

## Supplementary Information

### Prognostic significance of bone marrow FDG uptake in patients with gynecological cancer

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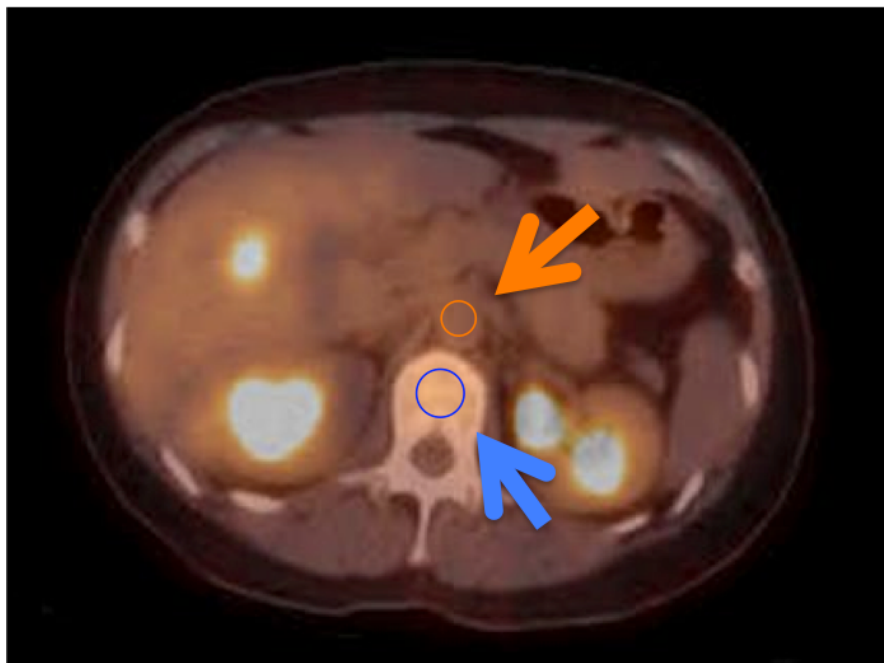
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## Supplementary Information

Supplementary Figure 1-8

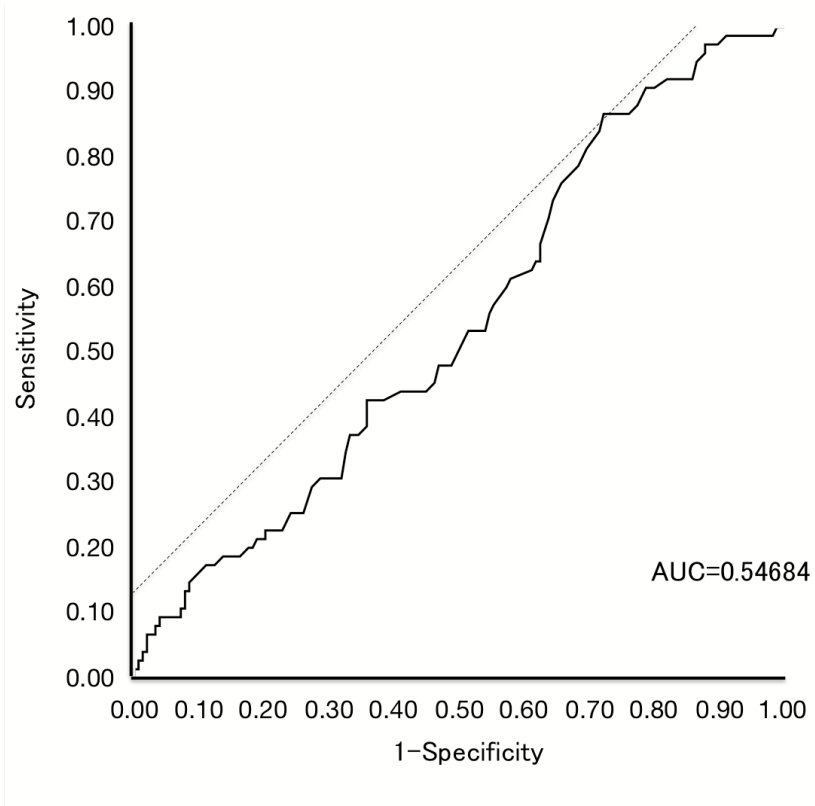
Supplementary table 1-10

Supplemental figure 1

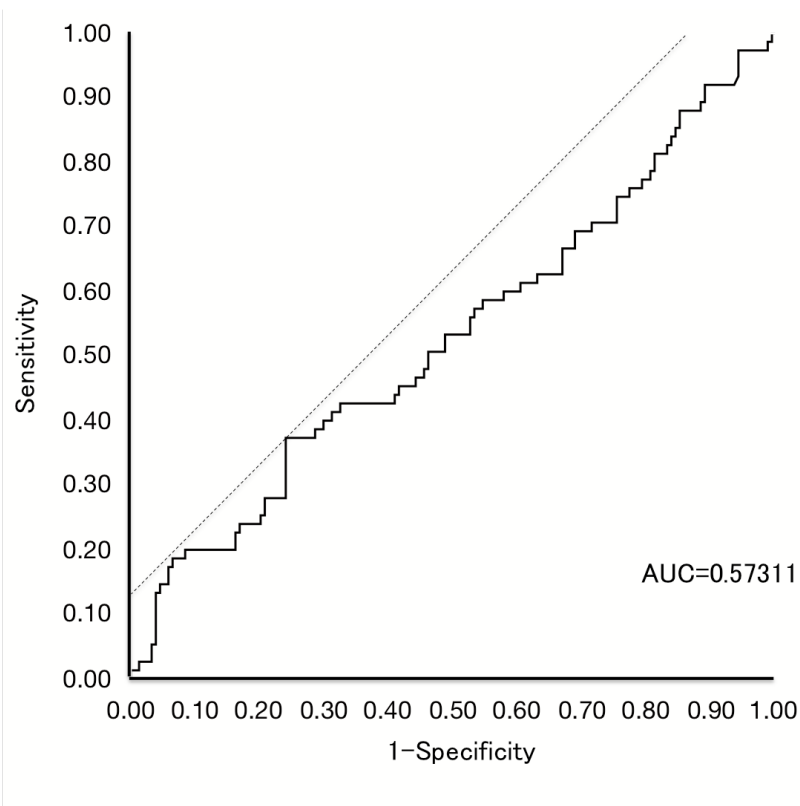


Supplemental figure 2

(A)

