STATEC

A randomised trial of non-Selective versus selective adjuvant Therapy in high risk Apparent sTage 1 Endometrial Cancer

Adjuvant Treatment Guidance

Version 3.0, 22nd June 2018

This document provides guidance for sites regarding adjuvant treatment of patients randomised to the STATEC trial. Its contents are not mandatory but strongly recommended for participating sites.

Where a participating site, or site in setup, is considering adjuvant treatment outside of those listed in this document, the proposed treatment(s) should be submitted to the trial management group (TMG) at ctc.STATEC@ucl.ac.uk to ensure compatibility with the trial.

Women treated on the previous guidance prior to the results of the studies below, will continue on the trial as before. Sites wishing to use the previous adjuvant guidance can continue to do so but should contact the TMG via ctc.STATEC@ucl.ac.uk.

For questions concerning this, please contact the TMG at ctc.STATEC@ucl.ac.uk

Summary of recommended adjuvant treatment schedules based on PORTEC 2 and 3, GOG-249 and GOG-258 clinical trials

Lymphadenectomy Patients

1) **Node Positive:** External beam radiotherapy (EBRT) and chemotherapy - two options:
   a. PORTEC-3 schedule: EBRT with 2 cycles of cisplatin followed by 4 cycles of carboplatin-paclitaxel, or
   b. Sequential radiotherapy (RT) and chemotherapy: EBRT with 6 cycles of carboplatin-paclitaxel (either before or after RT).

2) **Node Negative:** Vaginal brachytherapy alone
   Unless: Node negative but otherwise stage III (e.g. ovarian involvement, growth beyond serosa) please see table 1 below.

No Lymphadenectomy Patients

Lymph nodes unknown: Please use Table 1.

Table 1. *Outlines the recommended treatment based on the results from the PORTEC 2 and 3, GOG-249 and GOG-258 trials. This also includes if the final histology on the post hysterectomy specimen has a different pathology to the initial high grade biopsy*

Final stage	Grade	LVSI*	Treatment	Text Reference	Paper Reference
IA	1-2	No	no adjuvant treatment	n/a	ASTEC, PORTEC-1
IA	3	No	Vaginal brachytherapy alone	Section 2	PORTEC-2
IA	3	Yes	EBRT alone	Section 1c	GOG-249/PORTEC-3
IB	1-2	No	Vaginal brachytherapy alone	Section 2	PORTEC-2, ASTEC
IB	1-2	Yes	EBRT alone	Section 1c	GOG-249
IB	3	any	EBRT alone	Section 1c	GOG-249/PORTEC-3
IB	serous	any	RT and chemo	Section 1b	PORTEC-3[#]
II	1-2	any	EBRT alone	Section 1c	GOG-249/ PORTEC-3
II (after surgery)	3	any	RT and chemo	Section 1b	PORTEC-3[#]
III (after surgery)	any	any	RT and chemo	Section 1b	PORTEC-3/GOG-258

* *LVSI should be unequivocal / substantial (Bosse et al, EJC 2015)*

*** Carcinosarcoma, clear cell: same as for serous cancer*

[#] *No details yet on serous and stage II grade 3 from GOG-249*

1. Arm 1 node positive and Arm 2 patients- systemic adjuvant treatment details

A) Recommended systemic adjuvant treatment regimen details

The following systemic adjuvant treatment options are used internationally for high-risk endometrial cancer based on phase II/III studies:

Chemotherapy and external beam radiotherapy

- *Pelvic external beam radiotherapy with concurrent and adjuvant chemotherapy in the schedule as published by the RTOG phase II study and used in both the PORTEC-3 and GOG-258 trials*:

  Pelvic external beam radiotherapy with 2 concurrent cycles of cisplatin 50 mg/m2 (on days 1 and 22), followed by 4 cycles of carboplatin AUC 5/6 and paclitaxel 175 mg/m2 (starting within 3 weeks of completion of pelvic external beam radiotherapy and 4 weeks after the last cycle of cisplatin).

