future pharmacology

MDPI

# Suplementary Materials: Current Methods and Advances in the Immunotherapy Treatment of Non-Ovarian Gynaecological Cancers

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**Table S1.** Summary of the treatment of endometrial cancer based on current guidelines [39,45,46].

| Stage | Treatment considerations | | Treatment recommendations | |
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| | | | **Strongly recommended (A)** | **Generally recommended (B)** |
| Early-stage disease: FIGO I/II | Surgery | Minimally invasive surgery | This is the preferred surgical approach, including high-risk EC | Avoid intra-peritoneal tumour spillage, including tumour rupture or morcellation |
| | | Standard surgical procedure | Total hysterectomy with bilateral salpingo-oophorectomy without vaginal cuff resection | In stage I serous EC, carcinosarcoma, undifferentiated carcinoma: staging infra-colic omentectomy should be performed |
| | | | | Consider surgical restaging in previously incompletely staged patients with high- intermediate-risk/high-risk disease for adjuvant treatment |
| | | | | Relative contraindications: metastases outside uterus and cervix (excluding lymph node metastases) |
| | Palliative radiotherapy | | N/A | Can be considered for primary tumours where surgery is contra-indicated for medical reasons |
| | | | | For high-grade tumours and/or deep myometrial invasion: use combination of EBRT and brachytherapy |
| | | | | For low-grade tumours: consider brachytherapy alone |
| | Systemic treatment including hormonal therapy | | N/A | Consider in medically unfit patients unsuitable for curative surgery or radiotherapy |
| | LN staging | SLNB | Consider in low-/intermediate-risk disease<br>Indocyanine green with cervical injection is the preferred detection technique<br>If sentinel LN is not visualised upfront, consider tracer re-injection<br>If sentinel LN not detected on either pelvic side, perform side-specific systematic lymphadenectomy in high-intermediate-risk/high-risk disease<br>Pathologic ultra-staging of sentinel LN is recommended | N/A |
| | | Systematic lymphadenectomy | N/A | Consider surgical LN staging in high-intermediate-risk/high-risk disease; SLNB can be an alternative. |
| | | | | If pelvic lymph node involvement is found intra- operatively, further systematic pelvic lymph node dissection should be omitted. However, debulking of enlarged lymph nodes and para- aortic staging can be considered. |

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| | | | Consider pelvic and para-aortic infrarenal LN dissection |
| | Ovarian preservation | Consider in pre-menopausal patients <40 years with low-grade endometrioid EC with myometrial invasion <50% and no obvious ovarian or other extra-uterine disease | Salpingectomy is recommended in cases of ovarian preservation |
| | | | Not recommended for patients with family history involving ovarian cancer risk (e.g. BRCA mutation, Lynch syndrome, etc) |
| | Fertility preservation | Consider only in patients with AH/ EIN or grade 1 endometrioid carcinoma without myometrial invasion and without genetic risk factors:<br>Endometrial biopsy, preferably through hysteroscopy must be performed<br>AH/EIN or grade 1 endometrioid EC must be confirmed/diagnosed by a pathologist experienced in gynaecological pathology | Radiologic imaging (pelvic MRI) to assess disease extension must be performed. An expert ultrasound examination can be an alternative. |
| | | | Medroxyprogesterone acetate (400–600 mg/day) or megestrol acetate (160–320 mg/day) is the recommended treatment. Treatment with levonorgestrel intrauterine device in combination with oral progestins with/without gonadotropin- releasing hormone analogues can also be considered. |
| | | | Hysteroscopic guided biopsy and imaging at 3–4 and 6 months must be performed. If no response is achieved after 6 months, standard surgical treatment is recommended. |
| | | Patients must be informed that fertility-sparing treatment is not a standard treatment, as well as the need for future hysterectomy in case of treatment failure and/or after pregnancies. Patients must be willing to accept close follow-up. | Consider continuous hormonal treatment in responders who wish to delay pregnancy |
| | | | Hysterectomy and bilateral salpingo-oophorectomy is recommended after childbearing due to a high recurrence rate. |
| | Adjuvant treatment | Low risk | For patients with endometrial carcinoma stage I–II, low- risk based on pathogenic POLE- mutation, no adjuvant treatment is recommended. | N/A |
| | | Intermediate risk | Adjuvant brachytherapy can be considered to decrease vaginal recurrence | N/A |
| | | | Omission of adjuvant brachytherapy can be considered for patients aged <60 years. | |
| | | High–intermediate risk (pN0 after LN staging) | N/A | Adjuvant brachytherapy can be considered to decrease vaginal recurrence |
| | | | | EBRT can be considered for substantial LVSI and for stage II |
| | | High–intermediate risk cN0/pNx (LN staging not performed) | Adjuvant EBRT is recommended especially for substantial LVSI and/or for stage II | Additional adjuvant chemotherapy can be considered, especially for high- grade and/or substantial LVSI. |
| | | | | Adjuvant brachytherapy alone can be considered for high- grade LVSI negative and for stage II grade 1 endometrioid carcinomas. |
| | | High risk | EBRT with concurrent and adjuvant chemotherapy is recommended | Alternatively sequential chemotherapy and radiotherapy, or chemotherapy alone. |
| | | | | Carcinosarcomas should be treated as high-risk carcinomas (not as sarcomas) |
| Advanced disease: FIGO III and IV | Surgery | Primary systemic therapy should be used if upfront surgery is not feasible or acceptable. | Consider surgical tumour debulking including enlarged LNs when complete macroscopic resection is feasible with an acceptable morbidity and quality of life profile. Primary debulking surgery (PDS) is usually combined with metastasis resection. Following PDS, chemotherapy is recommended to improve survival |

