FIGO IVB cervical cancer patients benefit from locoregional surgery: a retrospective study from the SEER database

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Research article

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Abstract

Background: We aimed to analyze the clinical value of primary site surgery in improving survival of initial metastatic cervical cancer. Methods: A population-based retrospective study which analyzed clinical data extracted from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database was conducted. Stratified analysis was employed to evaluate the effect of cervical surgery on cervical cancer specific survival (CCSS) and overall survival (OS). Then COX regression models were performed to adjust potential confounders, and assess the survival benefit of cervical surgery for patients with primary metastatic cervical cancer. Results: The median CCSS and OS in the surgery group were more than twice of that in the group without surgery. Primary site surgery conferred prognosis superiority for patients with metastases merely to lung, and other site or distant LN, but not multiple metastasis and bone, liver. Pelvic lymph node dissection conducted in combination with cervical surgery provided a survival advantage over hysterectomy. Moreover, an aggressive treatment that integrated locoregional surgery with radiotherapy or chemotherapy showed the better survival when compared to surgery alone. The survival advantage provided by primary site surgery was not influenced by the histological type, lymph node status. Finally, after adjusting confounders using COX regression, local cervical surgery reduced the cancer related and overall mortality rate by about 30%. Conclusions: Surgical procedures could promote the survival of patients with primary metastatic cervical cancer, and should be considered as a therapeutic option for carefully chosen patients.

Background

Cervical cancer remains to be one of the most common tumors affecting women worldwide, ranking third for cancer incidence and fourth for mortality(1). Among patients with newly diagnosed cervical cancer, roughly 10% have distant metastasis at their initial diagnosis (2), and have a dismal prognosis, with poor median survival time usually less than 1 to 2 years (3, 4).

For International Federation of Gynecology and Obstetrics (FIGO) stage IVB cervical cancer, platinum-based chemotherapy, angiogenesis inhibitor bevacizumab and immunotherapy are the choice of treatment, and continuous to be considered palliative. Moreover, the studies of locoregional radiation therapy combined with system therapy for primary metastatic cervical cancer are emerging, and showed that locoregional radiotherapy would confer a substantial longer survival than system therapy alone(5-10). Nevertheless, the role of local surgery for these cervical cancer patients is still not established. In tradition, since FIGO IVB cervical cancer is considered incurable, surgical treatment is only recommend as a palliative treatment to relieve symptom such as pain, bleeding, and obstruction. Additionally, it has been reported that primary tumor mass inhibit remote metastasis by a circulating angiongenesis inhibitor, and once tumor removal, metastasis neovascularize and grow (11), but this viewpoint has not supported by clinical evidence. Growing studies have demonstrated prolonged survival of metastatic diseases when aggressive local surgeries were carried out (12-16). Sriram Venigalla and his colleagues proved that cervical cancer patients with disseminated disease would benefit from locally definitive treatment (concurrent chemotherapy or definitive surgery), and median OS time elevated 9.1 months. However, only

14% patients of definitive treatment group undergo definitive surgery, and the relative role of surgery on survival was not investigated (7).

To further examine the benefits of primary tumor resection for cervical cancer patients, we analyzed a large data from the National Cancer Institute's Surveillance, Epidemiology, and End Result (SEER) program database to conduct this population-based epidemiologic study. Sites of metastasis, histological type, surgical pattern, chemotherapy, radiotherapy, T stage and lymph node status were stratified in the analysis of OS and cervical cancer specific survival (CCSS). We hypothesized that FIGO IVB cervical cancer patients would benefit from locoregional surgery.

Methods

Data Acquisition and Processing

We identified cervical cancer cases from the SEER database using the official software SEERStat 8.3.6 on September 20, 2019. The demographic, clinicopathological and follow-up data of 23873 women with cervical cancer diagnosed from 2010 to 2016 was obtained. After screening the data based on the 7th AJCC staging system, 1483 IVB patients with at least one distant metastasis and definite information on surgery of primary site were included in this study.

Patients were classified based on whether they underwent locoregional surgery to remove the primary cervical tumor after the initial diagnosis. Age at diagnosis was categorized into three groups, younger than 40, 41 to 60, 61 to 80, 81 and older. Based on race, patients were categorized as White, Black, and others. Histological type included squamous cell carcinoma (SCC), adenocarcinoma (ADC), and others. Based on 7th AJCC staging system, patients with N0 were allocated as lymph node negative, N1 were positive. According to surgery pattern, patients were assigned into the "Hysterectomy" and "Radical Hysterectomy" groups. Data on chemotherapy, radiation, distant surgery were extracted, but the exact regimens, cycles, dose, and site were not in the SEER database.

