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Re-evaluating prognostic factors for cervical cancer with lymph node metastasis: a Japanese multicenter cohort study based on FIGO 2018

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34

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36 All authors contributed to the study conception and design. Material preparation and data collection
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41

42 **Abstract**

43 Background: In 2018, the International Federation of Gynecology and Obstetrics (FIGO) revised its
44 cervical cancer staging system to enhance clinical relevance, notably by categorizing lymph node metastases
45 (LNM) as an independent stage IIIC. This multicenter study evaluates the prognostic implications of the
46 FIGO 2018 classification within a Japanese cohort.

47 Methods: This study included 1,468 patients with cervical cancer. Initial FIGO 2009 stages were
48 restaged under FIGO 2018. Stage IIIC was further compared based on the location of LNM (pelvic or para-
49 aortic, i.e., IIIC1 and IIIC2, respectively), local tumor stage, and histology.

50 Results: A total of 345 cases (27.4%) were upstaged to stage IIIC, which exhibited a poorer
51 prognosis compared to stage II (HR, 2.12; 95% CI, 1.29–3.48; p=0.004) and better than stage IIIAB (HR,
52 0.46; 95% CI, 0.27–0.78; p=0.004). Notably, stage IIIC2 showed a significantly worse prognosis than IIIC1
53 (HR, 2.32; 95% CI, 1.37–3.93; p=0.003). Subdivisions of stage IIIC1 (T1, T2, and T3AB) displayed
54 significantly varied prognoses, with the prognosis for IIIC1-T3AB similar to that of stage IIIAB. In contrast,
55 all subdivisions of IIIC2 showed uniformly poor outcomes. Multivariate analysis of stage IIIC patients
56 revealed that para-aortic LNM, adenocarcinoma and adenosquamous carcinoma histology, and local T3AB
57 tumor remained significant.

58 Conclusions: The classification of para-aortic LNM as stage IIIC2 has proven to be of critical
59 relevance in the Japanese cohort. However, the prognostic impact of stage IIIC1 remains influenced by local
60 tumor factors and histological subtypes. (235 words)

61
62 <Key words>

63 International Federation of Gynecology and Obstetrics, FIGO, staging, cervical cancer, lymph node,
64 prognosis

65

66 **Introduction**

67 Cervical cancer is a major cause of death among women. In 2020, the global incidence of cervical
68 cancer exceeded 600,000 new cases, with approximately 340,000 deaths [1,2]. In Japan, over 10,000
69 individuals are newly diagnosed with cervical cancer each year [3], and the Gynecologic Tumor Registry of
70 the Japanese Society of Obstetrics and Gynecology (JSOG) includes 7,689 patients who newly initiated
71 treatment in 2020. [4]. The prognosis for cervical cancer is favorable in the early stages when the tumor is
72 confined to the cervix. However, the prognosis worsens when the tumor spreads to surrounding tissues or
73 metastasizes to the lymph nodes.

74 In 2018, the International Federation of Gynecology and Obstetrics (FIGO) revised the staging
75 system for cervical cancer [5], with key changes including the establishment of stage IIIC based on the
76 lymph node metastasis (LNM) status, further stratification of stage IB, and inclusion of postsurgical findings
77 as part of the staging criteria [6,7]. Specifically, incorporating the LNM status has reportedly made the FIGO
78 2018 staging system a better reflection of prognosis [8-11]. However, several reports have highlighted that
79 FIGO 2018 stage IIIC represents a heterogeneous group with varying prognoses [9-17]. Specifically,
80 multiple reports indicated a significant difference in the prognosis depending on whether LNM is confined to
81 the pelvic nodes (IIIC1) or extends to the para-aortic nodes (IIIC2) [9-11,13,16,18]. Additionally, prognosis
82 is reported to vary depending on the local tumor factors [9,10,12,15,16]. Therefore, there is debate on
83 whether all LNM should be classified as stage IIIC in a single category. However, reports from Japan are
84 limited to cases with early T-stages [18,19], and no recent reports have covered all T-stages.

85 Another important aspect of FIGO 2018 is the use of imaging findings for diagnosis. Therefore,
86 differences in medical systems may affect staging outcomes. The percentage of patients reclassified as FIGO
87 2018 stage IIIC owing to LNM varies between reports, ranging from 19% to 41% [10,20-22], which may
88 indicate the influence of different imaging techniques. Magnetic resonance imaging (MRI) is generally
89 considered superior for measuring the size of local tumors, while positron emission tomography/computed
90 tomography (PET/CT) is preferred for detecting lymph node metastasis [5,23]. In Japan, due to the
91 availability of universal health insurance, MRI and PET/CT scans are more easily accessible, and clinical
92 staging is based on these examinations in most cases. Given the possibility of accurate clinical staging in

93 Japan, it is crucial to assess the impact of this revision on the staging of patients with cervical cancer and
94 their prognosis.

95 Thus, we conducted a multicenter study to assess the validity of the new FIGO 2018 classification
96 and the prognosis of Japanese patients with stage IIIC disease. Our analysis was based on the LNM status
97 (IIIC1 or IIIC2) and local tumor factors (T1, T2, and T3AB), as well as the impact of histological type on
98 prognosis.

99

100 **Materials and methods**

101 ***Data source***

102 The JSOG created a standardized registry system for gynecological malignancies in designated
103 cancer treatment hospitals nationwide. This enables consistent data collection comprising patient
104 backgrounds, treatment courses, and prognoses. Using data collected from the JSOG registry, this study was
105 conducted by the KAMOGAWA study group, involved eight designated cancer treatment hospitals (Kyoto
106 University Hospital, Kobe City Medical Center General Hospital, Kindai University Hospital, National
107 Hospital Organization Osaka National Hospital, Kurashiki Central Hospital, National Hospital Organization
108 Kyoto Medical Center, Japanese Red Cross Wakayama Medical Center, and Kyoto Katsura Hospital). A
109 total of 1,468 patients with cervical cancer who began treatment between 2011 and 2019 were included.

110

111 ***Ethical approval***

112 This study was approved by the Ethics Committee of the Kyoto University Graduate School and
113 Faculty of Medicine (approval number: R4409). Informed consent was obtained from the websites of the
114 institutions using an opt-out option.

115

116 ***Data integration process***

117 Guidelines for cervical cancer registration were revised in Japan in 2012, 2015, 2018, and 2019. The
118 staging system was based on the FIGO 2009 staging system for all guidelines including the 2019 edition,
119 despite the release of the FIGO 2018. The TNM classification was based on Union for International Cancer
120 Control version 7 or 8. For other information, revisions to the registration form were carefully reviewed, and

121 the contents were integrated. The clinical characteristics of patients after integration are shown in Table 1.
122 Patient statuses at 3 and 5 years after the start of initial treatment were available in this registry. The
123 definitive treatment group included patients who received surgery, concurrent chemoradiotherapy (CCRT),
124 or neoadjuvant chemotherapy followed by surgery as their initial treatment.

125

126 ***FIGO 2018 restaging***

127 All patients with FIGO 2009 stage IA to IIIB disease were restaged according to the new FIGO 2018
128 staging system. The FIGO 2009 staging system determines the stage prior to treatment and does not change
129 it based on postoperative findings. In contrast, the FIGO 2018 staging system incorporates pre-treatment
130 imaging findings and postsurgical findings to determine the stage comprehensively. The JSOG registry
131 includes information on the presence of pelvic node (PeN) and para-aortic node (PAN) enlargement in
132 imaging studies (corresponding to cN and cM, respectively). For patients who underwent surgery,
133 postsurgical findings on PeN or PAN metastasis (corresponding to pN and pM, respectively) are also
134 available. For patients who underwent surgery, the stage was upstaged if pN or pM were positive (even if cN
135 or cM were positive in imaging studies, the stage was not upstaged if pN or pM were negative after surgery).
136 In cases where surgery was not performed, the stage was upstaged if cN or cM were positive in imaging
137 studies. In summary, patients who underwent surgery and were LNM positive (pN or pM positive) were
138 classified as having stage IIICp. Patients who had not undergone surgery and who were clinically LNM
139 positive (cN or cM positive) were classified as having stage IIICr. Patients who underwent surgery and had
140 both clinically and surgically confirmed LNM positive were classified as stage IIICrp. A stage-conversion
141 flowchart with respect to LNM status is shown in Figure 1. Subsequently, patients who underwent surgery
142 were restaged according to the local pathological tumor status (pT). Furthermore, based on local tumor
143 factors, stage IIIC cases were classified into substages IIIC-T1, IIIC-T2, and IIIC-T3AB.

144

145 ***Statistical analysis***

146 Statistical analyses were performed using Python version 3.10. Cumulative survival probabilities
147 were calculated using the Kaplan–Meier method. Univariate and multivariate Cox proportional hazards
148 regression analysis was used to calculate p-values, hazard ratios (HR), and 95% confidence intervals (CI).