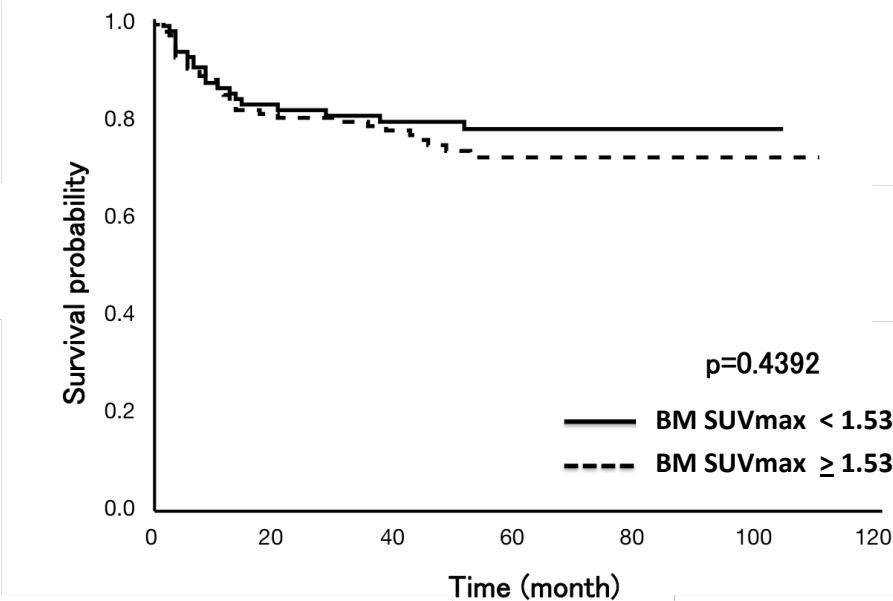


(B)