Statistical analysis

Chi-square tests or Wilcoxon signed-ranks test were used to compare the distribution difference of locoregional surgery and demographic characteristics. For CCSS, only death due to cervical cancer was considered as an event occurrence, while for OS, it was death due to any cause. Survival time was calculated using Kaplan-Meier methods, and compared by log-rank test. Univariate and multivariate Cox proportional hazards model was performed to evaluate the effects of demographic factors on CCSS and OS using the hazard ratio (HR) and 95% confidence intervals (95% CI). Variables that showed statistical significance in the univariate analysis or were considered as important for survival were then enrolled in multivariate analysis using a stepwise conditional method. Data analysis was performed using the software SPSS 22.0 and a 2-sided p value of less than 0.05 was considered to be statistically significant.

Results

Demographic characteristics of the patients

Among 1483 patients with FIGO IVB cervical cancer diagnosed between 2010 and 2016, 336 (22.6%) of them underwent surgery, while 1147 (77.3%) did not. The clinicopathological characteristics of patients with metastatic cervical cancer are summarized in Table1. The median age for the non-surgery group was 56 years, while it was 52 years for surgery group, indicating that older patients were more prone to choose conservative treatment. Race did not appear to affect the decision to excision the primary site tumor. The tumors resected from patients who had cervix surgery were less likely to be squamous cell carcinoma, and more likely to be T1 and T2 (both $p<0.0001$). Compared to non-surgery group, the surgery group had more patients with negative lymph node (27.4% vs. 36.6%, $p=0.001$). Less patients with multiple metastatic sites would opt for surgery, and more patients in the surgery group had other site or distant LN affected. There were more patients in surgery group deciding to remove distant metastases and received systemic chemotherapy. More patients received radiotherapy if they did not undergo cervix surgery.

Analysis of CCSS and OS

To analyze the effects of local surgery on CCSS and OS in patients with metastatic cervical cancer, log-rank test were performed between surgery and non-surgery groups. As illustrated in Fig. 1, locoregional surgical treatment conferred a prominent survival advantage. The median CCSS and OS were 37 and 28 months for the surgery group, 13 and 11 months for the non-surgery group (Fig. 1A and Additional file 1).

In order to eliminate the bias of site-specific metastasis on survival analysis, data were stratified based on the distant organs involved (multiple site, bone, liver, brain and lung, other site or distant LN), and CCSS was evaluated based on whether or not surgery of the primary tumor was performed in mentioned-above patient groups. Owing to the limited number of patients with isolated brain metastasis, they were excluded from this evaluation. Patients with isolated lung and other site or distant LN involved benefitted from primary site surgery ($p = 0.03$ for lung only; $p < 0.0001$ for other site or distant LN) (Fig. 1E, F). Nevertheless, the locoregional treatment could not prolong the survival of patients with bone, liver and multiple sites metastasis. Furthermore, the aggregate effects of surgical resection of primary and metastatic lesions on survival were also evaluated. It showed that survival was better for patients who underwent resection for distant organs, and significantly better for patients whose primary cervical tumors were resected (Fig. 2A).

Local surgeries were categorized into the “Hysterectomy” group (without regional lymph node dissection) and “Radical hysterectomy” group (with regional lymph node dissection). In all cases, pelvic lymph node dissection provided additional survival advantage to the cervical cancer patients (Fig. 2B).

The effects of chemotherapy and/or radiotherapy together with local surgery on survival in patients with metastatic cervical cancer were next analyzed (Fig. 2C-F). Prognosis was better for patients who underwent locoregional resection combined with chemotherapy or radiation compared with those received surgery/chemotherapy/radiation alone. Chemotherapy conferred similar OS and CSSS to locoregional surgery, while radiation provided worse survival compared to surgical treatment.

Data stratified on the basis of histology, and lymph node status showed that they did not affect the survival advantage provided by locoregional surgery. More advanced AJCC T stage, less advantage gained from primary site surgery. Eventually, survival benefit disappeared for T4 tumor.

