prognosis of patients with one or two extramesorectal lymph node metastases was favorable.[16] Our data, however, showed that three patients obtained long-term RFS, even when the number of PALN metastases reached seven or more. Additionally, there are very few reports about the relationship between the number of metastatic PALNs and prognosis, so no influencing factors have been established. Hence, the number of metastatic PALNs cannot guide the indication for PALN dissection at this moment.

Recently, several studies have reported an optimum cutoff for lymph node size to identify patients positive for lateral lymph node metastases of lower rectal cancer on preoperative imaging.[17, 18] However, reports on preoperative diagnosis of PALN metastasis are rare. Further studies on accurate preoperative imaging diagnosis and patient selection for PALN dissection are therefore necessary.

The benefits associated with removing PALN metastasis should be weighed up against the risk of morbidity. In the present study, postoperative morbidity occurred in 31.0% of patients, which was comparable with that of other studies (7.8–38.9%).[10–14] The main morbidity was surgical site infection, and the rate of Clavien and Dindo classification grade Ⅲ or above was only 10.3%, with no perioperative death. These results suggest that the incidence of postoperative morbidities associated with PALN dissection is within acceptable limits.

There were several limitations to the present study, including the single institutional experience, the small sample size due to the rarity of this metastatic pattern, and the retrospective analysis. The study period was long, lasting over 30 years; and during this time, the optimal indication for PALN dissection and treatment strategy, e.g. chemotherapeutic regimens, would have changed. Additionally, assessment of sexual dysfunction was not performed. A global assessment method, such as the International Index of Erectile Function, should be used for all cases. However, our results clearly showed that favorable prognosis could be expected in select patients with left-sided colon and rectal cancer using isolated PALN metastasis. In light of our results supporting the role of PALN dissection, large and multi-institutional prospective studies are required to overcome these problems.

Conclusions

In conclusion, PALN dissection for patients without other organ metastases in left-sided colon or rectal cancer can be a feasible treatment option as it is for liver and lung metastasis.

Abbreviations

CI
confidence interval
CRC
colorectal cancer
CT
computed tomography
HR
hazard ratio
OS
overall survival
PALN
para-aortic lymph node
RFS
recurrence-free survival
ROC
receiver operating characteristic

Declarations

Ethics approval and consent to participate

Institutional approval for this retrospective study was obtained from the Ethical Advisory Committee of Tochigi Cancer Center before initiating the study.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

Funding

No funding was received for this research.

Authors' contributions

Conception or design of the research; or the acquisition, analysis, or interpretation of data for the research: JS, HO, HN, SF

Drafting the manuscript or revising it critically for important intellectual content: JS, HO, HN, SF

Final approval of the version to be published: JS, HO, HN, SF

All other authors have contributed to data collection and interpretation, and critically reviewed the manuscript. All authors approved the final version of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Acknowledgements

This study was supported by Tochigi Cancer Center founded by Tochigi prefecture. All authors listed have contributed sufficiently to this study to be included as authors.

References

1. Watanabe T, Itabashi M, Shimada Y, Tanaka S, Ito Y, Ajioka Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2010 for the treatment of colorectal cancer. Int J Clin Oncol. 2012;17:1–29.
2. Choi PW, Kim HC, Kim AY, Jung SH, Yu CS, Kim JC. Extensive lymphadenectomy in colorectal cancer with isolated para-aortic lymph node metastasis below the level of renal vessels. J Surg Oncol. 2010;101:66–71.
3. Choti MA, Sitzmann JV, Tiburi MF, Sumetchotimetha W, Rangsin R, Schulick RD, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg. 2002;235:759–66.
4. Shah SA, Haddad R, Al-Sukhni W, Kim RD, Greig PD, Grant DR, et al. Surgical resection of hepatic and pulmonary metastases from colorectal carcinoma. J Am Coll Surg. 2006;202:468–75.
5. Lehnert T, Knaebel HP, Dück M, Bülzebruck H, Herfarth C. Sequential hepatic and pulmonary resections for metastatic colorectal cancer. Br J Surg. 1999;86:241–3.

