The Importance of Choosing the Right Strategy to Treat Small Cell Carcinoma of the Cervix: A Comparative Analysis of Treatments

Mariko Kawamura (mkawamura@med.nagoya-u.ac.jp)
Nagoya University https://orcid.org/0000-0001-9211-4934
Yutaro Koide
Aichi Cancer Center: Aichi-ken Gan Center
Taro Murai
Nagoya City University: Nagoya Shiritsu Daigaku
Shunichi Ishihara
Toyohashi Municipal Hospital: Toyohashi Shimin Byoin
Yuuki Takase
Japanese Red Cross Nagoya First Hospital: Nagoya Daiichi Sekijuji Byoin
Takayuki Murao
Matsuyama Shimin Hospital: Matsuyama Shimin Byoin
Dai Okazaki
Okazaki City Hospital: Okazaki Shimin Byoin
Takahiro Yamaguchi
Gifu University Hospital: Gifu Daigaku Igakubu Fuzoku Byoin
Kaoru Uchiyama
Kariya Toyota General Hospital: Kariya Toyota Sogo Byoin
Yoshiyuki Itoh
Nagoya University Hospital: Nagoya Daigaku Igakubu Fuzoku Byoin
Takeshi Kodaira
Aichi Cancer Center: Aichi-ken Gan Center
Yuta Shibamoto
Nagoya City University: Nagoya Shiritsu Daigaku
Mika Mizuno
Aichi Cancer Center: Aichi-ken Gan Center
Fumitaka Kikkawa
Nagoya University Hospital: Nagoya Daigaku Igakubu Fuzoku Byoin
Shinji Naganawa
Nagoya University Hospital: Nagoya Daigaku Igakubu Fuzoku Byoin

Research article

Keywords: small cell carcinoma, cervical cancer, rare cancer, chemotherapy

Posted Date: December 1st, 2020

DOI: https://doi.org/10.21203/rs.3.rs-115819/v1

Abstract

Background: Standard treatments for small cell carcinoma of the cervix (SCCC) is unclear. We aimed to estimate the optimal treatment strategy for SCCC.

Methods: This was a multicentre retrospective study. Medical records of patients with pathologically proven SCCC treated between 2003 and 2016 were retrospectively analyzed. Overall survival (OS) was plotted using the Kaplan-Meier method. The log-rank test and cox regression model were used to assess the differences in survival due to the stage, treatment strategy, and chemotherapy regimen.

Results: Seventy-seven patients were evaluated. Their median age was 47 (range: 24-83) years. The number of patients with stage I, II, III, and IV, as defined according to the Union for International Cancer Control (UICC), was 28, 9, 24, and 16, respectively. Of 64 patients who had undergone chemotherapy, 43 received a small cell carcinoma regimen and 21 received a non-small cell carcinoma regimen as their first-line chemotherapy regimen. The 5-year OS for all patients was 51%. The 5-year OS rates for the patients with UICC stage I, II, III, and IV were 61%, 76%, 54%, and 18%, respectively. The 5-year OS rates for patients who underwent treatments with a small cell carcinoma and non-small cell carcinoma regimen were 62% and 15% (p<0.001), respectively. This trend was observed in all UICC stages, except in stage I. Multivariate analysis showed that presence of metastasis was a significant prognostic factor in all the patients. Application of surgery was not a significant prognostic factor in multivariate analysis. The 5-year OS was similar in the concurrent chemoradiotherapy (CCRT) and surgery group if CCRT with small cell carcinoma regimen was selected.

Conclusion: The role of chemotherapy in stage I SCCC is unclear; however, if chemotherapy is applicable, SCCC patients should be treated with a chemotherapy regimen used for localized small cell carcinoma.

1. Background

Small cell carcinoma of the cervix (SCCC) is a rare cancer. It comprises approximately 1–3% of all cervical neoplasms [1, 2]. Owing to its rarity, it is very difficult to plan a prospective study involving these patients. In addition its standard treatment is unclear; therefore, debates regarding whether it should be treated with the same treatments used for localized small cell carcinoma or for advanced cervical cancer are ongoing. The Society of Gynecologic Oncology published a clinical document reviewing neuroendocrine tumors of the gynecologic tract in 2011 [3]. In this document, surgery is proposed as an optional therapy for early-stage SCCC, followed by adjuvant chemotherapy, Meanwhile, chemoradiotherapy is recommended for patients with advanced disease or those without an indication for surgery, and chemoradiotherapy with etoposide/cisplatin (EP) combined with pelvic radiation is recommended from multiple small series of retrospective cohort studies on prognostic factors of SCCC. Although multiple studies recommend EP as the first-line chemotherapy regimen for SCCC, the number of patients who had been treated with EP in prior studies is very small. Since the EP regimen often causes severe pancytopenia, the use of EP combined with whole pelvic radiotherapy is not very common in

Japan. However, after the publication of the document from the Society of Gynecologic Oncology in 2011, more institutions started to treat this disease as localized small cell carcinoma, and the treatment outcomes are our interest. Farther, it has been reported that the irinotecan/cisplatin (IP) regimen for small cell lung cancer is as effective as EP [4], and since small cell carcinoma of the cervix and lungs have a similar protein expression [5], IP can be effective in both the SCCC and SCC of the lungs; however, the existing data is limited.

Therefore, the purpose of this study was to evaluate the treatment strategy for SCCC by analyzing patients who had undergone different treatments in 9 major cancer care hospitals in Tokai area, Japan. This study aimed to capture today's treatment trend of SCCC and to address how treatment outcomes differed with the treatment strategy, as well as the first-line chemotherapy regimen.