Univariate and multivariate analysis

Univariate and multivariate analysis were then performed to evaluate the effects of the clinicopathological factors on CSSS and OS (Table 2). As illustrated in Table 2, patients with age between 41 and 80 were at a lower risk of cancer-related death compared to those younger than 40. Compared to white race, black women were at a higher risk of mortality. Tumors with higher AJCC T stage had a poor prognosis. When the lymph node was affected, CCSS was worse than in cases with negative nodes. For treatment, regional LN surgery, chemotherapy and radiation prolonged cancer-related and overall survival for cervical cancer with primary metastasis, while surgery of distant metastasis did not show any significance in CSSS and OS. Except for only brain metastasis, women with isolated organ metastases had better OS and CSSS compared to those with multiple distant organ involved.

Local cervix surgery reduced the cancer-associated and overall mortality rate by about 33% and 31%, which demonstrated that regional resection of primary tumor is an independent prognosis factor and is of vital significance in prolonging the survival of cervical cancer patients with primary metastasis.

Discussion

Usually, the treatment for FIGO IVB cervical cancer has been and continues to be considered palliative. And systemic therapies including platinum-based chemotherapy, target therapy and immunotherapy have been mainstay of care for patients with metastatic cervical cancer (3). In recent years, the efficacy of locoregional management on improving survival in M1 cervical cancer has been highlighted in multiple retrospective studies. A retrospective study by Tomoyuki *et al*. indicates that treatment with definitive radiotherapy was associated with improved survival compared with chemotherapy or palliative care alone (2). Another study by Sriram *et al.,* with a large sample size of 2838 indentified from National Cancer Database, revealed that patients who underwent definitive local therapy (either concurrent chemoradiation or surgery) had a 43% reduced mortality risk compared to those who received conservative therapy (systemic therapy with or without palliative radiation)(7). Similar conclusion was drawn by a Chinese study, which illustrated that chemotherapy combined with definitive pelvic radiotherapy would significantly prolong the OS by 7.3 months when compared to chemotherapy alone or with palliative pelvic radiotherapy(5). Another two studies which enrolled patients from SEER or National

Cancer Database, also demonstrated that radiotherapy would decrease 28-31% mortality risk for primary metastatic cervical cancer (6, 8).

However, in the literature, the resection of primary tumor for patients with FIGO IVB cervical cancer is poorly documented. In this study, based on SEER database, we found that excision of the primary cervical tumor, in general, could bring a survival benefit for metastatic cervical cancer, reducing the risk of mortality by about 30%. Several plausible reasons might help to explain why pelvic surgery would contribute to improving the prognosis in patients with metastatic breast cancer. Firstly, local surgery could mitigate symptoms such as pain, bleeding and infection, which poses a risk of morbidity and mortality that is independent of distant disease(17). However, systemic therapy alone is often insufficient to address such consequences of local progression. Secondly, control of the primary site may reduce the risk of further seeding of malignant cells and thereby reduce the risk of development new distant dissemination (7). Thirdly, surgical removal of the primary tumor decreases the production of immunosuppressive cytokines thereby, reversing tumor-induced immunosuppression and allow the host immune system to regain immunologic control of systemic disease burden(18). Fourthly, surgery removes the necrotic centric areas that are hypoxic and resistant to chemotherapy and radiotherapy, therefore, increasing the efficacy of adjuvant treatment and improving prognosis (19-21).

Although local surgery poses a benefit of survival, it is worth underlining that such therapy is likely not suitable for all patients with metastatic disease. The stratified analysis in this study demonstrated that hysterectomy resulted in survival improvement in cervical cancer patients with metastasis to lung alone and other site or distant LN alone. In line with previous studies, patients with metastasis to pulmonary or distant lymph node alone has remarkably good prognosis and gains survival benefit from aggressive therapy (22, 23). Hence, local surgery may be an appropriate treatment option for a carefully selected group of patients with good performance status, symptomatic primary disease and a low metastatic disease burden. Multiple studies have emphasized the risk of a positive surgical margin on prognosis (24, 25). Unfortunately, we could not obtain data on surgical margin status from the SEER database. We found that the advantage of surgery did not showed in patients with T4 stage (invasion into neighboring structures such as bladder and rectum), and there were prominent survival differences between women who had hysterectomy and those had a radical hysterectomy. It’s well known that a clear surgical margin is difficult to achieve in patients with tumors progression to neighboring organs. Pelvic lymph node dissection would also contribute to lower the tumor burden, and stop cancer cell spreading to distant organs through lymphatic pathway. Consequently, we preferentially hold the opinion that definitive surgery to remove primary tumor clearly vitally improves the therapeutic efficacy by lowering the tumor burden.