6. Wong JS, Tan GH, Teo MC. Management of para-aortic lymph node metastasis in colorectal patients: A systemic review. Surg Oncol. 2016;25:411–8.
7. Mahmoud N, Bullard Dunn K. Metastasectomy for stage IV colorectal cancer. Dis Colon Rectum. 2010;53:1080–92.
8. Stearns MW Jr, Deddish MR. Five-year results of abdominopelvic lymph node dissection for carcinoma of the rectum. Dis Colon Rectum. 1959;2:169–72.
9. Leggeri A, Roseano M, Balani A, Turoldo A. Lumboaortic and iliac lymphadenectomy: what is the role today? Dis Colon Rectum. 1994;37(2 Suppl):54–61.
10. Sahara K, Watanabe J, Ishibe A, Suwa Y, Suwa H, Ota M, et al. Long-term outcome and prognostic factors for patients with para-aortic lymph node dissection in left-sided colorectal cancer. Int J Colorectal Dis. 2019;34:1121–9.
11. Yamada K, Tsukamoto S, Ochiai H, Shida D, Kanemitsu Y. Improving selection for resection of synchronous para-aortic lymph node metastases in colorectal cancer. Dig Surg. 2019;36:369–75.
12. Nakai N, Yamaguchi T, Kinugasa Y, Shiomi A, Kagawa H, Yamakawa Y, et al. Long-term outcomes after resection of para-aortic lymph node metastasis from left-sided colon and rectal cancer. Int J Colorectal Dis. 2017;32:999–1007.
13. Bae SU, Han YD, Cho MS, et al. Oncologic outcomes of colon cancer patients with extraregional lymph node metastasis: comparison of isolated paraaortic lymph node metastasis with resectable liver metastasis. Ann Surg Oncol. 2016;23:1562–8.
14. Song SH, Park SY, Park JS, Kim HJ, Yang CS, Choi GS. Laparoscopic para-aortic lymph node dissection for patients with primary colorectal cancer and clinically suspected para-aortic lymph nodes. Ann Surg Treat Res. 2016;90:29–35.
15. Bae SU, Hur H, Min BS, Baik SH, Lee KY, Kim NK. Which patients with isolated para-aortic lymph node metastasis will truly benefit from extended lymph node dissection for colon cancer? Cancer Res Treat. 2018;50:712–19.
16. Fujita S. Incidence and prognosis of lower rectal cancer with limited extramesorectal lymph node metastasis. Int J Colorectal Dis. 2014;29:1077–80.
17. Ogawa S, Hida J, Ike H, Kinugasa T, Ota M, Shinto E, et al. Selection of lymph node-positive cases based on perirectal and lateral pelvic lymph nodes using magnetic resonance imaging: Study of the Japanese Society for Cancer of the Colon and Rectum. Ann Surg Oncol. 2016;23:1187–94.
18. Akiyoshi T, Matsueda K, Hiratsuka M, Unno T, Nagata J, Nagasaki T, et al. Indications for lateral pelvic lymph node dissection based on magnetic resonance imaging before and after preoperative chemoradiotherapy in patients with advanced low-rectal cancer. Ann Surg Oncol. 2015;22(Suppl 3):614–20.

Tables

Due to technical limitations, tables are only available as a download in the supplemental files section.