149 The Benjamini-Hochberg method was used to adjust for multiple comparisons, controlling the false
150 discovery rate at 5% (Benjamini-Hochberg-adjusted $p < 0.05$). Multivariate analyses were performed using
151 PAN metastasis, histology, and local tumor factors as variables. Overall survival (OS) was defined as the
152 time from the initial treatment to death or last follow-up. Two-sided p values < 0.05 were considered
153 statistically significant in all analyses.

154

155 **Results**

156 ***Restaging between FIGO 2009 and 2018***

157 Of the 1,468 cases included in this study, 210 were stage IV according to FIGO 2009, and were
158 also classified as stage IV according to FIGO 2018. The remaining 1,258 patients comprised: FIGO 2009 IA;
159 $n=178$, IB1; $n=466$, IB2; $n=123$, IIA1/2; $n=75$, IIB; $n=288$, IIIA; $n=20$, IIIB; $n=104$. After the restaging
160 process, 345 cases (27.4%) were upstaged to stage IIIC in FIGO 2018, according to LNM status. One, 24,
161 and eight cases in FIGO 2009 IA, IB1, and IB2 (0.6, 5.2, and 6.5%, respectively) were upstaged to stage II in
162 FIGO 2018 according to their pT status. In FIGO 2009 IIA, 11 patients (14.7%) were downstaged to stage I,
163 and six (8.0%) were upstaged to stage IIB in FIGO 2018. In FIGO 2009 IIB, six cases (2.1%) were
164 downstaged to stage I, and one (0.3%) were downstaged to stage IIA in FIGO 2018. Details of the stage
165 changes between FIGO 2009 and FIGO 2018 staging systems are presented in Table 2. Additionally, a
166 subset focusing on squamous cell carcinoma (SCC) and adenocarcinoma or adenosquamous carcinoma
167 (Adeno/Adesq) cases is presented in Supplementary Tables S1 and S2.

168

169 ***Survival analysis among FIGO 2018 stages***

170 We conducted a survival analysis based on the FIGO 2018 staging, including 1,264 cases with
171 available prognostic information (median follow-up period: 50.0 months). First, we compared the OS among
172 patients with FIGO 2018 stages I, II, IIIAB, IIIC, and IV (Figure 2A, Table 3A). Stage IIIC was associated
173 with a poorer prognosis compared to stage II (HR, 2.12; 95% CI, 1.29–3.48; $p=0.004$); however, it was
174 significantly better than stage IIIAB (HR, 0.46; 95% CI, 0.27–0.78; $p=0.004$). Next, we classified stage IIIC
175 patients into stages IIIC1 and IIIC2 and compared them with stages II and IIIAB (Figure 2B, Table 3B). The
176 results showed a significant difference between IIIC2 and IIIC1 (HR, 2.32; 95% CI, 1.37–3.93; $p=0.003$),

177 and the prognosis for IIIC2 was almost equivalent to that of stage IIIAB (HR, 1.10; 95% CI, 0.57–1.13;
178 p=0.76). Additionally, IIIC1 had a significantly poorer prognosis compared to stage II (HR, 1.80; 95% CI,
179 1.07–3.01; p=0.03). Similar analyses were conducted focusing only on SCC cases, Adeno/Adesq cases, and
180 patients who received the definitive treatment. The results were generally consistent (Supplementary Figure
181 S1, Supplementary Tables S3 and S4).

182 183 *Clinical impact of local tumor factors and histology on survival in stage IIIC*

184 We investigated the differences in prognosis among patients with stage IIIC disease based on local
185 tumor factors. First, we examined the differences in stage IIIC1 according to T1, T2, and T3AB.

186 The prognosis differed among stages IIIC1-T1, T2, and T3AB, with a trend toward poorer prognosis
187 in the order of IIIC1-T1, T2, and T3AB (IIIC1-T1 vs. IIIC1-T2, HR, 1.69; 95% CI, 0.82–3.47; p=0.18;
188 IIIC1-T2 vs IIIC1-T3AB, HR, 1.83; 95% CI, 0.95–3.53; p=0.11) (Figure 3A, Table 4A). Additionally, the
189 prognosis for IIIC1-T3AB was equivalent to that of stage IIIAB (IIIC1-T3AB vs IIIAB, HR, 1.44; 95% CI,
190 0.70–2.96; p=0.21). Similar analyses were conducted focusing on SCC and Adeno/Adesq cases. Regarding
191 SCC cases, there was little difference between T1 and T2, but T3AB was significantly associated with a
192 poorer prognosis (IIIC1-T1 vs IIIC1-T2, HR, 1.35; 95% CI, 0.53–3.43; p=0.63. IIIC1-T2 vs IIIC1-T3AB,
193 HR, 2.64; 95% CI, 1.26–5.55; p=0.02) (Supplementary Figure S2, Supplementary Table S5). For
194 Adeno/Adesq cases, IIIC1-T1 showed a trend toward better prognosis compared to IIIC1-T2 (IIIC1-T1 vs
195 IIIC1-T2, HR, 5.16; 95% CI, 1.11–24.0; p=0.07) (Supplementary Figure S2, Supplementary Table S5).

196 In contrast, regarding IIIC2, there was no significant difference in prognosis among T1, T2, and
197 T3AB (Figure 3B, Table 4B). This was also observed in the analyses focusing on SCC and Adeno/Adesq
198 (Supplementary Figure S2, Supplementary Table S5).

199 In summary, IIIC2 patients had a uniformly poor prognosis, regardless of their local condition or
200 histological type. Among IIIC1 patients, however, the prognostic impact of local conditions on prognosis
201 varied depending on the histological type. We then compared the prognosis for SCC and Adeno/Adesq at all
202 stages, including substages. The results showed that Adeno/Adesq had a significantly worse prognosis than
203 SCC in stages IIIAB, IV, and IIIC1-T2 (stage IIIAB, HR, 9.14; 95% CI, 2.65–31.5; p<0.001. stage IV, HR,

204 2.35; 95% CI, 1.45–3.75; p<0.001. stage IIIC1-T2, HR, 3.41; 95% CI, 1.52–7.67; p=0.003) (Supplementary
205 Figure S3).

206

207 ***Multivariate analysis of stage IIIC***

208 For a better understanding of prognostic factors in the stage IIIC population, we conducted a
209 multivariate analysis including PAN metastasis, histology, and local tumor factors. Histological types other
210 than SCC and Adeno/Adesq were excluded due to the small number of patients. PAN metastasis,
211 Adeno/Adesq histology, and T3AB remained significant (Table 5). Additionally, we investigated the impact
212 of postoperative treatment on prognosis in patients with stages IIIC-T1 and IIIC-T2 who underwent surgery.
213 Postoperative treatment information was available for 168 cases. After excluding the patients who received
214 radiotherapy alone due to the small number (n=12), we compared the CCRT group with the chemotherapy
215 group. There was no significant difference in prognosis between the CCRT and chemotherapy groups
216 (Supplementary Figure S4A). When we evaluated stages IIIC1 and IIIC2 separately, CCRT showed a trend
217 toward better prognosis in stage IIIC2; however, this was not statistically significant due to the limited
218 number of cases (Supplementary Figures S4B and S4C).

219

220 **Discussion**

221 We utilized a multicenter database of the Japanese population to investigate the proportion of
222 restaging in FIGO 2018. The analysis focused on overall stage IIIC and the differences between IIIC1 and
223 IIIC2. The impact of local tumor factors and histological types on the prognosis of patients with stage IIIC
224 disease was also examined.

225 In our study, total stage migration was observed in 32.0% of the cases. Among these, most stage
226 migrations were due to LNM (27.4 %), comparable to reports from other Japanese populations [18,19]. The
227 proportion of upstaging due to LNM increased at higher stages. However, the proportion of patients with
228 LNM was higher in stage IB2 than in stage IIA. Yan et al. reported that the proportions of upstaging to stage
229 IIIC in early-stage cases were IB1: 19.4%, IB2: 47.5%, and IIA: 33%, showing a similar trend [21]. In Japan,
230 where various imaging tests such as MRI, CT, and PET are extensively performed before treatment, it is

231 expected that the impact of the recent revision on Japanese cervical cancer cases is essentially stage
232 migration due to LNM.

233 Our results indicate that the prognosis for stage IIIC is intermediate between that of stage II and
234 stage IIIA/B, consistent with previous reports [15,17]. These findings indicate that LNM is a poor prognostic
235 factor, underscoring the significance of establishing stage IIIC. Furthermore, when comparing substages
236 IIIC1 and IIIC2, IIIC2 showed a significantly poorer prognosis. This is also consistent with previous reports
237 [9-11,13,16,18], suggesting that distinguishing between substages IIIC1 and IIIC2 is beneficial.