As for treatment, radiotherapy and chemotherapy were also independent prognostic factors for FIGO IVB cervical cancer. Moreover, an aggressive treatment approach that combines chemotherapy or radiation with surgical management of primary tumors may lead to improved survival compared with abovementioned treatments alone, and the survival advantage of combined treatment over palliative treatment is even greater than that of single treatment add together. Therefore, local surgical combined

with systemic therapy is recommended for primary metastatic cervical cancer with good performance. Regrettably, SEER database does not include information on chemotherapy regimen and cycles or radiation field size and dose, which would have allowed us to analyze survival based on chemotherapy modalities as well as the extent of radiotherapy administered.

There were several inevitable limitations in the present study. First, there is an inherent patient selection bias as it is a population-based retrospective study. Second, details of the systemic therapy, radiotherapy, performance status, and surgical margin were lacking, which could also affect prognosis. Third, the detail on how metastasis diagnosed was unavailable, which may affect the result to some extent. Consequently, these results should be prudently interpreted with these limitations in mind.

Conclusions

Surgical procedures in combination with lymph node resection, chemotherapy and radiotherapy have some positive effects on patients with metastasis to lung alone and other site or distant LN alone, a small primary tumor except for T4. Further well-designed studies should be initialed to indentify advantage of surgery over palliative therapy; also the surgical margin, systemic treatment strategy, and diagnosis method of metastasis deserve more attention.

Abbreviations

AJCC: American Joint Committee on Cancer

ADC: adenocarcinoma

CCSS: Cervical cancer specific survival

FIGO: International Federation of Gynecology and Obstetrics

LN: Lymph Node

OS: Overall Survival

SCC: squamous cell carcinoma

SEER: Surveillance, Epidemiology, and End Results

Declarations

Ethics approval and consent to participate

The SEER database was publicly available and all the research data were de-indentified. So no ethic approval and informed consents were needed in this study.

Consent for publication

Not applicable.

Availability of data and materials

The data were retrieved from publicly accessible database “Surveillance, Epidemiology, and End Results” (SEER), the website is “https://seer.cancer.gov/”. The definite data used in this study is available from the corresponding author on reasonable request.

Competing interests

All authors declare that they have no conflict of interest.

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Authors’ contributions

CQR and CXP participated in the design of the study. WYH and CQR collected the data from SEER database. SJJ and CQR did the literature search. OYY and BZG play a chief role in statistical part. WYH and OYY drafted the main manuscript. All authors have read and approved the final manuscript.

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Tables

Table 1. Clinicopathological characteristics of women diagnosed with primary metastatic cervical cancer included in SEER database.

	No surgery	Surgery	p
Age	56(47-65)	52(43-62)	0.000
Race			0.169
White	849(74.0)	256(76.2)	
Black	192(16.7)	43(12.8)	
Others	106(9.2)	37(11.0)	
Grade			0.598
I	49(4.3)	17(5.1)	
II	371(32.3)	117(34.8)	
III	661(57.6)	180(53.6)	
IV	66(5.8)	22(6.5)	
Histological type			0.000
SCC	792(69.0)	161(47.9)	
ADC	234(20.4)	116(34.5)	
Others	121(10.5)	59(17.6)	
T stage			0.000
T1	172(15.0)	108(32.1)	
T2	260(22.7)	106(31.5)	
T3	525(45.8)	87(25.9)	
T4	190(16.6)	35(10.4	
Lymph node status			0.001
Negative	314(27.4)	123(36.6)	
Positive	833(72.6)	213(63.4)	
Distant metastasis			0.000
Mutiple site	174(15.2)	19(5.7)	
Bone only	98(8.5)	9(2.7)	
Brain only	10(0.9)	0(0)	
Liver only	56(4.9)	11(3.3)	
Lung only	239(20.8)	35(10.4)	
Other site or distant LN only	570(49.7)	262(78.0)	
Distant surgery			0.000
No	1070(93.3)	247(73.5)	
Yes	77(6.7)	89(26.5)	
Chemotherapy			0.003
No/unknown	314(27.4)	65(19.3)	
Yes	833(72.6)	271(80.7)	
Radiation			0.001
No	332(28.9)	129(38.4)	
Yes	815(71.1)	207(61.6)	
Survival months	10(4-20)	22(11-36)	0.000
Vital status			0.000
Alive	243(21.2)	155(46.1)	
Dead for this cancer	782(68.2)	151(44.9)	
Dead for other cause	109(9.5)	25(7.4)	

