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Review article

Stage IIIC endometrial cancer review: Current controversies in adjuvant therapy

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A B S T R A C T

Stage IIIC is the most common stage of locally advanced sub-stage of endometrial cancer, nevertheless, the optimal management for these patients remains controversial. Adjuvant chemotherapy alone more effectively suppressed distant metastases but resulted in a higher rate of pelvic failure, while adjuvant radiation more effectively controlled pelvic recurrences but was associated with more frequent distant metastases. Two recent randomized trials, PORTEC3 and GOG 258, each have attempted to integrate multimodal therapy. However, heterogeneous cohorts analyzed together, including high risk stage I, stage III and stage IV, limit our ability to make conclusions specific to stage IIIC disease. Here, we review clinical evidence pertaining to management and outcomes with stage IIIC uterine carcinoma with brief discussion on evolving approaches. The studies reviewed demonstrate for stage IIIC disease radiation improves local control but does not confer an overall survival benefit and chemotherapy can improve overall survival. The data seem to suggest that aside from the possibility of defining subgroups that may confer an overall survival benefit from combined modality therapy, the future to improving survival lies in the exploration of better therapeutic regimens that will result from tailored biomarker-based therapy.

1. Background

Endometrial cancer (EC) remains the most common gynecologic malignancy in the United States, with an estimated 65,620 new cases and 12,590 deaths in 2020 (Surveillance, 2018; American Cancer Society. Cancer Facts and Figures, 2020). Approximately 30% of EC is diagnosed as locally advanced tumors or with distant metastasis. Five-year survival with regional or distant spread is approximately 69% and 17%, respectively. Stage IIIC disease accounts for 8% of EC diagnoses, making it the most common locally advanced sub-stage (Surveillance, 2018; American Cancer Society. Cancer Facts and Figures, 2020; American Cancer Society. Cancer Facts and Figures, 2017). FIGO 2009 staging subdivides locoregional nodal metastasis into IIIC1 (metastases to the pelvic lymph nodes) and IIIC2 (metastatic to *para*-aortic lymph nodes). Despite such refinement in staging based upon prognostic information, the optimal management remains controversial.

Post-operative pelvic radiotherapy (RT) proved effective in reducing local and regional recurrence of EC and became standard treatment. Nevertheless, high rates of distant metastases associated with advanced disease prompted the inclusion of chemotherapy (CT) in newer treatment protocols that are the subject of ongoing investigation and debate. Several single-institution retrospective series and single-arm prospective experiences have consistently reported the differential patterns of relapse associated with CT-only vs RT-only approaches (Mundt et al., 2001; Hicks et al., 1993; Sutton et al., 2005; Selman et al., 1998; Mundt et al., 2001; Faught et al., 1998; McMeekin et al., 2001). CT-alone more effectively suppressed distant metastases but resulted in a higher rate of pelvic failure, while RT more effectively controlled pelvic recurrences but was associated with more frequent distant metastases. Consequently, the two most recent randomized trials, PORTEC3 and GOG 258, each have attempted to integrate multimodal therapy. However, heterogeneous cohorts are analyzed together including high risk stage I, stage III and stage IV, thus limiting our ability to make conclusions specific to stage IIIC disease. The optimal management for stage IIIC EC is controversial. In this review, we propose to review clinical evidence pertaining to management and outcomes with stage IIIC1 and IIIC2 uterine carcinoma with brief discussion on evolving approaches, such as immunotherapy and personalized therapy (see Tables 1–3).

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2. Radiation alone

2.1. Retrospective studies

Mundt *et al.* reviewed 30 women with IIIC EC who were treated with postoperative RT. RT was not randomized or standardized; patients with positive, negative and unknown PALN status were treated with pelvic RT +/- extended field. Rates of pelvic (23%) and distant (40%) recurrences were similar in patients treated with EBRT alone or with systemic therapy. Patients with vaginal recurrence had not received vaginal brachytherapy (VB). All PALN failures occurred in patients treated with pelvic-only EBRT, while no *para*-aortic failures occurred in IIIC2 patients treated with extended fields. Based on the observed failure pattern, EBRT was concluded as optimal therapy and VB recommended for local control. However, systemic CT may be necessary to improve distant recurrence rate which was 40% in this series (Mundt et al., 2001).

Hicks *et al.* reviewed patients with endometrioid adenocarcinoma and histologically documented PALN metastases treated with pelvic EBRT (50.4 Gy) combined with either extended *para*-aortic fields (45 Gy) or progestin therapy. Of the 19 patients who demonstrated PALN metastases, eight received EBRT and progestin and 11 received extended EBRT. No patients treated with progestin therapy remained disease-free at 5 years while 27% of patients treated with pelvic and *para*-aortic fields remained disease free at 5 years. No patients treated with EBRT and *para*-aortic radiation developed recurrent pelvic or intra-abdominal disease. The most common site of recurrence was the lung. The authors concluded that addition of effective chemotherapy for patient with PALN metastases will improve survival (Hicks et al., 1993).