238 In the analysis of stage IIIC1, stages IIIC1-T1 and IIIC1-T2 were both significantly associated with a
239 poorer prognosis than stages I and II. In cases of T1/2, pelvic LNM is an important prognostic factor [15,22],
240 suggesting that it would be meaningful to subgroup pelvic LNM as IIIC1 in T1/2 patients. In contrast, stage
241 IIIC1-T3AB had a prognosis equivalent to that of stage IIIA/B. This is consistent with previous reports
242 stating that the prognosis differs among T1, T2, and T3AB in stage IIIC1 [9,10,12,16]. Kol et al. reported
243 that the impact of pelvic LNM on prognosis was only evident in T2 or below [22]. The clinical significance
244 of recognizing pelvic LNM as an independent group is debatable, particularly in T3AB cases.

245 In our analysis of patients with stage IIIC2, the prognosis was as poor as that of stage IIIAB,
246 regardless of local tumor factors, unlike in cases with stage IIIC1. This finding suggests that para-aortic
247 LNM has significant prognostic implications. Several reports have shown that progression-free survival
248 differs among T1, T2, and T3AB in stage IIIC2 [9,10]. However, the prognosis for stage IIIC2 disease often
249 varies between reports, and their interpretation may not be straightforward. Grigsby et al. reported that the 5-
250 year survival rates for IIIC2-T2 and IIIC2-T3 were below 40%, which is extremely poor compared to our
251 study [10]. The study by Kim et al. covered a wide data collection period from 1992 to 2018, during which
252 treatment policies may not have been uniform [9]. Given that para-aortic LNM is relatively rare in cervical
253 cancer and that its identification method varies, the differences in reports are understandable. Nonetheless,
254 the prognosis for stage IIIC2 cases is consistently extremely poor, and there seems to be little disagreement
255 regarding the classification of para-aortic LNM cases into an independent group, stage IIIC2.

256 Additionally, we investigated the prognostic effects of histological types. Compared to patients with
257 SCC, those with Adeno/Adesq are known to have a worse prognosis, especially in advanced cases [24].
258 Similarly, in our study, stages IIIA/B and IV cases had a clearly worse prognosis in Adeno/Adesq cases.

259 Additionally, when comparing IIIC1-T1 and IIIC1-T2, no significant difference in prognosis was observed in
260 SCC cases, whereas Adeno/Adesq cases showed a trend toward poorer prognosis in IIIC1-T2. Shigeta et al.
261 reported that patients with both surgically proven LNM and parametrial invasion had a significantly poorer
262 prognosis than those with only one of these factors in the overall population [18]. However, they did not
263 investigate the outcomes according to histological type. A previous report showed no difference in prognosis
264 between SCC and adenocarcinoma in cases without LNM, but adenocarcinoma was significantly associated
265 with poorer prognosis in cases with LNM [25]. However, this report did not investigate parametrial invasion
266 status. LNM positivity (stage IIIC1) and parametric invasion (T2) are well-known independent prognostic
267 factors; however, in Adeno/Adesq cases, the presence of both factors may simultaneously have a greater
268 impact on prognosis. This suggests that IIIC1-T1 and IIIC1-T2 could be considered clinically distinct
269 classifications, particularly in Adeno/Adesq cases. Currently, histological type does not affect stage
270 classification in cervical cancer. However, for endometrial cancer, recent attempts have been made to
271 incorporate histological types and underlying genetic alterations into the staging system from a prognostic
272 perspective [26,27]. In cervical cancer, there might be merit in attempting a separate classification based on
273 histological type. However, as these groups have a relatively small population, larger cohort studies are
274 required.

275 This study had several limitations. Although this was a multicenter study, the sample size was
276 limited. Furthermore, the national database does not provide detailed information on the date and location of
277 recurrence, preventing the evaluation of recurrence. Although treatment approaches vary considerably
278 among T1, T2, and T3, details of the surgical techniques and radiation fields are unavailable, making it
279 impossible to examine the impact of these treatment policies on prognosis. Furthermore, it is known that
280 postoperative treatments also affect prognosis. Although this study did not find a significant difference
281 between postoperative chemotherapy and CCRT, given the considerable differences in patient backgrounds
282 between the two groups [28], the results should be interpreted with caution. Studies on cohorts with better-
283 matched treatment backgrounds are needed, but our database lacked the necessary detail for such analyses,
284 which is another limitation of this study. However, by analyzing real-world data, we were able to clarify the
285 current situation in Japan and reevaluate the usefulness of FIGO 2018 beyond racial differences. Our results

286 also suggest that a comprehensive examination of LNM, local tumor factors, and histological type may
287 further reinforce and complement the findings of FIGO 2018.

288

289 <Data availability>

290 The data that support the findings of this study are available from the corresponding author upon
291 reasonable request.

292

293 <Tables>

294 **Table 1.** Clinical characteristics of the patients.

	Median (range)
Age	53 (16-95)
	N (%)
FIGO 2009 stage	
I	770 (52.5)
II	364 (24.8)
III	124 (8.4)
IV	210 (14.3)
FIGO 2018 stage	
I	650 (44.3)
II	209 (14.2)
III	399 (27.2)
IIIA/B	52 (3.5)
IIIC1	292 (19.9)
IIIC2	55 (3.7)
IV	210 (14.3)
Histology	
SCC	1047 (71.3)
Adeno	304 (20.7)
Adesq	47 (3.2)
Others	70 (4.8)
Treatment	
Surgery	807 (55.0)
CCRT	200 (13.6)
NAC followed by surgery	191 (13.0)
RT	181 (12.3)
Others	89 (6.6)
Total	1468 (100)

295
296 FIGO, International Federation of Gynecology and Obstetrics; SCC, squamous cell carcinoma; Adeno,
297 adenocarcinoma; Adesq, adenosquamous carcinoma; CCRT, concurrent chemoradiotherapy; NAC,
298 neoadjuvant chemotherapy; RT, radiotherapy.

299 **Table 2.** Stage migrations between FIGO 2009 and 2018 staging.

300

FIGO 2009 stage	FIGO 2018 stage														
	Not IIIC					IIIC1				IIIC2				IIIC Total (%)	Total
	I	IIA	IIB	III	Total (%)	r	p	rp	Total (%)	r	p	rp	Total (%)		
IA	174	1	0	0	175 (98.3)	0	2	1	3 (1.7)	0	0	0	0 (0.0)	3 (1.7)	178
IB1	388	10	14	0	412 (88.4)	2	26	17	45 (9.7)	2	6	1	9 (1.9)	54 (11.6)	466
IB2	68	2	6	0	76 (61.8)	21	13	9	43 (35.0)	1	0	3	4 (3.3)	47 (38.2)	123
IIA	11	37	6	0	54 (72.0)	10	6	4	20 (26.7)	0	0	1	1 (1.3)	21 (28.0)	75
IIB	6	1	133	0	140 (48.6)	97	13	19	129 (44.8)	15	2	2	19 (6.6)	148 (48.6)	288
IIIA	0	0	0	12	12 (60.0)	5	0	0	5 (25.0)	3	0	0	3 (15.0)	8 (40.0)	20
IIIB	0	0	0	40	40 (35.1)	45	0	0	45 (43.3)	19	0	0	19 (18.3)	64 (64.9)	104
Total	647	51	159	52	909 (72.5)	180	60	50	290 (23.1)	40	8	7	55 (4.4)	345 (27.5)	1254

301

302 **Table 3.** Pairwise univariate Cox proportional hazards regression survival analysis for OS.

303 Table 3A. Comparison of stages I, II, IIIAB, IIIC, and IV.

	I	II	IIIAB	IIIC
II	0.002, HR=2.56 (1.45- 4.52)			
IIIAB	<0.001, HR=11.6 (6.36-21.2)	<0.001, HR=4.56 (2.39-8.72)		
IIIC	<0.001, HR=5.37 (3.48-8.27)	0.004, HR=2.12 (1.29-3.48)	0.004, HR=0.49 (0.27-0.78)	
IV	<0.001, HR=23.4 (15.5-35.4)	<0.001, HR=9.24 (5.73-14.9)	0.004, HR=2.11 (1.27-3.52)	<0.001, HR=4.59 (3.41-6.19)

304

305 Table 3B. Comparison of stages II, IIIC1, IIIC2, and IIIAB.

	II	IIIC1	IIIC2
IIIC1	0.03, HR=1.80 (1.07-3.01)		
IIIC2	<0.001, HR=4.16 (2.22-7.81)	0.003, HR=2.32 (1.37-3.93)	
IIIAB	<0.001, HR=4.56 (2.39-8.72)	0.001, HR=2.59 (1.50-4.49)	0.76, HR=1.11 (0.57-2.13)

306

307 Benjamini-Hochberg-adjusted p-values and hazard ratios (HRs) with 95% confidence intervals (CI) are
308 shown. HRs are calculated using the row group as the reference and represent the risk of the column group
309 relative to the row group. OS, overall survival.

310

311 **Table 4.** Pairwise univariate Cox proportional hazards regression survival analysis for OS.