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| | | | | provided complete macroscopic resection or optimal PDS can be achieved (residual disease of <1–2cm) [46]. Full pre- operative staging and discussion by a multi- disciplinary team is advised |
| | | | | Only enlarged lymph nodes should be resected. Systematic lymphadenectomy is not recommended |
| | Post-surgery | Residual pelvis or para-aortic LNs | N/A | Treat with a combination of chemotherapy and EBRT or chemotherapy alone. |
| | | | | EBRT should be delivered to pelvis and para-aortic nodes with dose escalation to involved nodes using an integrated or sequential boost. |
| | | Residual pelvic disease (positive resection margin, vaginal disease, pelvic side wall disease) | N/A | Either radiotherapy or chemotherapy or a combination of both modalities should be considered by a multi-disciplinary team |
| | Unresectable locally advanced disease without distant metastases | | Image-guided brachytherapy is recommended to boost intrauterine, parametrial, or vaginal disease | Chemotherapy should be considered after definitive radiotherapy |
| Recurrent disease | Local treatment | | For locoregional recurrence, the preferred primary therapy should be EBRT±chemotherapy with brachytherapy. | In selected cases, palliative surgery can be performed to alleviate symptoms (e.g. bleeding, fistula, bowel obstruction). |
| | | | | In patients with a history of previous radiation, radical surgery, including exenteration, should be considered when the intention is complete resection with clear margins. |
| | | | For vaginal cuff recurrence:<br>Pelvic EBRT + intracavitary (±interstitial) image-guided brachytherapy is recommended<br>In case of superficial tumors, intracavitary brachytherapy alone can be considered. | Patients with oligometastatic disease should be considered for radical local therapy:<br>Surgery<br>Radiation therapy including stereotactic radiotherapy<br>Local ablating techniques<br>The additional benefit of chemotherapy is uncertain. |
| | Systemic treatment | Hormone therapy | Hormone therapy is the preferred front-line systemic therapy for patients with low- grade carcinomas without rapidly progressive disease:<br>Progestogens (medroxyprogesterone acetate 200 (–300) mg and megestrol acetate 160 mg) are recommended. | Patients with oestrogen/progesterone receptor-positive tumour may also benefit from hormone therapy. |
| | | Chemotherapy | The standard chemotherapy treatment is carboplatin AUC 5–6 + paclitaxel 175 mg/m$^2$ every 21 days for six cycles. | In oestrogen/progesterone receptor negative tumours, palliative chemotherapy (paclitaxel and carboplatin) is indicated. |
| | | Immunotherapy | | Anti-PD-1- based immune therapy with pembrolizumab could be considered for second-line therapy of MSI/MMRd carcinomas. The combination of pembrolizumab and the multi-tyrosine-kinase inhibitor lenvatinib could be considered for second- line treatment of microsatellite- stable carcinomas. However, its |