2. Methods

2.1. Patient eligibility

Nine cancer treatment cooperation base hospitals certified by the ministry of health for providing high quality cancer care, located in Tokai area, Japan, participated in this retrospective study; the institutional review board at each hospital approved their participation in this multi-center study (research representative facility approval: Nagoya University Ethics Committee 2017-0010). The need for informed consent was waived due to the retrospective design. Patients were eligible when they (1) were pathologically diagnosed with SCCC and (2) received an initial diagnosis between 2003 and 2016. Patients with a history of chemotherapy or radiotherapy used to treat a different malignant tumor and a double primary malignant tumor were excluded. Data regarding patient diagnosis, treatment regimen, treatment related toxicity, and treatment outcome were collected.

2.2. Patients diagnosis

Histopathologic diagnosis was based on morphological criteria, and immunohistochemical staining was not required; however, the immunohistochemical information of most patients (> 80%) was available (synaptophysin, chromogranin, and CD56). All tumors were staged clinically by the International Federation of Gynecology and Obstetrics 2009 (FIGO) [6] and radiologically by the Union for International Cancer Control ver. 7 (UICC). When patients underwent upfront surgery, pathological staging was prioritized over radiological staging; however, when patients underwent neoadjuvant chemotherapy prior to surgery, radiological staging prior to chemotherapy was prioritized for evaluation of the tumor UICC stage.

2.3. Treatment regimen

For chemotherapy recipients, the chemotherapy regimen was classified as either a small cell carcinoma regimen or non-small cell carcinoma regimen. The patients were divided into two groups depending on the regimen they had received. The patients were assigned into a small cell carcinoma regimen group when they received either cisplatin (CDDP) and irinotecan (IP) or EP, which is used for the treatment of

small cell carcinoma of the lungs. Changing CDDP to carboplatin due to kidney function impairment was allowed, and these patients were included in the small cell carcinoma regimen group. All other patients who had undergone chemotherapy with weekly CDDP or CDDP with fluorouracil (5-FU), which are often used in cervical cancer treatment, were assigned into the non-small cell carcinoma regimen group. We classified patients according to the first chemotherapy regimen they received after diagnosis. When a patient was administered the non-small cell carcinoma regimen first and then the small cell carcinoma regimen, the patient was assigned into the non-small cell carcinoma regimen group. Therefore, when a patient was administered weekly CDDP concurrently with radiotherapy upfront, followed by IP, she was assigned into the non-small cell carcinoma regimen group. However, when a patient had induction IP followed by weekly CDDP concurrently with radiotherapy, the patient was assigned into the small cell carcinoma regimen group.

Depending on the treatment strategy, patients were grouped as follows: (1) surgery only; (2) local first: surgery or radiotherapy first, followed by chemotherapy or chemoradiotherapy; (3) neoadjuvant chemotherapy or chemoradiotherapy (NAC) prior to surgery; (4) concurrent chemoradiotherapy (CCRT); and (5) chemotherapy only.

2.4. Statistical analyses

Overall survival (OS) was plotted using the Kaplan-Meier method, and the log-rank test was used to assess differences in survival between pairs of groups. Multivariate analysis was performed using the Cox regression model for variables that were significant in the univariate analysis. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patient characteristics and treatment strategies

Seventy-eight patients were eligible for this study. One patient who had not received any treatment and who died a month after diagnosis was excluded. Seventy- seven patients who had received any treatment were evaluated. Their median age was 47 (range: 24–83) years, and the number of patients with UICC stage I, II, III, and IV was 28 (36%), 9 (12%), 24 (31%), and 16 (21%), respectively. The number of patients with FIGO stage I-IIA and ≥ IIB was 39 (51%) and 38 (49%), respectively. Thirty-eight patients (49%) had lymph node metastasis at diagnosis and 64 (83%) had received chemotherapy. Thirty-nine patients (51%) had received radiotherapy; however, only 16 patients (21%) had undergone brachytherapy. Surgery was performed in 50 patients (65%) (Table 1).

Of 64 patients who had undergone chemotherapy, 43 received a small cell carcinoma regimen and 21 received a non-small cell carcinoma regimen as their first-line chemotherapy regimen. The application of the chemotherapy regimen along with the UICC stage and the number of patients in each stage are

shown in Supplementary Figure A. All but one patient who had not undergone chemotherapy had stage I disease.

The treatment strategy and corresponding UICC stages are shown in Fig. 1. Patients who had surgery alone or upfront surgery followed by systemic therapy were likely to have early stage cancer compared to those who had NAC or CCRT.

3.2. Survival

The 5-year OS for all patients was 51% (Fig. 2a). The differences in survival depending on the UICC stage are shown in Fig. 2b. Five-year OS rates for UICC stage I, II, III, and IV were 61%, 76%, 54%, and 18%, respectively. The survival of patients with metastasis was significantly lower than that of the rest (hazard ratio [HR], 3.92; 95%CI, 21.90–8.09; $p < 0.001$). Also, node positive patients had significantly lower OS rates than those without (HR2.16; 95%CI, 1.10–4.24; $p = 0.02$). However, OS did not differ significantly between FIGO stage I-IIA and ≥ IIB patients ($p = 0.74$). Because most of the patients who did not receive chemotherapy were in stage I, there was no significant difference in survival with or without chemotherapy ($p = 0.20$), but among patients who received chemotherapy, patients treated with small cell carcinoma regimens had significantly better OS (Fig. 3). The 5-year OS rates for patients who were administered a small cell carcinoma regimen and non-small cell carcinoma regimen were 62% and 15% ($p < 0.001$), respectively. A difference between IP and EP was not observed ($p = 0.77$). A trend towards better OS in patients treated with the small cell carcinoma regimen was observed for all UICC stages, except for stage I, for which there was no significant difference in OS regardless of chemotherapy use or application of surgery (Supplemental data, Figure B). The difference due to the application of surgery showed better OS with surgery (HR, 0.3908; 95%CI, 0.20-0.716; $p < 0.01$); However as shown in Fig. 2, patients who had surgery tended to have early stage cancer. The results of the univariate and multivariate Cox regression analysis of all patient variables for overall survival are given in Table 2. The presence of metastasis at diagnosis was the only significant factor with all patients in multivariate analysis. Although application of non-small cell carcinoma regimen was slightly less significant ($p = 0.055$) in all patients, the application of chemotherapy had significantly better OS in non-stage I patients (HR, 0.021; 95%CI, 0.0013-0.34; $p < 0.01$) and application of non-small cell carcinoma regimen had significantly worse OS in patients with chemotherapy if multivariate cox regression analysis was performed with or without metastasis (Table 2).

