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Oncology

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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1 List of the international development group

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2 Identification of scientific evidence

Literature search in MEDLINE	
Research period	2019/06/01 - 2023/10/01
Indexing terms	Adjuvant chemotherapy, adjuvant radiation therapy, adjuvant radiotherapy, adjuvant therapy, adjuvant treatment, advanced disease, advanced stage, adverse effect, adverse event, antiangiogenic-based treatment, antiangiogenic therapy, antiangiogenic treatment, aromatase, aromatase inhibitor, bariatric surgery, bevacizumab, bilateral salpingo-oophorectomy, biomarker, biopsy, brachytherapy, carbohydrate antigen 19.9, carbohydrate antigen 125, carboplatin, carcinoma, carcinosarcoma, CEA, cediranib, cell-free DNA, cervical cytology, chemoradiotherapy, chemotherapy, cisplatin, clinical examination, clinical manifestation, clinical staging, complications, comprehensive surgical staging, comprehensive staging, computed tomography, curettage, cytology, cytoreduction, cytoreductive surgery, definitive radiotherapy, definitive radiation therapy, definitive therapy, definitive treatment, diagnosis, diagnostic performance, differential diagnosis, diffusion-weighted imaging, diffusion-weighted magnetic resonance imaging, dilatation and curettage, disease, dovitinib, doxorubicin, early disease, early stage, endobag, endometrial biopsy, endometrial cancer, endometrial carcinoma, endometrial sampling, endometrioid endometrial cancer, ERAS, ERAS program, estrogen receptor, external beam radiation therapy, extra-fascial hysterectomy, everolimus, fluorescence in situ hybridation, follow-up, follow-up protocols, frozen section analysis, frozen section, fulvestrant, gene mutation testing, germline mutation, germline mutation analysis, gross examination, health-related quality of life, HER2, high-dose rate brachytherapy, high intermediate risk, high risk, hormonal therapy, hormonal treatment, hormone therapy, hormone treatment, human epididymis protein 4, hyperthermic chemotherapy, hyperthermic intraperitoneal chemotherapy, hysterectomy, hysteroscopy, hysteroscopic biopsy, hysteroscopic resection, imaging, immune checkpoint inhibitor, immunohistochemical diagnosis, immunohistochemistry, immunotherapy, incompletet surgery, infracolic omentectomy, intensity-modulated radiation therapy, intermediate risk, interstitial brachytherapy, intervall debulking surgery, intracavity brachytherapy, intraoperative frozen section, isolated tumor cell, L1 cell adhesion molecule, laparoendoscopic single-site approach, laparoscopic staging, laparoscopy, laparotomy, late recurrence, lenvatinib, levonorgestrel intrauterine device, levonorgestrel intrauterine system, local ablative technique, local control, local treatment, locally advanced cancer, locoregional disease, locoregional recurrence, locoregional recurrent disease, locoregional relapse, long-term survivorship, low dose rate brachytherapy, low risk, lymphadenectomy, lymphadenopathy, lymph node, lymph node assessment, lymph node dissection, lymph node involvement, lymph node staging, Lynch identification, Lynch syndrome, magnetic resonance imaging, management, marker, medically unfit patient, medroxyprogesterone, medroxyprogesterone acetate, megestrol acetate, MEK-1/2 inhibitor, metastatic disease, metastasis, microsatellite instability, mini-laparoscopic approach, mini-laparoscopic surgery, mini-laparoscopy, minimally invasive approach, minimally invasive surgery, mismatch repair, mismatch repair deficiency, mismatch repair proficient, MLH1, molecular biology, molecular classification, molecular marker, mortality rate, mortality analysis, MSH, MSH1, MSH2, MSH6, mTOR inhibitor, multidisciplinary board, multidisciplinary team, multivariate analysis, mutation, mutation analysis, myometrial invasion, myometrial involvement, neoadjuvant chemoradiation, neoadjuvant chemotherapy, nintedanib, nodal involvement, no specific molecular profile, omentectomy, oral progestogens, ovarian preservation, p53, paclitaxel, palliative care, palliative treatment, para-aortic lymph node, para-aortic lymphadenectomy, pathogenic mutation, pathology, pathology report, pathological assessment, pathological evaluation, patient, patient education, pelvic exenteration, pelvic lymph node, pelvic lymphadenectomy, perioperative care, peritoneal assessment, peritoneal cytology, physical examination, PI3K inhibitor, pilaralisib, platinum-based chemotherapy, platinum-based systemic therapy, platinum-based systemic treatment, platinum-based therapy, platinum-based treatment, platinum-based treatment, PMS2, *POLE*, *POLE* mutation, polymerase epsilon, positron emission tomography, positron emission tomography-computed tomography, postoperative care, postoperative complications, postoperative recurrence, preoperative care, preoperative staging, preoperative work-up, progesterone receptor, progestin, progestogen, prognosis, prognostic factor, prognostic value, programmed cell death ligand-1, proliferative endometrium, prophylactic hysterectomy, prophylactic surgery, psycho-oncology, psychological aspect, quality of health care, quality of life, radiation therapy, radical hysterectomy, radiotherapy, recurrence, recurrent disease, referral, relapse, reoperation, residual disease, residual pelvic disease, residual tumour, restaging, risk factors, risk groups, robot-assisted surgery, robotic laparoendoscopic single-site approach, robotic approach, robotic surgery, salpingectomy, salvage chemotherapy, salvage intraperitoneal chemotherappy, salvage radiation therapy, salvage radiotherapy, salvage therapy, salvage treatment, sandwich adjuvant chemotherapy, sandwich chemo-radiotherapy, sandwich method, sandwich radiation, salvage surgery, salvage treatment, sampling, screening, second line chemotherapy, second line treatment, selumetinib, sensitivity, sentinel lymph node, sentinel lymph node dissection, sentinel lymph node mapping, serous carcinoma, snail, side effects, specificity, specimen grossing, staging, staging procedures, sunitinib, surgery, surgical management, surgical outcome, surgical outcome criteria, surgical procedures, surgical resection, surgical treatment, surveillance, survival, survival rate, survival analysis, survivorship, systematic lymphadenectomy, systemic therapy, systemic treatment, tamoxifen, targeted therapy, taxane, temsirolimus, total hysterectomy, toxicity, TP53 mutation, transvaginal ultrasound, treatment, treatment outcome, trebananib, tumor-infiltrating lymphocytes, tumor spillage, tyrosine-kinase inhibitor, ultra minimally invasive approach, ultra minimally invasive surgery, ultrasonography, ultrastaging, unilateral salpingo-oophorectomy, vaginal brachytherapy, weight loss, weight loss interventions, weight reduction, work-up.
Language	English
Study design	Priority was given to high-quality systematic reviews, meta-analyses, and randomised controlled trials but lower levels of evidence were also evaluated. The search strategy excluded editorials, letters, case reports and *in vitro* studies.

3 List of the 225 external reviewers

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Javier**, pathologist (Spain); **Mateoiu Claudia**, pathologist (Sweden); **Mathevet Patrice**, gynecologic oncologist, obstetrician & gynecologist (Switzerland); **Matylevich Olga**, gynecologic oncologist (Belarus); **Melliou Kyriaki**, patient (Greece); **Menon Santosh**, pathologist (India); **Meydanli Mehmet Mutlu**, gynecologic oncologist (Türkiye); **Mitra Swarupa**, radiation oncologist (India); **Mlynček Miloš**, gynecologic oncologist (Slovakia); **Mozgovoi Sergei**, pathologist (Russia); **Muinelo Laura**, molecular biologist (Spain); **Murshudova Sabina**, gynecologic oncologist (Azerbaijan); **Mutyala Subhakar**, radiation oncologist (United States of America); **Myriokefalitaki Eva**, gynecologic oncologist (United Kingdom); **Nabais Henrique**, gynecologic oncologist (Portugal); **Neto de Vilhena Bernardino Margarida**, gynecologic oncologist (Portugal); **Niine-Roolaht Eva-Maria**, gynecologic oncologist, obstetrician & gynecologist (Estonia); **Nikolopoulos Manolis**, gynecologic oncologist (United Kingdom); **Nishio Shin**, gynecologic oncologist, obstetrician & gynecologist, medical oncologist (Japan); **Nobre Gois Ines**, radiation oncologist (Portugal); **Noriega-Álvarez Edel**, nuclear medicist (Spain); **Noventa Marco**, gynecologic oncologist (Italy); **Oliva Esther**, pathologist (United States of America); **Pakiz Maja**, gynecologic oncologist (Slovenia); **Papageorgiou Maria**, patient (Greece); **Park Jeong-Yeol**, gynecologic oncologist (Republic of Korea); **Pautier Patricia**, medical oncologist (France); **Pavlakis Kitty**, pathologist (Greece); **Peccatori Fedro Alessandro**, gynecologic oncologist, medical oncologist (Italy); **Perrone Anna Myriam**, gynecologic oncologist (Italy); **Persson Jan**, gynecologic oncologist (Sweden); **Pessini Suzana**, gynecologic oncologist, obstetrician & gynecologist (Brazil); **Pijnenborg Johanna MA**, gynecologic oncologist (Netherlands); **Ponomarova Olga**, medical oncologist (Ukraine); **Raimondo Diego**, gynecologic oncologist, obstetrician & gynecologist (Italy); **Razvi Khalil**, gynecologic oncologist (United Kingdom); **Redecha Mikuláš**, gynecologic oncologist, obstetrician & gynecologist (Slovakia); **Refky Basel**, gynecologic oncologist, surgical oncology (Egypt); **Ribeiro Vera**, gynecologic oncologist, obstetrician & gynecologist (Portugal); **Rodolakis Alexandros**, gynecologic oncologist (Greece); **Ronaghi Freydun**, gynecologic oncologist (Austria); **Rovira Ramon**, gynecologic oncologist (Spain); **Rovirosa Angeles**, radiation oncologist (Spain); **Sacristan Andres**, gynecologic oncologist (Spain); **Salutari Vanda**, gynecologic oncologist, obstetrics & gynecology, medical oncologist (Italy); **Sarivalasis Apostolos**, medical oncologist (Switzerland); **Scambia Giovanni**, gynecologic oncologist, obstetrician & gynecologist (Italy); **Schmidt Dietmar**, pathologist (Germany); **Segev Yakir**, gynecologic oncologist (Israel); **Silva Scott**, radiation oncologist (United States of America); **Simsek Tayup**, gynecologic oncologist, obstetrician & gynecologist (Türkiye); **Singh Shalini**, radiation oncologist (India); **Staff Synnöve**, gynecologic oncologist, obstetrician & gynecologist (Finland); **Stolnicu Simona**, pathologist

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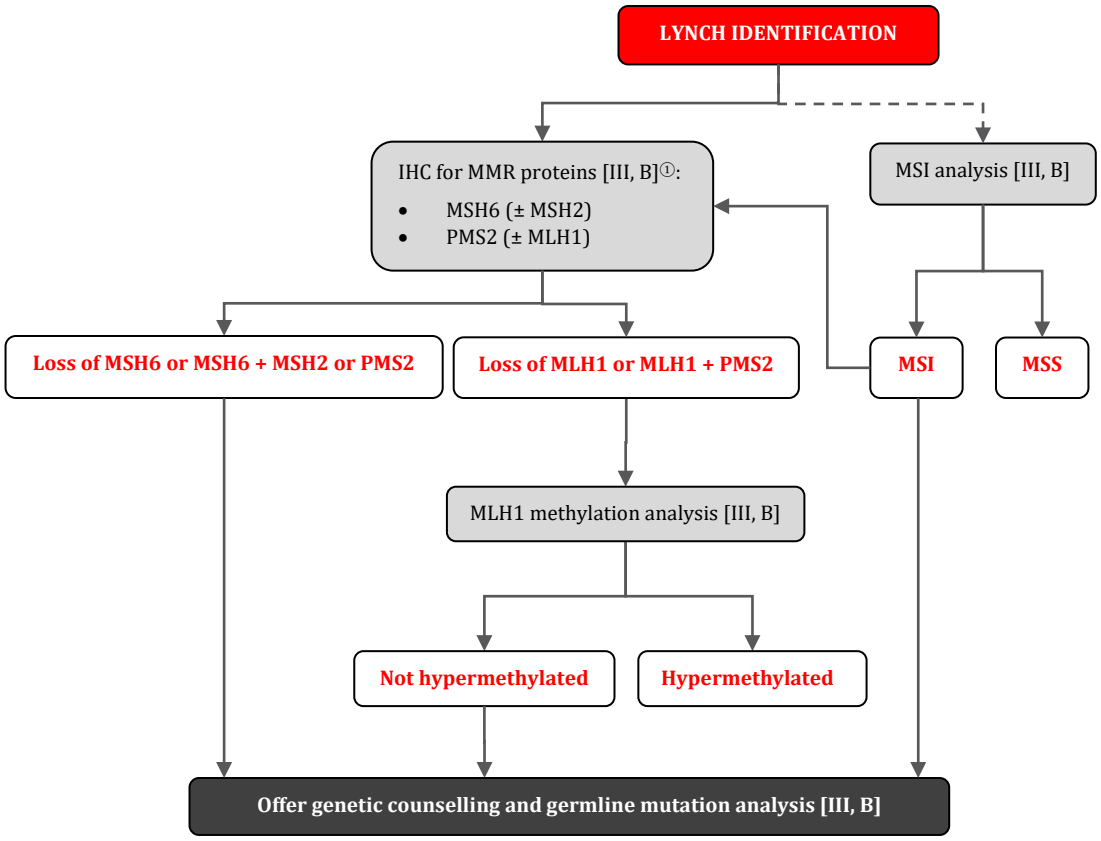
4 Algorithms

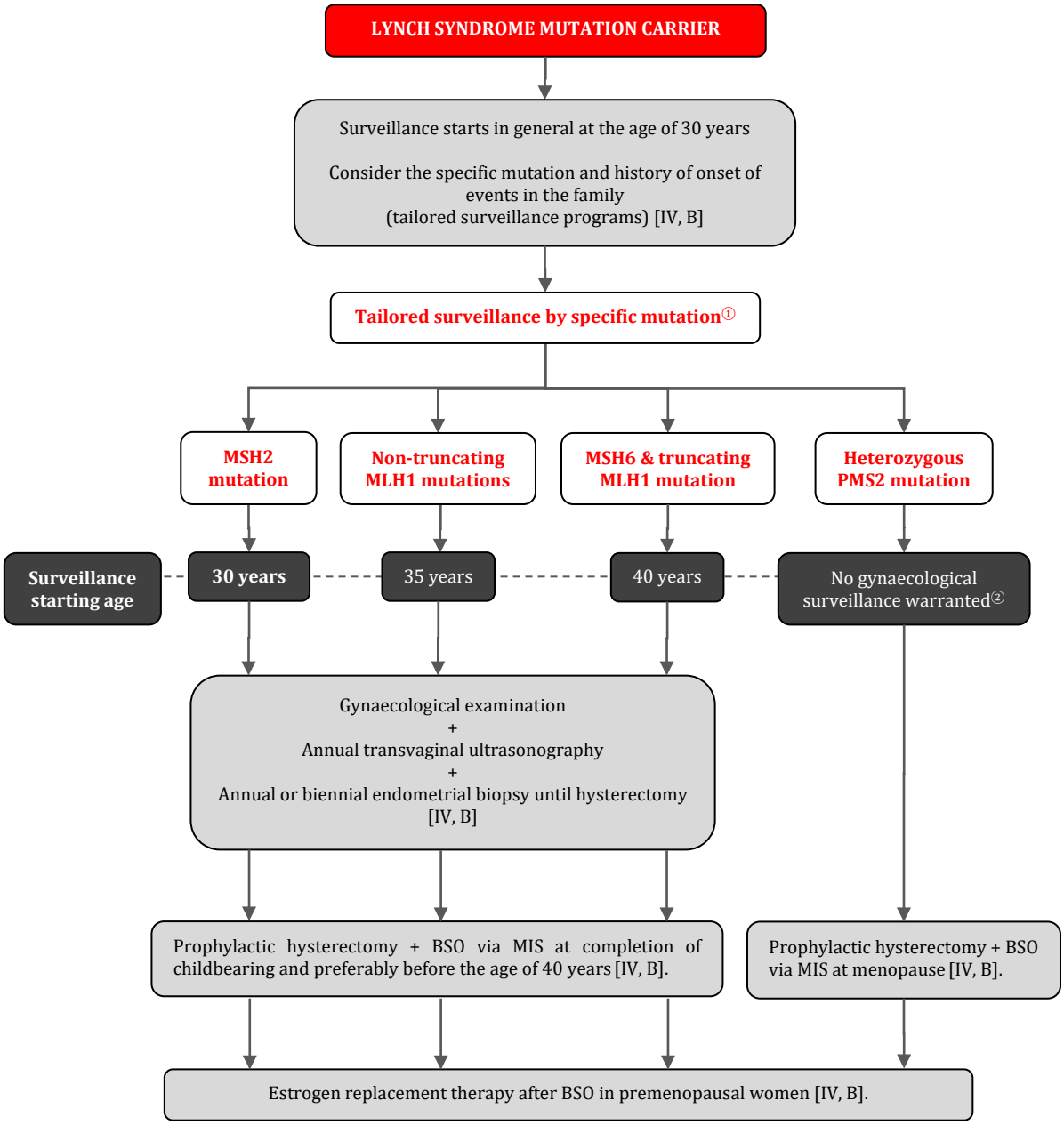
4.1 Algorithm #1 - Lynch identification



①The 2-antibody or 4-antibody approach can be used. The 2-antibody approach has the advantage of being more efficient while being equivalently reliable to detect MMR deficiency (see paragraph 5.2).