Dead(missing/Unknwon)	13(1.1)	5(1.5)

ıivariate and multivariate analysis between clinicopathological characteristic and CCSS and OS of cervical cancer patients

	CCSS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR(95%CI)	P	HR(95%CI)	P	HR(95%CI)	P	HR(95%CI)	P
0	Reference		Reference		Reference		-	-
50	1.01(0.84-1.22)	0.905	0.81(0.67-0.98)	0.029	1.10(0.92-1.31)	0.315	-	-
30	1.14(0.93-1.39)	0.213	0.79(0.65-0.97)	0.027	1.31(1.09-1.59)	0.005	-	-
1	2.07(1.48-2.90)	0.000	1.05(0.74-1.48)	0.802	2.59(1.91-3.50)	0.000	-	-
te	Reference		Reference		Reference		Reference	
ck	1.37(1.15-1.62)	0.000	1.34(1.12-1.59)	0.001	1.36(1.17-1.60)	0.000	1.31(1.12-1.53)	0.001
ers	0.94(0.91-1.40)	0.286	1.07(0.86-1.34)	0.554	1.10(0.89-1.35)	0.387	1.02(0.83-1.25)	0.879
type								
C	Reference		-	-	Reference		-	-
C	0.87(0.75-1.02)	0.088	-	-	0.90(0.78-1.04)	0.143	-	-
ers	1.08(0.89-1.32)	0.444	-	-	1.08(0.90-1.30)	0.426	-	-
	Reference		-	-	Reference		-	-
	1.20(0.85-1.70)	0.296	-	-	1.18(0.86-1.62)	0.302	-	-
	1.55(1.10-2.16)	0.012	-	-	1.48(1.09-2.02)	0.012	-	-
	1.64(1.08-2.49)	0.020	-	-	1.71(1.17-2.50)	0.005	-	-
	Reference		Reference		Reference		Reference	
2	1.45(1.17-1.80)	0.001	1.34(1.08-1.68)	0.009	1.39(1.14-1.69)	0.001	1.33(1.09-1.62)	0.006
3	2.11(1.73-2.56)	0.000	1.92(1.57-2.35)	0.000	1.94(1.63-2.33)	0.000	1.78(1.48-2.14)	0.000
4	2.15(1.70-2.72)	0.000	1.64(1.29-2.08)	0.000	2.06(1.67-2.55)	0.000	1.54(1.24-1.492)	0.000
status	1.14(0.99-1.31)	0.077	1.20(1.04-1.39)	0.015	1.07(0.94-1.22)	0.308	-	-
surgery	0.43(0.36-0.51)	0.000	0.67(0.53-0.84)	0.001	0.44(0.38-0.52)	0.000	0.69(0.56-0.85)	0.000
l surgery	0.41(0.34-0.50)	0.000	0.68(0.53-0.84)	0.002	0.40(0.33-0.48)	0.000	0.63(0.50-0.79)	0.000
ery	0.60(0.48-0.75)	0.000	-	-	0.62(0.51-0.76)	0.000	-	-
ıpy	0.37(0.32-0.43)	0.000	0.37(0.32-0.43)	0.000	0.36(0.31-0.41)	0.000	0.36(0.32-0.42)	0.000
	0.66(0.57-0.75)	0.000	0.71(0.61-0.81)	0.000	0.62(0.54-0.70)	0.000	0.66(0.58-0.76)	0.000
astasis								
e sites	Reference		Reference		Reference		Reference	

only	0.54(0.41-0.71)	0.000	0.55(0.42-0.73)	0.000	0.59(0.46-0.76)	0.000	0.60(0.47-0.78)	0.000
only	0.77(0.38-1.56)	0.462	0.66(0.32-1.36)	0.259	0.87(0.46-1.65)	0.668	0.65(0.35-1.24)	0.194
only	0.62(0.45-0.86)	0.003	0.65(0.47-0.90)	0.008	0.61(0.45-0.83)	0.001	0.59(0.44-0.80)	0.001
ɔnLy	0.56(0.45-0.69)	0.000	0.51(0.41-0.63)	0.000	0.60(0.49-0.73)	0.000	0.52(0.43-0.64)	0.000
ɔr distant nly	0.30(0.25-0.36)	0.000	0.34(0.29-0.42)	0.000	0.31(0.26-0.37)	0.000	0.37(0.31-0.44)	0.000