The 5-years OS of CCRT patients was 39% in all the patients and 58% in the non-stage IV patients. The 5-year OS of CCRT with small cell carcinoma regimen and non-small cell carcinoma regimen were 25% and 67%, respectively. Patients who had surgery were all non-stage IV and their 5-year OS was 61% in all patients, 68% in the patients who were administered the adjuvant small cell carcinoma chemotherapy regimen, and 0% in those who were administered the adjuvant non-small cell carcinoma regimen.

Regarding the primary treatment strategy for non-stage IV patients, the 5-year OS rates for surgery only, local first, NAC, and CCRT were 73%, 50%, 86%, and 58% ($p = 0.49$), respectively (Supplemental data,

Figure C). When patients treated with the non-small cell carcinoma regimen were excluded, the 5-year OS rates for the local first, NAC, and CCRT groups were 60%, 100%, and 80% ($p = 0.20$), respectively (Supplemental data, Figure D).

3.3. Local control

Fourteen patients experienced local recurrence or local residuals. Of 14 patients who had a locally recurrence, 4 were treated with surgery only; 4 underwent surgery, followed by the small cell carcinoma chemotherapy regimen; 2 underwent surgery, followed by CCRT with the non-small cell carcinoma regimen; 1 had radiotherapy alone, followed by small cell carcinoma chemotherapy regimen; 2 received CCRT with the non-small cell carcinoma regimen; and one received the small cell carcinoma chemotherapy regimen alone. Local recurrence was not observed in patients who were treated with CCRT using the small cell carcinoma regimen or who received NAC.

3.4. Cause of death

All the 37 patients who were dead at the time of analysis died from SCCC metastasis, and there were no treatment-related deaths. Metastatic sites were reported in 28 of the 37 patients who died of the disease; 10 had dissemination to the brain and/or meninges. No patient underwent prophylactic cranial irradiation. Other metastatic sites included the lung, liver, bone, and pleura/peritoneum.

4. Discussion

Although the necessity of adjuvant chemotherapy for stage I SCCC remains unclear, application of a small cell carcinoma chemotherapy regimen such as EP or IP may have a better prognosis in patients requiring chemotherapy. Wang *et al* [7] retrospectively analyzed 179 patients with SCCC and found that patients treated with five cycles of EP had better outcomes; however, in their series, only eight patients had been treated with five cycles of EP. Thus, the information on outcomes for patients with SCCC treated as having localized small cell carcinoma is essential since such data are lacking. We believe that our report provides a stronger evidence than the past reports where more than 40 patients were treated with the SCCC chemotherapy regimen and still performed better than a non-small cell carcinoma regimen such as weekly CDDP or CDDP with 5-FU. Some retrospective studies have reported that clinical stage at diagnosis and application of CDDP-based chemotherapy are prognostic factors for SCCC [8–11]. However, no prospective studies compared CCRT with surgery and adjuvant systemic therapy; thus, the primary treatment recommendation for early stage SCCC is still unclear. Ishikawa *et al* [12] identified the superiority of surgery over CCRT in early stage SCCC, but they included only five patients treated by CCRT and they did not report chemotherapy regimens for CCRT. According to our results, most Japanese institutions are using CCRT with a cervical cancer regimen and not with a small cell carcinoma regimen. We consider that this strategy may have caused the poor outcome in CCRT because in our series, CCRT using small cell carcinoma regimen was not inferior to surgery with an adjuvant small cell carcinoma chemotherapy regimen, as shown by 5-year OS of 67% and 68%, respectively. Furthermore, we did not experience any local recurrence in patients who had CCRT using small cell carcinoma regimen.

Hoskins *et al* [13] reported the efficacy and safety of CCRT with EP in 31 patients, and this may be the largest study reporting CCRT with EP for SCCC patients. They reported a 3-year OS rate of 60%, which is similar to our results; the patient background was also similar. Only one of nine institutions included in our cohort had used EP for CCRT. Other institutions employed weekly CDDP or CDDP with 5FU concurrently with radiotherapy and then applied a small cell carcinoma regimen probably because EP frequently causes severe pancytopenia. There were 11 patients who had CCRT with EP in our series and seven patients (64%) experienced G4 hemato-toxicity, and required granulocyte colony-stimulating factors (G-CSF). However, by using G-CSF, patients were able to complete five cycles of EP and there were no late adverse effects. Again, we included those who received a non-small cell carcinoma regimen concurrently with radiotherapy, followed by a small cell carcinoma regimen in the non-small cell carcinoma regimen group, so we believe that the order in which chemotherapy are used is as important.

Noda et al. [4] reported that IP for small cell lung cancer was as effective as EP; thus, we included IP in the small cell carcinoma regimen group as well. Our study demonstrated that IP in SCCC is as effective as EP in lung carcinoma. However, because irinotecan causes diarrhea which also occurs as major toxic adverse effect of abdominal irradiation, patients who underwent CCRT had EP and those who had upfront surgery followed by chemotherapy were likely to undergo IP. Although there was no difference in OS between the patients who received either IP or EP, considering that upfront surgery patients tended to have an earlier stage tumor, there may have been a patient selection bias.