IHC immunohistochemistry; MMR mismatch repair; MSI microsatellite instability; MSS microsatellite stability.

4.2 Algorithm #2 - Surveillance of Lynch syndrome mutation carrier

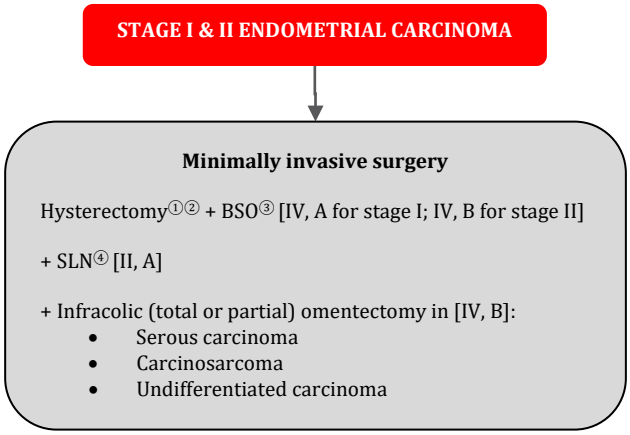


①The cumulative incidences for cancer and the age of cancer onset in women with Lynch syndrome depend on the specific mutation.

②Absolute risk of gynaecological cancer is very low.

BSO bilateral salpingo-oophorectomy; MIS minimally invasive surgery.

4.3 Algorithm #3 - Surgical management in stage I & II disease



①Intra-operative frozen section of the uterus is not encouraged for myometrial invasion assessment because of poor reproducibility and interference with adequate pathologic processing.

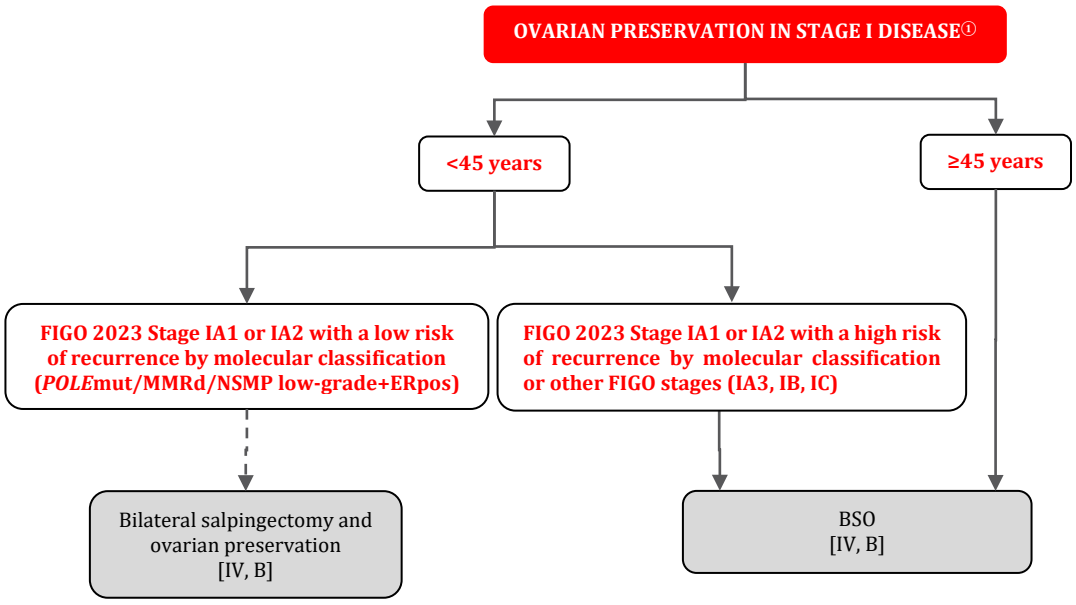
②For stage II cases, more extensive procedures should only be performed if required to achieve free surgical margins. This includes vaginal cuff and parametria resection.

③For ovarian preservation, see algorithm #4.

④If sentinel lymph node is not detected: side specific systematic lymphadenectomy should be performed in high-intermediate/high risk patients and can be considered in presumed intermediate risk patients.

BSO bilateral salpingo-oophorectomy; SLN sentinel lymph node.

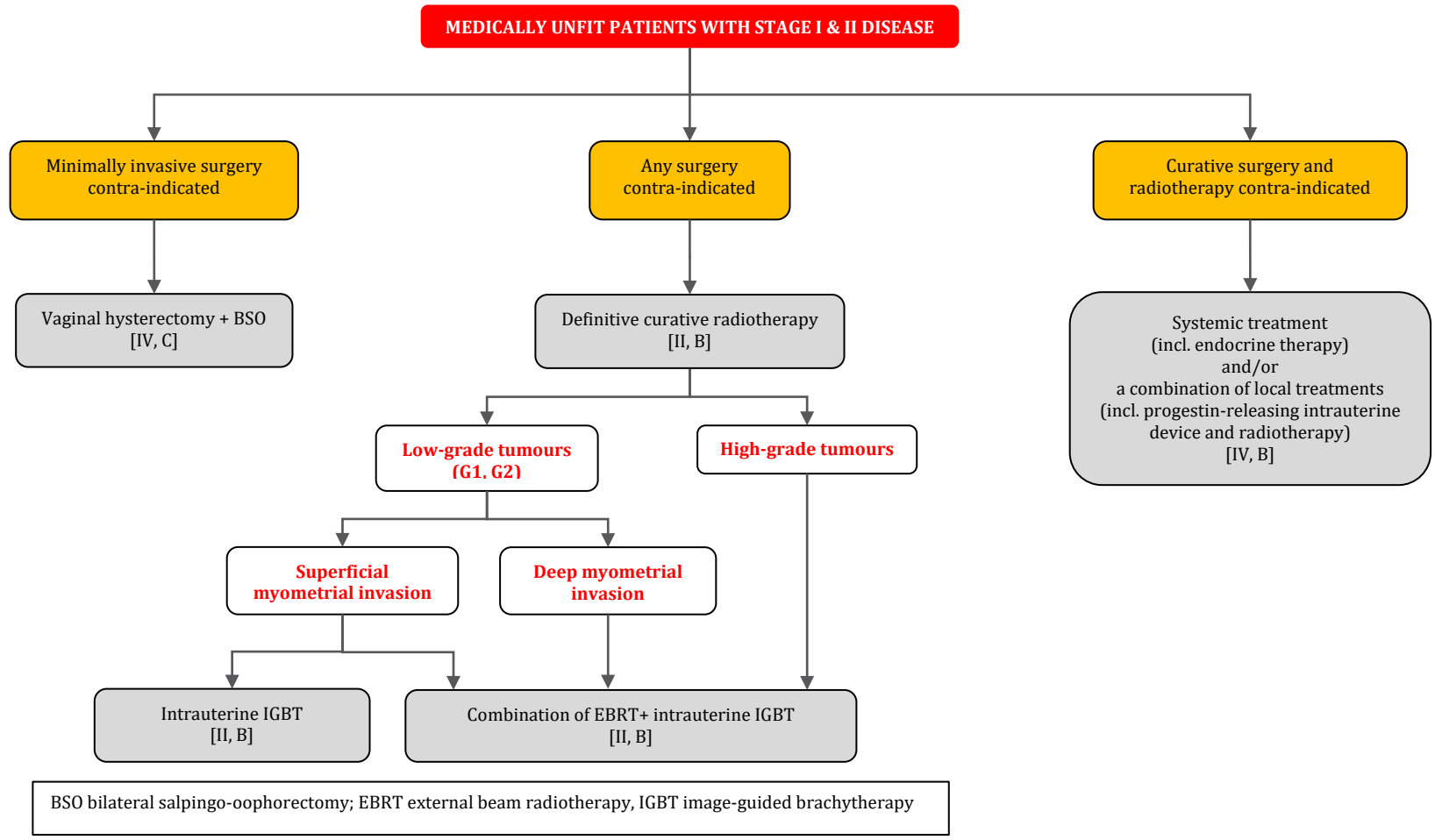
4.4 Algorithm #4 - Ovarian preservation in stage I disease



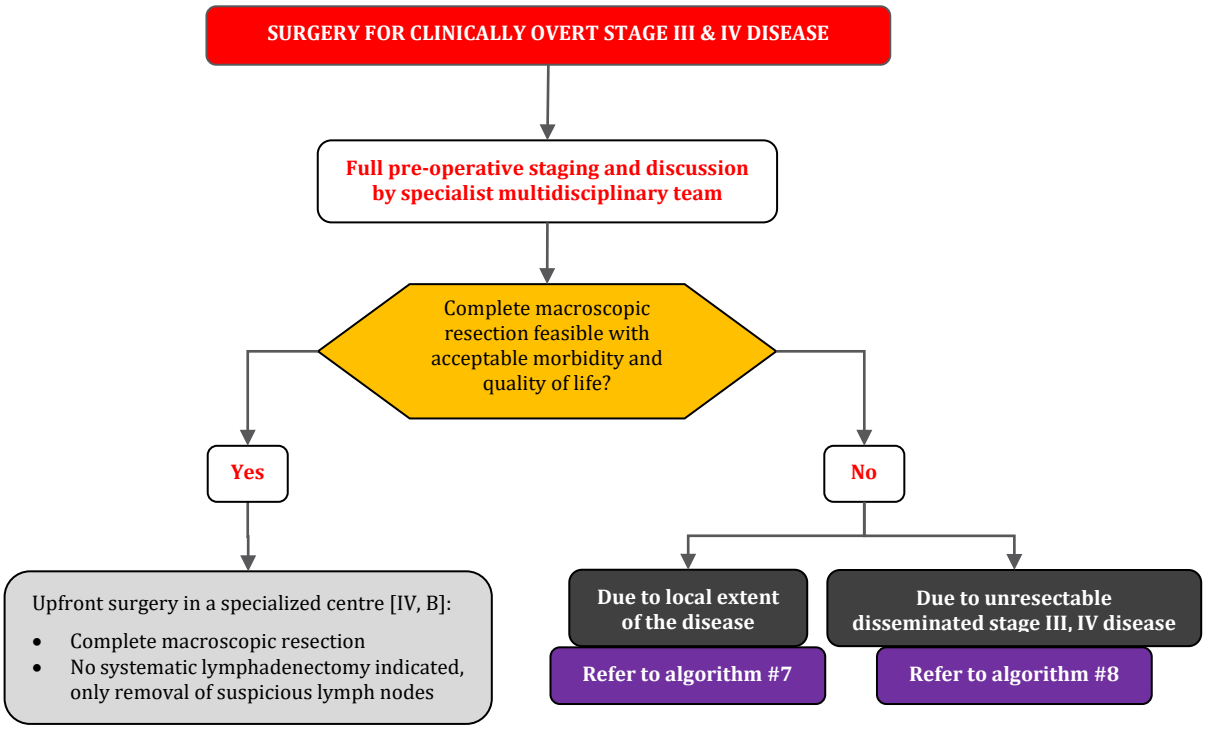
①Ovaries should not be preserved in patients at hereditary risk of ovarian cancer such as carriers of germline *BRCA* mutations or *MLH1/MSH2/MSH6* mutations (Lynch syndrome), and ovarian preservation should be carefully discussed in patients with ovarian or breast cancer family history.

BSO bilateral salpingo-oophorectomy; ERpos oestrogen receptor positive; MMRd mismatch repair deficient; NSMP no specific molecular profile.

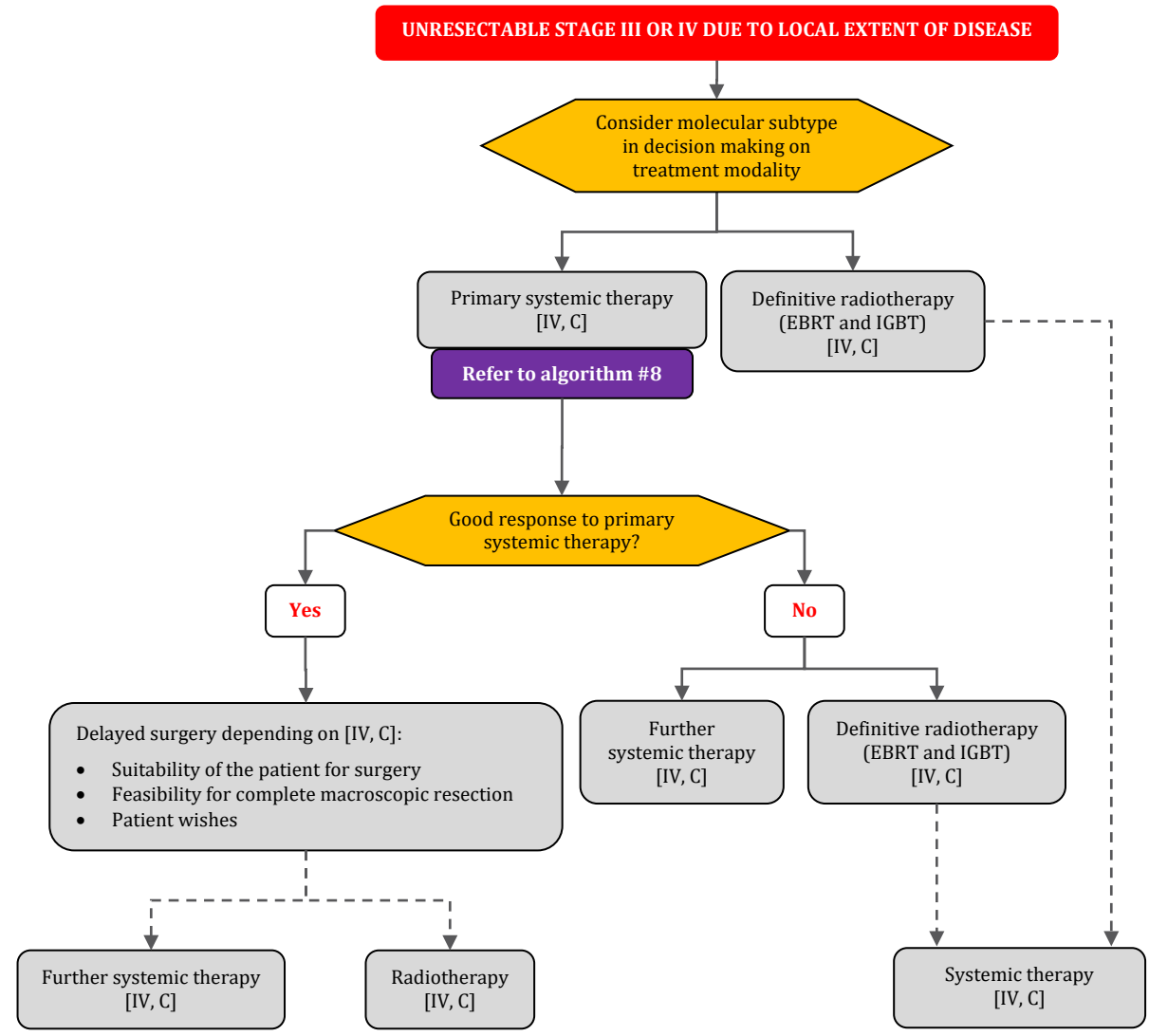
4.5 Algorithm #5 - Medically unfit patients with stage I & II disease



4.6 Algorithm #6 - Surgery for clinically overt stage III & IV disease

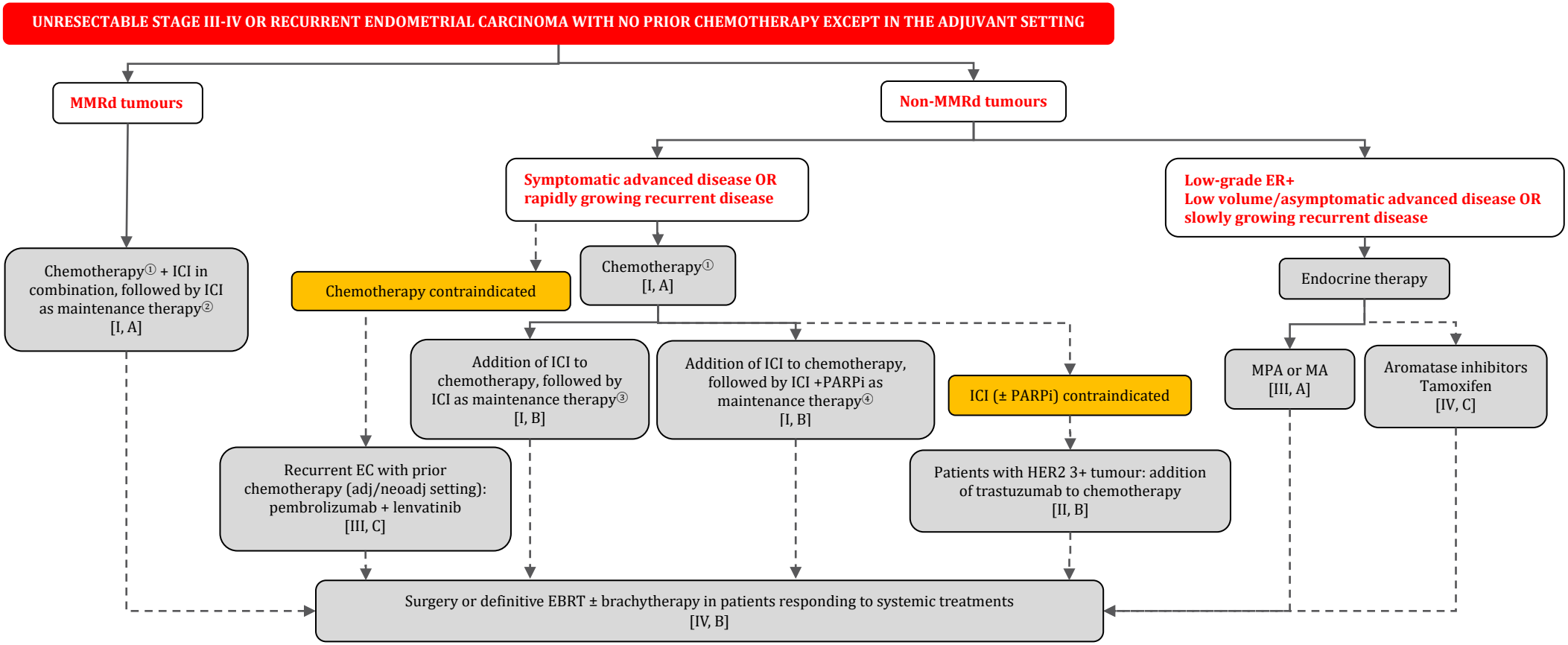


4.7 Algorithm #7 - Unresectable stage III or IV due to local extent of disease



EBRT external beam radiotherapy; IGBT image-guided brachytherapy.