Figures

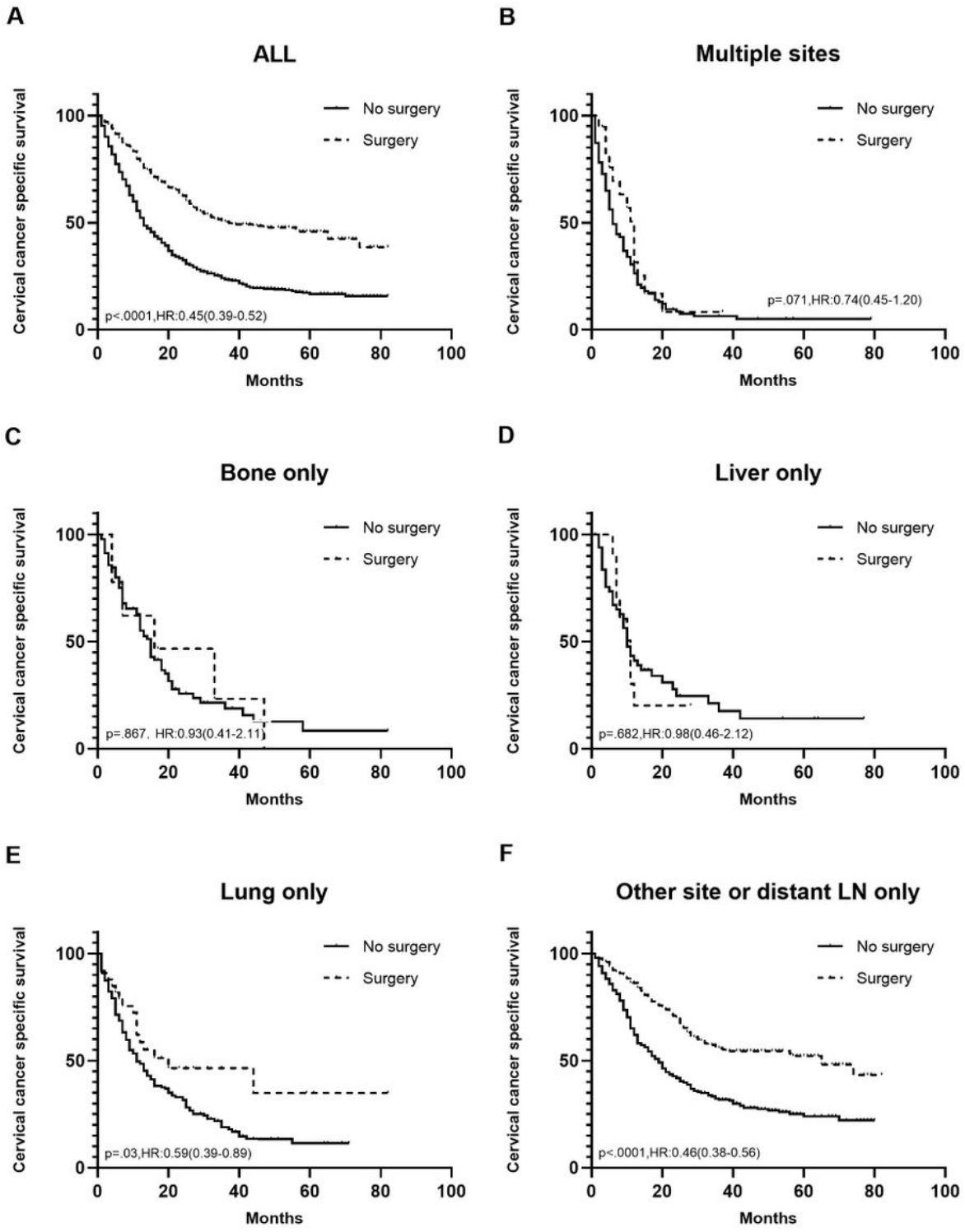

Figure 1

Cancer specific survival of FIGO IVB cervical cancer patients. Survival curve showing CCSS (A) in the surgery and no-surgery groups. B-F, CCSS curves classified by distant involved organs.