  An optional brachytherapy boost is permitted for patients with documented cervical involvement – see section D i)

- *Sequential chemotherapy and pelvic external beam radiotherapy*
  6 cycles of carboplatin (AUC 5/6) and paclitaxel 175 mg/m2 at 3 weekly intervals before or after pelvic external beam radiotherapy.

  An optional brachytherapy boost is permitted for patients with documented cervical involvement – see section D i)

Chemotherapy without external beam radiotherapy

- 6 cycles of carboplatin (AUC 5/6) and paclitaxel 175 mg/m2 at 3 weekly intervals.

  Optional brachytherapy is permitted for patients treated with this regimen – see section D ii)

NB Chemotherapy without pelvic external beam radiotherapy is **not** recommended adjuvant treatment in these patients, based on the following:

- Studies showing no difference in survival and relapse-free survival when comparing chemotherapy alone (3-5 cycles) to pelvic external beam radiotherapy alone (Susumu, Maggi, GOG249);
- Data indicating the combination of chemotherapy and radiotherapy has a significant improvement of progression-free survival over pelvic external beam radiotherapy alone (Hogberg).

B) Chemotherapy recommendations (combined and sequential schedules)

- **Cisplatin recommendations** (combined schedule - concurrent phase):

Agent	Dose/day	Route	Days
Cisplatin	50 mg/m^2 in 1000 ml sodium chloride 0.9% or 2.5-3%*	IV in 2 hours	1, 22

* According to local standard protocol

Supportive care for cisplatin

Pre-medication
Aprepitant 125 mg
Dexamethasone 12 mg
Ondansetron 8 mg; or
A standard combination of a corticosteroid and a 5HT-antagonist (the use of aprepitant is at the discretion of the participating site).

Post-medication
After administration of chemotherapy anti-emetic therapy is at the discretion of the participating site.

Pre- and post- hydration for cisplatin

Pre-hydration
1000 ml sodium chloride 0.9% in 2 hours

Post-hydration
2000 ml sodium chloride 0.9% in 4 hours, with adequate IV supplementation of potassium and magnesium.

Other schedules may be used but there must be a minimum total hydration volume of 1500 ml.

In the concurrent schedule, the first cycle of cisplatin should be given within days 1-3 of radiotherapy, and the second cycle 3 weeks after the first cycle (4^{th} week of radiotherapy).

Dose modifications for cisplatin:

Toxicity	**Adjustment**	**Remarks**
Haematological adverse events		
ANC < 1.5 x 10^9/L	Postpone 1 week	If recovery requires > 1 week stop cisplatin
Platelets < 100 x 10^9/L	Postpone 1 week	If recovery requires > 1 week stop cisplatin
Renal adverse events		
GFR < 50 ml/min (Cockroft-Gault) GFR < 40 ml/min (measured creatinine or EDTA clearance)	Postpone 1 week	If recovery requires > 1 week stop cisplatin If GFR < 40 ml/min (Cockroft-Gault) or remains < 40 ml/min (measured): Stop cisplatin
Neurological adverse events		
Neuropathy ≥ grade 2	Stop cisplatin	
Other adverse events		
Other toxicity > grade 2	Postpone 1 week	If recovery requires > 1 week stop cisplatin

- **Carboplatin and paclitaxel recommendations**:

Agent	**Dose/day**	**Route**	**Days**
Paclitaxel	175 mg/m^2	IV in 3 hours	1, 22, 43, 64
Carboplatin	AUC 5 (calculated AUC)	IV in 1 hour	1, 22, 43, 64

Combined schedule - adjuvant phase or sequential schedule:
4 cycles (combined schedule) or 6 cycles (sequential schedule) of carboplatin and paclitaxel given at 3 weekly intervals.

Adjuvant chemotherapy should be started within 3 weeks after completion of external beam radiotherapy, and preferably within 4 weeks after the last administration of cisplatin.
Before starting adjuvant chemotherapy, the toxicity of the (chemo) radiotherapy should be resolved to < grade 2.

