

## SUPPLEMENTAL MATERIAL

**Figure S1** Flow chart of patient inclusion with locally advanced cervical cancer and suspicious bulky nodes  $\geq 1.5$  cm.

**Abbreviations:** cN1, presence of regional lymph node metastasis bases on clinical examination and imaging; C(H)RT, radiotherapy with or without chemotherapy and/or hyperthermia. \* Data were collected on project basis for cervical cancer patients diagnosed between 2009 and 2017.

**Table S1** Logistic regression analysis for total patients experiencing surgery, radiotherapy or chemotherapy related toxicities.

| Variables                 | OR   | 95% CI    | p-value |
|---------------------------|------|-----------|---------|
| <b>Therapy group</b>      |      |           |         |
| Debulking                 | 1.00 | Reference |         |
| Boosting                  | 0.37 | 0.16-0.83 | 0.017*  |
| Neither                   | 0.89 | 0.30-2.70 | 0.84    |
| <b>Age†</b>               | 1.04 | 1.01-1.07 | 0.003*  |
| <b>Primary treatment</b>  |      |           |         |
| CRT                       | 1.00 | Reference |         |
| (C)HRT                    | 1.17 | 0.42-3.24 | 0.23    |
| RT only                   | 0.06 | 0.01-0.59 | 0.015*  |
| <b>Radiotherapy field</b> |      |           |         |
| Pelvic                    | 1.00 | Reference |         |
| Pelvic + para-aortic      | 1.20 | 0.58-2.47 | 0.62    |
| <b>Bulky node size†</b>   | 1.03 | 0.99-1.07 | 0.18    |
| <b>Constant</b>           | 0.04 | 0.01-0.23 | <0.001* |

**Abbreviations:** RT, radiotherapy; CRT, chemoradiation; (C)HRT, (chemotherapy with) hyperthermia and radiotherapy; OR, odds ratio; CI, confidence interval. † Continues scale; \* statistically significant.

14   **Table S2**   Multivariable subgroup analysis for nodal debulking with and without boost, and for bulky nodes ≥2 cm regarding overall and relapse-free survival.

| Variables                  | Debulking with/without boost<br>(n=60) |           |         |                       |           |         | Bulky nodes ≥2 cm<br>(n=92) |           |         |                       |           |         |
|----------------------------|--|-----------|---------|-----------------------|-----------|---------|-----------------------------|-----------|---------|-----------------------|-----------|---------|
|                            | Overall survival                       |           |         | Relapse-free survival |           |         | Overall survival            |           |         | Relapse-free survival |           |         |
|                            | HR                                     | 95% CI    | p-value | HR                    | 95% CI    | p-value | HR                          | 95% CI    | p-value | HR                    | 95% CI    | p-value |
| <b>Therapy group</b>       |  |           |         |                       |           |         |                             |           |         |                       |           |         |
| Debulking only             | 1.00                                   | Reference |         | 1.00                  | Reference |         |                             |           |         |                       |           |         |
| Debulking with boost       | 2.47                                   | 1.22-5.00 | 0.012*  | 2.37                  | 1.14-4.93 | 0.021*  |                             |           |         |                       |           |         |
| Boosting                   |  |           |         |                       |           |         | 0.67                        | 0.35-1.28 | 0.23    | 0.90                  | 0.48-1.69 | 0.75    |
| Neither                    |  |           |         |                       |           |         | 0.61                        | 0.23-1.65 | 0.33    | 0.73                  | 0.25-2.13 | 0.57    |
| <b>Age†</b>                | 1.03                                   | 1.00-1.06 | 0.07    | 1.02                  | 0.99-1.05 | 0.12    | 1.02                        | 1.00-1.04 | 0.023*  | 1.02                  | 1.00-1.04 | 0.08    |
| <b>Bulky node location</b> |  |           |         |                       |           |         |                             |           |         |                       |           |         |
| Pelvic                     | 1.00                                   | Reference |         | 1.00                  | Reference |         | 1.00                        | Reference |         | 1.00                  | Reference |         |
| Common iliac               | 0.80                                   | 0.24-2.69 | 0.72    | 0.57                  | 0.13-2.42 | 0.45    | 1.08                        | 0.33-3.54 | 0.90    | 0.37                  | 0.05-2.71 | 0.33    |
| Para-aortic                | 3.10                                   | 1.04-9.23 | 0.042*  | 2.16                  | 0.64-7.29 | 0.22    | 1.70                        | 0.69-4.18 | 0.25    | 1.92                  | 0.74-4.99 | 0.18    |
| <b>Bulky nodes size†</b>   | 1.01                                   | 0.98-1.04 | 0.49    | 1.02                  | 0.99-1.05 | 0.29    | 1.01                        | 0.98-1.03 | 0.57    | 1.01                  | 0.98-1.03 | 0.59    |

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16   *Abbreviations:* HR, hazard ratio; CI, confidence interval. † Continues scale; \* statistically significant.