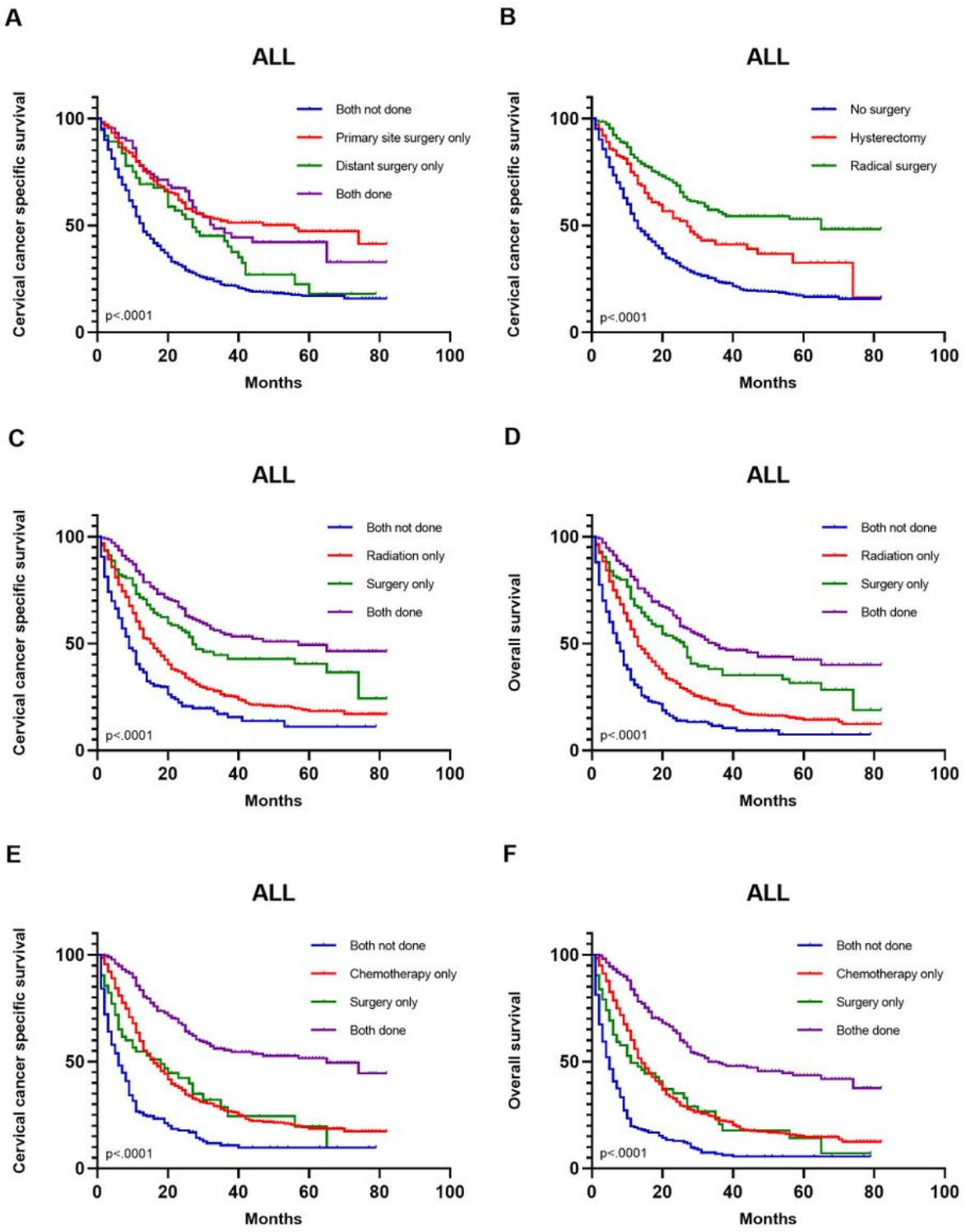

Figure 2

Survival of different treatment procedures. A, CCSS of FIGO IVB cervical cancer patients combined with primary site surgery and removal of distant metastasis. B, CCSS of patients with no primary surgery and patients who underwent hysterectomy, or radical surgery. C-D, survival of FIGO IVB cervical cancer with surgery combined with radiation or chemotherapy.