2.2. Prospective studies

GOG 94 enrolled 180 patients with surgically staged III-IV, optimally debulked (<2cm residual disease) EC including both endometrioid (43%) and high-risk histologies (serous and clear cell) (57%). Roughly half of both endometrioid and high-risk groups were Stage IIIC1 (45% and 51%, respectively). Approximately 15% of patients had gross residual disease. Patients were treated with post-operative WAI (30 Gy) followed by field reduction and boost to the pelvic and PALNs (45–49.8 Gy). A similar proportion of recurrences happened in patients with endometrioid histology (64.9%) and high-risk histology (67%). Over 50% of these recurrences occurred outside the WAI fields. Three-year recurrence free survival (RFS) and OS for patients with Stage III, endometrioid histology was 34.5% and 34.5%, respectively, and 40.1% and 48.1% for those with serous or clear cell histology. No patients with gross disease after surgery survived. 15% of patients experienced severe or life-threatening GI toxicity. WAI was deemed limited as a curative modality. Importantly, this trial prospectively reaffirmed the high rates of out-of-field metastatic progression when radiation is used for node-positive endometrial carcinoma and the authors concluded that systemic therapy was needed to improve poor survival outcomes (Sutton et al., 2005).

3. Chemotherapy alone

3.1. Retrospective studies

Three retrospective studies evaluating CT alone for adjuvant treatment of advanced EC are presented but contain heterogeneous staging and histologies. Nevertheless, they underscore the problem of high distant failure and localized pelvic recurrences seen when CT is given alone.

Selman *et al* reviewed 31 cases of node-positive EC including 25 cases of stage IIIC and 6 cases of stage IV ECs to evaluate survival and recurrence with adjuvant CT. Histologic subtypes included 45.0% adenocarcinoma/adenosquamous, 19.4% papillary serous, 19.4% clear cell and 16.2% other. CT regimens varied but were doxorubicin or cisplatin-based. Five patients additionally received RT. At a median follow up of 53 months, 32.6% patients experienced a recurrence and 12.9% had persistent disease. Recurrences were equally distributed among vagina, lung, liver, and intraabdominal sites. Of those with pelvic recurrence, only one patient received EBRT. Five-year OS and disease specific survival (DSS) for the patients with IIIC were 49% and 43% respectively. Despite systemic treatment, distant failures remained common (Selman et al., 1998).

Mundt *et al* reviewed 43 high-risk stage I-IV EC patients who underwent surgical staging followed by doxorubicin or cisplatin-based CT; no patients received adjuvant RT. 83.7% had stage lll-IV disease and 74.4% had high-risk histologies. 23.3% of patients had stage IIIC disease. 67.4% of patients relapsed with 31% of these relapses confined to the pelvis. Notably, of the patients that had pelvic only recurrence, 88% had stage I-II disease. 55.5% of patients had an extra-pelvic recurrence. These results were extrapolated to support continued used of

Table 1
Study Design and Patient Characteristics.

Study	Year	Design	Treatment	Age (Median & Range)	Stage	Histology (%)			
						Endometriod	Serous	Clear Cell	Mixed/Other
Mundt	2001	Retrospective	RT	62 (41–82)	IIIC	86	7	7	0
Hicks	1993	Prospective	RT	65 (34–81)	IIIC2	NR	NR	NR	NR
			RT, HT	59 (40–79)					
GOG 94	2005	Prospective	RT	63 (E) & 68.5 (32–85) (S/C)	III-IV	43		24	0
Selman	1998	Retrospective	CT		IIIC-IV	29	19	19	32
Mundt	2001	Retrospective	CT	65 (35–75)	I-IV	35	53	5	7
Faught	1998	Retrospective	CT	NR	IIIC	100	0	0	0
Aghajanian	2018	Prospective	CT	62–65 (36–89)	IIIC-IV, recurrent	62	21	4	13
McMeekin	2001	Retrospective	CT, RT, HT	62 (44–87)	IIIC	70	30	0	
Alvarez Secord	2007	Retrospective	CT, RT, CRT	66 (35–92)	III-IV	38	24		3
Klopp	2009	Retrospective	CT, RT, HT	NR	IIIC	100	0	0	0
Brown	2013	Retrospective	NAT, RT, CT, CRT	65 (26–88)	IIIC	59	41		
Milgrom	2013	Retrospective	CRT	59 (33–77)	III	80	15	5	0
Binder	2017	Retrospective	CT, RT, CRT	(27–90)	IIIC	77	19	4	0
Boothe	2016	Retrospective	CT, RT, CRT	NR	III	81	15	3	0
Maggi	2006	Prospective	RT, CT	NR	IC-III	100	0	0	0
GOG 122	2006	Prospective	RT, CT	63	III-IV	50	21	4	25
GOG184	2008	Prospective	CRT	58 (26–84)	III-IV	69	13	5	13
PORTEC 3	2018	Prospective	RT, CRT	(55.8–68.2)	I-III	67	16	9	8
RTOG9708	2006	Prospective	CRT	NR	III	100	0	0	0
GOG 258	2019	Prospective	CT, CRT	60 (31–88)	III-IV	70	18	3	9