4.8 Algorithm #8 - First line systemic therapy in unresectable stage III-IV or recurrent endometrial carcinoma with no prior chemotherapy except in the adjuvant setting (including patients with residual disease after surgery)



①The standard chemotherapy regimen is carboplatin + paclitaxel.

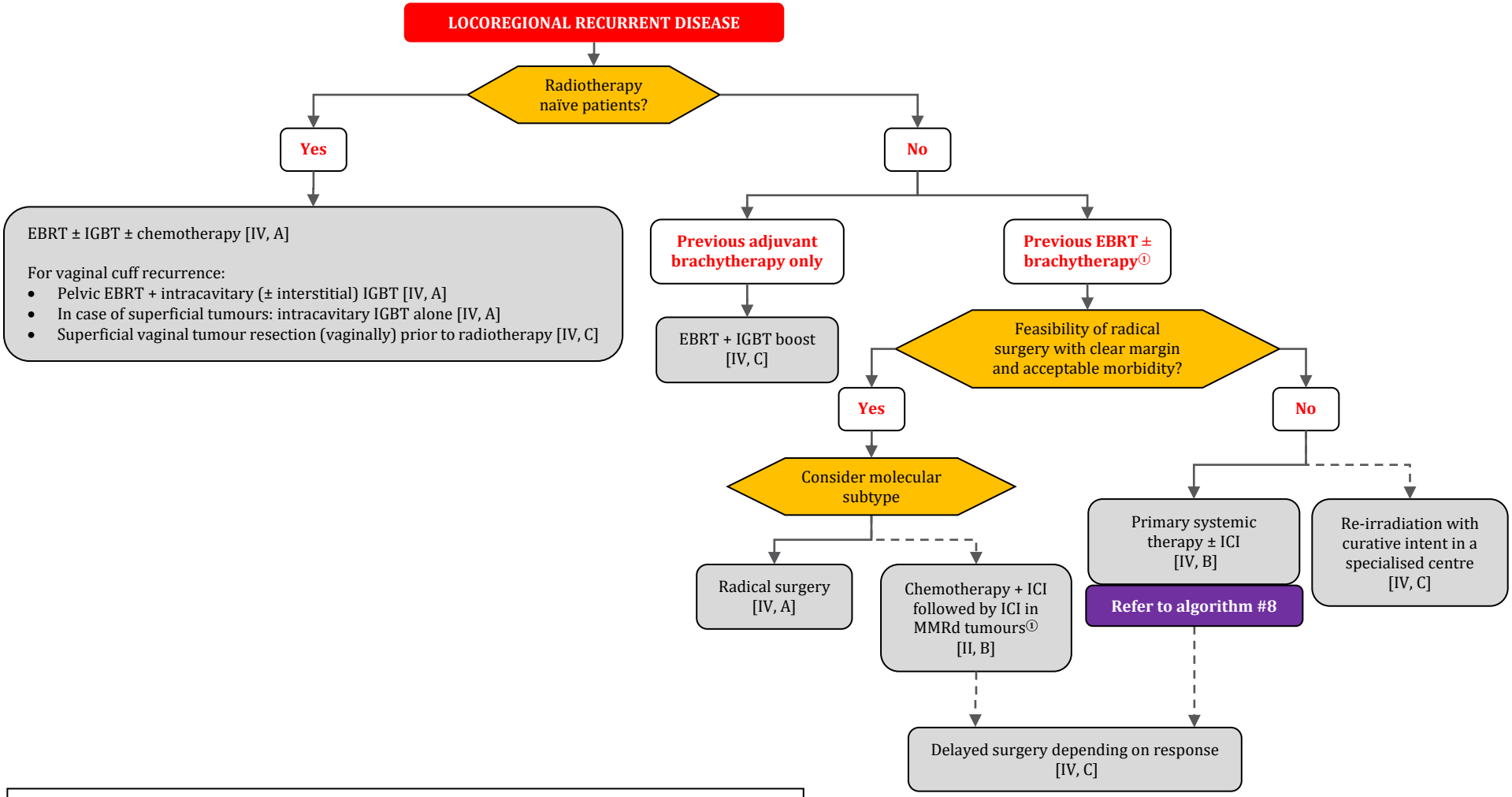
②Immune checkpoint inhibitor (ICI): dostarlimab or durvalumab or pembrolizumab (drugs in alphabetical order).

③ICI: dostarlimab or pembrolizumab.

④ICI + poly(ADP-ribose) polymerase inhibitor (PARPi): durvalumab + olaparib.

Adj/neoadj adjuvant/neoadjuvant; EBRT external beam radiotherapy; ER+ estrogen receptor positive; MA megestrol acetate; MMRd mismatch repair deficiency, MPA medroxyprogesterone acetate; non-MMRd non-mismatch repair deficiency; NSMP no~~n~~-specific molecular profile.

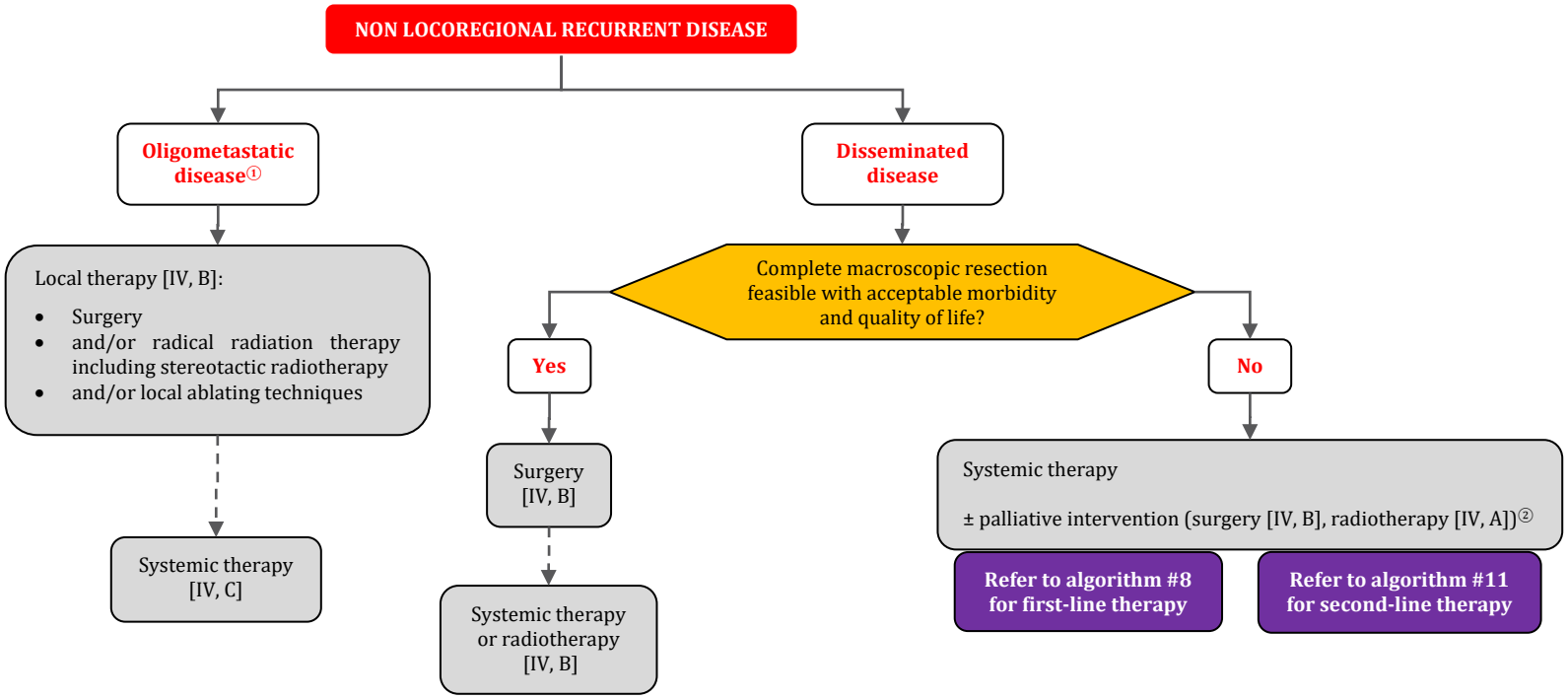
4.9 Algorithm #9 - Locoregional recurrent disease



①If the patient is immune checkpoint inhibitor (ICI) naïve.

EBRT External beam radiotherapy; MMRd mismatch repair deficiency; IGBT image-guided brachytherapy.

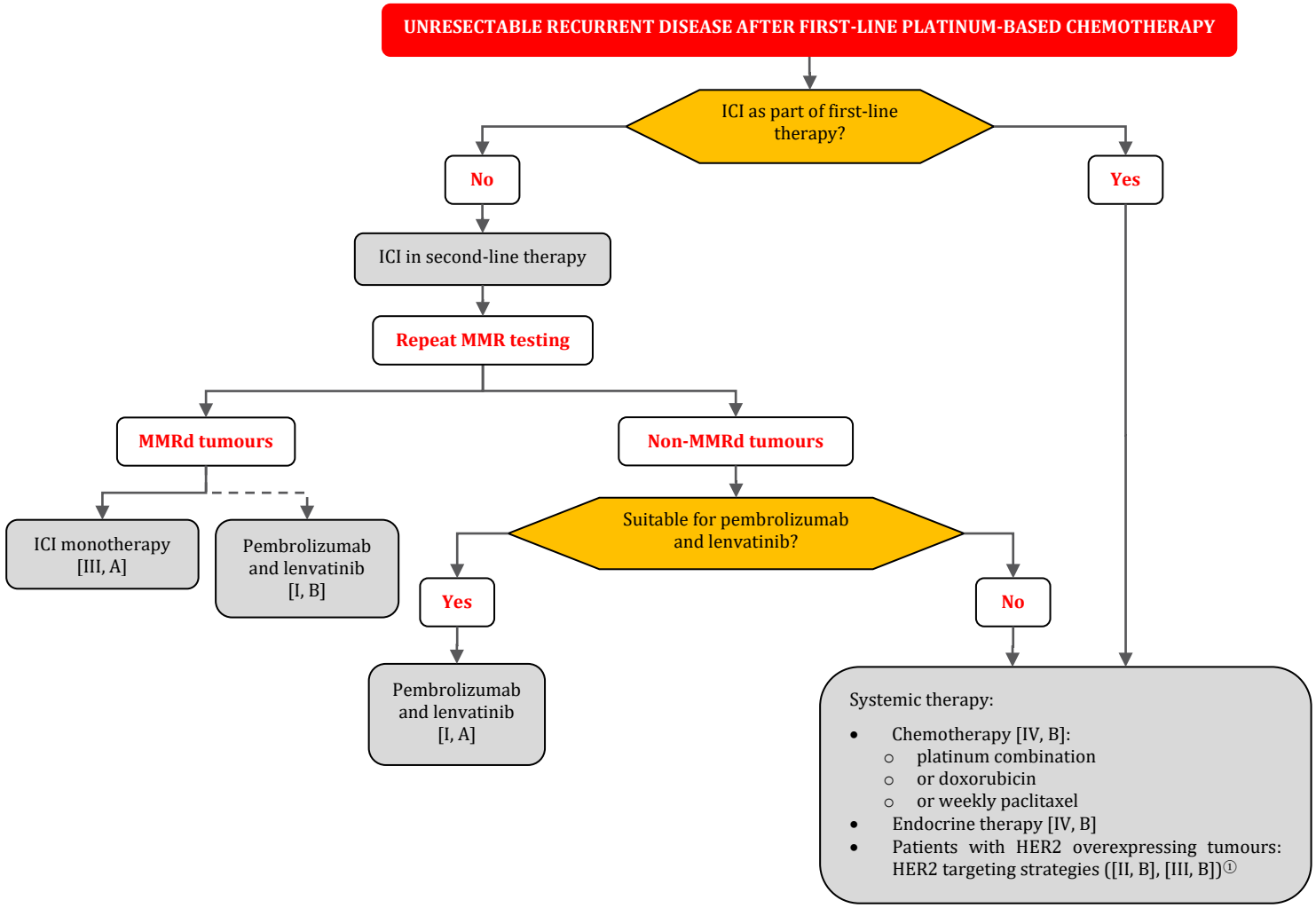
4.10 Algorithm #10 - Non locoregional recurrent disease (oligometastatic or disseminated recurrent disease)



①1-5 metastases/up to 3 regions.

②Palliative surgery can be performed in selected cases to alleviate symptoms (e.g. bleeding, fistula, bowel obstruction). Palliative radiotherapy is indicated for symptoms related to pelvic or systemic disease.

4.11 Algorithm #11 - Second line systemic therapy in unresectable, recurrent disease after first-line platinum-based chemotherapy



①Carboplatin + paclitaxel + trastuzumab (in HER2 3+ tumours by immunohistochemistry) if chemotherapy re-challenge is an option [II, B]; Trastuzumab deruxtecan (in HER2 2/3+ tumours by immunohistochemistry) [III, B].

MMRd/MSI-H mismatch repair deficiency/microsatellite instability-high; ICI immune checkpoint inhibitor; MMRp/MSS mismatch repair proficient/microsatellite stable.

5 Summary of evidence

5.1 Lynch identification and surveillance

Approximately 3% of all endometrial carcinomas (ECs) and about 10% of mismatch repair deficient (MMRd)/microsatellite instable ECs are causally related to germline mutations of one of the MMR genes *MLH1*, *PMS2*, *MSH2* and *MSH6*(1). Testing for MMR status/microsatellite instability (MSI) in EC patients has been shown to be relevant for four reasons:

1) diagnostic, as MMRd/MSI is considered a marker for endometrioid-type EC;
2) pre-screening to identify patients with a higher chance for having Lynch syndrome;
3) prognostic as identified by The Cancer Genome Atlas (TCGA, see below for molecular classification);
4) predictive for response to immune checkpoint inhibitor (ICI) therapy.