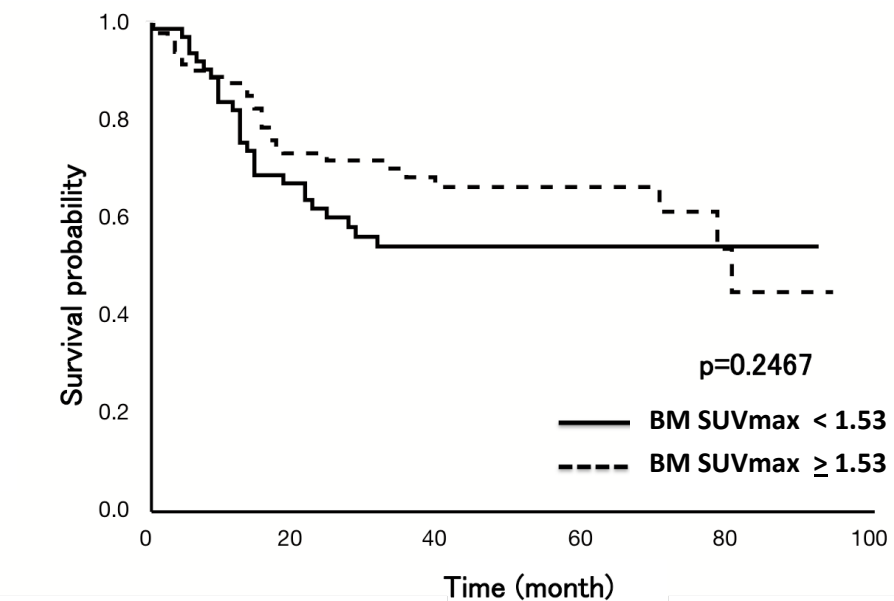


Supplemental figure 3

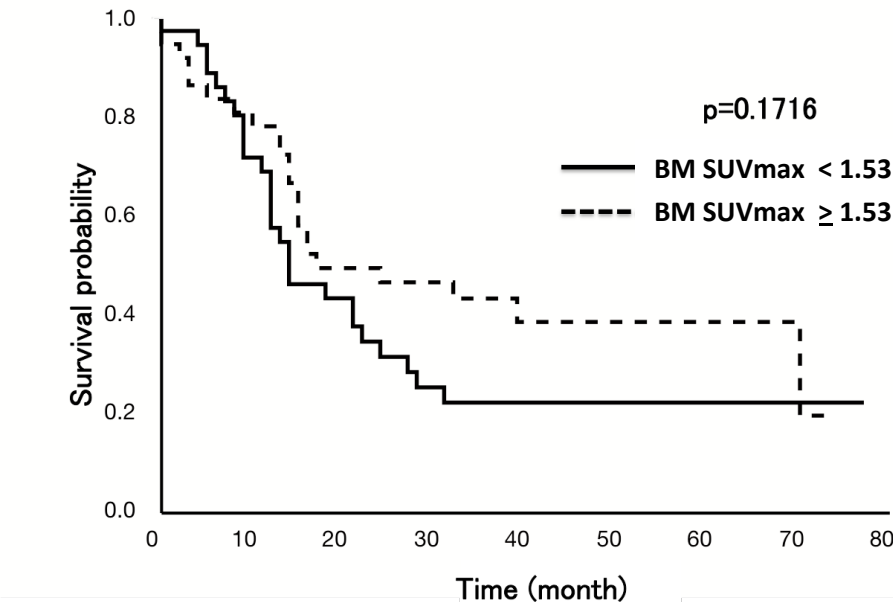
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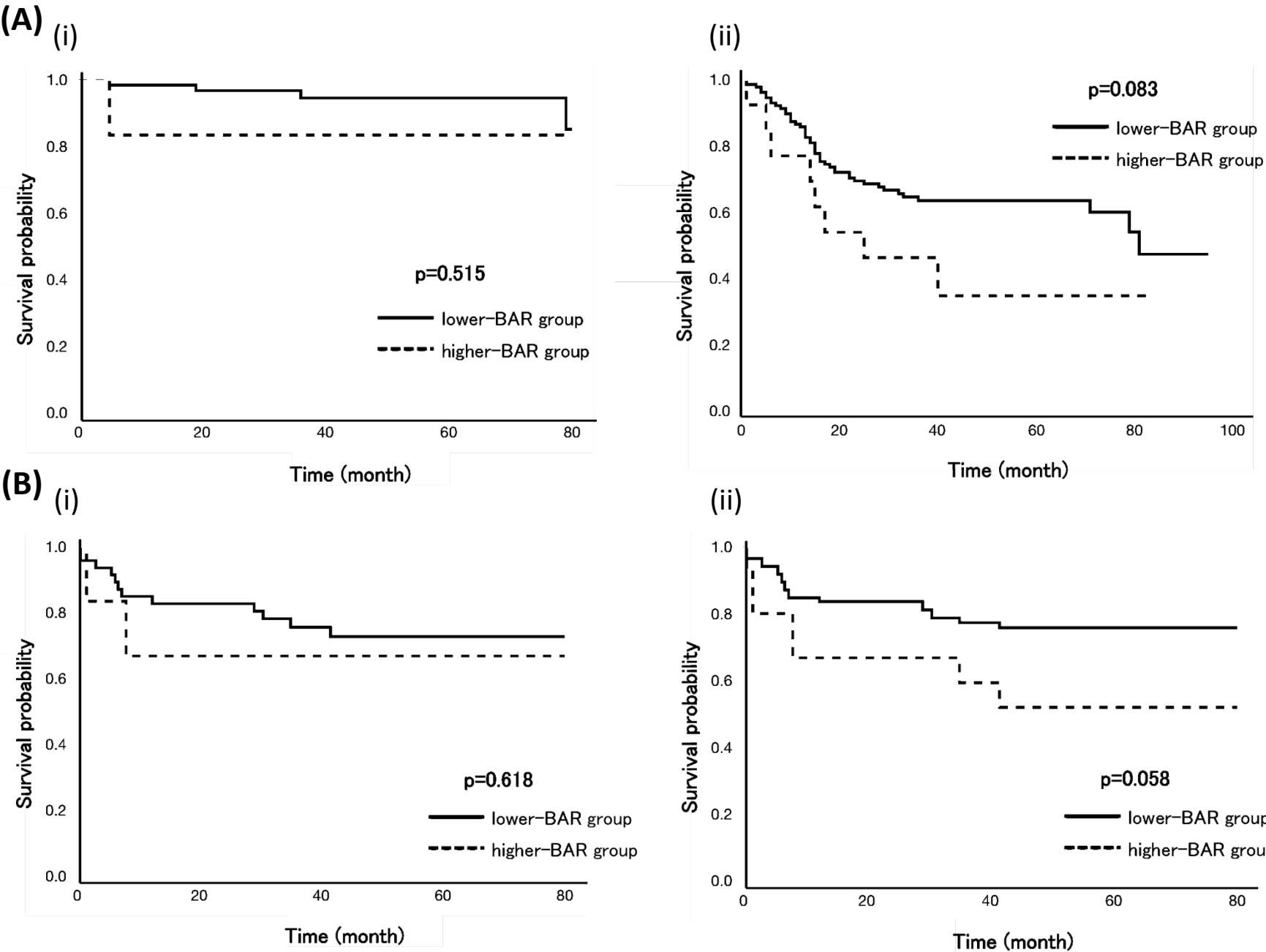
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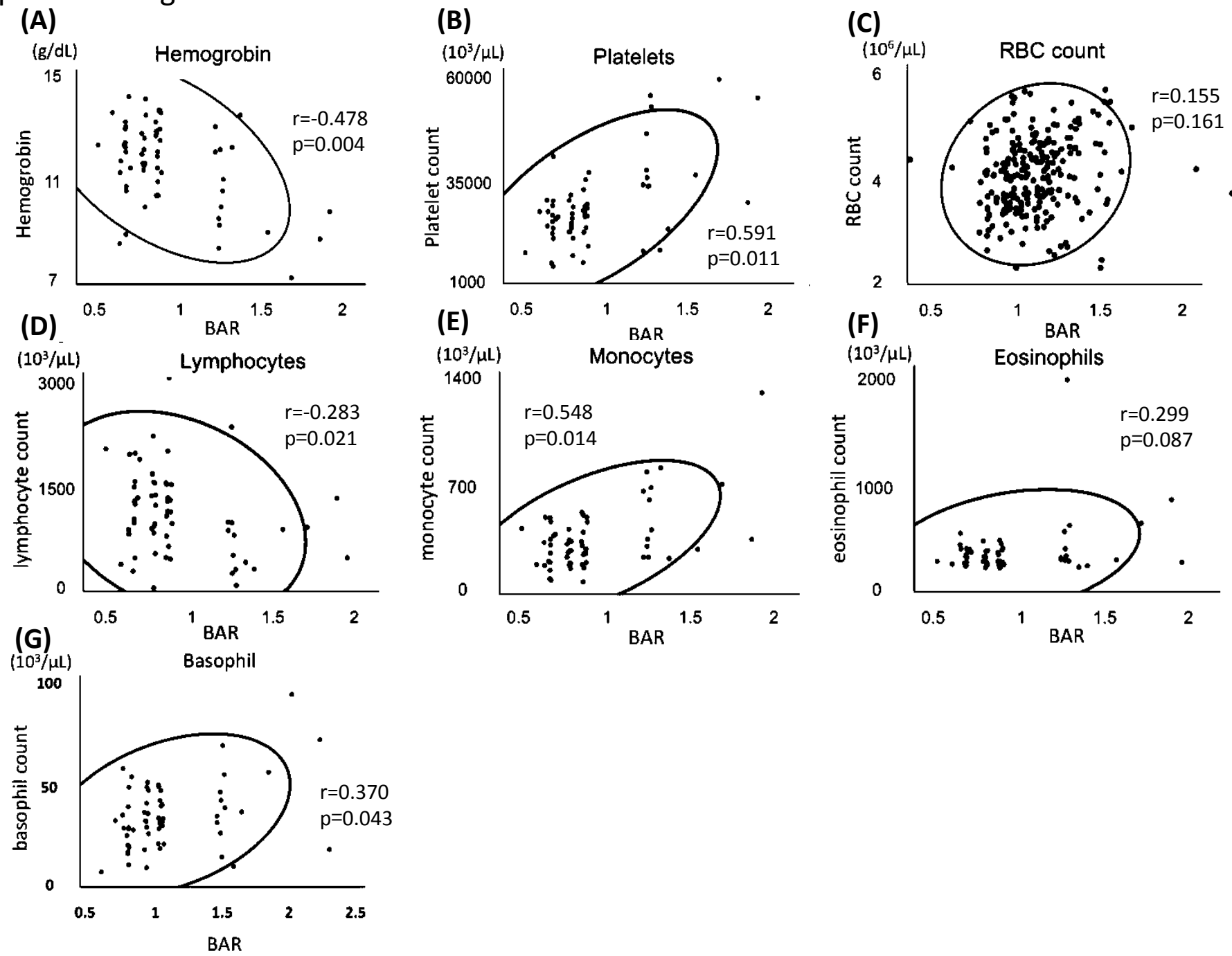
(C)