312 Table 4A. Comparison of stages IIIC1-T1, IIIC1-T2, IIIC1-T3AB, and IIIAB.

	IIIC1-T1	IIIC1-T2	IIIC1-T3AB
IIIC1-T2	0.18, HR=1.69 (0.82-3.47)		
IIIC1-T3AB	0.02, HR=3.04 (1.33-6.95)	0.11, HR=1.83 (0.95-3.53)	
IIIAB	0.002, HR=4.21 (1.93-9.22)	0.007, HR=2.54 (1.39-4.62)	0.21, HR=1.44 (0.70-2.96)

313
314 Table 4B. Comparison of stages IIIC2-T1, IIIC2-T2, IIIC2-T3AB, and IIIAB.

	IIIC2-T1	IIIC2-T2	IIIC2-T3AB
IIIC2-T2	0.83, HR=0.64 (0.20-2.04)		
IIIC2-T3AB	0.83, HR=0.69 (0.22-2.18)	0.91, HR=0.94 (0.33-2.70)	
IIIAB	0.83, HR=0.82 (0.30-2.22)	0.83, HR=1.21 (0.50-2.91)	0.83, HR=1.23 (0.51-2.97)

315
316 Benjamini-Hochberg-adjusted p-values and HRs with 95% CI are shown. HRs are calculated using the row
317 group as the reference and represent the risk of the column group relative to the row group.
318

319 Table 5. Multivariate Cox proportional hazards regression survival analysis for OS.
 320

Variables	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Local tumor factors	1 (reference)			1 (reference)		
T1						
T2	0.91	0.56-1.48	0.70	1.62	0.84-3.11	0.15
T3AB	2.02	1.19-3.47	0.01	2.56	1.22-5.36	0.01
PAN metastasis	1 (reference)			1 (reference)		
Negative						
Positive	2.36	1.35-4.11	0.002	2.05	1.14-3.66	0.02
Histology	1 (reference)			1 (reference)		
SCC						
Adeno/Adesq	1.65	0.93-2.91	0.08	1.98	1.11-3.53	0.02

321
 322 HR, hazard ratio; CI, confidence interval; PAN, para-aortic node; SCC, squamous cell carcinoma; Adeno,
 323 adenocarcinoma; Adesq, adenosquamous carcinoma.

324 <Figure legends>

325 **Fig. 1** Stage conversion flowchart with respect to LNM status from FIGO 2009 to FIGO 2018. This diagram
326 illustrates the transition between the staging systems, evaluating both postsurgical nodal and metastatic status
327 (pN and pM) and clinical nodal and metastatic status (cN and cM). PeN, pelvic lymph node; PAN, para-
328 aortic lymph node; NA, not assessed; FIGO, International Federation of Gynecology and Obstetrics.

329
330 **Fig. 2** Survival analysis based on FIGO 2018 staging. (A, B) Kaplan–Meier curves comparing overall
331 survival (OS). (A) Stages I, II, IIIA/B, IIIC, and IV were compared. (B) Stage IIIC was subdivided into IIIC1
332 and IIIC2.

333
334 **Fig. 3** Survival analysis based on FIGO 2018 staging, with stages IIIC1 and IIIC2 subdivided by local tumor
335 factors. Kaplan–Meier curves comparing overall survival (OS) in (A) stages IIIC1 and IIIAB patients, (B)
336 stages IIIC2 and IIIAB patients.