In our series, stage I patients had worse survival than stage II patients. Furthermore, in stage I there were no survival differences between patients treated with the small cell carcinoma chemotherapy regimen and with the non-small cell carcinoma chemotherapy regimen. However, most stage I patients in our series had surgery alone or upfront surgery followed by chemotherapy; thus, we hypothesize that there are certain patients who may benefit from chemotherapy, but at the same time there are patients who do not require systemic therapy at all. Therefore, further investigation is required to determine which patients will require chemotherapy in stage I SCCC.

Another interesting finding was that although we failed to prove statistical significance due to the small number of patients, the patients in the NAC group tended to have a better 5-year OS than those in the local first group, although the NAC group had more patients with advanced stage diseases. This may be because there is a bias in selecting good responders for chemotherapy, which may be a prognostic factor. On the other hand, this may be the key to understand why our result showed a poor OS for stage I. Only 2 of 28 (7.1%) stage I patients received a systemic therapy prior to surgery or CCRT and the others had surgery alone or upfront surgery followed by chemotherapy. On the other hand, more than half of the patients with stage II or III had CCRT or systemic therapy prior to surgery. As described previously, certain stage I patients may not require chemotherapy; however, if we could identify patients with stage I SCCC who could benefit from chemotherapy and to whom we could administer chemotherapy prior to surgery, we may be able to improve their outcome.

SCCC is rare, but very aggressive, and the OS rate is usually very poor. About half of the patients died from this disease, and most died within 2 years after diagnosis. We had 10 patients (13%) who died from dissemination to the brain and/or meninges. Once dissemination occurs, every treatment is futile. In lung carcinoma, there are some reports recommending prophylactic cranial irradiation; however, in our series, there was no patient who received prophylactic cranial irradiation. In addition, since there are many treatment options, it is difficult to recommend or not to recommend prophylactic cranial irradiation.

The major limitation of our study is that we did not perform a central pathological review. However, we only included patients from government-certified cancer care hospitals, and we believe that all hospitals included in this study have the required level of diagnosing and treating SCCC. Another limitation is that this is a retrospective study, and thus there may be some inherent biases. However, because SCCC is a rare cancer, performing a prospective study in one institution may be difficult. Our results suggest that application of a small cell carcinoma regimen as first-line chemotherapy for SCCC patients is very important; however, in non-stage IV patients, their upfront treatment is usually surgery or CCRT with non-small cell carcinoma regimen followed by EP or IP. Therefore, we hope our results will trigger nationwide prospective clinical studies.

5. Conclusion

The role of chemotherapy for stage I SCCC is unclear, however, if chemotherapy is applicable, SCCC patients should be treated with the chemotherapy regimen used for localized small cell carcinoma.

6. Abbreviations

SCCC
Small cell carcinoma of the cervix
OS
Overall survival
UICC
Union for International Cancer Control
EP
Etoposide/cisplatin
FIGO
Federation of Gynecology and Obstetrics
CDDP
Cisplatin
IP
Irinotecan/cisplatin
5-FU
Fluorouracil
NAC

Neoadjuvant chemotherapy or chemoradiotherapy
CCRT
Concurrent chemoradiotherapy
HR
Hazard ratio

7. Declarations

Ethics approval and consent: This study was approved by the ethics committee of Nagoya University (2017-0010). The need for informed consent was waived due to the retrospective design.

Availability of data and materials: The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials. Also, all data that support the findings of this study are available from the corresponding author, MK, upon reasonable request.

COI and Funding: None

Authors' contributions: MK is the first and corresponding author of the paper, participated in study design, data analysis and drafted the manuscript. YI participated in study design and coordination. YK, TM, SI, YT, TM, DO, TY, and KU participated in collecting data. YI, TK, YS, FK, and SN conceived the study and helped to draft the manuscript. All authors read and approved the final manuscript.