Chemotherapy alone:
6 cycles of carboplatin and paclitaxel will be given at 3 weekly intervals.

AUC for carboplatin should in principle be recalculated at each cycle, but should at least be recalculated in case of increasing serum creatinine (increase of 10% and/or out of normal range) and/or weight changes.

Dose modifications for carboplatin and paclitaxel:

Toxicity	**Adjustment**	**Remarks**
Hematologic adverse events		
ANC < 1.5 x 10^9/L	Postpone 1 week	If recovery requires > 1 week postpone until recovery
Platelets < 100 x 10^9/L	Postpone 1 week	If recovery requires > 1 week postpone until recovery
Neurologic adverse events		
Neuropathy grade 2	Postpone 1 week Postpone second week if still grade 2	If recovery to grade 1 or less: dose reduction for paclitaxel to 135 mg/m^2 for subsequent cycles If no recovery to grade 1 after 2 weeks: Stop paclitaxel and continue carboplatin AUC 6
Neuropathy > grade 2	Stop paclitaxel	Continue carboplatin with AUC 6 (higher dose for single agent carboplatin)
Other adverse events		
Non-hematologic and non-neurologic toxicity > grade 2	Postpone 1 week	If recovery requires > 1 week postpone until recovery of toxicity < grade 2

In case of severe hypersensitivity to paclitaxel, where re-challenge is not medically indicated **or** if repeated severe reaction at re-challenge, paclitaxel should be substituted by docetaxel 75 mg/m^2. In case of hypersensitivity to docetaxel as well, continue with carboplatin AUC 6.

In case of severe hypersensitivity to carboplatin, where re-challenge is not medically indicated **or** if repeated severe reaction at re-challenge, carboplatin should be substituted by cisplatin 50 mg/m^2.
In case of fever with grade 3 or 4 neutropenia, consider use of G-CSF (see Supportive Care), or prophylactic antibiotics at subsequent cycles.

Supportive care for carboplatin and paclitaxel

Pre-medication:
For paclitaxel, dexamethasone 20 mg IV
Clemastine 2 mg IV
Ranitidine 50 mg IV or
A similar schedule at the discretion of the participating site**.**

Post-medication:
5HT-antagonist. The use of aprepitant is at the discretion of the participating site.

Use of G-CSF is permitted for secondary prophylaxis after a neutropaenic complication according to the American Society of Clinical Oncology guideline (2006 Update of ASCO Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline).

Hypersensitivity reaction to paclitaxel or carboplatin:
Stop infusion immediately and administer 10 mg dexamethasone IV, clemastine 2 mg IV, epinephrine 1 mg. After recovery of symptoms, infusion may be rechallenged:

0-15 min: paclitaxel or carboplatin flow 15 ml/hour
15-30 min: sodium chloride 0.9% + 2 mg clemastine
30-45 min: paclitaxel or carboplatin flow 84 ml/hour
45-90 min: If no reaction occurs, paclitaxel flow 170 ml/hour or carboplatin flow 500 ml/hour

C) External beam radiotherapy recommendations

Target Volume
The clinical target volume (CTV) consists of:

- Upper 1/2 of the vagina
- Parametrial tissues
- Internal, external and distal common iliac lymph node regions up to the upper S1 level.
- Presacral nodes in the event of cervical snd/or iliac lymph node involvement, the. It is advisable to use an ITV for the vaginal vault area with CT scans with full and empty bladders and delineation and integration of CTV on both scans.

In case of external and/or internal iliac lymph node involvement, the common iliac lymph node regions are to be included up to the aortic bifurcation. In case of common iliac node involvement the aortic bifurcation should be included up to the lower peri-aortic region (margin of at least 2 cm above the highest lymph node region involved).

In case of peri-aortic involvement, the peri-aortic lymph node region should be included up to the higher para-aortic region (margin of at least 2 cm above the highest lymph node region involved).

The Planning Target Volume (PTV) consists of the CTV with a 7-10 mm margin. A detailed description and guidelines for delineation of the CTV are provided by atlases (Taylor et al; RTOG).