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 433

Figure 1

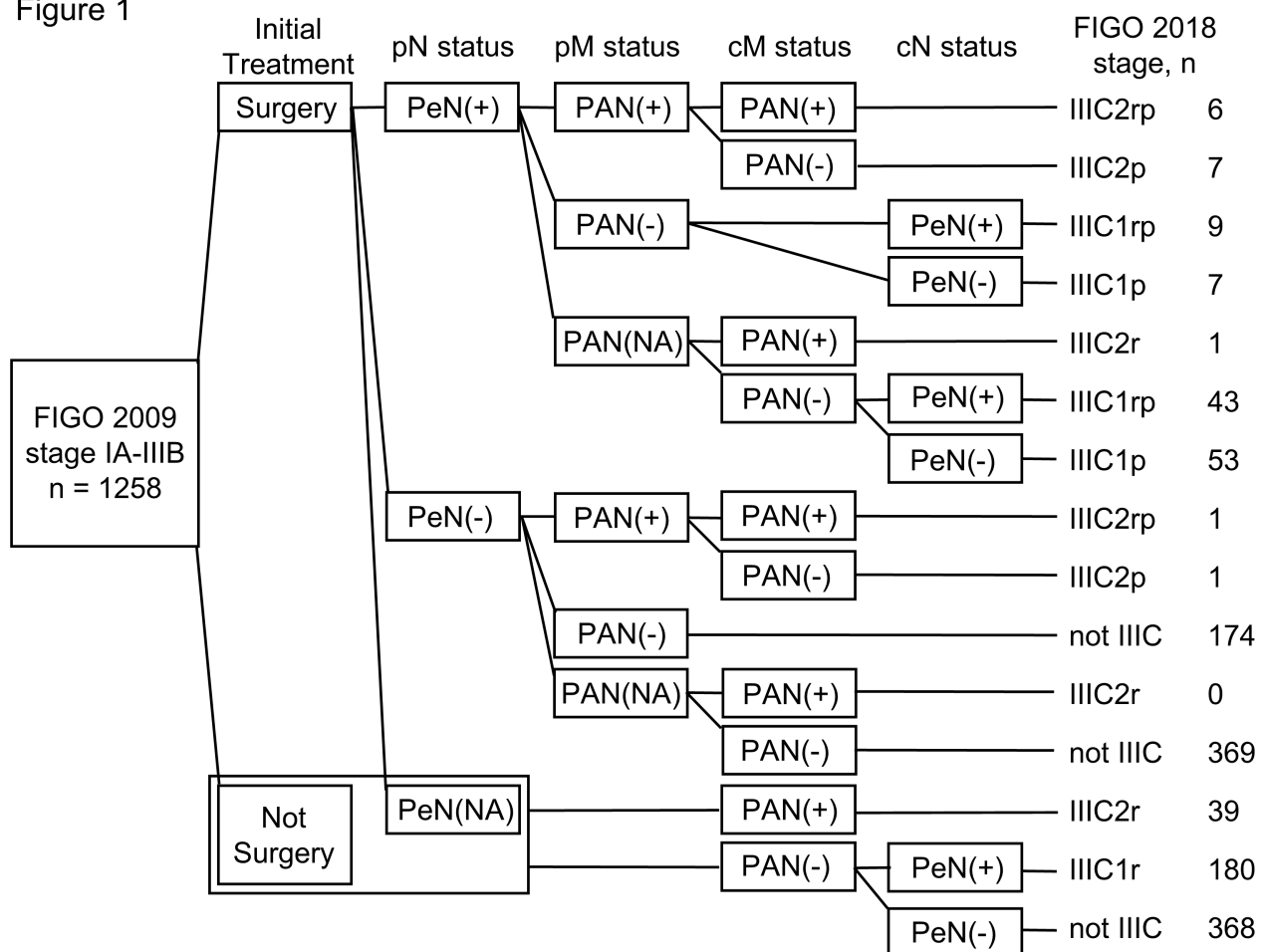


Figure 2

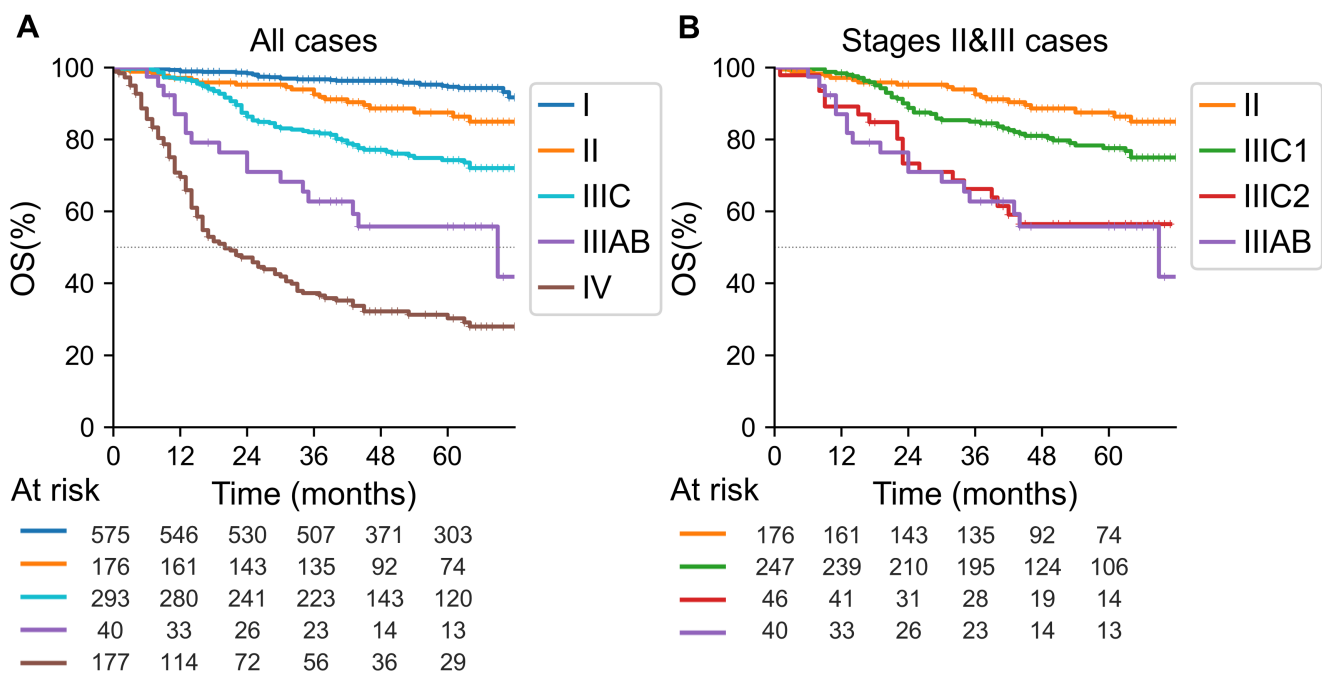
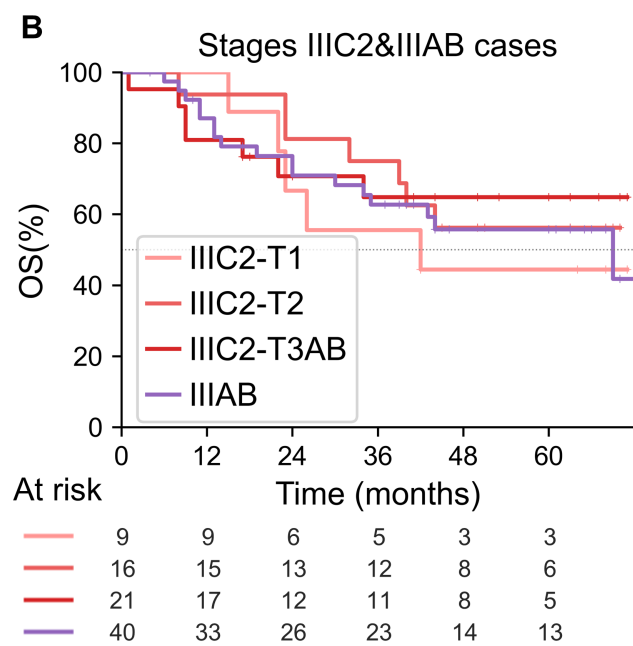
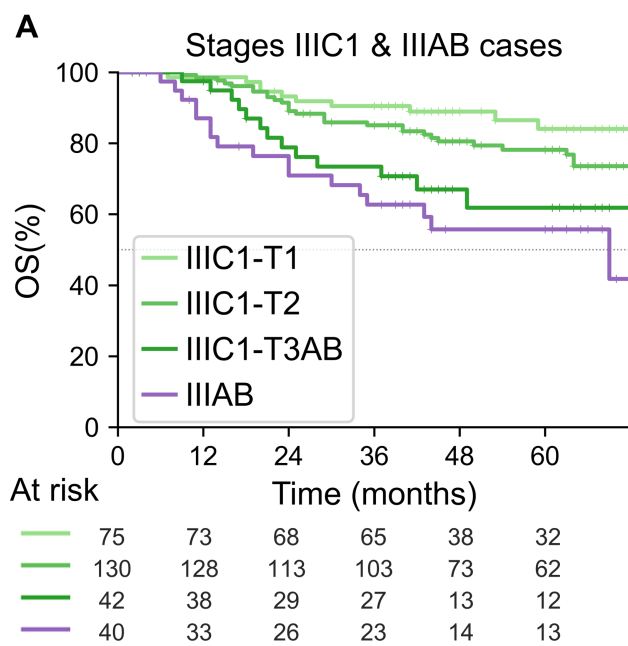


Figure 3



1 **Supplementary Table S1.** Stage migrations between FIGO 2009 and 2018 staging in SCC cases.

FIGO 2009 stage	FIGO 2018 stage														
	Not IIIC					IIIC1				IIIC2				IIIC Total (%)	Total
	I	IIA	IIB	III	Total (%)	r	p	rp	Total (%)	r	p	rp	Total (%)		
IA	144	1	0	0	145 (98.0)	0	2	1	3 (2.0)	0	0	0	0 (0.0)	3 (12.0)	148
IB1	219	7	11	0	237 (85.9)	2	21	11	34 (12.3)	1	3	1	5 (1.8)	39 (14.1)	276
IB2	42	2	5	0	49 (60.5)	15	8	6	29 (35.8)	1	0	2	3 (3.7)	32 (39.5)	81
IIA	8	31	5	0	44 (72.1)	8	5	3	16 (26.2)	0	0	1	1 (1.7)	17 (27.9)	61
IIB	3	0	106	0	109 (47.6)	81	10	13	104 (45.4)	12	2	2	16 (7.0)	120 (52.4)	229
IIIA	0	0	0	10	10 (66.7)	3	0	0	3 (20.0)	2	0	0	2 (13.3)	5 (33.3)	15
IIIB	0	0	0	34	34 (37.8)	41	0	0	41 (45.6)	15	0	0	15 (16.7)	56 (62.2)	90
Total	416	41	127	44	628 (70.0)	150	46	34	230 (25.6)	31	5	6	42 (4.7)	272 (30.2)	900

2
3 FIGO, International Federation of Gynecology and Obstetrics; SCC, squamous cell carcinoma.

4 **Supplementary Table S2.** Stage migrations between FIGO 2009 and 2018 staging in Adeno/Adesq cases.

FIGO 2009 stage	FIGO 2018 stage														
	Not IIC					IIC1				IIC2				IIC Total (%)	Total
	I	IIA	IIB	III	Total (%)	r	p	rp	Total (%)	r	p	rp	Total (%)		
IA	29	0	0	0	29 (100.0)	0	0	0	0 (0.0)	0	0	0	0 (0.0)	0 (0.0)	29
IB1	147	1	3	0	151 (91.5)	0	5	6	11 (6.7)	1	2	0	3 (3.3)	14 (8.5)	165
IB2	23	0	1	0	24 (68.6)	4	3	3	10 (28.6)	0	0	1	1 (2.8)	11 (31.4)	35
IIA	2	6	1	0	9 (66.7)	2	1	0	3 (33.3)	0	0	0	0 (0.0)	3 (33.3)	12
IIB	3	1	23	0	27 (51.9)	14	2	6	22 (42.3)	3	0	0	3 (5.8)	25 (48.1)	52
IIIA	0	0	0	1	1 (33.3)	2	0	0	2 (66.7)	0	0	0	0 (0.0)	2 (66.6)	3
IIIB	0	0	0	6	6 (50.0)	3	0	0	3 (25.0)	3	0	0	3 (25.0)	6 (50.0)	12
Total	204	8	28	7	247 (80.2)	25	11	15	51 (16.6)	7	2	2	11 (3.6)	62 (20.1)	308

5

6 Adeno, adenocarcinoma; Adesq, adenosquamous carcinoma.

7 **Supplementary Table S3.** Pairwise univariate Cox proportional hazards regression survival analysis among
8 stages I, II, IIIAB, IIIC, and IV **for OS.**

SCC cases				
	I	II	IIIAB	IIIC
II	0.03, HR=2.28 (1.13- 5.06)			
IIIAB	<0.001, HR=549 (50.2-5998)	<0.001, HR=4.36 (1.96-9.71)		
IIIC	<0.001, HR=5.24 (2.97-9.22)	0.01, HR=2.29 (1.22-4.31)	0.04, HR=0.52 (0.27-0.97)	
IV	<0.001, HR=22.6 (13.1-39.0)	<0.001, HR=9.74 (5.28-18.0)	0.008, HR=2.29 (1.24-4.22)	<0.001, HR=4.42 (3.06-6.37)
Adeno/Adesq cases				
	I	II	IIIAB	IIIC
II	0.01, HR=4.30 (1.49- 12.41)			
IIIAB	0.99, HR=1.12 (0.007-183)	0.89, HR=0.46 (0.008-25.6)		
IIIC	<0.001, HR=8.37 (3.57-19.6)	0.23, HR=1.95 (0.76-4.98)	<0.001, HR=0.07 (0.02-0.22)	
IV	<0.001, HR=53.3 (22.3-127)	<0.001, HR=12.6 (4.89-32.5)	0.99, HR=0.99 (0.37-2.64)	<0.001, HR=7.31 (3.71-14.4)
Definitive treatment cases				
	I	II	IIIAB	IIIC
II	0.002, HR=2.78 (1.48- 5.20)			
IIIAB	<0.001, HR=7.42 (3.04-18.1)	0.05, HR=2.67 (1.04-6.83)		
IIIC	<0.001, HR=5.83 (3.65-9.30)	0.01, HR=2.11 (1.22-3.67)	0.57, HR=0.79 (0.34-1.82)	
IV	<0.001, HR=21.0 (12.3-35.8)	<0.001, HR=6.92 (3.81-12.6)	0.04, HR=2.56 (1.07-6.10)	<0.001, HR=3.34 (2.20-5.08)

9
10 **Benjamini-Hochberg-**adjusted p-values and hazard ratios (HRs) with 95% confidence intervals (CI) are
11 shown. HRs are calculated using the row group as the reference and represent the risk of the column group
12 relative to the row group. OS, overall survival.