Figures

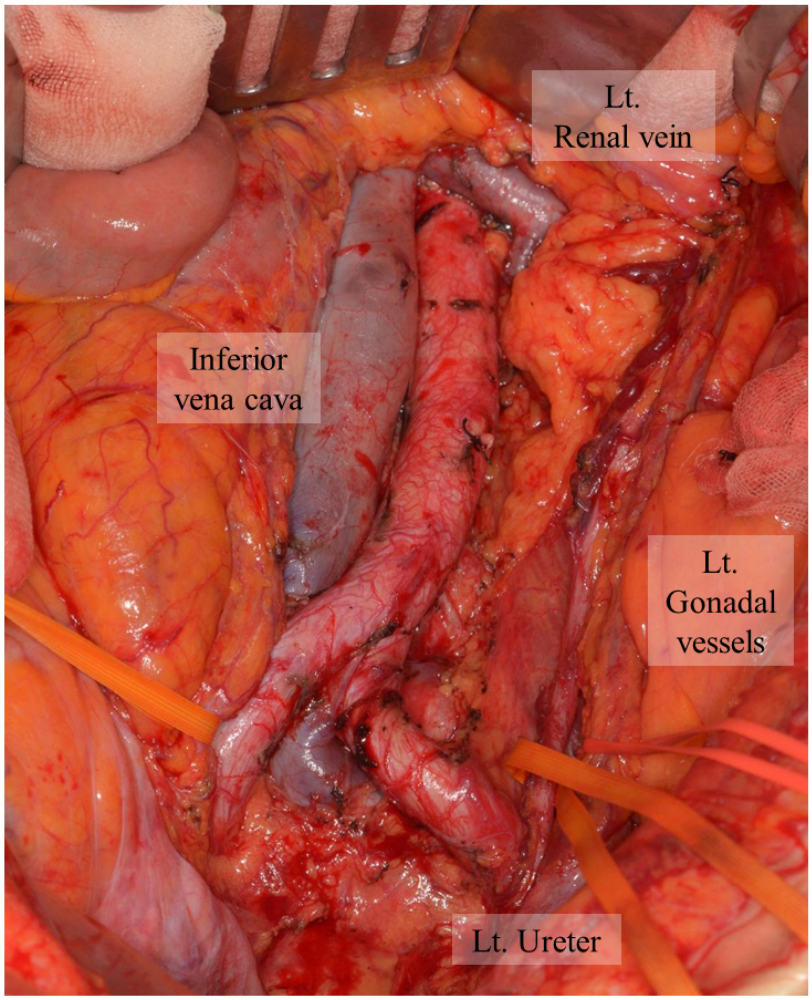

Figure 1

Intraoperative findings of PALN dissection PALN, para-aortic lymph node

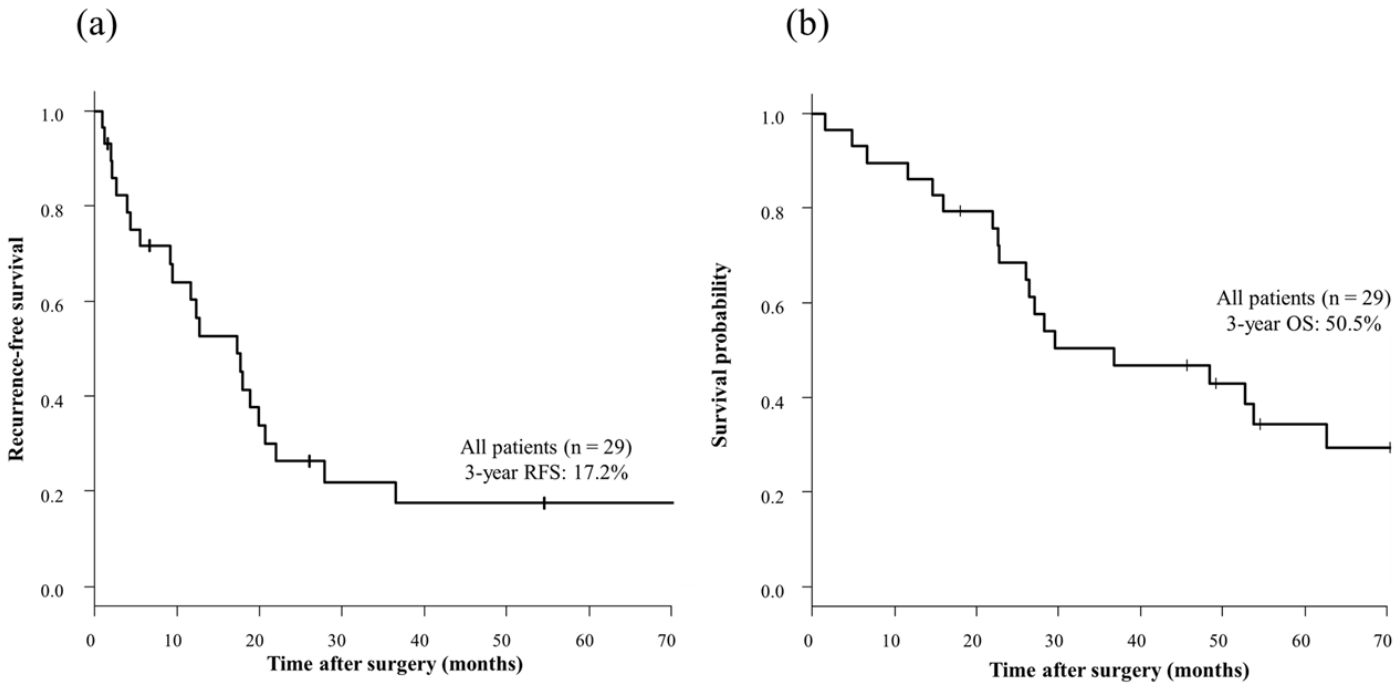

Figure 2

(a) Kaplan-Meier OS curve for all patients (b) Kaplan-Meier RFS curve for all patients OS, overall survival; RFS, recurrence-free survival

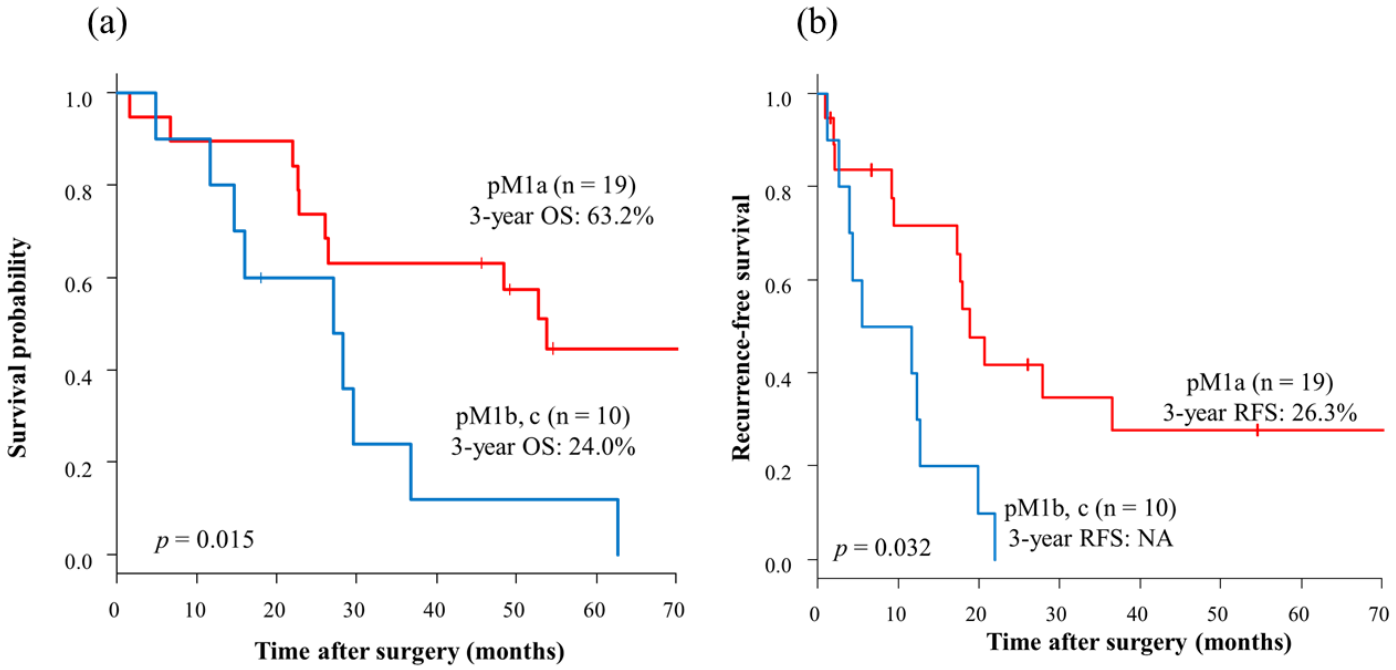

Figure 3

(a) Kaplan-Meier OS curve for patients with each M-category pM1a and pM1b, c (red, pM1a; blue, pM1b and pM1c) (b) Kaplan-Meier RFS curve for patients with each M-category pM1a and pM1b, c (red, pM1a; blue, pM1b and pM1c) OS, overall survival; RFS, recurrence-free survival; NA, not applicable

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 4.jpg
- Table1.jpg
- 2.jpg
- 4.jpg
- 3.jpg

- Table1.jpg
- 2.jpg
- 3.jpg