The GOG conducted 2 trials that included patients with early-stage nonendometrioid histologies.[17,20] GOG 258 randomized patients to either EBRT with concurrent chemotherapy (2 cycles of cisplatin) followed by 4 cycles of sequential chemotherapy (paclitaxel and carboplatin) or to chemotherapy alone for 6 cycles (paclitaxel and carboplatin).[20] Although the study included patients with FIGO stage I to II nonendometrioid histology with positive peritoneal cytology, there were too few patients enrolled to draw any conclusions. For the overall patient population, the study concluded that EBRT with concurrent chemotherapy followed by sequential chemotherapy did not improve RFS compared with chemotherapy alone. In GOG 249, patients with serous carcinoma comprised 15% of the those enrolled, yet they accounted for 29% of the recurrences.[17] Clear cell carcinoma comprised only 5% of the accrual. On subgroup analysis, there was no difference in RFS between EBRT alone and VBT with chemotherapy arms, yet the study was likely underpowered given the relatively few patients enrolled with high-risk histologies.[17]

In PORTEC-3, patients with serous carcinoma had significantly lower RFS and OS than the other histologic subtypes. There was a significantly greater improvement in RFS and OS among patients with serous carcinoma with the addition of chemotherapy, with a 5-year survival improvement from 52.8% to 71.4%.[16]

There are several retrospective studies that have evaluated the role of chemotherapy in patients with early-stage high-risk histologies.[82–84] In a retrospective study of FIGO stage I to II serous carcinoma, there was improved OS with the addition of chemotherapy among patients who were surgically staged.[82] Another large retrospective study of patients with high-risk endometrial cancer showed that chemotherapy was associated with a worse DFS compared with observation, VBT, or EBRT. A similar trend was observed with the serous carcinoma group but did not reach statistical significance.[83] A multicenter study pooled patients with FIGO stage I nonendometrioid histologies and demonstrated that adjuvant chemotherapy was associated with improved local control (96% vs 84%) and DFS (84% vs 69%) compared with no adjuvant therapy.[84]

The role of chemotherapy for FIGO stage I to II clear cell carcinoma remains unclear. Although clear cell carcinomas are often classified together with other high-risk histologies, their patterns of failure and response to adjuvant therapy seem to differ. Therefore, treatment recommendations may differ for serous and clear cell carcinomas, as outlined in Figure 2. One retrospective study showed no OS benefit from chemotherapy in patients with clear cell carcinoma of any stage.[82] A study of adjuvant therapy for FIGO stage I to II clear cell carcinoma and serous carcinoma demonstrated similar clinical outcomes despite significantly less use of chemotherapy among patients with clear cell carcinoma.[85] Molecular analysis of clear cell carcinomas suggests features representative of all molecular subtypes of endometrial cancer. Therefore, it is possible that prognosis may align more with the molecular subtyping than the histology itself.[86]

Uterine carcinosarcoma is a less common endometrial cancer variant, comprising <5% of cases, but it is responsible for 16.4% of endometrial cancer-related deaths.[87] Although prospective data are limited by patient numbers, GOG conducted a prospective randomized trial of whole abdominal radiation (WAI) versus chemotherapy (cisplatin and ifosfamide) in patients with FIGO stage I to IV carcinosarcoma (about half were FIGO stage I-II).[19] Five-year survival rates were 65% and 45% for patients with FIGO stage I and stage II disease, respectively. The study did not find a statistically significant advantage in recurrence rate or OS for adjuvant chemotherapy over WAI, likely because of small numbers. However, given the observed differences in recurrence and survival endpoints, the authors favored the use of combination chemotherapy in future trials.[19] In summary, although systemic therapy is often recommended for patients with endometrial cancer with high-risk histologies, the quality of the data is low, and the routine use of adjuvant chemotherapy is only conditionally recommended.

FIGO stage III to IVA endometrial cancer with endometroid or high-risk histologies

Patients with FIGO stage III to IVA endometrial cancers are a heterogeneous group who are at high risk for local recurrence, distant metastases, and cancer-related death. Given the high rates of relapse, advanced endometrial cancer has been treated with a variety of combinations of RT, chemotherapy, or combined modality adjuvant therapy.

Historically, WAI was used to treat FIGO stage III or IV endometrial cancer after surgery. WAI was effective at decreasing risk of pelvic recurrence but less successful at preventing distant metastases. GOG 122 was an RCT comparing WAI to chemotherapy alone (cisplatin and doxorubicin) in patients with FIGO stage III or IV endometrial cancer with <2 cm of residual disease after surgery. This study demonstrated improved PFS and OS with chemotherapy compared with WAI, establishing chemotherapy as part of the standard therapy for patients with advanced disease.[56] Unfortunately, the efficacy of RT in this study was limited by the low doses used and the associated high local failure rates because of this WAI technique. Two other similarly designed RCTs randomized patients to EBRT alone (not WAI) or chemotherapy alone, and neither showed any difference in PFS or OS.[21,88]

As previously described, the PORTEC-3 trial demonstrated that patients with FIGO stage III endometrial cancer who were randomized to EBRT with concurrent chemotherapy followed by sequential chemotherapy had improved 5-year RFS and OS compared with EBRT alone, and these results were most significant for patients with FIGO stage III or serous carcinoma.[16] In contrast, the GOG 258 trial demonstrated no differences in RFS