Table 2
Treatment Regimens.

Study	N	RT Regimen	CT Regimen	HT Regimen
Mundt	30	50.4 Gy Pelvis (20) 45 Gy Para-aortic boost (10) 25–30 Gy VB (10)	Not standardized (5)	Progestin not standardized (7)
Hicks	19	50.4 Gy Pelvis + 45 Gy Paraaortic (11)	NA	NA
		50.4 Gy Pelvis + HT (8)	NA	Progestin not standardized
GOG 94	180	30 Gy WAI	NA	NA
Selman	31	45 Gy Pelvis (4) Pelvis + Paraaortic (1)	Cisplatin or Doxorubicin containing regimens	Megestrol acetate 4 mg QID after CT (8)
Mundt	43	NA	Cisplatin + Doxorubicin (25) Other Cisplatin or Doxorubicin containing regimens	NA
Faught	20	NA	PAC Cisplatin 50 mg/m^2 Adriamycin 50 mg/m^2 Cyclophosphamide 500 mg/m^2	NA
Aghajanian	349	NA	Paclitaxel 175 mg/m^2 + Carboplatin AUC6+ Bevacizumab 15 mg/kg or Temsirlimus 25 mg/kg or ixabepilone 30 mg/m^2 carboplalin AUC 6 Bevacizumab 15 mg/kg	NA
McMeekin	47	Pelvis (8) Pelvis + extended field (9) WAI (17)	Not standardized (8)	Progestin not standardized (5)
Alvarez Secord	356	Gy Unspecified Pelvis ± extended field ± VB WAI	Regimens not standardized Majority platinum based	NA
Klopp	68	45–57 Gy Pelvis ± extended field ± 15–30 Gy VB	PAC (11) Carboplatin (4)	Megestrol acetate (3)
Brown	116	45–54 Gy Pelvis ± extended field ± VB	Regimens not standardized Majority platinum + taxane	NA
Milgrom	40	Cisplatin 50.4 Gy Pelvis ± extended field	Carboplatin Paclitaxel	NA
Binder	199	51.2 Gy (median) Pelvis ± VB or VB alone	Not standardized All regimens included a platinum	NA
Boothe	21,027	Not standardized Pelvis ± VB or VB alone	Not standardized	NA
Maggi	345			NA
		45–50 Gy Pelvis	Cyclophosphamide 600 mg/m^2 Doxorubicin 45 mg/m^2 Cisplatin 75 mg/m^2	
GOG 122	388	30 Gy WAI + 15 Gy Boost Pelvis	Doxorubicin 60 mg/m^2 Cisplatin 50 mg/m^2	NA
GOG184	552	50.4 Gy Pelvis ± VB ± extended field	Doxorubicin 45 mg/m^2 Cisplatin 50 mg/m^2 ± Paclitaxel 160 mg/m^2	NA
PORTEC 3	660	48.6 Gy Pelvis ± VB 14 Gy ± Cisplatin 50 mg/m2	Paclitaxel 175 mg/m^2 Carboplatin AUC5	NA
RTOG9708	27	Cisplatin 50 mg/m^2 45 Gy Pelvis + VB	Cisplatin 50 mg/m^2 Paclitaxel 175 mg/m^2	NA
GOG258	736	Cisplatin 50 mg/m^2 days 1 & 29 45 Gy Pelvis +/- VB +/- extended field	Paclitaxel 175 mg/m^2 Carboplatin AUC5 −6	NA

locoregional EBRT in patients undergoing adjuvant CT (Mundt et al., 2001).

Faught and colleagues reviewed 20 patients with surgically staged, microscopic, IIIC1 endometrioid endometrial carcinoma, to understand patterns of recurrence and survival. No patients had *para*-aortic lymphadenectomy. Patients were treated with cisplatin, adriamycin and cyclophosphamide every 28 days for 9 cycles. Twenty five percent of patients developed a recurrence, at a median of 12 months. One had recurrence in the pelvis, and one had first recurrence in the brain. Recurrences were treated with a combination of radiation and hormonal therapy; all who recurred died of disease. Estimated 5-year survival was 70% (Faught et al., 1998).