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19 **Table S3** Patients and treatment characteristics categorized per treatment group for patients with  
 20 bulky nodes  $\geq 2$  cm.

| Characteristics   | Overall<br>(n=92)   | Boosting<br>(n=35) | Debulking<br>(n=48) | Neither<br>(n=9)  | P-value     |
|---|---------------------|--------------------|---------------------|-------------------|-------------|
| <b>Age (years)</b>  | 53 (27-86)          | 50 (25-77)         | 54 (31-82)          | 52 (25-77)        | 0.07        |
| <b>Charlson comorbidity index</b>                         |                     |                    |                     |                   | 0.19        |
| 0   | 55 (60%)            | 20 (57%)           | 21 (67%)            | 16 (62%)          |             |
| 1   | 14 (15%)            | 7 (20%)            | 5 (10%)             | 2 (8%)            |             |
| $\geq 2$  | 7 (8%)              | 4 (11%)            | 3 (6%)              | 3 (12%)           |             |
| Unknown   | 16 (17%)            | 4 (11%)            | 8 (17%)             | 5 (19%)           |             |
| <b>Squamous cell antigen†<br/>(ng/mL)</b>                 | 11.4<br>(0.3-224.3) | 7.5<br>(0.5-224.3) | 14.8<br>(1.0-176.0) | 5.0<br>(0.3-79.5) | 0.24        |
| <b>FIGO 2009 stage</b>                                    |                     |                    |                     |                   | 0.21        |
| IB2   | 17 (18%)            | 4 (11%)            | 13 (27%)            | -                 |             |
| II  | 48 (52%)            | 18 (51%)           | 22 (46%)            | 8 (89%)           |             |
| III   | 23 (25%)            | 11 (31%)           | 11 (23%)            | 1 (11%)           |             |
| IVA   | 4 (4%)              | 2 (6%)             | 2 (4%)              | -                 |             |
| <b>Primary tumor size (cm)</b>                            |                     |                    |                     |                   | 0.42        |
| $\leq 4$  | 16 (18%)            | 4 (11%)            | 11 (23%)            | 1 (13%)           |             |
| $> 4$   | 75 (82%)            | 31 (89%)           | 37 (77%)            | 7 (88%)           |             |
| <b>Histology</b>  |                     |                    |                     |                   | $> 0.99$    |
| Squamous  | 82 (89%)            | 31 (89%)           | 43 (90%)            | 8 (89%)           |             |
| Non-squamous  | 10 (11%)            | 4 (11%)            | 5 (10%)             | 1 (11%)           |             |
| <b>Bulky node size (mm)</b>                               | 25 (20-86)          | 24 (20-86)         | 24 (20-83)          | 26 (20-60)        | 0.64        |
| <b>Bulky node location‡</b>                               |                     |                    |                     |                   | 0.64        |
| Pelvic  | 81 (88%)            | 29 (83%)           | 44 (92%)            | 8 (89%)           |             |
| Common iliac  | 4 (4%)              | 2 (6%)             | 2 (4%)              | -                 |             |
| Para-aortic   | 7 (8%)              | 4 (11%)            | 2 (4%)              | 1 (11%)           |             |
| <b>Diagnosis to primary<br/>treatment interval (days)</b> | 55 (11-125)         | 50 (11-71)         | 62 (28-107)         | 61 (34-125)       | $< 0.001$   |
| <b>Primary treatment</b>                                  |                     |                    |                     |                   | 0.005*      |
| CRT   | 75 (82%)            | 24 (69%)           | 45 (94%)            | 6 (67%)           |             |
| (C)HRT  | 10 (11%)            | 8 (23%)            | 1 (2%)              | 1 (11%)           |             |
| RT only   | 7 (8%)              | 3 (9%)             | 2 (4%)              | 2 (22%)           |             |
| <b>Brachytherapy (yes)</b>                                | 85 (92%)            | 33 (94%)           | 46 (96%)            | 6 (67%)           | 0.023*      |
| <b>Nodal boost (yes)</b>                                  | 57 (62%)            | 35 (100%)          | 22 (46%)            | -                 | $< 0.001^*$ |
| <b>Radiotherapy field</b>                                 |                     |                    |                     |                   | 0.09        |
| Pelvic  | 48 (52%)            | 19 (54%)           | 22 (46%)            | 7 (78%)           |             |
| Pelvic + para-aortic                                      | 40 (43%)            | 16 (46%)           | 23 (48%)            | 1 (11%)           |             |
| Other/unknown   | 4 (4%)              | -                  | 3 (6%)              | 1 (11%)           |             |
| <b>Recurrence</b>   | 48 (52%)            | 19 (54%)           | 25 (52%)            | 4 (44%)           | 0.91        |
| <b>Recurrence location§</b>                               |                     |                    |                     |                   | 0.75        |
| Central pelvic  | 6 (13%)             | 3 (16%)            | 3 (12%)             | -                 | $> 0.99$    |

|                     |          |          |          |         |      |
|---------------------|----------|----------|----------|---------|------|
| Lateral pelvic      | 10 (21%) | 4 (21%)  | 6 (24%)  | -       | 0.87 |
| Para-aortic         | 17 (35%) | 5 (26%)  | 11 (44%) | 1 (25%) | 0.48 |
| Distant             | 37 (77%) | 14 (74%) | 20 (80%) | 3 (75%) | 0.88 |
| Unknown             | 1 (2%)   | 1 (5%)   | -        | -       | -    |
| <b>Vital status</b> |          |          |          |         | 0.83 |
| Alive               | 43 (47%) | 18 (51%) | 21 (44%) | 4 (44%) |      |
| Deaths              | 49 (53%) | 17 (49%) | 27 (56%) | 5 (56%) |      |

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22 *Abbreviations:* FIGO, International Federation of Gynecology and Obstetrics; CRT, chemoradiation;

23 (C)HRT, (chemotherapy with) hyperthermia and radiotherapy; RT, radiotherapy. † Pretreatment level for

24 squamous cell type only; ‡ most cranial lymph node region was decisive; § some patients had multiple

25 recurrence locations; \* statistically significant.