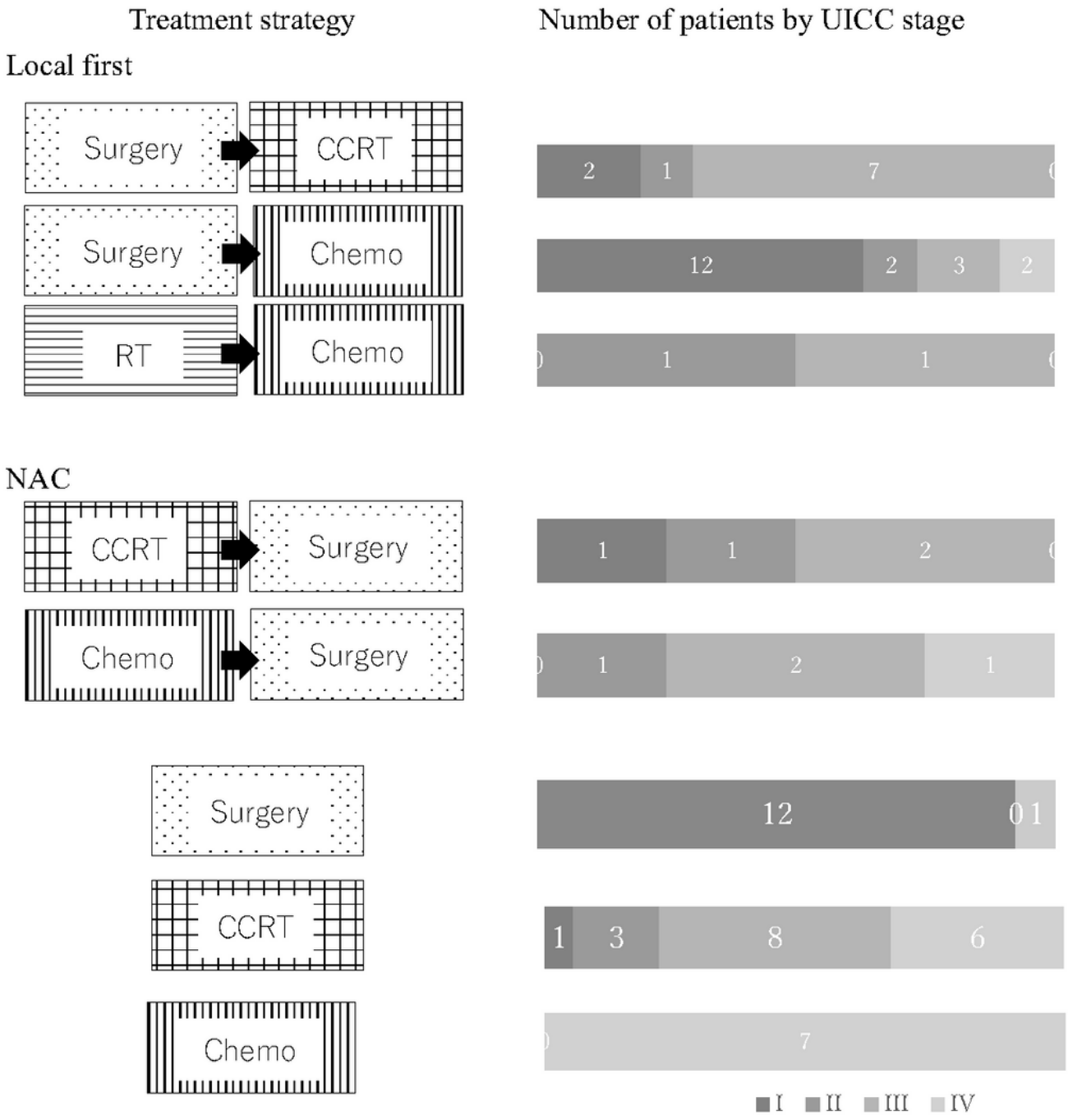
Acknowledgements: None

References

1. McCusker ME, Cote TR, Clegg LMX, et al. Endocrine tumors of the uterine cervix: incidence, demographics, and survival with comparison to squamous cell carcinoma. Gynecol Oncol. 2003;88:333–9.
2. Alfsen GC, Thoresen SO, Kristensen GB, et al. Histopathologic subtyping of cervical adenocarcinoma reveals increasing incidence rates of endometrioid tumors in all age groups - A population based study with review of all nonsquamous cervical carcinomas in Norway from 1966 to 1970, 1976 to 1980, and 1986 to 1990. Cancer. 2000;89:1291–9.
3. Gardner GJ, Reidy-Lagunes D, Gehrig PA. Neuroendocrine tumors of the gynecologic tract: A Society of Gynecologic Oncology (SGO) clinical document. Gynecol Oncol. 2011;122:190–8.
4. Noda K, Saijo N, Kawahara M, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med. 2002;346:85–91.
5. Egawa-Takata T, Yoshino K, Hiramatsu K, et al. Small Cell Carcinomas of the Uterine Cervix and Lung: Proteomics Reveals Similar Protein Expression Profiles. Int J Gynecol Cancer. 2018;28(9):1751–7.

6. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int Gynaecol Obstet. 2009;105(2):103–4.
7. Wang KL, Chang TC, Jung SM, et al. Primary treatment and prognostic factors of small cell neuroendocrine carcinoma of the uterine cervix: A Taiwanese Gynecologic Oncology Group study. Eur J Cancer. 2012;48:1484–94.
8. Lee JM, Lee KB, Nam JH, et al. Prognostic factors in FIGO stage IB-IIA small cell neuroendocrine carcinoma of the uterine cervix treated surgically: results of a multi-center retrospective Korean study. Ann Oncol. 2008;19:321–6.
9. Viswanathan AN, Deavers MT, Jhingran A, et al. Small cell neuroendocrine carcinoma of the cervix: outcome and patterns of recurrence. Gynecol Oncol. 2004;93:27–33.
10. Cohen JG, Kapp DS, Shin JY, et al. Small cell carcinoma of the cervix: treatment and survival outcomes of 188 patients. American Journal of Obstetrics and Gynecology. 2010;203.
11. Chan JK, Loizzi V, Burger RA, et al. Prognostic factors in neuroendocrine small cell cervical carcinoma - A multivariate analysis. Cancer. 2003;97:568–74.
12. Ishikawa M, Kasamatsu T, Tsuda H, et al. Prognostic factors and optimal therapy for stages I-II neuroendocrine carcinomas of the uterine cervix: A multi-center retrospective study. Gynecol Oncol. 2018;148:139–46.
13. Hoskins PJ, Swenerton KD, Pike JA, et al. Small-cell carcinoma of the cervix: Fourteen years of experience at a single institution using a combined-modality regimen of involved-field irradiation and platinum-based combination chemotherapy. J Clin Oncol. 2003;21:3495–501.