The preferred approach (widely available, cost-effective and informative on which specific MMR protein is affected) to identify patients with a higher chance of having Lynch syndrome is by MMR-immunohistochemistry (IHC) on well preserved tumour tissue. MMR testing is discussed in the chapter on molecular classification in EC. Testing for MMRd by IHC or MSI by PCR-based methods, does not allow direct identification of Lynch syndrome patients (pre-screening), since MMRd/MSI is frequently due to sporadic events such as bi-allelic somatic mutations or hypermethylation. In the absence of hypermethylation, referral to genetic counselling is recommended to evaluate the presence of a germline mutation. When familial history is highly suspicious of Lynch syndrome, genetic counselling is recommended independent of the MMR status. Mutation of EPCAM has recently also been identified in 0.2% of patients with Lynch Syndrome(2).
The cumulative incidences for cancer depend on the specific mutation in women with Lynch syndrome. For EC, the cumulative incidences at 70 years are 34%, 51%, 49% and 24% for *MLH1*, *MSH2*, *MSH6* and *PMS2* mutation carriers, respectively, and for ovarian cancer 11%, 15%, 0% and 0%, respectively(3). Furthermore, the age of cancer onset in Lynch syndrome varies among specific mutated genes and type of mutations(4). The youngest cases of endometrial cancers in patients having Lynch syndrome are in general observed after the age of 30 years, this particularly concerns MSH2 carriers. For MLH1, MSH2 and MSH6 carriers the highest incidence of EC is observed between 50 and 54 years and for PMS2 carriers between 55 and 59 years (5). These characteristics explain the different guidelines in relation to the starting-age of screening and age of prophylactic surgery. Ryan *et al.* suggest gynaecological surveillance to be appropriate from age 30 years for those with MSH2 mutations, from age 35 years for those with non-truncating MLH1 mutations, and from age 40 years for those with MSH6 and truncating MLH1mutations. Women with heterozygous PMS2 mutations do not warrant gynaecological surveillance because their absolute risk of gyanecological cancer is very low. As part of a retrospective study, Lachiewicz *et al.* reported a risk of any occult malignancy during prophylactic surgery for women with Lynch syndrome or Hereditary Non-Polyposis Colorectal Cancer to be up to 17%(6). Thus, these patients should be counselled about the risk of detection of gynaecological cancer at prophylactic surgery (Algorithms #1 & #2).

5.2 Integration of molecular classification and other biomarkers

Molecular classification provides important information on diagnosis, prognosis and response to therapy and is therefore recommended in all newly diagnosed ECs. Molecular classification should include all histological types. It is based on three key markers: pathogenic *POLE* mutations in the exonuclease domain, mismatch repair deficiency (MMRd)/microsatellite instability (MSI) and p53 abnormal immunohistochemical staining/*TP53* mutations (7). The whole continuum of these 3 markers should be tested to properly allocate each EC to one molecular subtype. Molecular testing includes IHC for MMR and p53 proteins. For MMR protein analysis a two-step IHC procedure can start with two antibodies detecting MSH6 and PMS2 (the minor partners) and uses the corresponding major partner (MLH1 and MSH2, respectively) only, when the minor partner is not expressed (immunohistochemically negative)(8). This procedure has in comparison to the all four-antibody upfront approach, the advantage of being more efficient while being equivalently reliable to detect MMR deficiency. IHC should be performed on an automated platform using IVD-CE or validated in-house antibodies. The interpretation of MMR IHC may be hampered by inconclusive staining patterns or artifacts (dot-like or granular staining). Molecular analysis for MSI is encouraged when IHC is equivocal. For p53 there are 4 major immunoreactive patterns

indicating abnormality (p53abn), i.e. diffusely nuclear positivity ("all") or negativity ("null"), focal nuclear ("subclonal") and cytoplasmic staining (9, 10). The "all" and "null" patterns account for almost 80% of the cases whereas cytoplasmic is rare. Subclonal p53 expression is usually seen in *POLE*mut or MMRd tumours, and in this scenario, it does not have significant relevance. When seen in the absence of a pathogenic *POLE* mutation or MMRd, a cut-off of 10% has been proposed to classify the tumors as NSMP (less than 10% p53 expression) or as p53abn (more than 10% p53 expression)(11).

Equivocal or heterogenous p53 IHC should be supplemented by *TP53* sequencing. It is important to be aware that a small subset of low-grade stage I endometrioid carcinomas harbour *TP53* mutations and is characterized by increased recurrence risk(12). *POLE* mutational analysis should cover all 11 pathogenic mutations within the exonuclease domain and can be performed by sequencing or alternative PCR techniques(13). It needs to be emphasized that other *POLE* mutations do not have a documented prognostic impact. Access to *POLE* mutation testing is not uniformly available and might be associated with higher cost, thus *POLE* mutation analysis may be omitted in low-risk stage I EC if the *POLE* mutational status does not influence the adjuvant treatment decision.

In general, estimated less than 5% of EC (depending on cohort) shows more than one molecular feature, which is sometimes referred to as "multiple classifiers"(14). Carcinomas that are *POLE*mut + MMRd or *POLE*mut + p53abn or *POLE*mut + MMRd + p53abn behave clinically similarly to pure *POLE*mut carcinomas and therefore should be categorized as *POLE*mut(15). In combination with MMR deficiency and/or mutant-type p53 staining, the pathogenic *POLE* mutations are considered the genomic driver. Similarly, in case of double classifiers of MMRd and mutant-type p53 staining the carcinoma should be categorised as MMRd.

Patients with MMRd EC (prescreening) should be further investigated for potential germline mutations in the *MMR* genes (Lynch syndrome). MLH1 loss detected by IHC can be caused either by a *MLH1* mutation or by *MLH1* promotor methylation. It is important to know that in the majority of cases the MLH1 loss is caused by promotor methylation and that *MLH1* germline mutations are rather rare(16). To know the mechanism behind the MLH1 loss is important for the triage of patients to genetic counselling and germline testing for Lynch syndrome. Methylation analysis for *MLH1* might be replaced by the immunohistochemical surrogate marker EPM2AIP1(17).

Molecular characterization is encouraged on endometrial biopsy/ curettage material where it can supplement the histological diagnosis of EC(18). Molecular testing only needs to be repeated on the hysterectomy specimen in special situations including scant tumour tissue, equivocal or inconclusive results or technical problems on biopsy or in the case of presence of an additional tumour component in the hysterectomy specimen that was not present in the biopsy. Hysterectomy specimens often suffer from inadequate handling and fixation, which may strongly influence the quality of IHC and molecular analyses. In contrast, curettages and biopsies usually undergo prompt fixation which allows optimal preanalytical conditions.

The four molecular subgroups have a distinctly different prognosis. This was first demonstrated by TCGA using extensive molecular characterization and later repeated with surrogate markers in multiple independent cohorts, including randomized trials(18-21). Patients with *POLE*mut tumours have an excellent prognosis, which is probably related to increased immunogenicity of related neoepitopes. In contrast, those with p53abn tumours have the poorest prognosis. Both MMRd and no specific molecular profile (NSMP) tumours have an intermediate prognosis.

It is also recommended to assess oestrogen receptor (ER) IHC on all ECs, since it is diagnostically useful and allows to stratify NSMP carcinomas in two distinct prognostic subgroups (22, 23). As for molecular testing, ER IHC can be done on the biopsy/curettage material. For ER positivity, a cut-off of 10% positive tumours cells is proposed.

Amplification of the *ERBB2* gene leading to overexpression of HER2 are found in approximately 20% of ECs with a *TP53* mutations (24, 25). This affects particularly endometrial serous carcinomas and carcinosarcomas(26, 27). Since overexpressed HER2 represents a potential therapeutic target, all recurrent and advanced stage p53 abnormal EC and all serous carcinomas and carcinosarcomas may be tested for HER2 by IHC using a standardized procedure(28-30). Tumours with an immunoreactive score 2+ need to be additionally tested by in situ

hybridization(31). The optimal scoring system for predicting response to different anti HER2 targeting drugs is under discussion. Tumour heterogeneity may cause differences in the HER2 expression between curettage materials and surgical specimens(27). There is some evidence that HER2 overexpression represents a poor prognostic marker in early-stage serous carcinoma(32).

The presence of lymphovascular space invasion (LVSI) is observed in approximately 10-15% of stage I EC, with reported incidences of LVSI across all EC cases varying widely (6-60%), and increasing with higher tumour grade, depth of invasion, and stage. Diagnosing any LVSI can be challenging for pathologists due to factors such as artifacts and MELF-type invasion; however, recent guidance has been developed(33). Approximately 5% of stage I EC cases exhibit obvious LVSI that can be easily recognized at low magnification, leading to a high level of agreement among pathologists. In contrast, focal LVSI requires high magnification and thorough inspection for identification, is therefore underreported, and is associated with significant interobserver variability. The presence of substantial LVSI is a reproducible, independent prognostic factor in stage I EC, with its significance particularly evident in stage I NSMP EC(34-40). Substantial LVSI has established itself as a robust H&E-based prognosticator capable of stratifying prognosis in stage I EC patients globally without additional costs. Data from the PORTEC-2 trial indicate that pelvic recurrence risk is reduced in stage I patients with substantial LVSI who receive external beam radiotherapy (EBRT)(41). The clinical relevance of substantial LVSI is characterized by an incremental increase in the hazard ratio for recurrence with the number of vessels involved among stage I EC patients without adjuvant treatment(41). In stage I EC patients with ≥4 vessel involved, the risk of pelvic recurrence reaches 10%, warranting adjuvant treatment(41). Most LVSI cases do not fall within the 3-5 vessel range, complicating the study of precise thresholds in this ambiguous range. Focal LVSI is significantly more dependent on sampling than substantial LVSI, with the average number of LVSI-positive vessels for focal LVSI reported as 1.9 in the PORTEC-1/2 studies. A recent meta-analysis(38) concluded that both focal and substantial LVSI are associated with poorer survival, higher recurrence rates, and increased incidence of lymph node metastasis compared to patients without LVSI, with the substantial LVSI group demonstrating an even worse prognosis. In addition, two recent studies show discordant findings with regard to the prognostic role of focal LVSI compared to the earlier reports, favouring a binary reporting system (LVSI detected or not)(39, 40). In these studies, the average number of positive vessels for focal LVSI was not reported. Together, the prognostic signal for focal LVSI shows variability across studies, likely due to higher interobserver variability, the propensity for misidentification, differential diagnoses with suspected LVSI or artifacts, and variations in the definition used for focal LVSI. Current data are insufficient to advocate for differential treatment based on the presence of focal LVSI, which parallels discussions around isolated tumour cells (ITC) - important to report but not actionable due to insufficient data. Reverting to a binary reporting system will also introduce new challenges, including the risk of overtreatment. Therefore, we recommend maintaining the three-tiered LVSI system, as substantial LVSI demonstrates robust and consistent prognostic results. For definition of substantial LVSI, we endorse WHO (≥ 5 vessels in 2021) and FIGO 2023 but recognize that the ≥ 4 vessels score can be used, since the scientific evidence between the two different scores (≥4 versus ≥5) is not strong, and vast majority of LVSI cases do not fall within the 4-5 vessel range. While we recognize the complexity of studying optimal thresholds for clinical management, we recommend future studies to focus on this important topic. Prospective data on (focal) LVSI in the context of molecularly classified uterus confined EC are eagerly awaited, such as in the forthcoming PORTEC-4a trial(34) (Figure 2).

5.3 Definition of risk groups

Definition of risk groups integrating molecular classification

At the outline of this updated guideline the previous risk group table was revised to: 1) accommodate FIGO 2023 staging system; 2) incorporate any new and relevant prognostic molecular marker; and 3) assign a risk group status. Tables 1 and 2 in the manuscript depict such an integrated approach towards prognostic risk group allocation either based on FIGO 2023 staging system with known molecular classification (Table 1) or on tumour extension, LVSI status and known molecular classification (depicting the corresponding FIGO 2023 stages in the table`s cells; Table 2), respectively. Thus, these tables offer two different starting points for risk group allocation for a specific patient and it is at the discretion of the reader which of the two Tables is more convenient to use. Three different retrospective analysis have shown that ER negativity and/or histological high-grade defines a group of NSMP EC

associated with a poor prognosis(22, 23, 42). This has been taken into account in the tables where now NSMP has been split in: 1) NSMP low-grade+ERpos; and 2) NSMP high-grade/ERneg.

Taking published outcome data from clinical trials and available data on outcomes for the different molecular subgroups as well as FIGO 2023 stages into account, a risk status was assigned. The respective groups are defined according to estimated 5-year risk of any recurrence as:

- low risk group: risk less than 8%;
- intermediate risk group: risk between 8 and 15%;
- high-intermediate risk group: risk between 15 and 25%;
- high risk group: risk higher than 25%.

Definition of risk groups without molecular classification

Tables 3 and 4 depict prognostic risk groups either based on 2023 FIGO staging without molecular classification (Table 3) or based tumor extension, LVSI status, grading & histological subtype, without molecular classification (Table 4), respectively.

Adjuvant treatment guidelines for the respective risk groups are provided in figure 3 of the manuscript. Of note, particularly in high-grade histologies, molecular classification has a large impact on risk group allocation and associated management(43).

Table 3. Definition of risk groups based on FIGO 2023 staging, without molecular classification.

2023 FIGO staging			Molecular classification unknown
I	**Confined to the uterine corpus**		
IA	IA1	Low-grade endometrioid, limited to polyp/endometrium (no myoinvasion)	
	IA2	Low-grade endometrioid, myoinvasion <50%, no/focal LVSI	
	IA3	Low-grade endometrioid carcinoma of the endometrium & ovary#	
IB		Low-grade endometrioid, myoinvasion ≥50%, no/focal LVSI	
IC		High-grade histologies^, limited to polyp/endometrium	
II	**Confined to the uterus**		
IIA		Low-grade endometrioid, invasion of the cervical stroma	
IIB		Low-grade endometrioid, substantial LVSI*	
IIC		High-grade histologies^, myoinvasion	High-grade endometrioid, myoinvasion <50%, no/focal LVSI
			High-grade endometrioid, myoinvasion ≥50%, no/focal LVSI
			High-grade endometrioid, cervical invasion, no/focal LVSI
			High-grade endometrioid, substantial LVSI
			All other high-grade histotypes, any myoinvasion ± cervical invasion
III	**Local and/or regional spread**		
IIIA	IIIA1	Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)	
	IIIA2	Involvement of uterine subserosa or spread through the uterine serosa	
IIIB	IIIB1	Metastasis or direct spread to the vagina and/or the parametria	
	IIIB2	Metastasis to the pelvic peritoneum	
IIIC	IIIC1	Pelvic lymph node metastasis	
	IIIC1i	Micrometastasis	
	IIIC1ii	Macrometastasis	
	IIIC2	Para-aortic lymph node metastasis (up to renal vessels)	
	IIIC2i	Micrometastasis	
	IIIC2ii	Macrometastasis	
IV	**Locally advanced and/or metastatic disease**		
IVA		Invasion of the bladder mucosa and/or the intestinal mucosa	
	Metastatic disease or residual disease after surgery		
III/IVA		With residual disease	
IVB		Peritoneal metastasis beyond the pelvis	
IVC		Distant metastasis	

Green denotes low risk for recurrence; yellow denotes intermediate risk; orange denotes high-intermediate risk and red denotes high risk.

myoinvasion <50% + no/focal LVSI + ovarian tumour pT1a

^High-grade histologies are the FIGO 2023 aggressive histotypes that include high-grade endometrioid (grade 3), serous, clear cell carcinomas, carcinosarcomas, undifferentiated, mixed, mesonephric-like, and gastrointestinal mucinous type carcinoma.

*Substantial LVSI is defined according to WHO criteria in at least one H&E slide (refer to appendix for information on LVSI, pp 18-20).