Supplemental figure 4

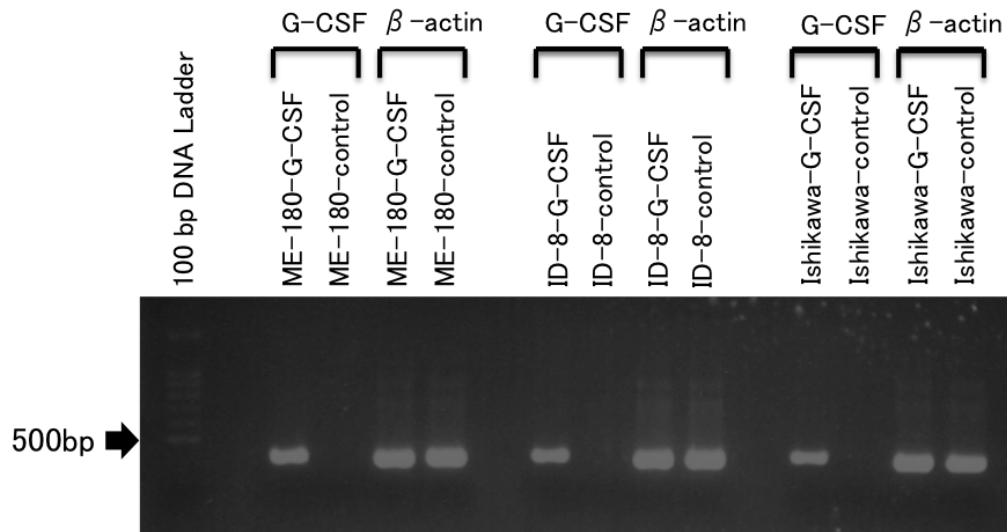


# Supplemental figure 5

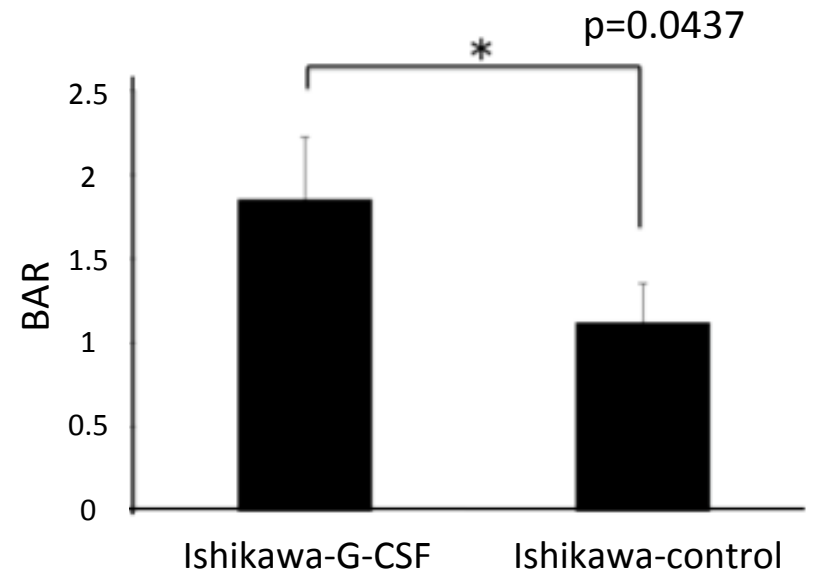


## Supplemental figure 6

(A)

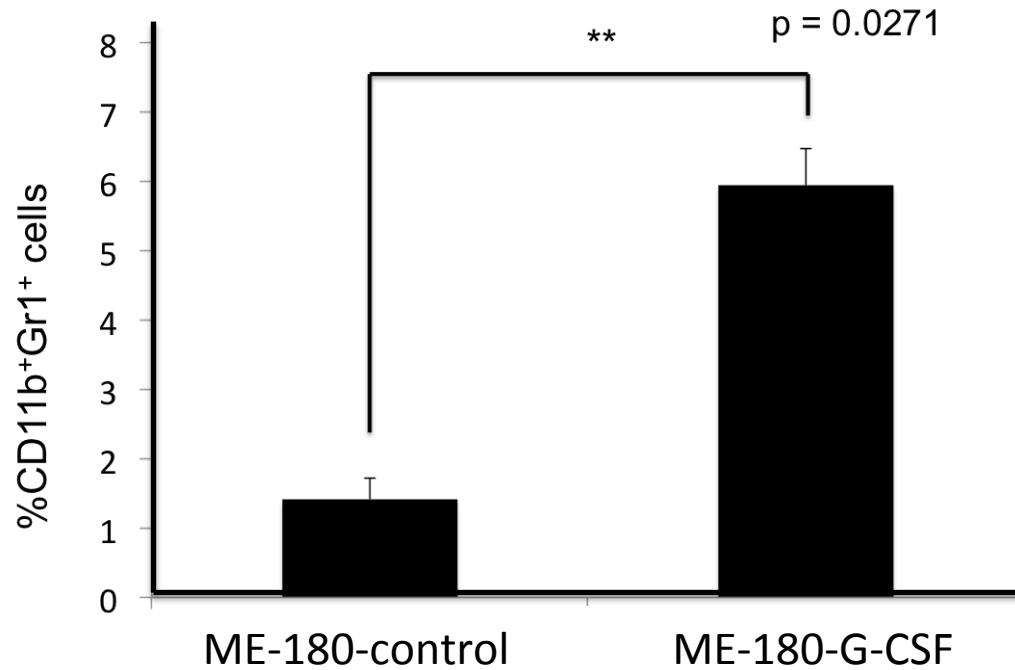


(B)