13 **Supplementary Table S4.** Pairwise univariate Cox proportional hazards regression survival analysis among
14 stages II, IIIC1, IIIC2, and IIIAB **for OS.**

SCC, stages II&III cases			
	II	IIIC1	IIIC2
IIIC1	0.06, HR=1.93 (1.00-3.72)		
IIIC2	<0.001, HR=4.60 (2.10-10.1)	0.02, HR=2.34 (1.24-4.43)	
IIAB	<0.001, HR=4.36 (1.96-9.71)	0.02, HR=2.31 (1.20-4.45)	0.98, HR=0.98 (0.45-2.17)
Adeno/Adesq, stages II&III cases			
	II	IIIC1	IIIC2
IIIC1	0.30, HR=1.68 (0.63-4.47)		
IIIC2	0.10, HR=4.00 (1.12-14.22)	0.17, HR=2.50 (0.80-7.77)	
Definitive treatment, stages II&III cases			
	II	IIIC1	IIIC2
IIIC1	0.07, HR=1.80 (1.01-3.18)		
IIIC2	<0.001, HR=4.12 (2.06-8.26)	0.01, HR=2.31 (1.30-4.09)	
IIAB	0.07, HR=2.66 (1.04-6.83)	0.37, HR=1.50 (0.64-3.53)	0.37, HR=0.65 (0.26-1.67)

15 **Benjamini-Hochberg-**adjusted p-values and HRs with 95% CI are shown. **HRs are calculated using the row**
16 **group as the reference and represent the risk of the column group relative to the row group.**
17
18

19 **Supplementary Table S5.** Pairwise univariate Cox proportional hazards regression survival analysis for OS.

20 Supplementary Table S5A: Comparison of stages IIIC1-T1, IIIC1-T2, IIIC1-T3AB, and IIIAB.

SCC, stages IIIC1&IIIAB cases

	IIIC1-T1	IIIC1-T2	IIIC1-T3AB
IIIC1-T2	0.63, HR=1.35 (0.53-3.43)		
IIIC1-T3AB	0.02, HR=3.42 (1.28-9.12)	0.02, HR=2.64 (1.26-5.55)	
IIIAB	0.02, HR=3.68 (1.38-9.84)	0.02, HR=2.73 (1.30-5.72)	0.87, HR=1.07 (0.48-2.38)

Adeno/Adesq, stages IIIC1&IIIAB cases

	IIIC1-T1	IIIC1-T2	IIIC1-T3AB
IIIC1-T2	0.07, HR=5.16 (1.11-24.0)		
IIIC1-T3AB	0.32, HR=5.83 (0.36-93.3)	0.98, HR=0.78 (0.10-6.29)	
IIIAB	0.002, HR=45.5 (5.03-412)	0.002, HR=12.9 (3.29-51)	0.99, HR=36.8 (0-inf)

21

22 Supplementary Table S5B. Comparison of stages IIIC2-T1, IIIC2-T2, IIIC2-T3AB, and IIIAB.

SCC, stages IIIC2&IIIAB cases

	IIIC2-T1	IIIC2-T2	IIIC2-T3AB
IIIC2-T2	0.92, HR=0.88 (0.17-4.40)		
IIIC2-T3AB	0.92, HR=0.86 (0.17-4.43)	0.92, HR=0.84 (0.26-2.77)	
IIIAB	0.92, HR=0.88 (0.20-3.97)	0.92, HR=0.95 (0.36-2.53)	0.92, HR=1.11 (0.39-3.17)

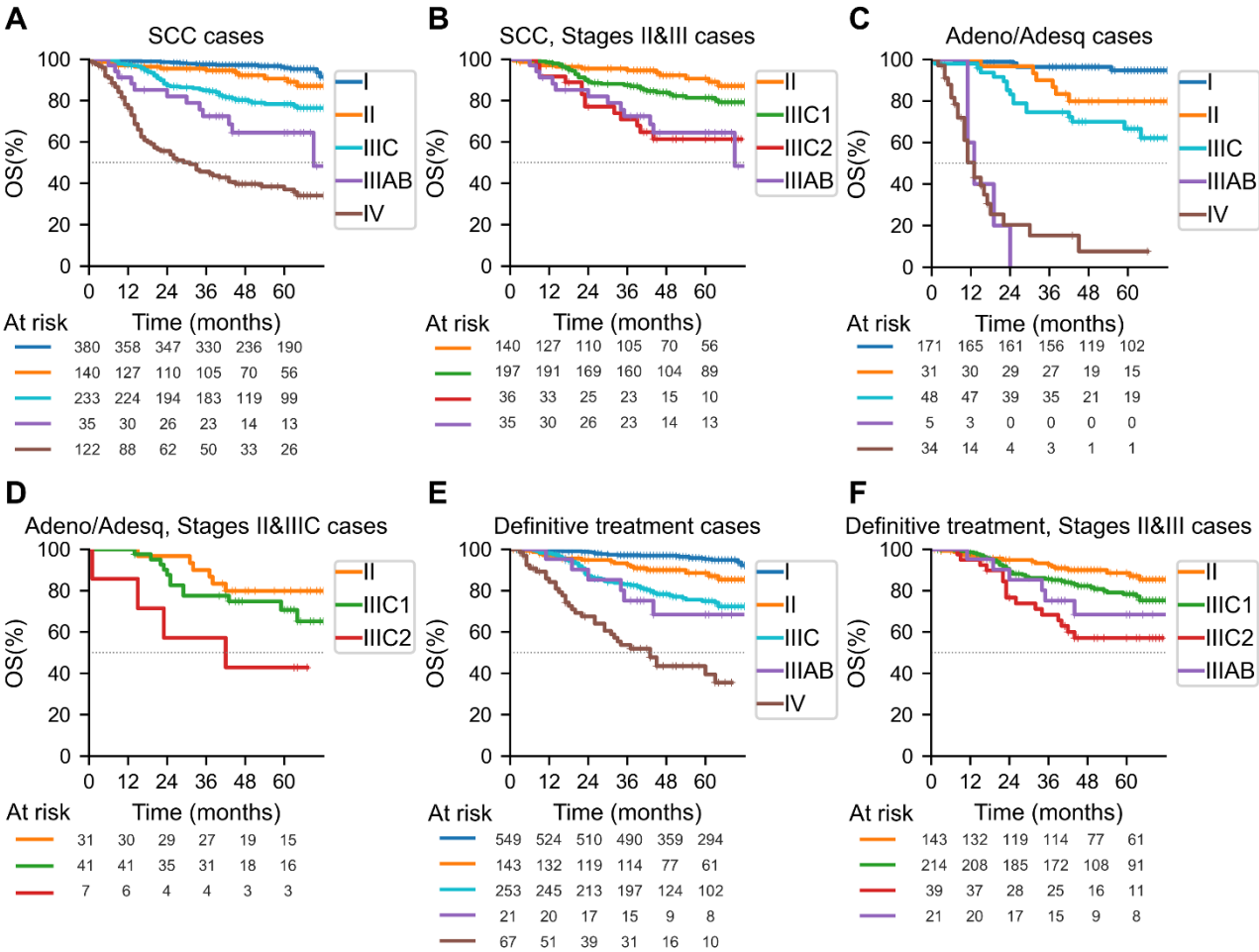
Adeno/Adesq, stages IIIC2&IIIAB cases

	IIIC2-T1	IIIC2-T2	IIIC2-T3AB
IIIC2-T2	0.97, HR=0.71 (0.06-8.02)		
IIIC2-T3AB	0.98, HR=1.02 (0.09-11.6)	0.97, HR=1.41 (0.08-23.6)	
IIIAB	0.56, HR=5.55 (0.63-48.7)	0.56, HR=4.40 (0.49-39.4)	0.97, HR=2.11 (0.23-19.0)

23

24 Benjamini-Hochberg-adjusted p-values and HRs with 95% CI are shown. HRs are calculated using the row
25 group as the reference and represent the risk of the column group relative to the row group.

26 **Supplementary Fig. S1** Subgroup analysis based on FIGO 2018 staging.



27
28 Kaplan–Meier curves comparing overall survival (OS) in (A, B) patients with SCC, (C, D) patients with
29 Adeno/Adesq, and (E, F) patients who received definitive treatment. (B, D, F) Stage IIIC was subdivided
30 into IIIC1 and IIIC2.