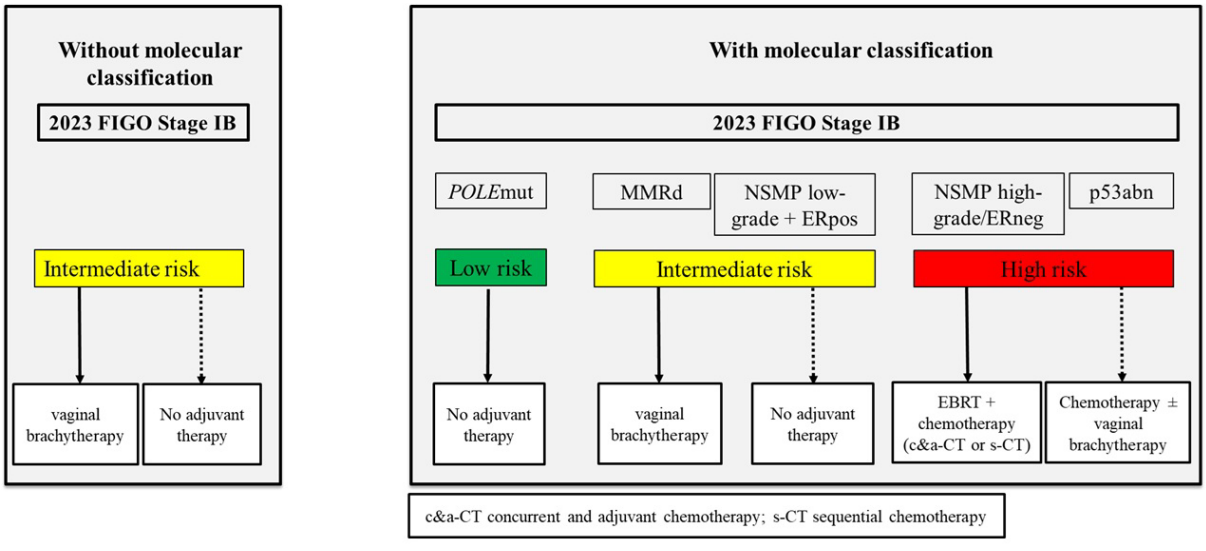
Table 4. Definition of risk groups based on tumour extension, LVSI status, grading & histological subtype, without molecular classification, showing corresponding FIGO 2023 stages in the table`s cells

		Molecular classification unknown		
		Low-grade endometrioid	High-grade endometrioid	High-grade non endometrioid
Confined to the uterine corpus				
	No myoinvasion, limited to polyp/endometrium	IA	IC	IC
	Myoinvasion <50%, no/focal LVSI	IA2	IIC	IIC
	Myoinvasion ≥50%, no/focal LVSI	IB	IIC	IIC
Confined to the uterus (uterine corpus ± cervical invasion)				
	Cervical stromal invasion, no/focal LVSI	IIA	IIC	IIC
	Uterine corpus ± cervical invasion, substantial LVSI*	IIB	IIC	IIC
Local and/or regional spread beyond uterus				
	Spread to ovary or fallopian tube (except for #)	IIIA1	IIIA1	IIIA1
	Involvement of uterine subserosa or spread through the uterine serosa	IIIA2	IIIA2	IIIA2
	Metastasis or direct spread to the vagina and/or the parametrium	IIIB1	IIIB1	IIIB1
	Metastasis to the pelvic peritoneum	IIIB2	IIIB2	IIIB2
	Metastasis to the pelvic lymph nodes	IIIC1	IIIC1	IIIC1
	Metastasis to the para-aortic lymph nodes	IIIC2	IIIC2	IIIC2
Locally advanced				
	Invasion of bladder mucosa and/or intestinal mucosa	IVA	IVA	IVA
Low-grade endometrioid carcinoma of both the endometrium + ovary				
	Myoinvasive <50%, no/focal LVSI, ovarian tumour pT1a	IA3	n.a	n.a
Advanced or metastatic or residual disease after surgery				
	Local and/or regional spread with residual disease	III with residual disease		
	Invasion of bladder mucosa and/or intestinal mucosa with residual disease	IVA with residual disease		
	Peritoneal metastasis beyond pelvis	IVB		
	Distant metastasis	IVC		

Green denotes low risk for recurrence; yellow denotes intermediate risk; orange denotes high-intermediate risk and red denotes high risk.
*Substantial LVSI is defined according to WHO criteria in at least one H&E slide (refer to appendix for information on LVSI, pp 18-20).
myoinvasion <50% + no/focal LVSI + ovarian tumour pT1a

An example for the impact of the molecular classification on the risk group allocation and the management of EC patients is provided in Figure 4 for FIGO 2023 stage IB EC. Other examples are FIGO 2023 stage IIC high-grade endometrioid cancers with substantial LVSI which are high-risk without molecular classification, while are low risk in the presence of a pathogenic *POLE* mutation, high-intermediate if MMRd, and high risk if p53abnormal, resulting in different treatment guidelines. This exemplifies the importance of the molecular classification.

Figure 4. Example of the impact of the molecular classification on patient management in FIGO 2023 stage IB endometrial carcinoma.



5.4 Surgical management in presumed stage I & II disease

Standard surgical procedure

In a randomised controlled trial comparing modified radical (Piver-Rutledge class II) hysterectomy to the simple hysterectomy (Piver-Rutledge class I) in stage I EC, no differences in locoregional control and survival were found(44). Also in a meta-analysis of 2,866 patients with stage II EC, radical hysterectomy did not show a significant survival benefit for either overall survival (OS) or progression-free survival (PFS) as compared to simple hysterectomy(45). The result remained consistent after it was adjusted for the possible impact from adjuvant radiotherapy.

The high risk of microscopic omental metastases in stage I serous and undifferentiated EC suggests that infracolic (total or partial) omentectomy should be part of staging surgery in these patients(46). The low rate of omental metastases in apparent clinical stage I endometrioid and clear cell carcinoma does not justify the procedure(47). Although the risk of having occult (microscopic) omental metastases in carcinosarcoma is relatively low (about 6%), staging omentectomy in these women is suggested. Identification of these cases will allow inclusion of patients with advanced stage disease into clinical trials(48). There is little evidence from retrospective data on the incidence of omental/peritoneal metastases per molecular subtype in preoperatively presumed early-stage disease(49, 50). A study including all stages of EC patients demonstrated metastatic omental/peritoneal disease in 23.8% of p53abn carcinomas across all histologies (without providing specific numbers in high-grade endometrioid histological subtype)(49). Prospective data on the pattern of spread according to molecular subtype are warranted, particularly in patients with preoperatively presumed early-stage EC, to further tailor surgical management in the future. Positive peritoneal cytology correlates with poor prognostic factors and poor survival; however, it is not part of FIGO staging and unclear if this should influence treatment decisions(51-53).

Minimally invasive approach

Two randomised prospective studies comparing minimally invasive with open surgeries showed similar survival with quicker recovery with the minimally invasive approach(54, 55). More recently, pooled analyses of randomised prospective studies including notably these 2 studies, and multiple retrospective and prospective studies support also the use of minimally invasive surgery (MIS) for patients including those with high risk EC(56-121). Transcervical uterine manipulators are commonly used devices for minimally invasive hysterectomy in endometrial cancer. A variety of disposable and reusable systems are available worldwide and can aid the surgeon in tissue exposure and successful completion of the operation. On the one hand the majority of studies do not demonstrate a higher risk of mortality in EC patients who underwent surgery with a uterine manipulator; furthermore, uterine manipulators are not associated with increased risk of LVSI on final pathology(122-125). However, some recent studies raise doubts regarding the safety of the use of intra-uterine manipulators(126, 127). Some manipulators have an intrauterine component, and some only provide a circular ring in the vaginal fornixes to facilitate colpotomy. There is no high-level evidence to show advantage or risk to either model. In any case, rupture of the uterus (e.g. also due to an intrauterine component of a manipulator) needs to be avoided by all means to prevent spilling of the tumour (26).

Lymph node staging

Multiple studies, including prospective cohort studies, confirmed the high sensitivity of sentinel lymph node (SLN) biopsy to detect metastatic disease for the purpose of lymph node staging in early-stage EC patients(128-190). SLN biopsy without dissection of other pelvic lymph nodes is associated with subtantially lower risk of intra-operative complications and post-operative morbidity, especially lower leg lymphoedema(191-193). Also in high-intermediate/high risk patients several prospective cohort studies and meta-analyses confirmed high bilateral SLN detection rate and high sensitivity of SLN biopsy in surgical staging (130, 131, 186, 194, 195). More intensive pathological assessment of SLN (ultrastaging) increases the accuracy of lymph node staging by the detection of small volume disease (micrometastases and ITCs) which can be missed more often by standard evaluation(163, 181, 196). Presence of both macrometastases and micrometastases (micrometastases defined as greater than 0.2 mm and/or more than 200 cells, but not greater than 2.0 mm, pN1(mi)) is regarded as a metastatic involvement(197). There are conflicting data on the impact of ITCs on prognosis, and similar to other tumour

sites, the stage would be pN0(i+). Based on the low morbidity associated with SLN biopsy, it can be recommended even in the low risk group of patients in which lymph node involvement was reported at a rate of 6% (197). Several retrospective studies and meta-analysis showed no difference in the overall recurrence rate or lymph node recurrence rate after systematic pelvic lymphadenectomy and SLN biopsy, respectively (128, 150, 169). Based on all the above arguments, SLN biopsy without a need for further lymph node dissection should be the preferred procedure for LN staging universally applied to all patients with presumed early-stage endometrial cancer. Because the drainage of the central pelvic organs, including the uterus, is to both sides of the pelvis, surgical lymph node staging should be bilateral. Therefore, in case of the SLN is unsuccesful on one side of the pelvis, it is recommended to perform a unilateral systematic pelvic lymphadenectomy at this side in high-intermediate/high-risk patients. A side-specific systematic lymphadenectomy can be considered in presumed intermediate-risk patients. However, a systematic lymphadenectomy has a higher morbidity than SLN biopsy, and its implementation should be considered on an individual basis, keeping in mind that the purpose of lymph node staging is to assess the extenet of disease and to tailor adjuvant treatment, while a therapeutic value has not been demonstrated in two large randomised trials (198, 199). SLNs should undergo the pathological work-up of ultrastaging. In the literature no consensus among pathologists has been reached regarding the minimal number of levels for ultrastaging. The initial section followed by, at least, two additional levels (50µ to 250µ apart, combining H&E and IHC) might be a reasonable approach to combine cost-effectiveness and efficacy to detect low volume metastasis. With respect to the optimal tracer for SLN biopys, a randomised controlled trial highlighted that the use of indocyanine green instead of methylene blue dye resulted in a significant increase of sentinel lymph node detection rates per hemipelvis in women with EC undergoing minimally invasive surgery(200). Higher sentinel lymph node detection rate has been reported using near-infrared fluorescence in comparison to other techniques(201). The standard dose of IGC from clinical trials is 1.25mg/ml and a total of 4 ml is injected into the cervix at 3 and 9 o'clock, usually 1 ml superficial (2-3mm) and 1 ml deep (1-2cm) on each side(201, 202). Variations to this protocol are acceptable as long as a high detection rate (≥85%) is achieved. A multicenter Italian study recently reported higher SLN detection rate after cervical versus hysteroscopic tracer injection(203).

Ovarian preservation in stage I disease

Ovarian preservation in patients with stage 1, grade 1 EC was shown to have no impact on overall survival and to improve quality of life in premenopausal women(204). It has been suggested to extend the option for ovarian preservation to patients with grade 2 or 3 disease (but with a limited number of high-grade cases)(205). Integration of molecular markers had been proposed for the first time by the Memorial Sloane Kettering Cancer Center, however data on molecular subtypes and ovarian preservation are sparse(206). The new FIGO classification and the ESGO/ESTRO/ESP guidelines integrate molecular classification to improve identification of distinct prognostic patient populations. Ovarian preservation in premenopausal patients aged <45 years can be considered in low-risk patients as defined by FIGO stage IA1/ IA2 and a low risk of recurrence by molecular classification. These cases are represented by FIGO 2023 stage IA1 (low-grade endometrioid limited to a polyp/the endometrium) and stage IA2 (low-grade endometrioid <50% myometrial invasion, no/focal LVSI) of the molecular subtypes *POLE*mut, MMRd and NSMP low-grade+ERpos, respectively(207).

In patients with ovarian preservation, salpingectomy during standard surgery for EC is recommended to decrease the risk of high-grade serous ovarian carcinoma(208). Ovarian preservation is not recommended in patients with a hereditary cancer risk including tubo-ovarian cancer (e.g. germline *BRCA* mutation, Lynch syndrome, etc.), however, oocyte cryopreservation might be considered in these patients(209). Ovarian preservation should be carefully discussed in patients with ovarian or breast cancer family history without verified hereditary mutations (Algorithm #3).

5.5 Medically unfit patients with stage I & II disease

Medical co-morbidities, which increasingly include morbid obesity, can preclude surgery due to high operative and peri-operative risks. Ideally, frailty and/or geriatric assessments should be performed, as well as evaluation by an anaesthesiologist who is skilled in managing these high-risk patients. Definitive radiotherapy is the curative treatment of choice for patients in whom surgery (including vaginal hysterectomy) is contra-indicated for medical reasons(210-216): the combination of EBRT and brachytherapy is indicated for high-grade tumours and/or deep

myometrial invasion; curative brachytherapy alone can be considered for low-grade tumours without deep myometrial infiltration. When patients are medically ineligible for curative therapies, systemic treatment (including endocrine therapy) and/or a combination of local treatments (including progestin-releasing intrauterine device and haemostatic radiotherapy) can be considered(217, 218) (Algorithm #5).

5.6 Adjuvant therapy

Adjuvant therapy guidelines for patients with EC strongly depend on the prognostic risk group (see tables 1 and 2 for definitions of the prognostic risk groups with molecular classification; and tables 3 and 4 for risk stratification without molecular classification). Low risk (including molecular class) is defined as estimated overall 5-year risk of any recurrence less than 8%; intermediate risk between 8 and 15%; high-intermediate risk between 15 and 25%, and high risk higher than 25%.

Low risk

For patients with low-risk EC (marked in green in risk group Tables 1 and 2), no adjuvant therapy is recommended based on data from multiple randomized trials(219-222). The molecular classification is essential particularly in high-grade carcinomas (endometrioid and non-endometrioid) as they have different outcomes by molecular subgroup, most being p53abn(18, 20, 223, 224).

For patients with the molecularly defined FIGO 2023 stage IAm *POLE*mut (i.e uterus confined *POLE*mut ECs), no adjuvant therapy seems justifiable. This guideline is based on the rapidly cumulating data from independent series - although mostly from post-hoc molecular testing from large prospective series - showing very few recurrences and an excellent prognosis, also in case of no adjuvant therapy after surgery (20, 207, 225, 226). Prospective studies are encouraged.

FIGO 2023 stages IA1m NSMP high-grade/ERneg or p53abn & ICm NSMP high-grade/ERneg or p53abn

Patients with p53abn or NSMP high-grade/ERneg tumours in 2023 FIGO stage IA1/ICm (limited to a polyp or to the endometrium without myometrial invasion) have a slightly less favourable prognosis compared to patients in the low risk category (223, 224). Predominantly high-grade tumours without myometrial invasion (i.e. 2023 FIGO stage 1C) were not included in the randomized trials, and the value of adjuvant chemotherapy or radiotherapy is uncertain. There are very few specific data on treatment for FIGO 2023 stage IC non-endometrioid carcinomas (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion. Some case series and a US National Cancer Data Base analysis suggested that adjuvant chemotherapy (with or without vaginal brachytherapy) could be considered to improve survival; however, other reports showed good outcomes with vaginal brachytherapy only or without any adjuvant therapy(227, 228). Adjuvant treatment should therefore be decided on a case-by-case basis in the multidisciplinary team meeting and in shared decision making with the patient. Prospective studies or registries are highly encouraged.

Intermediate risk

Adjuvant brachytherapy provides excellent vaginal control and high survival rates, similar to those after adjuvant EBRT in this intermediate risk population, as shown in case series and large randomised trials, particularly the PORTEC-2 trial and Swedish trial(227, 229-236). It was also shown that only the small minority of patients with higher risk based on substantial LVSI, p53abn, or L1CAM overexpression had a slightly higher risk of pelvic recurrence with vaginal brachytherapy than those who had EBRT(229, 232-234). Therefore, the intermediate risk category includes FIGO 2023 stage IBm MMRd and NSMP low-grade+ERpos, stage IIAm NSMP low-grade+ERpos, and stage IICm MMRd with no/focal LVSI regardless of depth of myometrial invasion (marked in yellow in risk group Tables 1 and 2).

In a Danish population study, it was confirmed that the risk of locoregional relapse was higher (about 14%) with omission of vaginal brachytherapy, but that OS was not different due to effective treatment of relapse(237). Therefore, no adjuvant therapy is an option in this group. As age has consistently been proven to be an independent prognostic risk factor in endometrial cancer, both as a continuous variable and when used in age categories with

best cut-off around 60 years of age, no adjuvant therapy can be considered especially for patients with intermediate risk features aged <60 years. While advanced age is associated with more aggressive tumour features in endometrial cancer, age has also been shown to be independently and causally related to worse oncological outcomes(238).

MMRd and, especially, NSMP low-grade+ERpos EC form the majority of endometrioid carcinomas and have an intermediate prognosis. Findings of prior large, randomised trials in high–intermediate risk EC are therefore mainly applicable to MMRd and NSMP low-grade+ERpos endometrioid carcinomas in this intermediate risk category.

High-intermediate risk

The definition of high–intermediate risk includes FIGO 2023 stage IIAm MMRd, stage IIBm NSMP low-grade+ERpos or MMRd, stage IICm MMRd with cervical invasion and/or with substantial LVSI (marked in orange in risk group Tables 1 and 2). In the case of substantial LVSI or cervical involvement, pelvic EBRT is recommended as it has been shown to reduce the risk of pelvic and para-aortic nodal relapse(229, 239, 240). In the GOG249 trial, pelvic EBRT was compared with brachytherapy and 3 cycles of carboplatin and paclitaxel, with similar rates of relapse-free and OS but with better pelvic and para-aortic control and better quality of life(239). In the 10-year analysis of the PORTEC-2 trial, EBRT was shown to improve pelvic control for cases with substantial LVSI(229). An additional brachytherapy boost can be considered, especially for those with substantial LVSI and cervical stromal invasion. The unselected use of chemotherapy in this group seems not justified. In two older randomized controlled trials there was no difference between adjuvant chemotherapy alone and EBRT alone in recurrence-free and OS(241, 242). In unselected patients with stage I-II EC with risk factors, the PORTEC-3 and NSGO/EORTC trials suggested a benefit in recurrence-free and overall survival for the combination of chemotherapy and radiotherapy compared with radiotherapy alone; however, this benefit was likely caused by the p53abn cancers in these trials(21, 243, 244). Molecular analysis of PORTEC-3 trial tissues suggested no benefit of chemotherapy for MMRd carcinomas that mostly represent this risk group(21). In the GOG-249 trial no benefit in recurrence-free and overall survival was found with 3 cycles of chemotherapy and brachytherapy over EBRT alone, with higher nodal relapse rates in the chemotherapy arm(239, 245).