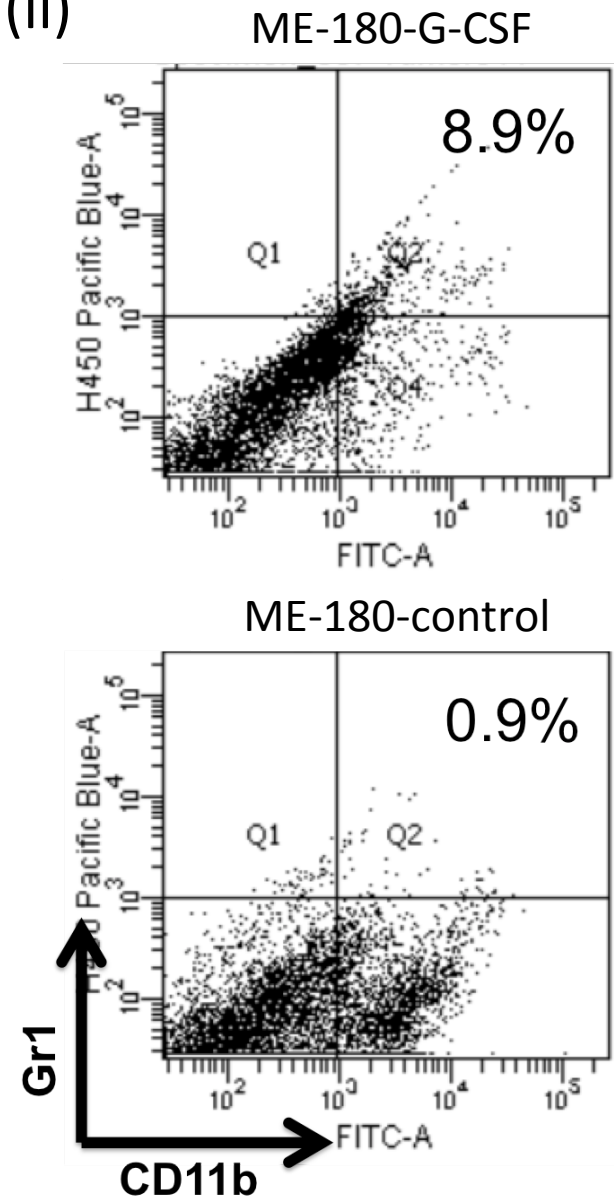


Supplemental figure 7

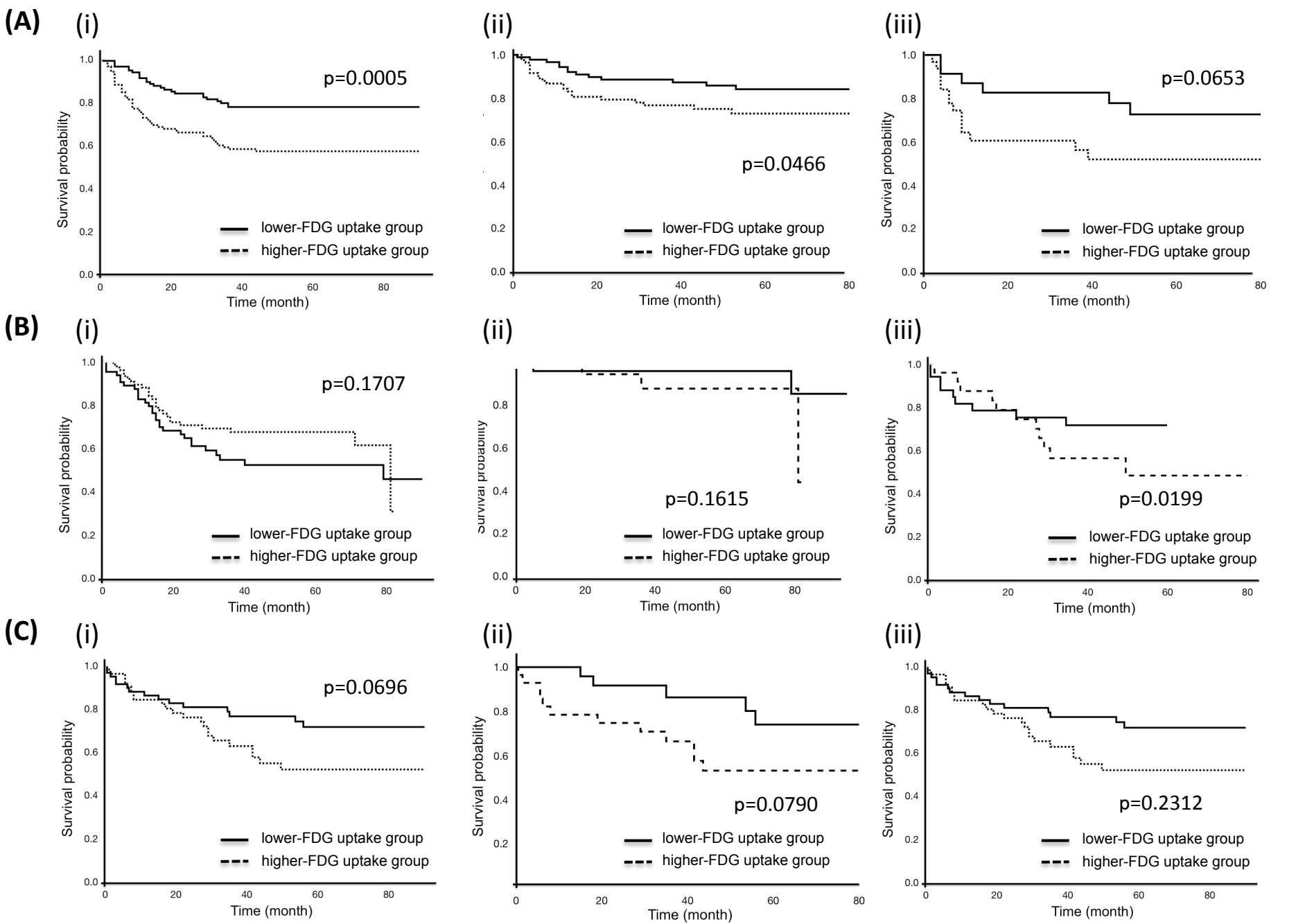
(i)



(ii)



# Supplemental figure 8



Supplemental Table 1. Clinical characteristics of the 231 cervical cancer patients

|                        |              | No. of Patients (%) | BM SUVmax $\leq 1.5$ | BM SUVmax $> 1.5$ | p-value |
|------------------------|--------------|---------------------|----------------------|-------------------|---------|
|                        |              | Median (Range)      | (n=99)               | (n=132)           |         |
| Age (y.o.)             |              | 54 (26-96)          | 51 (28-96)           | 56 (26-88)        | 0.512   |
| FIGO stage             | I            | 100 (43)            | 44 (44)              | 56 (42)           | 0.123   |
|                        | II           | 75 (33)             | 32 (32)              | 43 (33)           |         |
|                        | III          | 26 (11)             | 4 (4)                | 22 (17)           |         |
|                        | IV           | 30 (13)             | 19 (19)              | 11 (8)            |         |
| Primary treatment      | Surgery      | 119 (51)            | 48 (48)              | 71 (55)           | 0.721   |
|                        | Radiotherapy | 110 (48)            | 51 (51)              | 59 (44)           |         |
|                        | Others       | 2 (1)               | 1 (1)                | 1 (1)             |         |
| Histology              | SCC          | 161 (70)            | 88 (89)              | 73 (55)           | 0.067   |
|                        | Adeno        | 57 (25)             | 8 (8)                | 49 (37)           |         |
|                        | Others       | 13 (5)              | 3 (3)                | 10 (8)            |         |
| Lymph node metastasis* | Positive     | 47 (20)             | 22 (22)              | 25 (19)           | 0.691   |
|                        | Negative     | 184 (80)            | 77 (78)              | 107 (81)          |         |
| Tumor size (cm) **     |              | 35 (5-100)          | 45 (5-100)           | 35 (5-88)         | 0.171   |
| Hemoglobin (g/dl)      |              | 12.6 (7.2-15.3)     | 8.4 (7.3-12.7)       | 12.1 (8.2-15.3)   | 0.137   |
| CRP (mg/l)             |              | 0.04 (0-18.1)       | 0.21 (0-18.1)        | 0.04 (0-13.6)     | 0.141   |
| BM SUVmax              |              | 1.6 (0.56-2.8)      | 1.13 (0.56-1.53)     | 1.82 (1.55-2.8)   | <.0001  |

BM, bone marrow; SUV, standard uptake value; FIGO, International Federation of Gynecology and Obstetrics; SCC, squamous cell carcinoma; Adeno, adenocarcinoma ; CRP, C-reactive protein.