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| | | | use may be limited due to regulatory approvals or reimbursement in different countries. Clinical trial participation should be offered to all patients with relapse disease. |
| | Palliative therapy | Radiotherapy is indicated for palliation of symptoms related to pelvic or systemic disease. | Hypofractionated small volume EBRT can be used for treating primary disease in patients not fit for radical treatment. |

Abbreviations: FIGO: International Federation of Gynecology and Obstetrics; EC: endometrial cancer/carcinoma; LN: lymph node; SLNB: sentinel lymph node biopsy; EBRT: external beam radiation therapy; AH/EIN: atypical hyperplasia/endometrioid intraepithelial neoplasia; MRI: magnetic resonance imaging; LVSI: lymphovascular space invasion; AUC: area under the time vs concentration curve; MSI/MMRd: microsatellite instability/MMR deficient; PD-1: programmed cell death protein 1. Only grades A and B recommendations have been included in this table. (A: Strong evidence for efficacy with a substantial clinical benefit, strongly recommended; B: Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended.).

**Table S2.** Summary of the treatment for cervical cancer based on tumour stages [47–50].

| Stage | Treatment considerations | | Treatment recommendations | |
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| | | | **Strongly recommended (A)** | **Generally recommended (B)** |
| CIN2/CIN3 | | | **Conisation** | |
| | | | Invasive CC early disease | |
| FIGO IA1 | Surgery | No LVSI | N/A | Conisation (only if negative margins on frozen section) in squamous cell and adenocarcinoma of the cervix [47] or simple trachelectomy to preserve fertility[a]. Alternatively, conisation may be preferred if adequate margins can be achieved. |
| | | With LVSI | Simple hysterectomy + PLND ± PALND ± SLNB | |
| FIGO IA2 to IB2 | Surgery | | The standard management for stage IB1 and IB2 cervical cancer is radical hysterectomy and bilateral salpingectomy with bilateral pelvic lymphadenectomy +/- bilateral oophorectomy (with or without SLN). | In stage IA2: to preserve fertility, conisation / simple or radical trachelectomy can be considered if clear margins can be achieved without pathological LNs being identified in staging [47]. |
| | | | | In stage IB1: radical trachelectomy with pelvic lymphadenectomy is considered a standard fertility-sparing procedure in tumours ≤2 cm in diameter[a]. Studies have shown that conservative surgical management with laparoscopic hysterectomy, simple trachelectomy or loop cone biopsy may be appropriate in patients with small volume stage IB1 cervical cancer [49,50]. |
| | CRT | | Alternative to radical surgery, usually offered for those unfit for surgery or where a double treatment modality (i.e., surgery and radiotherapy) is to be avoided. | N/A |
| | | | Locally advanced disease | |
| FIGO IB3/IIA2 | CRT | | Treatment strategy should aim to avoid the combination of radical surgery and postoperative EBRT, due to significant increase of morbidity and no impact on survival. | N/A |
| | | | Definitive treatment is platinum-based CRT and brachytherapy | N/A |
| | Chemo + surgery/RT | | | Neoadjuvant chemotherapy followed by surgery or RT |