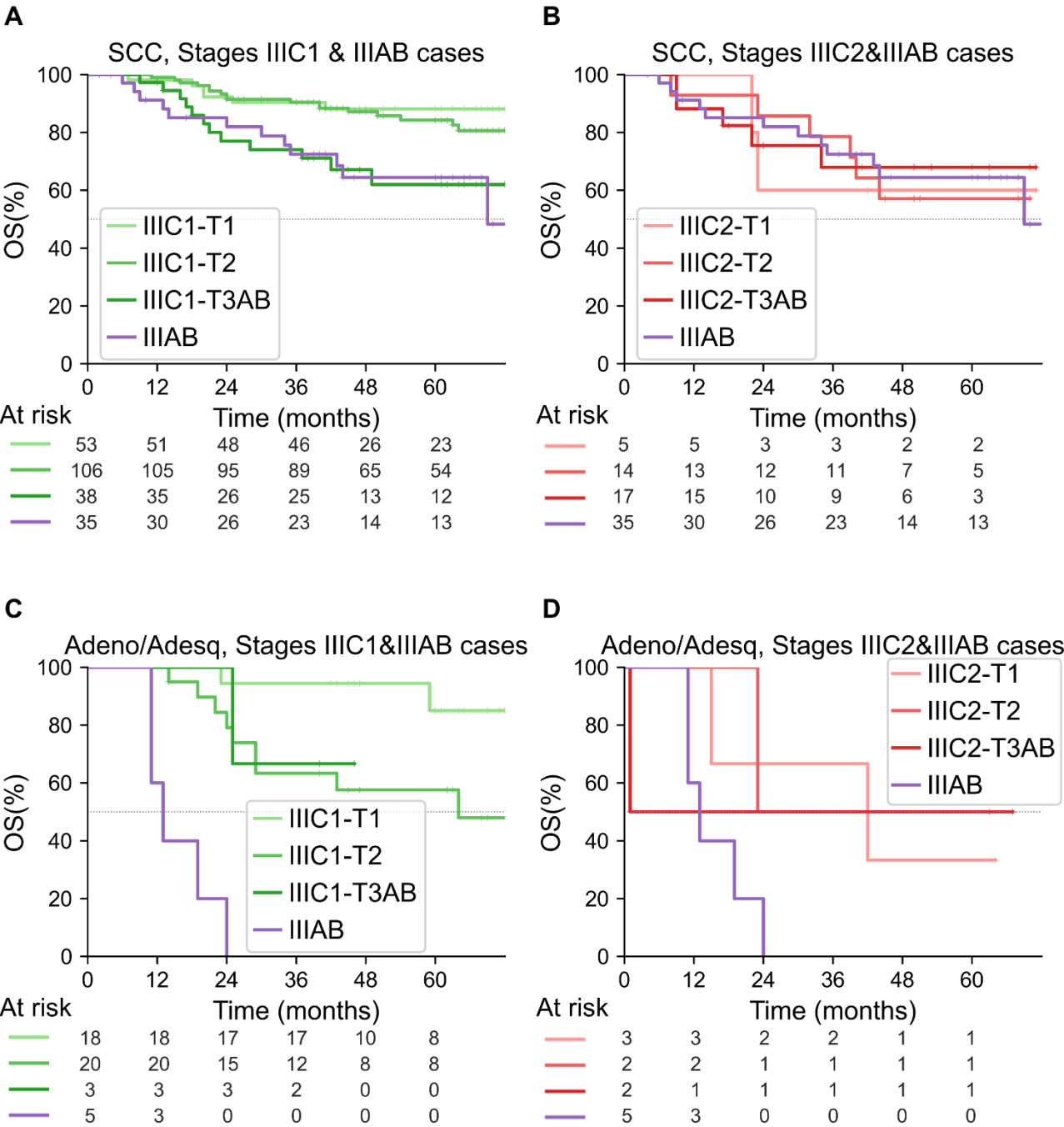
31 Adeno/Adesq, adenocarcinoma and adenosquamous carcinoma; SCC, squamous cell carcinoma; FIGO,
32 International Federation of Gynecology and Obstetrics

33
34 First, we focused only on SCC cases and compared the prognosis among re-staged FIGO groups.
35 Stage IIIC was associated with a poorer prognosis compared to stage II (HR, 2.29; 95% CI, 1.22–4.31;
36 $p=0.01$), but it was significantly better than stage IIIAB (HR, 0.52; 95% CI, 0.27–0.97; $p=0.04$)
37 (Supplementary Figure S1A, Supplementary Table S3). When comparing stages IIIC1 and IIIC2, there was a
38 significant difference between IIIC2 and IIIC1 (HR, 2.34; 95% CI, 1.24–4.43; $p=0.02$), while the prognosis
39 for stage IIIC2 was almost equivalent to that of stage IIIAB (HR, 0.98; 95% CI, 0.45–2.17; $p=0.98$)

(Supplementary Figure S1B, Supplementary Table S4). Additionally, IIIC1 had a poorer prognosis compared to stage II (HR, 1.93; 95% CI, 1.00–3.72; $p=0.06$). Furthermore, when considering only Adeno/Adesq cases, the prognoses for stages IIIAB and IV were almost equivalent, with both showing extremely poor outcomes (median survival: 390 and 404 days, respectively) (Supplementary Figure S1C, Supplementary Table S3). Additionally, stage IIIC had a significantly better prognosis compared to that of stage IIIAB (HR, 0.07; 95% CI, 0.02–0.22; $p<0.001$). When distinguishing between stages IIIC1 and IIIC2, stage IIIC1 showed a trend toward better prognosis (HR, 2.50; 95% CI, 0.80–7.77; $p=0.17$), and when compared to stage II, stage IIIC1 showed a trend toward poorer prognosis (HR, 1.68; 95% CI, 0.63–4.47; $p=0.30$) (Supplementary Figure S1D, Supplementary Table S4). Similar results were observed in the group that received the definitive treatment (Supplementary Figure S1E, F, Supplementary Table S3,4).

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Supplementary Fig. S2 Subgroup analysis based on FIGO 2018 staging, with stages IIIC1 and IIIC2 subdivided by local tumor factors.



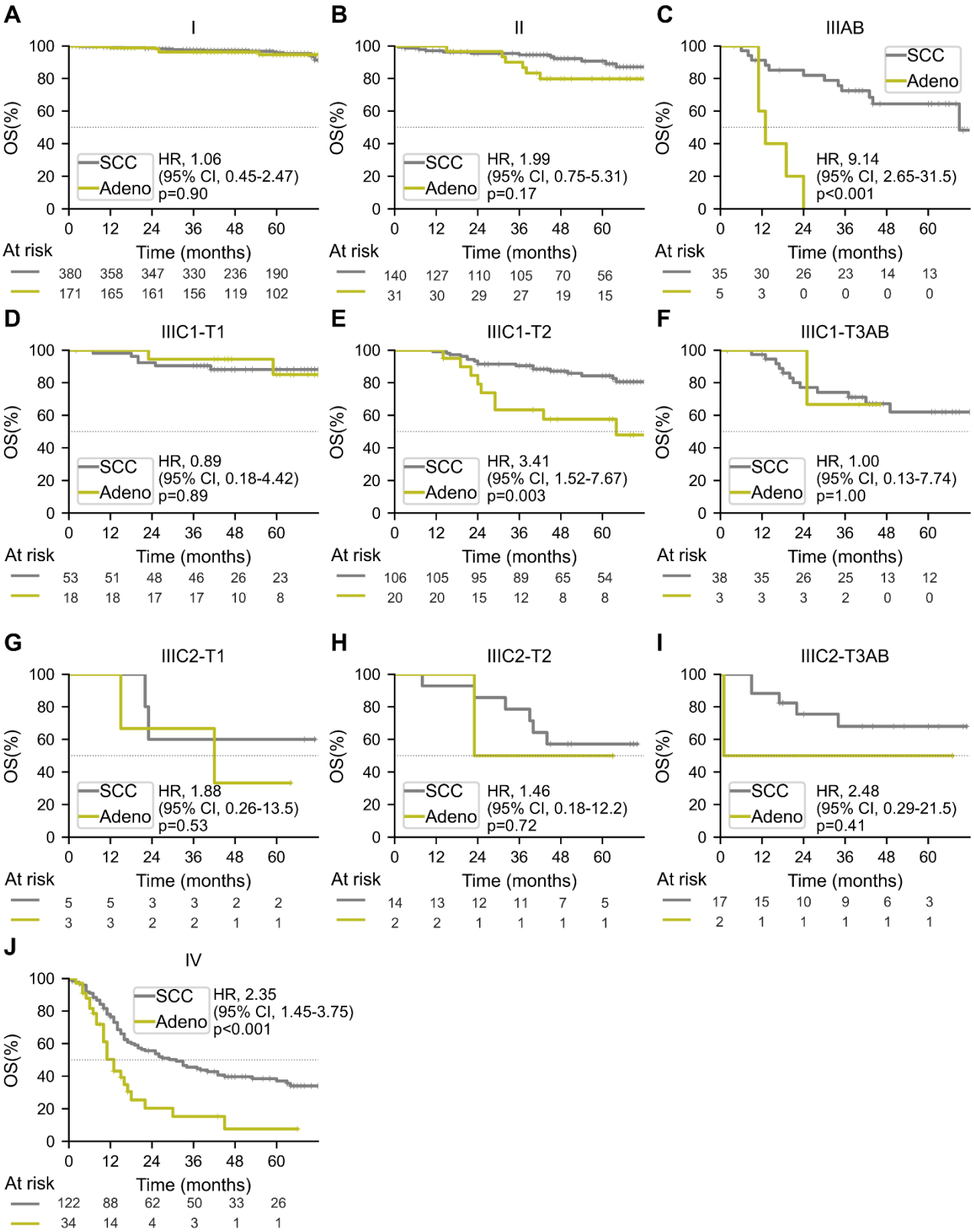
Kaplan–Meier curves comparing overall survival (OS) in (A, B) patients with SCC, and (C, D) patients with Adeno/Adesq. (A, C) Stages IIIC1 and IIIAB patients. (B, D) Stages IIIC2 and IIIAB patients.