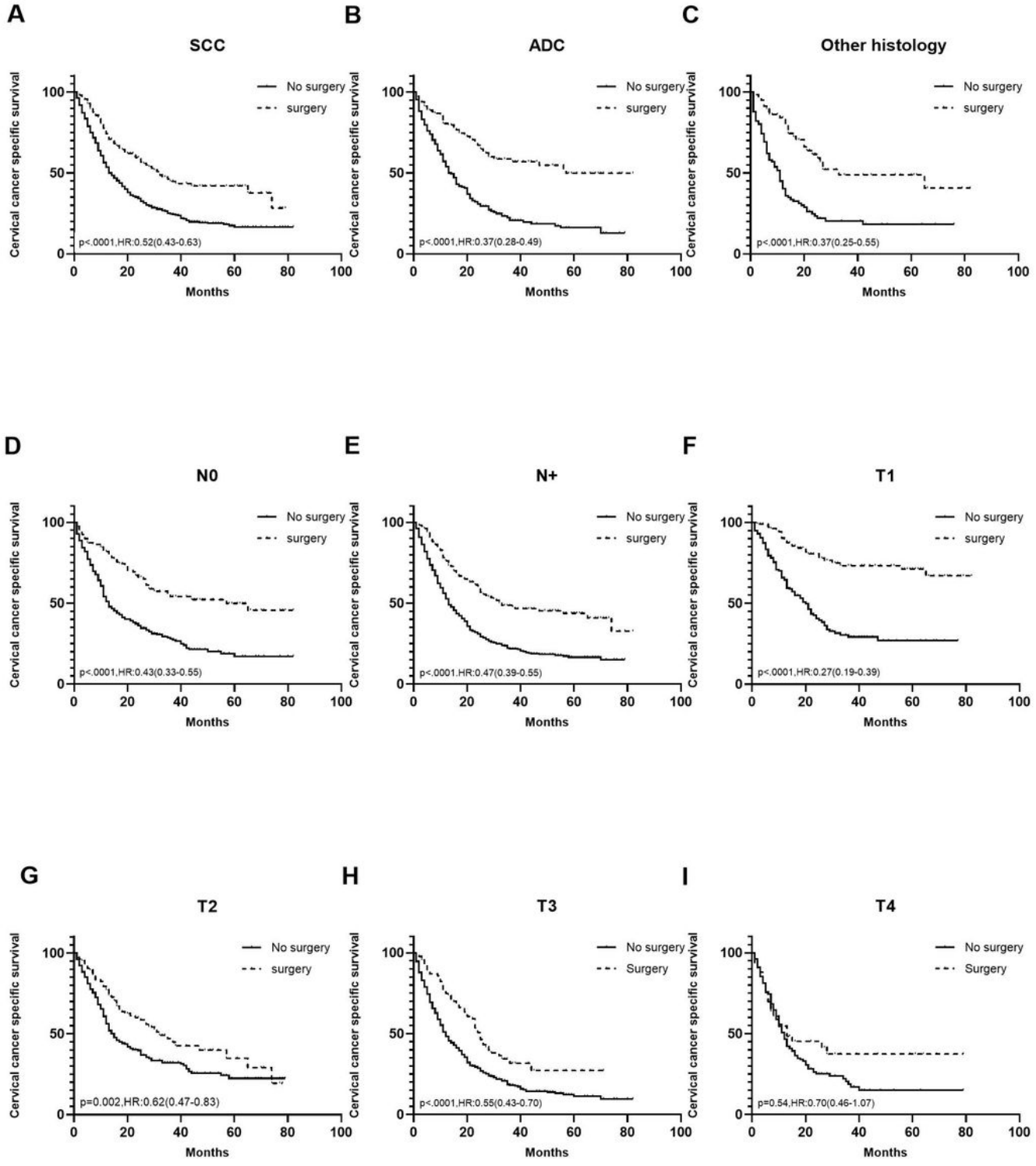

Figure 3

CCSS curves stratified by histological type, lymph node status and T stage.'

Supplementary Files

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

- Additionalfile1.tif