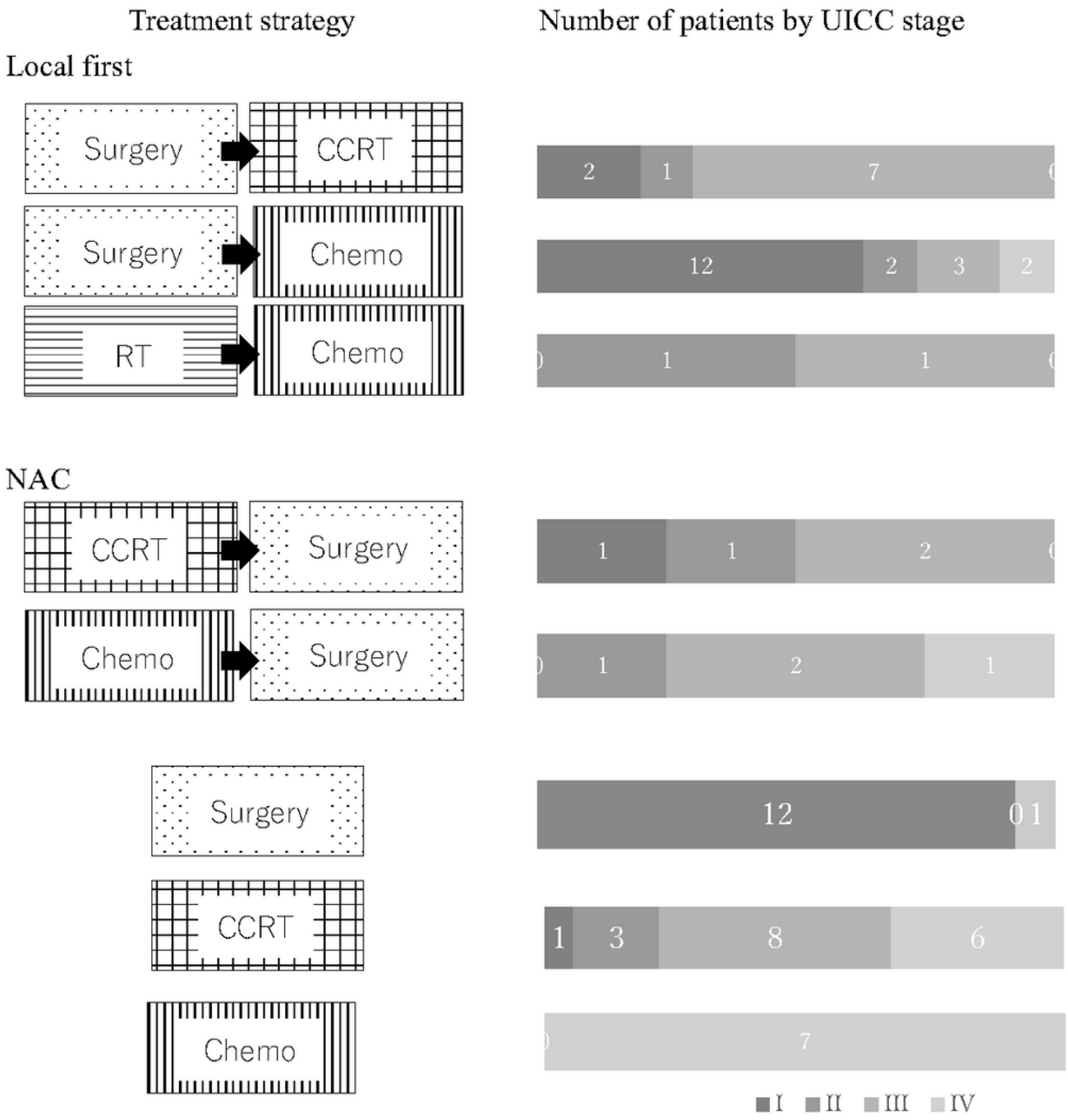
Figures



CCRT: concurrent chemo-radiotherapy, RT: radiotherapy

Figure 1

Treatment strategies for all patients as classified by UICC staging. Local first patients and surgery alone patients tended to have earlier UICC stages.

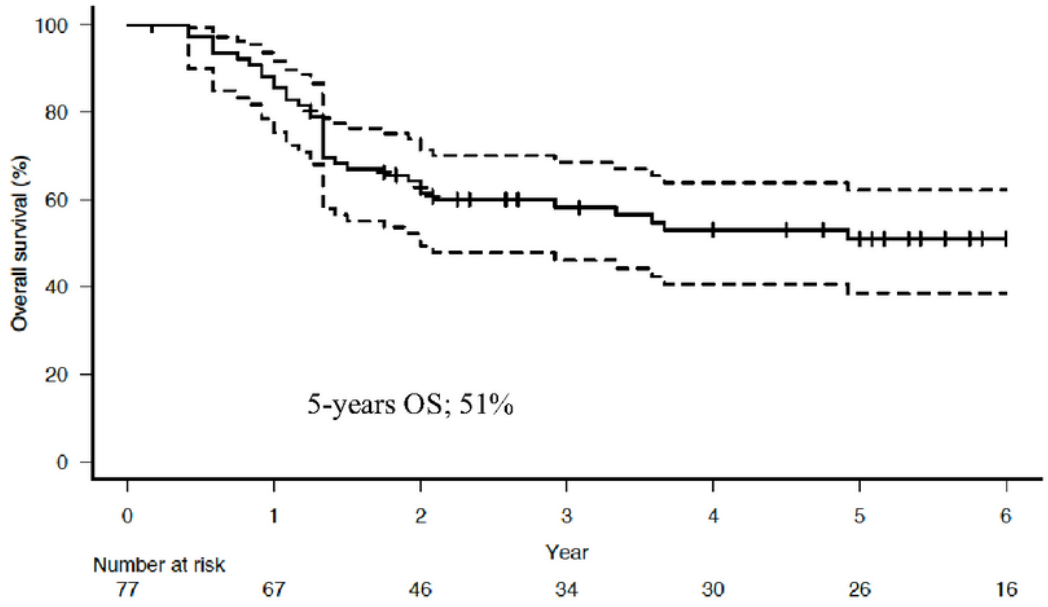


CCRT: concurrent chemo-radiotherapy, RT: radiotherapy

Figure 1

Treatment strategies for all patients as classified by UICC staging. Local first patients and surgery alone patients tended to have earlier UICC stages.