Adeno/Adesq, adenocarcinoma and adenosquamous carcinoma; SCC, squamous cell carcinoma; FIGO, International Federation of Gynecology and Obstetrics

60 We focused on SCC and Adeno/Adesq cases classified as IIIC in FIGO 2018 and investigated the
61 differences in prognosis among different local tumor factors independently. Regarding SCC cases, there was
62 little difference between T1 and T2, but T3AB was significantly associated with a poorer prognosis (IIIC1-
63 T1 vs IIIC1-T2, HR, 1.35; 95% CI, 0.53–3.43; p=0.63. IIIC1-T2 vs IIIC1-T3AB, HR, 2.64; 95% CI,
64 1.26–5.55; p=0.02) (Supplementary Figure S2A, Supplementary Table S5A). In contrast, regarding IIIC2,
65 there was little difference in prognosis among T1, T2, and T3AB (Supplementary Figure 2B, Supplementary
66 Table S5B).

67 For Adeno/Adesq cases, IIIC1-T1 showed a trend toward better prognosis compared to IIIC1-
68 T2/T3AB (IIIC1-T1 vs IIIC1-T2, HR, 5.16; 95% CI, 1.11–24.0; p=0.07. IIIC1-T1 vs IIIC1-T3AB, HR, 5.83;
69 95% CI, 0.36–93.3; p=0.32) (Supplementary Figure S2C, Supplementary Table S5A). As for IIIC2 cases,
70 there was little difference in prognosis among T1, T2, and T3AB, and all were associated with a poor
71 prognosis (Supplementary Figure S2D, Supplementary Table S5B).

72



74
75 Kaplan–Meier curves comparing overall survival (OS) in patients with SCC and Adeno/Adesq for each
76 stage: (A) Stage I, (B) Stage II, (C) Stage IIIAB, (D) Stage IIIC1-T1, (E) Stage IIIC1-T2, (F) Stage IIIC1-
77 T3AB, (G) Stage IIIC2-T1, (H) Stage IIIC2-T2, (I) Stage IIIC2-T3AB, and (J) Stage IV.

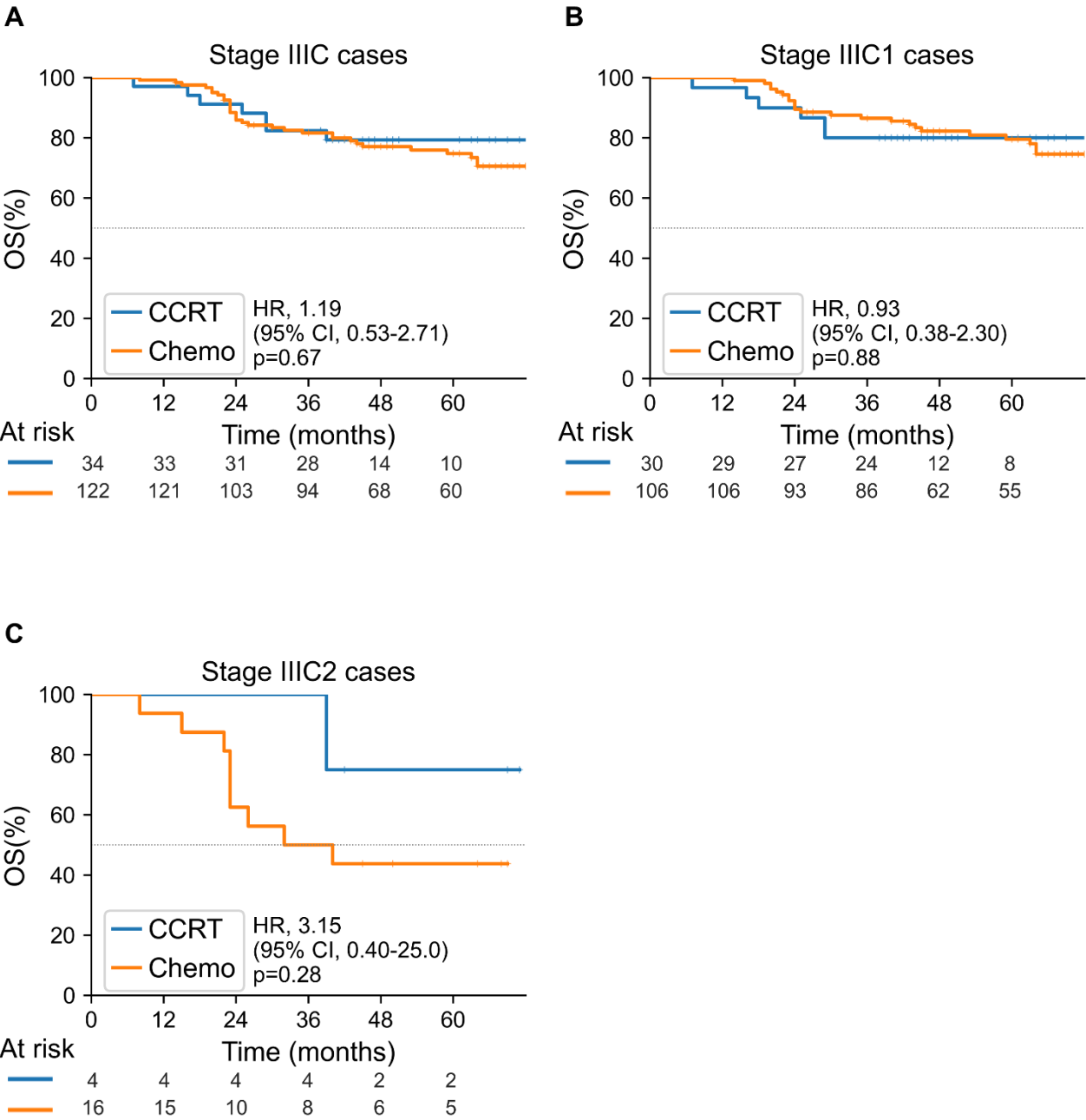
78 HR, hazard ratios; CI, confidence intervals; Adeno/Adesq, adenocarcinoma and adenosquamous carcinoma;
79 SCC, squamous cell carcinoma; FIGO, International Federation of Gynecology and Obstetrics.

80

81 We subsequently compared the prognosis for SCC and Adeno/Adesq across all stages, including substages.
82 In stage I, where the tumor is confined to the cervix, there was little difference in prognosis between SCC
83 and Adeno/Adesq; both demonstrated a relatively favorable prognosis (Supplementary Figure S3A). Even in
84 stage IIIC1-T1, where the primary tumor is confined to the cervix but has metastasized to the pelvic lymph
85 nodes, the prognosis was comparable between the two groups (Supplementary Figure S3D). However, in
86 stage II, where the cancer has extended beyond the cervix, there was a trend toward a poorer prognosis in the
87 Adeno/Adesq group, although this was not significant (HR: 1.99, 95% CI: 0.75–5.31; Supplementary Figure
88 S3B). This difference became more pronounced in stage IIIC2-T2, where the local tumor had progressed to
89 T2 and was accompanied by pelvic lymph node metastasis, with Adeno/Adesq showing a significantly
90 poorer prognosis (HR: 3.41, 95% CI: 1.52–7.67; Supplementary Figure S3E). Furthermore, in stages IIIAB
91 and IV, Adeno/Adesq showed a significantly poorer prognosis compared to SCC (HR: 9.14, 95% CI: 2.65–
92 31.5; HR: 2.35, 95% CI: 1.45–3.75, respectively; Supplementary Figures S3C and S3J).

93

94 **Supplementary Fig. S4** Survival analysis by postoperative treatment in patients with stages IIIC-T1 and
95 IIIC-T2 who underwent surgery.



96

97

98 Kaplan–Meier curves comparing overall survival (OS) in patients who received concurrent
99 chemoradiotherapy (CCRT) and chemotherapy (Chemo).