\* Lymph node metastasis assessed by FDG-PET/CT (SUV max $>2.5$  was considered positive for metastasis).

\*\* Tumor diameter was measured three dimensionally based on T2-weighted MRI images.

Supplemental Table 2. Clinical characteristics of the 161 endometrial cancer patients

| Charactristics         |                      | No. of Patients (%) | BM SUVmax $\leq 1.53$ | BM SUVmax $> 1.53$ | p-value |
|------------------------|----------------------|---------------------|-----------------------|--------------------|---------|
|                        |                      | Median (Range)      | (n=77)                | (n=84)             |         |
| Age (y.o.)             |                      | 58 (23-89)          | 59 (23-89)            | 53 (27-83)         | 0.717   |
| FIGO stage             | I                    | 27 (16)             | 15 (19)               | 12 (14)            | 0.031   |
|                        | II                   | 21 (13)             | 16 (21)               | 5 (6)              |         |
|                        | III                  | 54 (34)             | 20 (26)               | 34 (40)            |         |
|                        | IV                   | 59 (37)             | 26 (34)               | 33 (39)            |         |
| Primary treatment      | Surgery              | 33 (20)             | 19 (25)               | 14 (17)            | 0.066   |
|                        | Surgery+Chemotherapy | 112 (70)            | 49 (64)               | 63 (75)            |         |
|                        | Chemotherapy         | 13 (8)              | 9 (12)                | 4 (4)              |         |
|                        | Others               | 3 (2)               | 0 (0)                 | 3 (4)              |         |
| Histology              | Endometrioid         | 130 (81)            | 66 (86)               | 64 (71)            | 0.582   |
|                        | Non-endometrioid     | 31 (19)             | 11 (14)               | 20 (29)            |         |
| Lymph node metastasis* | Positive             | 49 (30)             | 22 (29)               | 27 (32)            | 0.814   |
|                        | Negative             | 112 (70)            | 55 (71)               | 57 (68)            |         |
| Tumor size (cm) **     |                      | 15 (0.5-88)         | 14 (0.5-72)           | 17 (1-88)          | 0.112   |
| Hemoglobin (g/dl)      |                      | 11.7 (6.3-14.4)     | 13.1 (8.8-14.4)       | 8.4 (6.3-10.7)     | 0.029   |
| CRP (mg/l)             |                      | 0.04 (0-8.53)       | 0.033 (0-4.14)        | 0.41 (0-8.53)      | 0.313   |

BM, bone marrow; SUV, standard uptake value; FIGO, International Federation of Gynecology and Obstetrics; CRP, C-reactive protein.

\* Lymph node metastasis assessed by FDG-PET/CT (SUV max $>2.5$  was considered positive for metastasis).

\*\* Tumor diameter was measured three dimensionally based on T2-weighted MRI images.

Supplemental Table 3. Clinical characteristics of the 167 ovarian cancer patients

|                        |                        | No. of Patients (%) | BM SUVmax $\leq 1.53$ | BM SUVmax $> 1.53$ | p-value |
|------------------------|------------------------|---------------------|-----------------------|--------------------|---------|
|                        |                        | Median (Range)      | (n=85)                | (n=82)             |         |
| Age (y.o.)             |                        | 57 (19-81)          | 53 (22-81)            | 59 (19-78)         | 0.811   |
| FIGO stage             | I                      | 67 (40.1)           | 30 (35)               | 37 (45)            | 0.652   |
|                        | II                     | 13 (7.8)            | 6 (7)                 | 7 (9)              |         |
|                        | III                    | 50 (29.9)           | 29 (34)               | 21 (26)            |         |
|                        | IV                     | 37 (22.2)           | 20 (24)               | 17 (21)            |         |
| Primary treatment      | Surgery                | 18 (11)             | 14 (17)               | 4(5)               | 0.173   |
|                        | Surgery + Chemotherapy | 147 (88)            | 70 (82)               | 77 (94)            |         |
|                        | Others                 | 2 (1)               | 1 (1)                 | 1 (1)              |         |
| Histology              | Serous                 | 88 (53)             | 51 (60)               | 37 (45)            | 0.107   |
|                        | Mucinous               | 16 (10)             | 10 (12)               | 6 (7)              |         |
|                        | Clear cell             | 35 (21)             | 14 (16)               | 21 (26)            |         |
|                        | Endometrioid           | 27 (16)             | 10 (12)               | 17 (21)            |         |
| Lymph node metastasis* | Positive               | 44 (26)             | 31 (25)               | 13 (38)            | 0.047   |
|                        | Negative               | 123 (74)            | 54 (75)               | 69 (62)            |         |
| Tumor size (cm) **     |                        | 9.8 (0.6-27)        | 9.0 (0.6-27)          | 12.1 (1.7-25)      | 0.399   |
| Hemoglobin (g/dl)      |                        | 11.1 (6.9-14.3)     | 13.1 (6.9-14.3)       | 9.9 (7.2-11.2)     | 0.273   |
| CRP (mg/l)             |                        | 0.04 (0-14.3)       | 0.04 (0-11.6)         | 0.21 (0-14.3)      | 0.130   |
| BM SUVmax              |                        | 1.53 (1.08-2.36)    | 1.69 (1.08-1.53)      | 2.22 (1.55-2.8)    | <.0001  |

BM, bone marrow; SUV, standard uptake value; FIGO, International Federation of Gynecology and Obstetrics; CRP, C-reactive protein.

\* Lymph node metastasis assessed by FDG-PET/CT (SUV max>2.5 was considered positive for metastasis).

\*\* Tumor diameter was measured three dimensionally based on T2-weighted MRI images.