a



b

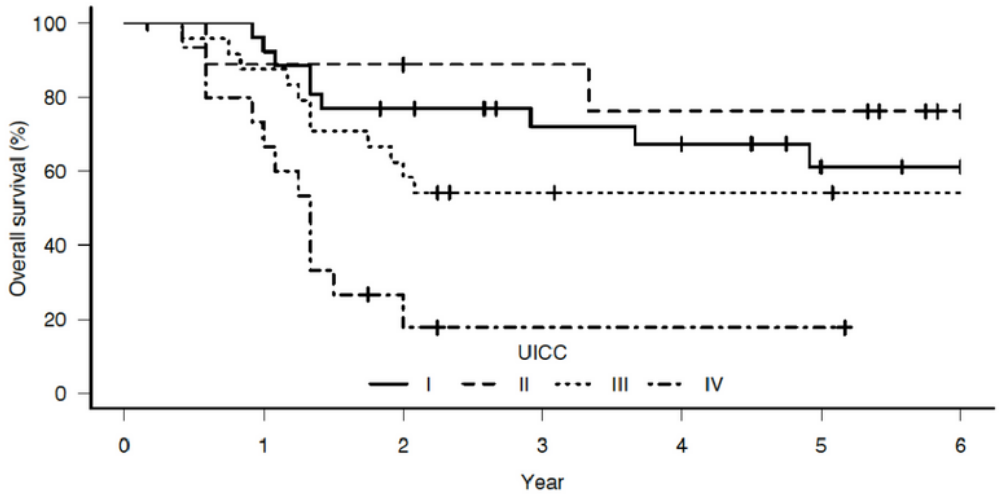
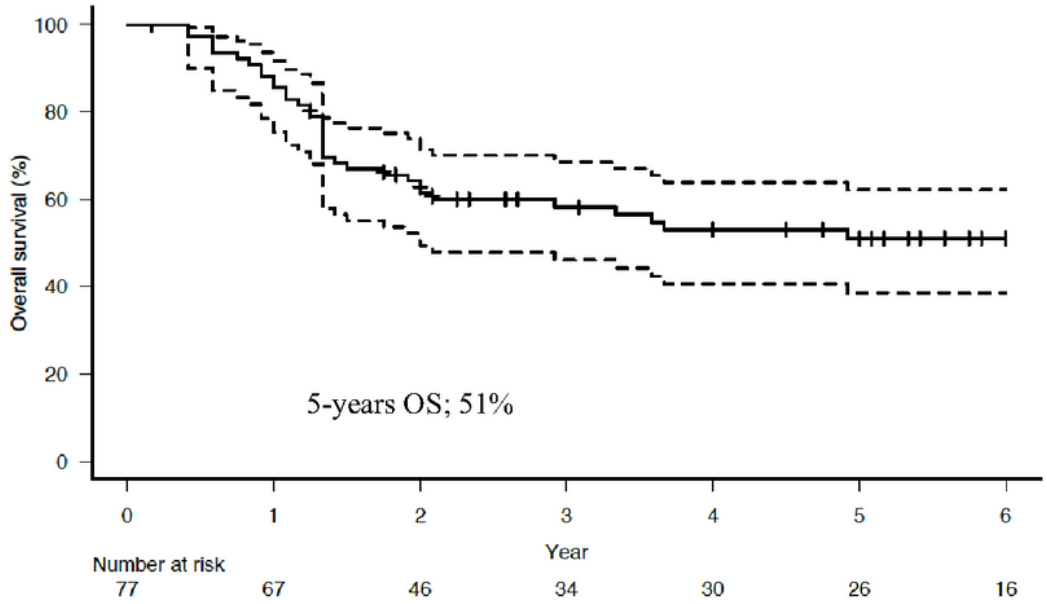


Figure 2

a. Overall survival of all patients with 95% CI. The patients deceased from this disease tended to die within 2 years from diagnosis. b. Overall survival of patients as classified by UICC staging. Stage IV patients had the worst survival.

a



b

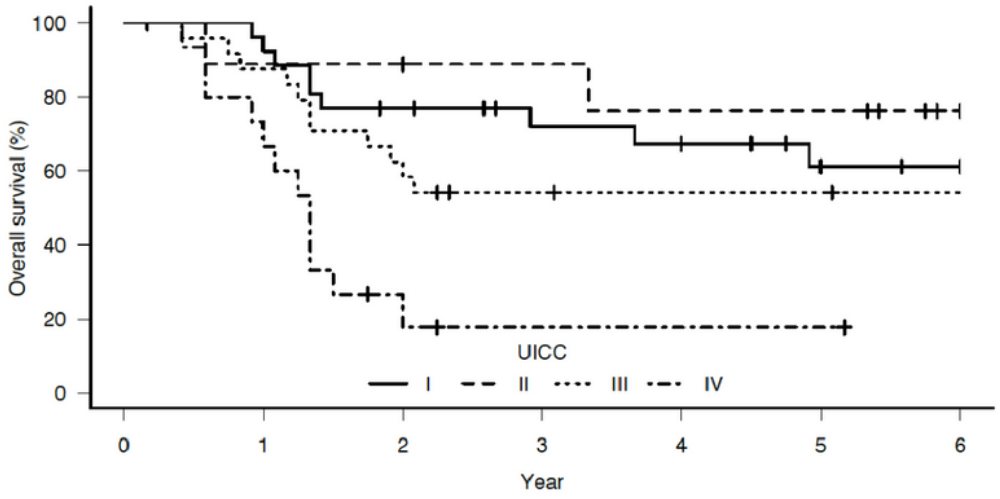


Figure 2

a. Overall survival of all patients with 95% CI. The patients deceased from this disease tended to die within 2 years from diagnosis. b. Overall survival of patients as classified by UICC staging. Stage IV patients had the worst survival.