The majority of FIGO 2023 stage IIC tumours (high-grade histology with myometrial invasion) fall into the molecular subtypes of p53abn and NSMP high-grade/ERneg carcinomas, the remaining cases of IIC tumours primarily demonstrate grade 3 MMRd (endometrioid and non-endometrioid carcinomas and carcinosarcomas). Grade does not seem to be an important factor in MMRd carcinomas(207, 246). MMRd non-endometrioid carcinomas and carcinosarcomas have a clearly better outcome than the p53abn and NSMP ERneg carcinomas, but seem less favorable than their endometrioid counterparts. Especially high-grade stage I MMRd carcinomas have a favourable prognosis, and the molecular analysis of the PORTEC-3 trial suggested no efficacy of adding adjuvant chemotherapy to EBRT(21). Overall, while more data are warranted, taking the previously mentioned randomised controlled trials (NSGO/EORTC, GOG-249 and PORTEC-3) into account, EBRT is effective in the management of stage I/II non-endometrioid ECs.

A first study, i.e. ENGOT-EN11-Keynote B21, using adjuvant chemotherapy (± EBRT ± cisplatin) with an immune checkpoint inhibitor (ICI) for advanced stage disease and specific early stage disease with a higher risk for relapse (uterus confined, non-endometrioid carcinomas with myometrial invasion and/or p53abnormal/*TP53*mutated carcinomas with myometrial invasion) suggest favourable results for MMRd(247). In patients with early stage 2023 FIGO stage IIC non-endometrioid MMRd carcinomas, a combination of adjuvant ICI with chemotherapy could be considered in view of the results of the MMRd subgroup in the ENGOT-EN11-Keynote B21 trial, with the aim to deliver an ICI. However, the number of patients with uterus confined non-endometrioid MMRd cancers in this study was small with a low number of events and short follow-up, and specific studies for this group are needed. Some studies are underway, and more are encouraged as the question remains if ICI should optimally be given alone or in conjunction with EBRT or with chemotherapy.

In view of the higher risk of recurrence in this newly classified high-intermediate risk group (even with negative nodes after lymphadenectomy, pN0), adjuvant brachytherapy can be recommended to decrease vaginal recurrence.

Omission of adjuvant therapy is an option especially if pN0 after lymph node staging, with low-grade and without substantial LVSI, and this should be considered only when close follow-up is guaranteed to ensure detection and prompt salvage treatment of recurrence at an early stage.

High risk

The high-risk category includes all p53abn and NSMP high-grade/ERneg ECs, except those with FIGO 2023 stage IA1m (low-grade endometrioid without myometrial invasion), or ICm (high-grade histology without myometrial invasion). It also includes all FIGO 2023 stage III and IVA carcinomas, except those with a *POLE* mutation (stages IIIm *POLE*mut and IVAm *POLE*mut) (marked in red in risk group Tables 1 and 2). The PORTEC-3 trial comparing combined platinum-based chemotherapy and radiotherapy (two cycles of cisplatin during radiotherapy followed by four cycles of triweekly carboplatin-paclitaxel) with radiotherapy alone showed a statistically significant 7% failure-free survival benefit and 5% OS benefit at 5 years in the treatment arm with added chemotherapy(243). The greatest OS difference with addition of concurrent and adjuvant platinum-based chemotherapy was seen in stage III carcinomas and in serous carcinomas, regardless of stage. The GOG-258 trial compared the same chemotherapy-radiotherapy schedule used in PORTEC-3 with six cycles of carboplatin-paclitaxel chemotherapy alone, and found overlapping relapse-free and OS rates(248). However, the chemotherapy alone arm had significantly higher rates of pelvic and paraaortic nodal relapse. Quality of life results showed no clinically meaningful differences between the arms(249). Therefore, chemotherapy alone is an alternative option based on the GOG-258 results for stage III-IVA disease. Multiple retrospective studies have demonstrated a survival benefit in patients with advanced stage EC treated with postoperative combined treatment including radiotherapy and chemotherapy, delivered by either the sandwich or sequential method, compared with radiotherapy alone or chemotherapy alone(250-266). A recent meta-analysis comprising the data of 15 studies and 18,375 patients with stage III EC who underwent either chemotherapy and radiotherapy or chemotherapy alone showed statistically significant superiority of chemotherapy and radiotherapy for total recurrence rate and for OS compared to chemotherapy alone(267). While no OS effect was observed in patients with EC involving the uterine serosa, the adnexa or the parametria, a significant benefit was observed in patients with lymph node involvement (stage IIIC).

Uterus-confined serous and clear cell carcinomas (20% of the trial population) and other early stage carcinomas with unfavourable factors (G2-G3, LVSI, $\geq$50% myoinvasion) were included in the GOG249 trial. The trial showed similar survival outcomes of EBRT compared to 3 cycles of carboplatin-paclitaxel and vaginal brachytherapy and a better nodal control with EBRT. Therefore, chemotherapy (± brachytherapy) alone is an option in early stage, high risk disease. Some uncertainty remains as to the survival benefit of adjuvant chemotherapy for p53abn or NSMP high-grade/ERneg tumours with only minimal myometrial invasion. EBRT alone could be considered, especially in cases with comorbidities posing relative contra-indications to chemotherapy.

Extended field radiotherapy is used only in the case of involved paraaortic nodes or involvement of high common iliac nodes, both with or without chemotherapy. The combination of extended field radiotherapy with chemotherapy using modern intensity-modulated radiation therapy/volumetric modulated arc therapy techniques has been shown to be feasible in the PORTEC-3 and GOG-258 trials. An additional brachytherapy boost can be considered, especially for those with substantial LVSI and cervical stromal invasion. Post-hoc molecular analysis of PORTEC-1, 2 and 3 studies showed a substantial effect in terms of pelvic control of EBRT in p53abn carcinoma regardless of tumour stage, and a clear role of chemotherapy in addition to EBRT, especially in stage III disease and in serous carcinomas (21, 268). The molecular analysis of the PORTEC-3 trial suggested some added benefit of adjuvant chemotherapy for the NSMP group, especially in case of stage IIIm NSMP. This is likely driven by the high-grade/ERneg NSMP carcinomas, which have an unfavourable prognosis(22, 23). Prospective evaluation of the molecular characteristics in randomized trials is highly recommended. MMRd and NSMP ECs are included in the high-risk category if FIGO 2023 stage III–IVAm with no residual disease. The molecular analysis of the PORTEC-3 study showed no clear role of chemotherapy in MMRd stage III disease, but there is currently not enough evidence for not recommending chemo-radiotherapy followed by chemotherapy in this group(21). The role of immune checkpoint inhibition (ICI) in the adjuvant therapy of the high-risk group has been evolving. In advanced stage III/IV and recurrent MMRd carcinomas, the RUBY, the NRG GY-018, the AtTEnd and the DUO-

E trials have shown significant survival benefit by the addition of ICI to platinum-based chemotherapy (269-273). The RUBY trial also included 54 (10%) patients with stage IIIC non-endometrioid carcinomas without measurable disease. The role of ICI for MMRd carcinomas was confirmed in the ENGOT-EN11-Keynote-B21 trial, which included 725 patients with FIGO 2009 stage III-IVA EC of any histology and 371 patients with stage I-II endometrial carcinomas of non-endometrioid histology or with p53 abnormalities/*TP53* mutation and myometrial invasion(247). EC patients were randomized to adjuvant chemotherapy with pembrolizumab or with placebo. Radiotherapy was at investigator's discretion; over 50% received EBRT. Recently published results showed no improvement of disease-free survival for all-comer EC patients included into this trial (HR 1.02). However, subgroup analysis among the 281 (26%) patients with MMRd tumours showed significant disease-free survival improvement (2-year disease-free survival 92.4% versus 80.2%, HR 0.31), this improvement being of similar magnitude as in the RUBY, NRG GY-018, AtTEnd and DUO-E trials. Of note, more than 80% of patients with MMRd tumours in the chemotherapy + ICI arm also received radiotherapy: 92% of these had EBRT. Based on these studies, adjuvant ICI with chemotherapy (± EBRT) should be considered for patients with FIGO 2023 stage IIIm MMRd EC(247, 269, 274). For the 64 stage I-II MMRd carcinomas of non-endometrioid histology (23% of the MMRd carcinomas in the ENGOT- EN11-Keynote-B21 trial) the data of this subgroup analysis are promising (4/25 events in the placebo group versus 0/8 events with ICI occurred in stage I-II non-endometrioid cancers). Thus, adjuvant therapy with a combination of ICI and chemotherapy (± EBRT) could be considered for the reason to deliver an ICI in patients with stage IIC MMRd of non-endometrioid histology. However, further studies are urgently needed to further clarify the role of ICI in early stage MMRd cancers, and if ICI should be used alone or in combination with chemotherapy or with EBRT for the overall goal of highest efficacy with the least toxicity. Randomised trials comparing adjuvant chemotherapy with ICI alone for stage IIIm MMRd are ongoing or being initiated, as well as trials of EBRT with or without ICI for stages I-III MMRd with risk factors.

FIGO 2023 stage IIIm *POLE*$_{mut}$ and IVAm *POLE*mut

Patients with stage IIIm *POLEmut* and IVAm *POLE*mut (gray cells in tables 1 and 2) could not be classified into a risk group because of lack of data. For patients with stage IIIm *POLE*mut EC, there are only indirect data to support observation, as the few reported cases with advanced disease had adjuvant therapy. In the molecular analysis of the PORTEC-3 trial of high risk EC, those with *POLE*mut carcinomas had an excellent outcome in both arms, showing no added benefit of chemotherapy(21). However, both trial arms included adjuvant EBRT. *POLE*mut cancers treated with surgery alone in the Danish high-grade cohort had excellent outcomes without any adjuvant therapy(207). Adjuvant treatment should therefore be decided on a case-by-case basis in the multidisciplinary team meeting and in shared decision making with the patient. Prospective registration (preferably in national or international studies) of *POLE*mut EC cases with treatment and outcome data is strongly recommended. As *POLE*mut tumours might respond exceptionally to immunotherapy, specific studies are needed, especially on the roles of (neo)adjuvant therapy and treatment for advanced/relapsed disease(275).

5.7 Advanced disease

Surgery for clinically overt stage III and IV disease

In patients with stage III and IV EC, cytoreduction should be considered only if macroscopic complete resection is feasible with acceptable morbidity to avoid sequalae on patients quality of life without proven survival benefit (276-281). To have maximal oncologic benefit with the least morbidity, surgery should be performed in a specialised centre by an expert team. Indication for surgery, and all decision-making processes including pre-operative complete diagnostics should be assessed and reviewed by a multidisciplinary tumour board. Prospective randomised studies to date have failed to show a survival benefit from the systematic pelvic and paraaortic lymph node dissection and is therefore not recommended. Only bulky lymph nodes should be resected as part of the cytoreduction if complete resection is possible(282, 283) (Algorithm #6).

Unresectable stage III or IV disease due to local extent of disease

For patients presenting with unresectable locally advanced disease and no evidence of multiple distant metastases, treatment options include definitive radiotherapy or primary systemic therapy followed by delayed surgery in case of a meaningful response(284-288). Information on the molecular subtype can influence the decision making for

either radiotherapy or systemic therapy, e.g. considering patients with MMRd carcinomas to be particularly responsive to ICI addition to carboplatin and paclitaxel chemotherapy. Definitive radiotherapy comprises of EBRT to the pelvis (and paraaortic if involved) followed by image-guided brachytherapy (IGBT). Concurrent systemic therapy may be considered to enhance the radiation effect. IGBT should boost sites of macroscopic disease in the uterus, parametrium or vagina using the GEC-ESTRO principles. Macroscopic disease at locations not amenable for brachytherapy (e.g. pathologic lymph nodes) should be boosted with EBRT. Systemic therapy should also be considered following local treatment (surgery or radiotherapy) to reduce the risk of distant metastases(289, 290) (Algorithm #7).

Unresectable, disseminated disease or residual disease after primary surgery for stage III or IV disease

See systemic therapy section 5.9 on first line treatment.

5.8 Incomplete primary surgery

An unexpected EC diagnosis may be obtained after surgery for benign indications. In these cases, patients have not received complete surgical staging for EC and cannot be assigned to a FIGO stage and an appropriate risk group. These women should be referred to a specialised centre. Post-surgical contrast enhanced abdominal computed tomography scan or positron emission tomography-computed tomography scan should be performed to exclude any metastatic disease, either as primary localisation or as an effect of surgical spreading. Patients should be evaluated for second surgery in a specialised centre based on results from imaging, the initial surgical report and based on clinical and prognostic factors.

No residual disease

In presumed early stage disease without the presence of residual tumour after initial surgery (based on postoperative imaging and initial surgical report) one or several components of standard surgical procedures such as the removal of the cervix, bilateral salpingo-oophorectomy (BSO), peritoneal and/or lymph node staging might not have been done. The decision to re-operate should always be individualised, considering the benefit for the patient, the morbidity of the procedure, and the delay of potential adjuvant treatment. The most common situation of incomplete primary surgery is the absence of surgical lymph node staging. When considering re-surgery, it is important to remember that after hysterectomy, SLN biopsy cannot be utilised, and a therapeutic effect of systematic lymphadenectomy has not been established. Therefore, a second surgery with the aim of performing a systematic lymphadenectomy should be avoided in low risk cases (defined by uterine pathological and molecular factors) with a very low probability of lymph node involvement, and should in all other risk groups be considered only if the lymph node status can alter adjuvant therapy.

Residual disease

Residual lymph node disease in pelvis or para-aortic region following surgery: if re-surgery in residual lymph node disease is not feasible, systemic therapy considering the molecular profile and/or EBRT using a simultaneous integrated or sequential boost to escalate the nodal dose should be applied. An IMRT technique reduces the risk of toxicity to surrounding tissue(291). Systemic therapy after radiotherapy reduces the risk of distant metastases for patients with lymph node involvement(248, 292, 293).

Residual pelvic disease (vaginal, pelvic side wall, bowel) following surgery: If not operable and/or resectable, an individualised approach with either radiotherapy and/or primary systemic therapy should be considered by a multidisciplinary team. Patients with residual pelvic disease following surgery have a high risk of both local and distant recurrence. Radiotherapy can achieve long-term local control while systemic therapy reduces the risk of distant metastases. An individualised approach with either (chemo)-radiotherapy to pelvis followed by systemic therapy or systemic therapy followed by radiotherapy to the pelvis (± para-aortic nodes) or systemic therapy alone should be considered. The molecular profile should be taken into consideration in the decision making on the type of systemic therapy.

5.9 Recurrent disease

Locoregional recurrent disease

Locoregional recurrence of EC is rare. Treatment of patients with recurrent EC involves a multi-disciplinary approach with radiotherapy, surgery, and/or systemic therapy depending on the fitness and wishes of the patient, the tumour dissemination pattern and prior treatment and the molecular profile. The interval between primary treatment and recurrence should also be considered.

Radiotherapy naïve patients: with the advent of modern image-guided radiation therapy, including IMRT and image-guided adaptive brachytherapy, radiotherapy has become the treatment of choice in previously not-irradiated patients with isolated vaginal recurrence or locoregional recurrence(294-305). Consideration can be given to surgically remove superficial solitary, easily accessible vaginal relapses not requiring exenterative procedures, for better local symptom control prior to radiotherapy. In patients with vaginal-only recurrences of grade 1 or 2 endometrioid endometrial cancer, EBRT + image-guided brachytherapy (IGBT) (without addition of chemotherapy) results in excellent outcome (DFS 73% at 3 years)(306). In case of superficial tumours, intracavitary IGBT alone can be considered(307).

Radiotherapy pretreated patients: if the patient had prior adjuvant brachytherapy only, EBRT and IGBT is recommended. In patients who have previously received EBRT ± brachytherapy, radical surgery with the intention of complete resection with clear margins should be considered in specialised centres after ruling out metastatic disease with detailed imaging. Pelvic exenteration for central local relapse should only be performed if clear margins can be achieved, and in the absence of extrapelvic disease in an curative intent (280, 308, 309). Considering the significant overall survival benefit seen in patients with advanced/recurrent MMRd carcinomas when adding and ICI to chemotherapy followed by ICI maintenance therapy, this systemic therapy approach is an option in radiotherapy pretreated, ICI naïve patients with MMRd tumours and a locoregional recurrent disease, potentially followed by delayed surgery depending on response to systemic therapy(269-273). Thus, the molecular subtype should be taken into account in the decision making about radical surgery or primary systemic therapy in ICI naïve patients with MMRd tumours and a locoregional, radiotherapy pretreated recurrence. When radical surgery with complete resection is not feasible, primary systemic therapy should be considered with a potential re-evaluation for surgery depending on response. Otherwise, re-irradiation could be considered as radical curative therapy in a specialised centre, with or without systemic therapy. Interstitial brachytherapy as sole modality of treatment or combined with EBRT can result in high and durable local control(300, 301, 310, 311). Other techniques such as permanent seed implant, intra-operative electron irradiation, proton therapy or stereotactic body radiotherapy may be an option in selected patients(312-314). The appropriate dose for each case needs to be individualised. In general, a longer time interval between the first and second course of radiation and recurrence with lesions <4 cm in diameter tend to have a better outcome. Multidisciplinary management is critical to develop individualised plans, and to communicate clearly to patients the potential side effects and expected treatment outcome (Algorithm #9).