Supplemental Table 4. Univariate and multivariate analyses for PFS in cervical cancer patients

|                   |        | Univariate Analysis   |         | Multivariate Analysis |         |
|-------------------|--------|-----------------------|---------|-----------------------|---------|
|                   |        | Hazard Ratio (95% CI) | p-value | Hazard Ratio (95% CI) | p-value |
| Age               | <55    | 1                     | 0.266   | 1                     | 0.064   |
|                   | 55≤    | 1.37 (0.78-2.45)      |         | 1.86 (0.96-3.67)      |         |
| Histology         | SCC    | 1                     | 0.843   | 1                     | 0.119   |
|                   | Adeno  | 1.06 (0.58-2.07)      |         | 1.78 (0.86-3.58)      |         |
| Tumor Size        | <40    | 1                     | 0.001   | 1                     | 0.041   |
|                   | 40≤    | 2.54 (1.43-4.58)      |         | 2.03 (1.03-4.05)      |         |
| Hemoglobin (g/dl) | <10    | 1                     | 0.001   | 1                     | 0.004   |
|                   | 10≤    | 0.34 (0.18-0.66)      |         | 0.32 (0.16-0.68)      |         |
| FIGO stage        | I-II   | 1                     | 0.013   | 1                     | 0.923   |
|                   | III-IV | 2.11 (1.18-3.66)      |         | 0.96 (0.44-1.94)      |         |
| CRP (mg/l)        | <1     | 1                     | 0.270   | 1                     | 0.270   |
|                   | 1≤     | 0.95 (0.50-1.72)      |         | 0.68 (0.32-1.32)      |         |
| BM SUVmax         | <1.53  | 1                     | 0.440   | 1                     | 0.472   |
|                   | 1.53≤  | 1.24 (0.72-2.19)      |         | 1.28 (0.65-2.61)      |         |

CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; CRP, C-reactive protein; BM, Bone marrow; SUV, standard uptake value.

P-values were calculated using the two-sided Wald test in the Cox proportional hazard model.

Supplemental Table 5. Univariate and multivariate analyses for PFS in ovarian cancer patients

|                   |            | Univariate Analysis   |         | Multivariate Analysis |         |
|-------------------|------------|-----------------------|---------|-----------------------|---------|
|                   |            | Hazard Ratio (95% CI) | p-value | Hazard Ratio (95% CI) | p-value |
| Age               | <55        | 1                     | 0.416   | 1                     | 0.268   |
|                   | 55≤        | 1.41 (0.25-1.81)      |         | 1.62 (0.89-2.37)      |         |
| Histology         | Serous     | 1                     | 0.276   | 1                     | 0.411   |
|                   | Non serous | 1.06 (0.58-5.07)      |         | 1.05 (0.72-3.63)      |         |
| Tumor Size        | <30        | 1                     | 0.011   | 1                     | 0.414   |
|                   | 30≤        | 2.07 (0.99-5.19)      |         | 1.76 (1.69-4.84)      |         |
| Hemoglobin (g/dl) | <10        | 1                     | 0.001   | 1                     | 0.032   |
|                   | 10≤        | 0.34 (0.13-1.04)      |         | 0.45 (0.11-1.73)      |         |
| FIGO stage        | I-II       | 1                     | 0.009   | 1                     | 0.873   |
|                   | III-IV     | 3.05 (1.01-4.11)      |         | 1.11 (0.44-2.12)      |         |
| CRP (mg/l)        | <1         | 1                     | 0.879   | 1                     | 0.531   |
|                   | 1≤         | 0.98 (0.61-1.56)      |         | 0.88 (0.53-1.63)      |         |
| BM SUVmax         | <1.53      | 1                     | 0.253   | 1                     | 0.312   |
|                   | 1.53≤      | 1.36 (0.80-2.32)      |         | 1.29 (0.17-3.92)      |         |

CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; CRP, C-reactive protein; BM, Bone marrow; SUV, standard uptake value.

P-values were calculated using the two-sided Wald test in the Cox proportional hazard model.

Supplemental Table 6. Univariate and multivariate analyses for PFS in endometrial cancer patients

|                   |                  | Univariate Analysis   |         | Multivariate Analysis |         |
|-------------------|------------------|-----------------------|---------|-----------------------|---------|
|                   |                  | Hazard Ratio (95% CI) | p-value | Hazard Ratio (95% CI) | p-value |
| Age               | <55              | 1                     | 0.226   | 1                     | 0.164   |
|                   | 55≤              | 1.47 (0.78-2.65)      |         | 1.86 (0.77-4.49)      |         |
| Histology         | Endometrioid     | 1                     | 0.345   | 1                     | 0.902   |
|                   | Non-endometrioid | 1.27 (0.57-2.17)      |         | 1.05 (0.43-2.46)      |         |
| Tumor Size        | <40              | 1                     | 0.013   | 1                     | 0.002   |
|                   | 40≤              | 2.12 (1.03-3.58)      |         | 4.21 (1.70-10.38)     |         |
| Hemoglobin (g/dl) | <10              | 1                     | 0.001   | 1                     | 0.082   |
|                   | 10≤              | 0.34 (0.18-0.66)      |         | 0.36 (0.13-1.14)      |         |
| FIGO stage        | I-II             | 1                     | 0.021   | 1                     | 0.437   |
|                   | III-IV           | 2.31 (1.38-3.51)      |         | 2.10 (0.40-8.73)      |         |
| CRP (mg/l)        | <1               | 1                     | 0.593   | 1                     | 0.187   |
|                   | 1≤               | 0.91 (0.40-1.54)      |         | 0.51 (0.16-1.35)      |         |
| BM SUVmax         | <1.53            | 1                     | 0.917   | 1                     | 0.323   |
|                   | 1.53≤            | 1.14 (0.48-2.33)      |         | 1.61 (0.62-4.15)      |         |

CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; CRP, C-reactive protein; BM, Bone marrow; SUV, standard uptake value.

P-values were calculated using the two-sided Wald test in the Cox proportional hazard model.

Supplemental Table 7. Clinical characteristics of the lower- and higher-BAR group patients with endometrial cancer

| Charactristics         |                      | lower-BAR group<br>(n=140) | higher-BAR group<br>(n=21) | p-value |
|------------------------|----------------------|----------------------------|----------------------------|---------|
| Age (y.o.)             |                      | 58 (23-89)                 | 49 (29-78)                 | 0.217   |
| FIGO stage             | I                    | 23 (16)                    | 4 (19)                     | 0.717   |
|                        | II                   | 17 (12)                    | 4 (19)                     |         |
|                        | III                  | 48 (34)                    | 6 (29)                     |         |
|                        | IV                   | 52 (37)                    | 7 (33)                     |         |
| Primary treatment      | Surgery              | 32 (23)                    | 1 (5)                      | 0.361   |
|                        | Surgery+Chemotherapy | 95 (68)                    | 17 (81)                    |         |
|                        | Chemotherapy         | 11 (8)                     | 2 (10)                     |         |
|                        | Others               | 2 (1)                      | 1 (6)                      |         |
| Histology              | Endometrioid         | 111 (79)                   | 19 (90)                    | 0.917   |
|                        | Non-endometrioid     | 29 (21)                    | 2 (10)                     |         |
| Lymph node metastasis* | Positive             | 38 (27)                    | 11 (52)                    | 0.024   |
|                        | Negative             | 102 (73)                   | 10 (48)                    |         |
| Tumor size (cm) **     |                      | 15 (0.5-88)                | 13 (1-60)                  | 0.412   |
| Hemoglobin (g/dl)      |                      | 12.1 (8.3-14.4)            | 9.4 (6.3-11.2)             | 0.037   |
| CRP (mg/l)             |                      | 0.048 (0-2.64)             | 0.28 (0-8.53)              | 0.083   |
| BM SUV                 |                      | 1.54 (0.68-2,16)           | 2.04 (1.56-3.46)           | 0.025   |
| BM/Ao ratio            |                      | 1.05 (0.76-1.49)           | 1.9 (1.50-3.09)            | <.0001  |