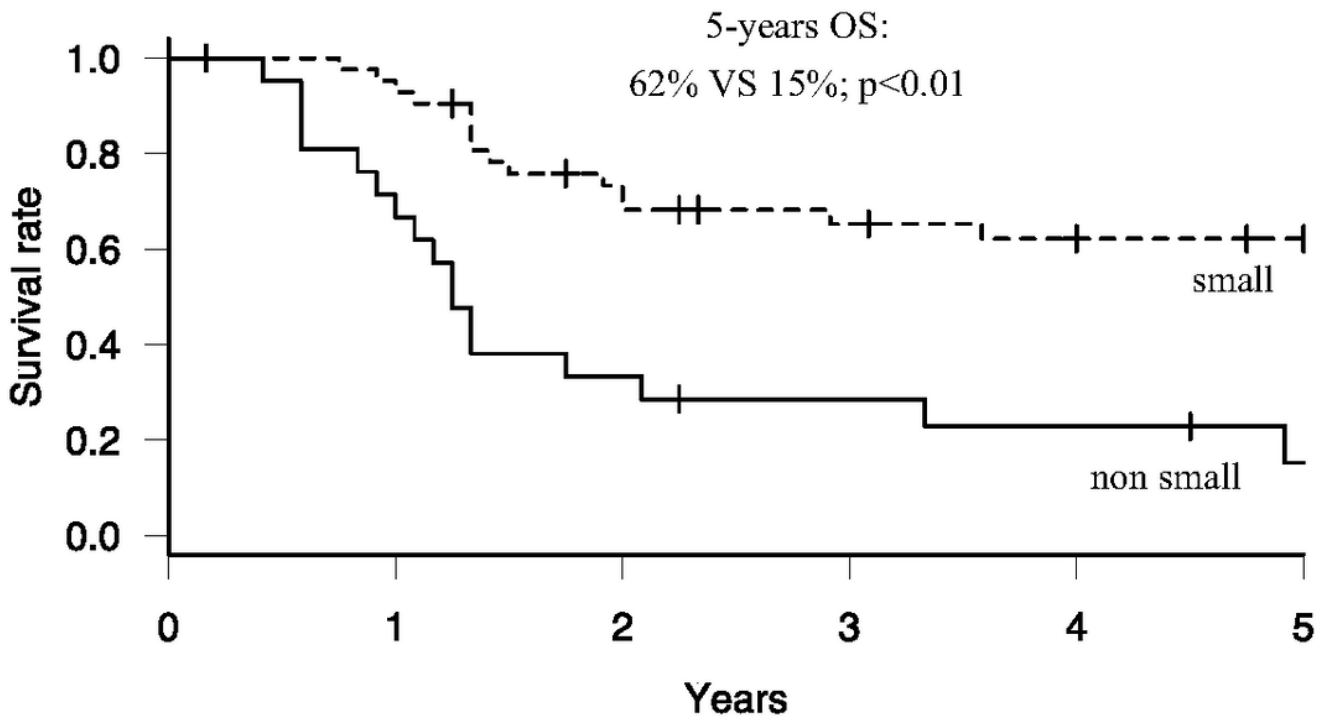


Figure 3

Survival difference depending on chemotherapy regimen. Patients treated with the non-small chemotherapy regimen tended to have worse survival than those treated with the small cell carcinoma regimen.

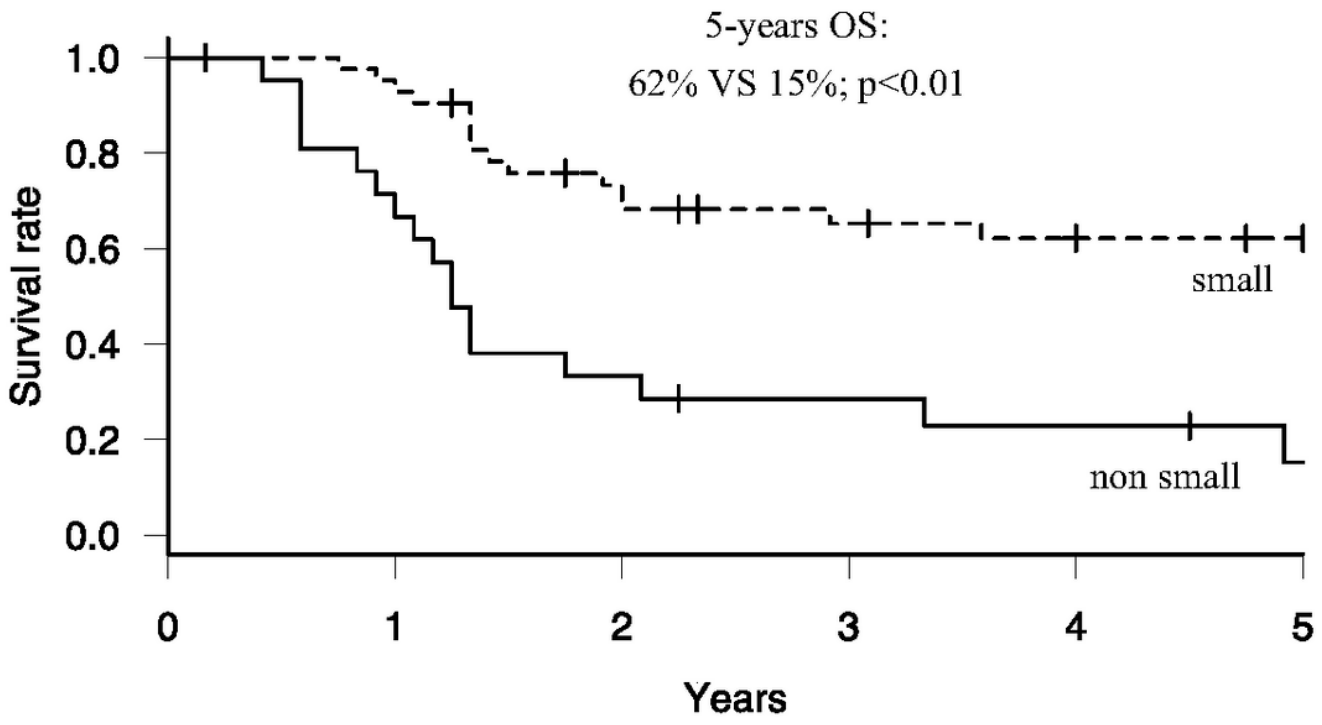


Figure 3

Survival difference depending on chemotherapy regimen. Patients treated with the non-small chemotherapy regimen tended to have worse survival than those treated with the small cell carcinoma regimen.

Supplementary Files

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

- supplement.pdf
- supplement.pdf