Oligometastatic recurrent disease

Oligometastases is defined by a state of limited metastatic tumours for which local ablative techniques including surgery, radical radiation and local ablative techniques could be used. It refers in general to cancer patients with 1 to 5 metastases in up to 3 regions in the recurrent setting (315-317). In recent years, the concept of oligometastatic relapse has evolved and has led to a change in the approach to treatment. A prolonged disease-free interval and perhaps even cure may be achieved in some situations where the primary cancer site (if still present) is controlled, and metastatic sites are ablated (surgically or with radiation)(318-321). If oligometastases occur in a previously treated area, and surgery is not an option, stereotactic radiotherapy or particle beam radiotherapy could be considered if the metastatic burden is low(322-325). Systemic therapy could be considered in selected patients in addition to local treatment. As mentioned above, multi-disciplinary management is critical (Algorithm #10).

Disseminated recurrent disease

Patients with recurrent disease, including resectable peritoneal and lymph node relapse, should only be considered for surgery if it is anticipated that complete resection of macroscopic disease can be achieved with an acceptable morbidity and quality of life (294, 295, 326-330). The extent of the operation will depend on the amount of tumour dissemination and the pattern of spread. Systemic therapy is recommended for patients when surgery is not feasible. Historically radiotherapy has been an efficient treatment to palliate bleeding and pain from pelvic disease or systemic metastases. This results in rapid pain relief and temporary cessation of bleeding in the majority of patients(331) (Algorithm #10).

5.10 Systemic therapy

First line systemic therapy in unresectable stage III/IV or recurrent EC with no prior chemotherapy except in the adjuvant setting (including patients with residual disease after surgery)

Carboplatin and paclitaxel are accepted as the standard chemotherapy treatment for advanced/recurrent EC following the results of a non-inferiority randomized phase 3 trial (GOG#209) in which carboplatin-paclitaxel was compared to carboplatin-paclitaxel-doxorubicin. There was overlapping PFS and overall but increased toxicity with the triple combination.

Following the compelling evidence of immune checkpoints inhibitors (ICI) in the recurrent setting following platinum-failure, several phase 3 trials addressed the role of ICI as part of the first line therapy (patients who have not received systemic therapy except in the adjuvant setting). These trials have shown that ICI in combination with carboplatin-paclitaxel followed by ICI as maintenance are more effective than carboplatin-paclitaxel alone. This applies mainly, but not exclusively to the MMRd population; a smaller benefit was also seen in the non-MMRd population. In the RUBY Part 1/ENGOT-en6/GOG-3031 trial patients with newly diagnosed stage III, IV (approximately half of included patients) or recurrent EC were randomised to receive dostarlimab or placebo and standard chemotherapy, with maintenance ICI or placebo for up to 3 years. There was a significant improvement in PFS and OS (HR, 0.69;95% CI, 0.54–0.89; P=0.002) in the whole population with a greater benefit in the MMRd group. In patients with non-MMRd tumours (exploratory subgroup analysis) there was a 24% reduction in the risk of death. The combination of dostarlimab and chemotherapy has been approved by the European Medicines Agency's (EMA) and by Federal Drug Agency (FDA) for all EC patients with advances/recurrent disease. In the NRG-GY018/KEYNOTE-868 phase 3 study in advanced/recurrent EC, carboplatin-paclitaxel was given with pembrolizumab or placebo, followed by pembrolizumab or placebo for up to 84 weeks(270). The primary endpoint was PFS and a benefit was seen in the MMRd cohort with pembrolizumab and to a lesser degree in the non-MMRd group (2 separate cohorts with PFS as primary endpoint in each cohort). OS data are still immature, but show favourable trends in OS for pembrolizumab, particularly in the MMRd cohort. In light of these results EMA and FDA approved pembrolizumab in combination with chemotherapy in all EC patients with advanced/recurrent disease. In a third study, AtTEnd/ENGOT-en7 with atezolizumab (anti-PDL1) in combination with chemotherapy, a positive outcome in PFS was met in the intention-to-treat population, however, there was no benefit in non-MMRd population (exploratory subgroup analysis). OS results are not yet mature(272).

Two trials have investigated the addition of PARPi to ICI maintenance(273, 332).

The first, DUO-E/ENGOT-en10/GOG-3041 trial, had two experimental arms, one with durvalumab added to carboplatin-paclitaxel followed by durvalumab as maintenance and the other one with olaparib added to durvalumab in the maintenance phase(273). The DUO-E trial showed a significant improvement in PFS for the two experimental arms compared with carboplatin-paclitaxel. In a pre-specified exploratory analysis, in the MMRd subgroup the addition of olaparib did not add any benefit to durvalumab. In contrast, in the non-MMRd group, the greatest benefit in PFS was observed with the combination of durvalumab and olaparib. The DUO-E trial has resulted in EMA approval of durvalumab in addition to chemotherapy in MMRd and the addition of olaparib maintenance to durvalumab in the non-MMRd population, while FDA approved durvalumab in all advanced and recurrent EC patients independent of MMRd status (and did not approve the combination of durvalumab and olaparib).

The second trial is RUBY Part 2/ENGOT-en6/GOG-3031 in which niraparib was added to dostarlimab in the maintenance phase(332). There was a statistically significant PFS benefit of this combination compared to

chemotherapy alone in the 'all-comer' population and in the non-MMRd groups, as well as a benefit in the MMRd group although this one was an exploratory subgroup analysis. However, the trial design was such that it is not possible to determine the contribution of PARPi added to dostarlimab in patients with advanced or recurrent endometrial cancer as there was no arm with dostarlimab alone included in RUBY Part 2 trial.

In those patients for which there is a contraindication to receive ICI (± olaparib) and their tumours overexpress HER2 as 3+, the addition of trastuzumab to carboplatin-paclitaxel may be considered. A phase 2 prospective, randomized clinical trial enrolled patients with Stage III to IV or recurrent, HER2/neu-positive EC. In this trial the addition of trastuzumab to carboplatin-paclitaxel resulted in significantly improved PFS and OS compared with PC, the greatest benefit in terms of PFS and OS were observed in women with stage III/IV disease undergoing primary therapy. In this population, the addition of trastuzumab showed an improvement greater than 8-month in PFS and the median OS has not yet been reached in the trastuzumab arm compared with 25.4 months in the control arm only with carboplatin-paclitaxel (333).

In the LEAP-001/ENGOT-en9 phase 3, randomised, open-label study, the efficacy and safety of lenvatinib/pembrolizumab was compared versus carboplatin-paclitaxel as first-line therapy for advanced/recurrent EC (patients with prior adjuvant and neoadjuvant chemotherapy included). The trial did not meet the primary endpoint of prolonging OS and PFS vs carboplatin-paclitaxel in patients with non-MMRd tumours. However, in the subgroup analysis of non-MMRd patients with recurrent disease and prior adjuvant/neoadjuvant chemotherapy the combination of lenvatinib/pembrolizumab seems to provide a benefit in comparison with carboplatin-paclitaxel with PFS HR 0.60 (95% CI 0,37-0,97) and OS HR 0.67 (95% CI, 0.41-1.11). Based on this analysis, the combination of lenvatinib/pembrolizumab may represent a treatment option in this population, when chemotherapy is contraindicated.

In the MMRd subgroup, lenvatinib/pembrolizumab prolonged PFS and OS vs carboplatin-paclitaxel with HRs 0.61 (95% CI, 0.40-0.92) and 0.57 (95% CI, 0.36–0.91), respectively. However, it is not clear what the contribution of lenvatinib could be in the MMRd population, pending the results of ongoing studies investigating the efficacy of single agent dostarlimab or pembrolizumab versus chemotherapy in the first line setting.

Hormone therapy is an option for small volume or slow growing tumours, or for patients in whom first-line chemotherapy is not suitable. Low-grade, slowly progressing, and hormone receptor positive tumours appear to gain the greatest benefit from treatment, but clinical benefit is also seen in hormone receptor negative tumours(334). Progestogens are generally recommended(334). Alternative options include aromatase inhibitors or tamoxifen(335). In patients undergoing hormonal therapy, the risk of thrombo-embolic events needs to be considered. Prophylaxis with anticoagulants should be considered in patients at high risk for thrombosis, and given according to local guidelines. Attempts to increase the activity of hormonal therapy by targeting the PI3K pathway with mTOR inhibitors such as everolimus and temsirolimus, alone or in combination with hormone therapy have not improved survival. They should be considered as experimental therapies. However, encouraging results in a single-arm study in ER-positive EC have been seen with the combination of CDK4/6 and aromatase inhibitors. Randomized Phase 2 trials combining palbociclib and letrozole were superior to letrozole alone(336, 337). However, phase 3 studies are needed to see if the activity of CDK4/6 inhibitors is confirmed (Algorithm #8).

<u>Second line systemic therapy in unresectable, recurrent disease after first line platinum-based chemotherapy</u>

ICI are considered the preferred second line therapy after platinum failure for patients who have not received previous therapy with ICI. The efficacy of anti PD-1 and anti PD-L1 checkpoint inhibitors as monotherapy has been clearly shown in MMRd EC recurring after prior chemotherapy for advanced disease. To date, dostarlimab has been approved by the EMA and FDA, based on the results of the GARNET Trial. Additionally, the FDA and EMA have approved pembrolizumab in the MMRd population following the Keynote-158 trial. Both studies demonstrated a compelling benefit in overall response rate and duration of response in patients with MMRd solid tumours that had progressed on conventional therapy(338, 339). The combination of intravenous pembrolizumab and lenvatinib, an oral multi-receptor tyrosine kinase inhibitor, in the MK-775 phase 3 trial was superior to standard chemotherapy in terms of PFS and OS for the non-MMRd and overall population. This led to FDA

approval of this combination after platinum failure approval for second-line systemic therapy of non-MMRd EC, and EMA approval for all EC patients after failure of platinum-based chemotherapy(340, 341).

For patients who have been treated with ICI in first line, no standard second line therapy has been identified; a response rate of about 10-15% has been seen among all the available treatment options. Thus, enrolment of patients in clinical trials is strongly encouraged. Weekly paclitaxel and anthracyclines (including pegylated liposomal doxorubicin) have some activity and the reintroduction of carboplatin may be considered after a prolonged interval from the last platinum-based treatment, based on the results of a single-centre retrospective series in patients treated with a median platinum-free interval of 25 (range 8-79) months. A response rate of 50%, and median PFS and median OS of 10 and 27 months, respectively, was reported after platinum re-challenge(342). Approximately 30% of uterine serous carcinomas show HER2/neu over expression for which the addition of trastuzumab to paclitaxel and carboplatin can be considered based on a small randomised phase II trial (343).

Recently, the Phase 2, open-label, multicentre study of the ADC trastuzumab deruxtecan (T-DXd) Destiny Pan-Tumor 02 (NCT04482309) enrolled an EC cohort of 40 patients whose tumours overexpressed HER2 (2+/3+) by IHC and had progressed on at least one prior line of therapy. The overall response rate was 57.5% in all EC patients and was 84.6% in patients with HER2 3+ tumours determined centrally; the median duration of response has not yet been reached. In light of these results, the FDA, in April 2024 granted accelerated approval to T-DXd for adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumours in progression after prior systemic treatment and with no satisfactory alternative treatment options (Algorithm #11).

5.11 Follow-up & patient education/empowerment of EC patients

The only randomised data on follow-up in EC patients are derived from the TOTEM trial(344), which showed that an intensified follow-up does not improve OS, not even in high-risk patients. Gynecological examination including vaginal ultrasound can be considered to detect local recurrence. Other imaging techniques are not indicated in asymptomatic patients. Patients should be educated on the importance of cardiovascular health and the risk of secondary cancer, to be motivated to participate in local screening programs and to be educated in regard to physical activity, diet, healthy weight and smoking cessation (secondary/tertiary) prevention. Quality of life, psycho-oncological support and sexual health should be addressed repeatedly. Individual survivorship care plans are recommended.

6 Principles of pathological evaluation

The following section presents the requirements for specimen submitted for pathological evaluation including specimen grossing and sampling, for the pathology report, and the molecular classification(7, 345-348). The following sections are proposed in agreement with the guidelines by ISGyP, the International Collaboration on Cancer Reporting, and the WHO Classification of Tumours (5th edition).

6.1 Requirements for specimen submitted for pathological evaluation

Patient information, family history of cancer or cancer-associated syndrome, prior history of cancer, prior therapy, previous cytology, histological specimens, clinical and radiological data, need to be included on the specimen request form, particularly if there is no electronic patient file. This needs to provide itemised details of biopsy, and surgical specimen (type of hysterectomy, presence of ovaries and fallopian tubes, presence of lymph nodes and designation of the lymph node sites). Biopsies should be sent to the pathology department in a container with liquid fixative (10% neutral formalin is preferred). Surgical specimens should be either sent in a fixative or preferably fresh if there is a specific workflow for it and if the microbiological risk is controlled. This allows proper opening of the uterus and sampling a fresh tissue for research purposes.

6.2 Specimen grossing and sampling

All pathology reports should include a detailed block code on which the origin/designation of all tissue blocks should be recorded. The specimen needs to be oriented, that means that the anterior and posterior walls of the uterus are identified using anatomic landmarks such as the peritoneal reflection and the round ligament/ovaries. Document all organs/structures received and record their measurements and gross appearance. The uterus should

be opened immediately upon receipt in the pathology laboratory and placed in formalin within an hour of opening whenever possible. If the uterus is not immediately sent to a pathology laboratory the uterine cavity needs to be opened technically correct to guarantee proper fixation. The uterus is preferably opened along the lateral uterine walls (3 and 9 o'clock), although 12 and 6 o'clock sectioning may be acceptable. The pathology laboratory personnel and/or pathologists should manage the requests for fresh tissue for banking and/or investigational protocols and this task should be completed as soon as the specimen is received in the pathology laboratory.

Inking of peritoneal and/or non-peritoneal surfaces is recommended in hysterectomy specimens and is mandatory in radical hysterectomy specimens in which parametrium and vaginal cuff are present. Providing of 3 dimensions of the tumour is recommended but at least the largest dimension of the tumour must be provided. Horizontal/transverse sectioning is recommended. Sampling one section per centimetre of the largest tumour dimension is recommended. In case of preoperative endometrial sampling with a malignant diagnosis and no visible lesion on gross examination or a history of atypical endometrial hyperplasia/EIN, the entire endometrium and adjacent inner myometrium should be submitted for microscopic examination. The same applies to hysterectomy specimens that have been obtained for other reasons (leiomyomas, adenomyosis, etc.) when the endometrium is grossly inconspicuous but EC or atypical endometrial hyperplasia/EIN are detected on the initial histological sections. At least, one full thickness section of the uterine wall-including serosa, is required to show the deepest point of myometrial invasion.

The number of sections submitted should not be altered in the context of adenomyosis. However, in cases where the assessment of myometrial invasion is difficult because of tumour involving adenomyosis taking additional sections of the uterine wall may be useful. Whenever possible, the interface between the tumour and its surrounding should be submitted for microscopic examination. This facilitates the measurement of the depth of myometrial invasion and the identification of precursor lesions. At least one representative section of non-neoplastic endometrium should be submitted for microscopic examination. In addition, any grossly identified endometrial lesions separate from the tumour should be submitted. All gross endometrial abnormalities need to be submitted for microscopic examination in hysterectomy specimen from Lynch syndrome patients. In the absence of a gross lesion, the endometrium should be submitted in toto, including the lower uterine segment. A minimum of 2 sections (1 anterior, 1 posterior) should be submitted from the lower uterine segment. If parametrial tissue/parametrium was resected it should be sampled before opening the uterus as this approach minimizes the chance of finding carryovers. All parametrial tissue/parametrium should be submitted for histologic examination. If macroscopic tumour is seen in the parametrial tissue/parametrium, the most proximal parametrial section should include the adjacent outer portion of the cervical wall.

The cervix should be left attached to the corpus during the gross examination of a hysterectomy specimen obtained for EC. At least 2 full thickness sections (1 anterior and 1 posterior) should be submitted from a grossly unremarkable cervix. At least 2 representative sections of tumour involving the cervix should be submitted when the cervix is grossly involved by EC. These sections must include the full thickness of the cervical wall and the ectocervical or vaginal cuff margin. Gross examination of a morcellated hysterectomy specimen requires special attention to identify any endometrial abnormality, although this may be extremely difficult to see in some cases. If such an abnormality is detected, the entire endometrial lesion and the adjacent myometrium should be submitted for microscopic examination. In addition, sampling of myometrial tissue containing any serosal surface should be undertaken. If the endometrium appears grossly unremarkable and the initial representative sections demonstrate the presence of atypical endometrial hyperplasia/EIN or EC, careful re-grossing is required with the submission of all the visible endometrial lining and adjacent myometrium. If the morcellated specimen contains the uterine cervix, this should be sampled representatively. Gross examination of the fallopian tube must be carefully undertaken and any areas with macroscopic abnormalities should be submitted for microscopic examination. For serous carcinoma and carcinosarcoma, the entire tube should be submitted for microscopic examination using the sectioning and extensively examining the fimbriated end (according to the SEE-FIM protocol), particularly, if grossly inconspicuous, while only the fimbriated end should be submitted in toto in other scenarios-using the guidelines of the SEE-FIM protocol, along with representative cross-sections of the remainder of the fallopian tube. Gross examination of the ovary must be carefully performed. In case of endometrial serous, clear cell carcinoma or carcinosarcoma, the entire ovary should be submitted after slicing it perpendicularly to its long axis

at 2 to 3mm intervals. If possible, the same protocol should be used for oophorectomy specimens accompanying hysterectomies for other EC histotypes. Should the latter not be possible, at least 2 sections of each ovary should be submitted.