Positioning and verification

The choice of the supine or prone position is left to the treating physician. In the case of prone positioning, the use of a belly-board is recommended. Treatment with a comfortably full bladder is advisable. A CT scan for simulation and planning is mandatory. The positioning of the patient during simulation and treatment should be reproduced with the aid of orthogonal laser beams. The positioning should be verified by electronic portal images and/or cone beam CT using a verification and correction procedure.

Dose and fractionation
45-48.6 Gy, at 1.8 Gy per fraction, specified at the isocenter, 5 fractions per week. Treatment should preferably be started within 4-6 weeks after surgery, but no later than 8 weeks after surgery. Treatment breaks should be avoided, and overall treatment time should be kept within 6 weeks. Treatment breaks due to public holidays and machine maintenance should not exceed 2 days.

Technique
The use of CT-scan based three-dimensional treatment planning is mandatory. The dose is be specified at the ICRU reference point. Homogeneity requirements should be according to ICRU-62 and 83, with 98% of the PTV receiving at least 95% of the prescribed dose. IMRT is preferred if a center has completed clinical introduction of standard IMRT for pelvic fields and adequate QA procedures are employed. Patients should be treated with megavolt photons from a linear accelerator, using at least 6 MV photons, but treatment with higher energies (10 MV or higher) is recommended.

D) Vaginal brachytherapy recommendations

i) Vaginal brachytherapy boost to external beam radiotherapy
A brachytherapy boost may be considered for patients with documented cervical involvement. Brachytherapy should be either incorporated within the last week of EBRT (not giving both on the same day), or be given in the first week after completion of EBRT (HDR sessions should be given at least 3 days apart). Overall treatment time for radiotherapy (EBRT and brachytherapy) should not exceed 50 days. Brachytherapy is either given with a ring, with ovoids or with a vaginal cylinder, with the reference isodose covering at least the proximal 2-3 cm of the vagina. High-dose-rate (HDR) schedules are used, which deliver an equivalent dose of 10-14 Gy at 5 mm from the vaginal mucosa.

Examples of such schedules
HDR 10 Gy in 2 fractions, or 12 Gy in 3 fractions, at least 3 days apart. PDR equipment may be used if the brachytherapy is given as HDR in fractions of 4-5 Gy (NB not using a PDR schedule).

CT/MRI planning is advised, with the cumulative (external beam and brachytherapy) EDQ2 dose in a 2cc volume of the rectum and bladder not exceeding 75 Gy and 80 Gy respectively.

ii) Vaginal brachytherapy in addition to chemotherapy, but without external beam radiotherapy

Target Volume
The target volume consists of the upper 4 cm of the vagina, including the vaginal tissues containing the lymphatic vessels to a depth of 3 mm from the mucosal surface.

Technique and dose
High-dose-rate (HDR) brachytherapy should be given using a vaginal cylinder and preferably be started between 4 and 6 weeks after surgery, and not less than 3 weeks after surgery. PDR equipment may be used if the brachytherapy is given as HDR in fractions of 7 Gy (NB not using a PDR schedule). At the first session and prior to delivery, vaginal inspection and pelvic examination should be performed to confirm that the vaginal cuff has healed. Care should be taken to obtain optimal contact of the cylinder to the vaginal apex mucosa, and the largest diameter cylinder that fits tightly in the vaginal vault should be chosen. The cylinder should be placed in a horizontal position i.e. parallel to the treatment table rather than pitching anteriorly or posteriorly.

Three fractions of 7 Gy should be delivered within an overall treatment time of 14 days. The interval between each fraction should be 3-7 days. The dose is specified at the 100% isodose at 5 mm from the cylinder surface. The loading pattern of the cylinder is chosen in such a way that the 100% isodose runs parallel to the cylinder surface at 5 mm distance. To account for the anisotropy in the longitudinal direction of the ^{192}Ir source, two points are defined at 5 mm from the top of the applicator:one along the central axis and the second 5 mm laterally from this point. The average dose in these two points should be approximately 100%. The most caudal dwell position is placed 3-3.5 cm from the first dwell position in the top of the cylinder, resulting in a 100% isodose length outside the applicator of approximately 4 cm.