BAR, BM-to-Aorta ratio of FDG uptake; FIGO, International Federation of Gynecology and Obstetrics; CRP, C-reactive protein. BM, bone marrow; SUV, standard uptake value; Ao, Aorta.

\* Lymph node metastasis assessed by FDG-PET/CT (SUV max>2.5 was considered positive for metastasis).

\*\* Tumor diameter was measured three dimensionally based on T2-weighted MRI images.

Supplemental Table 8. Clinical characteristics of the lower- and higher-BAR group patients with ovarian cancer

|                        |                        | lower-BAR group<br>(n=146) | higher-BAR group<br>(n=21) | p-value |
|------------------------|------------------------|----------------------------|----------------------------|---------|
| Age (y.o.)             |                        | 57 (19-81)                 | 61 (23-77)                 | 0.782   |
| FIGO stage             | I                      | 59 (42)                    | 8 (38)                     | <.0001  |
|                        | II                     | 12 (9)                     | 1 (5)                      |         |
|                        | III                    | 47 (34)                    | 3 (14)                     |         |
|                        | IV                     | 28 (20)                    | 9 (43)                     |         |
| Primary treatment      | Surgery                | 15 (10)                    | 3 (14)                     | 0.361   |
|                        | Surgery + Chemotherapy | 130 (89)                   | 17 (81)                    |         |
|                        | Others                 | 1 (1)                      | 1 (5)                      |         |
| Histology              | Serous                 | 77 (53)                    | 11 (52)                    | 0.408   |
|                        | Mucinous               | 13 (9)                     | 3 (14)                     |         |
|                        | Clear cell             | 28 (19)                    | 7 (33)                     |         |
|                        | Endometrioid           | 25 (17)                    | 2 (10)                     |         |
| Lymph node metastasis* | Positive               | 36 (25)                    | 8 (38)                     | 0.468   |
|                        | Negative               | 110 (75)                   | 13 (62)                    |         |
| Tumor size (cm) **     |                        | 9.8 (0.6-27)               | 11.4 (1.2-22)              | 0.377   |
| Hemoglobin (g/dl)      |                        | 11.7 (7.1-14.3)            | 8.9 (6.9-12.2)             | 0.293   |
| CRP (mg/l)             |                        | 0.04 (0-12.6)              | 0.41 (0-14.3)              | 0.130   |
| BM SUV                 |                        | 1.69 (1.08-2.66)           | 2.22 (1.39-2.8)            | 0.007   |
| BM/Ao ratio            |                        | 1.02 (0.82-1.49)           | 1.53 (1.50-1.69)           | <.0001  |

BAR, BM-to-Aorta ratio of FDG uptake; FIGO, International Federation of Gynecology and Obstetrics; CRP, C-reactive protein; BM, bone marrow; SUV, standard uptake value; Ao, Aorta.

\* Lymph node metastasis assessed by FDG-PET/CT (SUV max>2.5 was considered positive for metastasis).

\*\* Tumor diameter was measured three dimensionally based on T2-weighted MRI images.

Supplemental Table 9. Univariate analyses for PFS in ovarian cancer patients

|                   |            | Univariate Analysis   |         |
|-------------------|------------|-----------------------|---------|
|                   |            | Hazard Ratio (95% CI) | p-value |
| Age               | <55        | 1                     | 0.416   |
|                   | 55≤        | 1.41 (0.25-1.81)      |         |
| Histology         | Serous     | 1                     | 0.276   |
|                   | Non serous | 1.06 (0.58-5.07)      |         |
| Tumor Size        | <30        | 1                     | 0.011   |
|                   | 30≤        | 2.07 (0.99-5.19)      |         |
| Hemoglobin (g/dl) | <10        | 1                     | 0.001   |
|                   | 10≤        | 0.34 (0.13-1.04)      |         |
| FIGO stage        | I-II       | 1                     | 0.009   |
|                   | III-IV     | 3.05 (1.01-4.11)      |         |
| CRP (mg/l)        | <1         | 1                     | 0.879   |
|                   | 1≤         | 0.98 (0.61-1.56)      |         |
| BM/Ao Ratio       | <1.5       | 1                     | 0.083   |
|                   | 1.5≤       | 1.57 (0.88-2.12)      |         |

CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; CRP, C-reactive protein; BM, bone marrow; Ao, Aorta. P-values were calculated using the two-sided Wald test in the Cox proportional hazard model.

Supplemental Table 10. Univariate analyses for PFS in endometrial cancer patients

|                   |                  | Univariate Analysis   |         |
|-------------------|------------------|-----------------------|---------|
|                   |                  | Hazard Ratio (95% CI) | p-value |
| Age               | <55              | 1                     | 0.226   |
|                   | 55≤              | 1.47 (0.78-2.65)      |         |
| Histology         | Endometrioid     | 1                     | 0.345   |
|                   | Non-endometrioid | 1.27 (0.57-2.17)      |         |
| Tumor Size        | <40              | 1                     | 0.013   |
|                   | 40≤              | 2.12 (1.03-3.58)      |         |
| Hemoglobin (g/dl) | <10              | 1                     | 0.001   |
|                   | 10≤              | 0.34 (0.18-0.66)      |         |
| FIGO stage        | I-II             | 1                     | 0.021   |
|                   | III-IV           | 2.31 (1.38-3.51)      |         |
| CRP (mg/l)        | <1               | 1                     | 0.593   |
|                   | 1≤               | 0.91 (0.40-1.54)      |         |
| BM/Ao Ratio       | <1.5             | 1                     | 0.058   |
|                   | 1.5≤             | 1.61 (1.07-2.36)      |         |

CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; CRP, C-reactive protein; BM, bone marrow; Ao, Aorta. P-values were calculated using the two-sided Wald test in the Cox proportional hazard model.