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| [a]Surgery should only be considered in patients with earlier stages of cervical cancer (up to FIGO IIA) without risk factors necessitating adjuvant therapy, which results in a multi modal therapy without improvement of survival but increased toxicity | | | |
| FIGO IIB, IIB/IIIB, IVA | N/A | PALND may be considered before treatment for staging purposes if no evidence of disease on imaging (PET-CT). | |
| | CRT | Definitive CRT and brachytherapy with additional radiation boost to the involved LNs is recommended in patients with unequivocally involved PLNs on imaging. | |
| | Pelvic exenteration | Pelvic exenteration can be considered in selected cases with stage IVA (T4M0) disease. | |
| Metastatic disease | | | |
| FIGO IVB | Systemic treatment | N/A | First line treatment is cisplatin/paclitaxel or carboplatin/paclitaxel doublets with or without bevacizumab depending on the balance between efficacy and toxicity profile. Bevacizumab should be offered if not contraindicated. |
| Pregnancy | | | |
| Any stage | Multidisciplinary management | Surgery is usually avoided and radiotherapy are contraindicated.<br><br>During the first trimester pregnancy termination may be discussed alongside standard treatment especially in cases where nodal metastases is present. Cone biopsy can be used in Stage IA1 cases who present without LVSI however, for those with LVSI or stage IA2 and IB1 cancer, staging lymphadenectomy may be performed up to 22 weeks of gestation. | In pregnant patients with node positive or locally advanced disease, chemotherapy may be safe during the second or third trimester however it can be delayed until after delivery (caesarean section after 35 weeks). |

Abbreviations: CIN: cervical intraepithelial neoplasia; FIGO: International Federation of Gynecology and Obstetrics; LVSI: lymphovascular space invasion; LN: lymph node; PLND: pelvis lymph node dissection; SLN: sentinel lymph node; PALND: para-aortic lymph node dissection; CRT: chemoradiotherapy; EBRT: external beam radiotherapy; RT: radiotherapy. Only grades A and B recommendations have been included in this table. (A: Strong evidence for efficacy with a substantial clinical benefit, strongly recommended; B: Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended.).

**Table S3.** Summary of the treatment recommendations for vulval cancer based on tumour stages and types [58–60].

| **Tumour Type / Stage** | Treatment considerations | |
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| **VSCC** | | |
| Ia/Ib | Surgical excision | Large or multifocal tumours may necessitate a radical vulvectomy: remove the tumour with macroscopically-free margins, including the clitoris, bilateral vulva and the perineum. Management of the primary tumour by wide local excision without groin node dissection is recommended. If there is no clinical suspicion of lymph node involvement, unifocal tumours of less than 4cm diameter can be managed by removing by sentinel lymph node removal. |
| II | Surgical excision | Excision of distal urethra and vagina should also be considered. |
| | CRT | In cases where the anus is involved, concomitant CRT or neoadjuvant CRT may be considered to shrink the tumour size. In some cases maintenance of surgical margins may prevent the preservation of faecal continence. |
| III | Same procedures as early stages | |
| Adjuvant (C)RT should take place within 6 weeks of surgery if:<br>Positive excision margins of the primary tumour, and further surgical excision not possible<br>Pathological margins <2 mm where repeat excision not recommended<br>Presence of >1 metastatic lymph node and/or presence of extracapsular lymph node involvement | | |
| IV | Palliative | Chemotherapy, radiotherapy or combination. |
| Bartholin's Carcinoma | May need multi-modal treatment and full body imaging with CT CAP is recommended pre-surgery as disease is more likely to present at an advanced stage. | |

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| Vulval Malignancy Melanoma | Surgery: aim to achieve an R0 resection (no microscopic disease within <1mm of margins) with the least radicality. | |
| | Consider sentinel node dissection to help guide adjuvant immunotherapy. | |
| | Metastatic regional nodal disease may be considered for removal as treatment may improve quality of life, but without evidence of survival benefit. | |
| Locally unresectable disease | Definitive chemoradiation | Weekly cisplatin with IMRT |
| Recurrent disease | Surgical re-excision | May be considered in patients with relapsed disease amenable to surgery |
| | Palliative | Chemotherapy or radiotherapy or combination of both. |
| | Systemic | Systemic treatment may be considered in patients with distant metastases, but published data are insufficient to recommend a preferred protocol. |

Abbreviations: VSCC: vulval squamous cell carcinoma; CRT: chemoradiotherapy; IMRT: intensity-modulated radiation therapy.