Before or at the first brachytherapy session, a CT or MRI scan should be performed and the upper 3.5 cm of the vagina (as measured from the top of the cylinder) up to 3 mm from the cylinder surface should be contoured as CTV. Organs at risk (OAR), specifically the bladder, rectum, sigmoid and small bowel should be delineated up to a distance of at least 2 cm cranially from the cylinder. A standard treatment plan may be used for the first fraction, and dose distributions for the CTV and OAR should be recorded. The 2cc doses in the OAR should be calculated for documentation and evaluation purposes. If at CT/MRI planning the bladder, rectum or small bowel is located within 3 mm from the cylinder surface leading to a D2cc for bladder > 7.5 Gy, rectum > 7 Gy or small bowel > 7 Gy per fraction, it is acceptable to slightly adjust the loading pattern to keep to these constraints for the next fractions.

It is important to check the cylinder position and especially its contact with the vaginal apex mucosa. This can be done by applying light pressure to the applicator just before and after CT/ MRI scanning and just prior to starting each HDR treatment. It is advised that the bladder be moderately filled during each treatment.

2. Arm 1 node negative patients: vaginal brachytherapy alone

Vaginal brachytherapy recommendations

Target Volume
The target volume consists of the upper 4 cm of the vagina, including the vaginal tissues containing the lymphatic vessels to a depth of 3 mm from the mucosal surface.

Technique and dose

High-dose-rate (HDR) brachytherapy should be given using a vaginal cylinder and preferably be started between 4 and 6 weeks after surgery, and not less than 3 weeks after surgery. PDR equipment may be used if the brachytherapy is given as HDR in fractions of 7 Gy (NB not using a PDR schedule). At the first session and prior to delivery, vaginal inspection and pelvic examination should

be performed to confirm that the vaginal cuff has healed. Care should be taken to obtain optimal contact of the cylinder to the vaginal apex mucosa, and the largest diameter cylinder that fits tightly in the vaginal vault should be chosen. The cylinder should be placed in a horizontal position i.e. parallel to the treatment table rather than pitching anteriorly or posteriorly.

Three fractions of 7 Gy should be delivered within an overall treatment time of 14 days. The interval between each fraction should be 3-7 days. The dose is specified at the 100% isodose at 5 mm from the cylinder surface. The loading pattern of the cylinder is chosen in such a way that the 100% isodose runs parallel to the cylinder surface at 5 mm distance. To account for the anisotropy in the longitudinal direction of the ^{192}Ir source, two points are defined at 5 mm from the top of the applicator:one along the central axis and the second 5 mm laterally from this point. The average dose in these two points should be approximately 100%. The most caudal dwell position is placed 3-3.5 cm from the first dwell position in the top of the cylinder, resulting in a 100% isodose length outside the applicator of approximately 4 cm.

Before or at the first brachytherapy session, a CT or MRI scan should be performed and the upper 3.5 cm of the vagina (as measured from the top of the cylinder) up to 3 mm from the cylinder surface should be contoured as CTV. Organs at risk (OAR), specifically the bladder, rectum, sigmoid and small bowel should be delineated up to a distance of at least 2 cm cranially from the cylinder. A standard treatment plan may be used for the first fraction, and dose distributions for the CTV and OAR should be recorded. The 2cc doses in the OAR should be calculated for documentation and evaluation purposes. If at CT/MRI planning the bladder, rectum or small bowel is located within 3 mm from the cylinder surface leading to a D2cc for bladder > 7.5 Gy, rectum > 7 Gy or small bowel > 7 Gy per fraction, it is acceptable to slightly adjust the loading pattern to keep to these constraints for the next fractions.

It is important to check the cylinder position and especially its contact with the vaginal apex mucosa. This can be done by applying light pressure to the applicator just before and after CT/ MRI scanning and just prior to starting each HDR treatment. It is advised that the bladder be moderately filled during each treatment.