Omentectomy is part of the staging procedure of endometrial serous carcinoma, undifferentiated carcinoma and carcinosarcoma. The gross appearance and measurement of the omentum should be provided. Omental tissue should be sliced at 0.5 cm intervals to detect small abnormalities. If the omentum is grossly positive, one or 2 representative sections are enough for microscopic evaluation, but if it is grossly negative, one representative section per 2 or 3 cm of maximal omental dimension or at least a total of 4 blocks of tissue should be submitted.

Lymph nodes from different anatomical sites should be sent in separate appropriately labelled specimen containers and handled separately. They should be carefully dissected from the adipose tissue. This can be done with a thorough visual examination and palpation. A small amount of adipose tissue should be left around larger lymph nodes to evaluate the presence or absence of extranodal extension. Lymph nodes up to 2 mm are totally embedded. If larger than 2 mm, parallel slices at 2 to 3 mm intervals perpendicular to the long axis of the node should be performed. All grossly unremarkable lymph node tissue should be submitted for microscopic examination. The number of lymph nodes submitted per cassette and the way they have been submitted, for example in toto - if very small, or sectioned, should be specified in the section code. With grossly positive lymph nodes, representative sections to demonstrate the largest size of tumour involvement as well as the surrounding adipose tissue should be submitted for microscopic examination and noted in the section code. The description of the sentinel lymph node should include gross measurement and description of gross appearance including the presence of dye. The lymph node is sliced at 2-3 mm intervals perpendicular to its long axis. A small rim of adipose tissue should be left around the lymph node. The entire lymph node is submitted for microscopic examination in properly coded cassettes. Ultrastaging is encouraged (i.e. additional recuts and/or IHC for keratin). At the present time there is no universal ultrastaging protocol accepted in the pathology literature. However, an initial section followed by, at least, two additional levels (50µ apart, combining H&E and IHC) might be a reasonable approach to combine cost-effectiveness and efficacy to detect low volume metastasis.

Frozen section for intraoperative assessment is not encouraged for myometrial invasion assessment because of poor reproducibility and because it interferes with pre-analytical issues and possibility of carryovers. Frozen section in this setting has no clinical implications and is therefore obsolete.

6.3 Report of pathology results (required items, based on ICCR dataset)

- Operative procedure
- Description of the specimen(s) submitted for histological evaluation
- Tumour type (WHO Classification of tumours (5th edition))
- Tumour grade (FIGO 2023, and WHO Classification of tumours (5th edition)). Endometrioid EC is graded using FIGO grading criteria: grades 1, 2 and 3 tumours exhibit ≤ 5%, 6-50% and >50% solid non-glandular (including cribriform), non-squamous growth. The presence of severe cytologic atypia in more than 50% of cells increases the grade by one level. Serous carcinoma should be excluded in cases with nuclear atypia that is out of proportion to the architecture. Binary grading is recommended by the WHO Classification of tumours (5th edition) and FIGO 2023, whereby grades 1-2 tumours are classified as low-grade and grade 3 tumours as high-grade.
- Absence or presence and depth of myometrial invasion should be reported in all EC as “none or less than half” OR “half or more.” The measurement should be performed from the adjacent endometrial-myometrial interface. If myometrial invasion occurs from carcinoma within adenomyosis, the deepest myoinvasive point from the involved adenomyosis should be reported. In case of an exophytic tumour, the depth of myometrial invasion, and not tumour thickness, should be measured by identifying the adjacent endomyometrial junction and by correlating with the macroscopic appearance. For tumours involving polyps, measurement of invasion is performed only if the tumour invades the underlying myometrium and measurement.
- LVSI should be unequivocal, and reported as focal and extensive/substantial, according to WHO) in at least one slide. For definition of substantial LVSI, we endorse WHO (≥5 vessels in 2021) and FIGO 2023, but

recognize that the >4 vessels score can be used, since the scientific evidence between the two different scores (≥4 versus ≥5) is not strong, and vast majority of LVSI cases do not fall within the 4-5 vessel range.

- Cervical stromal invasion: for the purposes of standard reporting, the uppermost endocervical mucinous gland identified in the section should be taken as the upper limit of the endocervix.
- Vaginal involvement.
- Uterine serosal involvement. Tumour infiltrating the full myometrial thickness and reaching submesothelial fibro-connective tissue or the mesothelial layer should be reported as serosal involvement; tumour may or may not be present on the surface of the uterus; a desmoplastic response may or may not be present.
- Parametrial involvement.
- Adnexal involvement, According to FIGO 2023, Low-grade endometrioid carcinomas limited to the uterus and ovary (Stage IA3) must be distinguished from extensive spread of the EC to the ovary (Stage IIIA1), by the following criteria:
    1) no more than superficial myometrial invasion is present (<50%), and
    2) absence of extensive/substantial LVSI, and
    3) absence of additional metastases
    4) the ovarian tumour is unilateral, limited to the ovary, without capsule invasion/rupture (equivalent to pT1a).

In cases of serous EC with coexisting tubal intraepithelial (mucosal) carcinoma, with or without stromal invasion, ancillary techniques should be undertaken to help define whether the Fallopian lesion is independent or metastatic. In cases of endometrioid EC, a comment may be included on the unknown prognostic significance of this finding.

- Omental involvement.
- Peritoneal involvement; site of involvement.
- Margin status of paracervical soft tissue and ectocervical/vaginal cuff margins. The term paracervical soft tissue refers to the small part of the parametrium that is included in simple hysterectomy specimens. The distance to the margins should be stated in mm.
- Lymph node status including sentinel lymph node status reports the total number of nodes found and the number of positive lymph nodes, and the presence of extranodal extension (list for all separates sites). According to TNM8 and FIGO 2023, macrometastases are >2 mm, micrometastases are >0.2 to 2 mm and/or >200 cells, and ITCs are up to 0.2 mm and ≤200 cells.
- Pathologically proven distant metastases.
- Required ancillary techniques (see molecular classification).
- Provisional pathological staging in advance of the tumour board/multidisciplinary team meeting, according to FIGO 2023 and TNM staging system (Union for International Cancer Control and American Joint Committee on Cancer versions).

Report of pathology results (recommended items unrelated to stage and with limited supporting evidence)

- Clinical Information
- Tumour site.
- Maximum tumour dimension.
- Omentum dimensions
- Block identification key (clock code).
- Percentages of different components of mixed carcinoma and in carcinosarcoma, and neuroendocrine carcinoma subtype.
- Percentage of myometrium infiltrated by tumour.
- Cervical surface or crypt tumour involvement
- Lower uterine segment involvement
- Depth of cervical stromal invasion.
- Peritoneal cytology (if available).
- Pattern of myometrial invasion.

- Background endometrium
- Presence of extranodal extension
- Recommended ancillary investigations.

6.4 Molecular classification

Molecular classification is recommended to be performed by the TCGA-surrogate. The diagnostic algorithm requires testing of three immunohistochemical markers (p53, MSH-6, PMS-2) with expanded analysis of MLH1 when PMS2 is lost, and of MSH2 when MSH6 is lost; and somatic mutation analysis of *POLE* (exons 9, 11, 13, 14 or known pathogenic mutations). Four categories of tumours are recognized:

1) Ultramutated/with functional pathogenic *POLE* mutations (*POLE*mut EC).
2) Hypermutated with MSI/MMRd (loss of MMR protein immunoreactivity, MMRd EC).
3) High copy number/p53abn (p53 mutant immunoreactive pattern, p53abn EC).
4) Low copy number/NSMP EC (retained MMR protein immunoreactivity, and p53 wild type immunoreactive pattern). ECs with multiple classifying features are classified according to the diagnostic algorithm.

Carcinomas showing loss of MLH1 and PMS2 expression should be investigated for MLH1 promoter hypermethylation, or by IHC of the surrogate marker EPM2AIP1. Oestrogen receptor (ER) immunostaining can serve as a diagnostic marker. Rare histologic subtypes (eg. mesonephric-like EC, CCC and dedifferentiated EC) should be considered when ER expression is completely negative. ER expression may also serve as a prognostic marker within NSMP EC, for which the cut off 10% is proposed. Molecular classification data should be integrated into conventional pathologic diagnosis. It is recommended to include the molecular class in the pathologic diagnosis. The pathology report should include information regarding the methods used for IHC as well as for *POLE* mutation analysis. To avoid confusion, the molecular class should only be reported when the full molecular classification has been performed. Nonpathogenic *POLE* mutations should not be classified as *POLE*mut EC until more evidence comes available.

7 Principles of radiotherapy

The following sections present the general principles, the principles of adjuvant radiotherapy, of definitive treatment, and of radiotherapy for recurrent disease.

7.1 General principles

State of art techniques and radiotherapy dose are chosen based on clinical findings, pathology and patient factors including co-morbidities. For complex treatments or rare cases, referral to a specialized centre is recommended. Prospective assessment of toxicity is recommended. Patients should be carefully counselled about the suggested treatment plan and potential alternatives, including risks and benefits of all options.

7.2 Adjuvant radiotherapy

Radiotherapy should preferably commence within 6(-8) weeks of surgery or be scheduled in relation to chemotherapy.

External beam radiation therapy

Intensity-modulated radiotherapy/volumetric modulated arc therapy (IMRT/VMAT) techniques are recommended because the more conformal dose distribution increases normal tissue sparing compared to a four-field conventional or 3D-conformal plan. The clinical target volume (CTV) includes the pelvic nodes (external iliac, internal iliac, obturator, distal common iliac), parametria and upper vagina. The upper common iliac and sub-aortic presacral lymph nodes are included when there is cervical stromal involvement and/or pelvic lymph node involvement. The lymph node target volume may be extended to include the aortic bifurcation or para-aortic nodes, up to or just above the level of the renal vessels, depending on the location and number of positive lymph nodes, site of sentinel lymph nodes and whether there is extra-uterine primary tumour involvement. The clinical target volume should be individualised when there is a positive resection margin, pelvic peritoneal disease or vaginal

involvement. Treatment with a comfortably full bladder reduces the volume of irradiated small bowel and bladder. The planning target volume (PTV) should account of potential internal motion, depending on the method of verification used during treatment. Image-guided radiotherapy by repeated volumetric imaging with cone beam computed tomography (and use of so-called library of plans or plans of the day techniques) may enable the use of smaller CTV-PTV margins to reduce normal tissue toxicity. The prescription dose is commonly 45-48.6 Gy in 25-27 fractions over 5-6 weeks. A simultaneous integrated or sequential EBRT boost is given to residual lymph node disease, sites of extracapsular nodal spread and positive lateral resection margins (not amenable for brachytherapy) with a total dose of 55-60 Gy $EQD2_{10}$ for microscopic residual disease, or up to 66 Gy for macroscopic/bulky disease. Concurrent and adjuvant chemotherapy may be considered for high risk or recurrent disease.

Vaginal brachytherapy

Vaginal examination is undertaken to ensure the vaginal cuff is healed, and to assess the size and shape of vagina to guide applicator selection. Usually, a vaginal cylinder is used but other applicators can be used, depending on patient anatomy. The target volume is individually determined and is usually the upper third of the vagina to a depth of 5 mm (both superiorly and halfway along the active length). The high-dose rate brachytherapy dose is most commonly 21-24 Gy in 3-4 fractions prescribed at 0.5 cm from the applicator surface, or 8-11 Gy in 2-3 fractions when given as a boost following EBRT. An additional brachytherapy boost can be considered, especially for those with substantial LVSI and cervical stromal invasion. A higher dose is required for treatment of residual macroscopic disease or positive margins. Pulsed-dose rate brachytherapy can be used following EBRT to boost macroscopic residual disease with a dose of 15-25 Gy. The treatment planning options are to use a standard library plan for each applicator size and treatment length or to use image-guided adaptive brachytherapy. In institutions where image-guided adaptive brachytherapy is applied, imaging of the applicator with computed tomography scan or magnetic resonance imaging (MRI) evaluates whether the applicator is in close apposition to the vaginal mucosa and dose to organs at risk. This allows verification and calculation of cumulative doses, especially if vaginal brachytherapy is used as a boost after EBRT. Image-guided adaptive brachytherapy is strongly recommended when there is residual macroscopic vaginal disease following surgery using similar principles as for treatment of recurrent disease(349).

7.3 Definitive treatment

Definitive radiotherapy with EBRT, brachytherapy or a combination of both is indicated for primary tumours where surgery is contra-indicated for medical reasons. If patients are medically unfit for surgery, consider whether a long course of EBRT would be tolerated or if not, a more hypofractionated approach could be used. Intrauterine brachytherapy as a sole treatment modality can be used for low-grade, early-stage disease without deep myometrial infiltration, whereas the combination of EBRT and intracavitary brachytherapy is recommended for high-grade tumours and/or deep myometrial invasion. Frailty and/or geriatric assessments should be performed, as well as a specialist anaesthetic review may be required to assess suitability for brachytherapy, or whether brachytherapy could be applied with local anaesthesia only. More advanced inoperable disease is treated with a combination of pelvic EBRT and intrauterine brachytherapy with or without concurrent platinum-based chemotherapy. For EBRT the preferred technique is IMRT with adaptive image guidance to verify target volume coverage and to maximize normal tissue sparing. In selected cases, highly conformal EBRT boost (with IMRT or stereotactic body radiotherapy) can be used to escalate the total dose to the tumour site in the uterus to at least 65Gy if brachytherapy is not feasible.

Image-guided adaptive brachytherapy is recommended, preferably using MRI at the time of brachytherapy, to optimize tumour coverage and organ at risk doses. The brachytherapy applicator should consist of an intrauterine applicator (preferably a dedicated applicator with multiple channels for the larger uterus) and a vaginal component depending on the extent of any extra-uterine disease. Interstitial applications may be required to achieve adequate coverage. In view of the rarity of definitive treatment for EC, referral to a dedicated centre is recommended. The tumour-related target volumes include the (residual) gross tumour volume on MRI (GTV-res) and the CTV is the whole uterus and any extra-uterine sites of extension before EBRT. The treatment plan aims include a total dose ($EQD2_{10}$) of at least 80 Gy to GTV-res, CTV D90 of about 48-60Gy with brachytherapy alone and 65-75 Gy with the combination of EBRT and brachytherapy.

7.4 Recurrent disease

Radiotherapy treatment for recurrent EC depends on the site of disease and any previous treatment. It involves EBRT, brachytherapy or a combination of both modalities. Concurrent or sequential chemotherapy may also be considered.

Radiation naïve or previous brachytherapy only

Pelvic EBRT is used according to the guidelines above. Brachytherapy is used to boost recurrent disease in the vagina; in selected cases with superficial tumours (≤7 mm) brachytherapy alone can be considered. The brachytherapy applicator options include a vaginal cylinder or mould for superficial lesions whereas interstitial applicators can be used for bulkier tumours.

Image-guided adaptive brachytherapy is recommended, preferably using MRI at the time of brachytherapy, in order to optimize tumour coverage and organ at risk doses. When image-guided adaptive brachytherapy is used, the target volumes should be contoured according to the GEC-ESTRO guideline for vaginal recurrence, aiming for a total dose ($EQD2_{10}$) of 80-85Gy to CTV D90 with the combination of EBRT and image-guided brachytherapy(349, 350). If brachytherapy is not feasible due to tumour location or topography, a sequential EBRT boost with conformal radiotherapy, IMRT or stereotactic body radiotherapy is used to deliver a total GTV dose of at least 65 Gy $EQD2_{10}$.

Re-irradiation

Re-irradiation is individualized according to the extent of disease, previous radiation fields and time elapsed from the previous treatment. In general, recurrences with a longer disease-free interval as well as recurrences less than 2-4 cm tend to have improved outcomes. Ideally, this should be done in specialised centres with prospective collection of dosimetric and clinical data. The most common re-irradiation technique is intracavitary-interstitial brachytherapy, preferably MRI image-guided. However, in selected cases EBRT, stereotactic body radiotherapy, proton or carbon ion therapy is an option, particularly for pelvic sidewall or lymph node disease. Organ at risk dose constraints should consider prior radiotherapy treatment to derive cumulative doses. Some low-dose rate data suggest improved outcomes with doses more than 50 Gy. The high-dose rate data are more varied with some studies suggesting improved local control with doses more than 40 Gy $EQD2_{10}$.

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