4. Comparative and multimodal therapies

4.1. Retrospective studies

Given inadequate disease control where radiation or chemotherapy were given alone multimodal therapy has been explored.

McMeekin and colleagues performed a retrospective analysis of 47 patients with stage IIIC EC. All had a pelvic lymph node dissection, and 89% had a PALN dissection. Eighty-nine percent received adjuvant therapy including WAI (36%), pelvic RT with (19%) and without (17%) extended *para*-aortic field, CT (17%) or hormonal therapy (11%). Prognostic factors, however, were not well matched between treatment groups and overall sample size was small. Thirty-three percent of patients had recurrence after adjuvant therapy. There were 2 isolated pelvic, 9 distant, and 2 combined sites of recurrences. Of those with pelvic recurrences, three received adjuvant CT only (McMeekin et al., 2001). This study showed high distant recurrence despite multimodal therapy and that EBRT may decrease local recurrence.

Alvarez-Secord and colleagues performed a multicenter, retrospective review of 356 patients with stage III & IV, surgically-staged EC treated with CT alone (29%), radiation alone (48%) or combination CT and radiation (23%), to determine optimal adjuvant therapy. They found that women who were treated with CT alone were more likely to have both a pelvic and distant recurrence, compared with patients who had received RT or combined chemotherapy and radiation therapy

(CRT). The odds ratio of death for CT alone and RT alone were 2.33 (CI 1.12–4.86) and 2.64 (CI 1.38–5.07) respectively compared with multimodal therapy (HR 1.0) (Alvarez Secord et al., 2007).

Klopp *et al* reviewed 71 patients with stage IIIC endometrioid adenocarcinoma treated with systemic therapy alone (+/- brachytherapy) (n = 18) or combined with pelvic radiotherapy (n = 50). Five and ten-year DSS and OS was significantly worse for patients who received systemic therapy only, however a minority of these were treated with hormonal therapy only which may have negatively skewed these results. The most common site of relapse was distant for those who received pelvic RT and pelvic for those who did not. 5-year pelvic relapse free survival was 98% vs. 61% in those who did and did not receive RT, respectively. Tumor grade was a strong predictor of metastases with distant metastasis the primary mode of failure in grade 3 tumors. Patients with high grade disease may be most likely to benefit from combined modality treatment (Klopp et al., 2009).

Brown and colleagues conducted a retrospective review of 116 patients with stage IIIC EC treated with surgery alone 22.4%, RT37.1%, CT 6.9% and CRT 33.6%; 5-year OS was 40%, 58%, 50% and 54% respectively. Proportion hazard modeling, adjusting for tumor characteristics, demonstrated a HR 0.44 (95% CI 0.20–0.96) for patients treated with RT compared to those not treated with RT. After adjustment, histology and chemotherapy were not significant survival indicators. Notably, patients treated with RT alone were younger (mean age at diagnosis = 62 vs 71 years) and had a lower percentage of grade 3 tumors (45.6% vs 742%). The small number of patients treated with chemotherapy alone and the relatively large portion of patients treated with surgery only limit our ability to draw specific conclusions (Brown et al., 2013).

Milgrom *et al*, reported outcomes of 40 patients with stage III EC, 82% stage IIIC disease, 32% high-grade histology, treated with EBRT and radiation-sensitizing cisplatin, followed by 4 cycles of carboplatin/paclitaxel. Extended field RT (EFRT) was used in patients with histologic or radiographic PALN involvement. Twenty percent of patients relapsed including the following sites: 10% PALN, 10% distant sites, 5% peritoneal, 5% vagina or pelvis. Of the four patients with PALN recurrence, three had PALN involvement at diagnosis and were treated with EFRT; one had PLN disease at diagnosis, PALN dissection was not completed and received only conventional RT. 5-year OS and DFS were 85% and 79%, respectively. In patients treated with CT and RT, pelvic recurrence risk was low, though PALN recurrence risk remained despite selective use of extended field radiation and CT. The authors concluded that CT with RT is associated with good pelvic control (Milgrom et al., 2013).

Binder *et al* reviewed cases of IIIC EC to evaluate the survival benefit of treatments based on tumor grade. Of the 199 patients, 50.3% received CRT, 23.1% received CT alone, 16.1% received RT alone and 10.5% received no adjuvant treatment. Those with grade 1–2 tumors were more likely to be younger, have fewer positive lymph nodes and were more likely to receive adjuvant RT. Those with grade 3 endometrioid or serous histology were more likely to receive CT or CRT. OS was found to be superior with CRT compared with no adjuvant treatment, CT alone, and RT alone; HR for death for RT alone was 2.56 (CI 1.27–5.16) and CT alone was 2.24 (CI 1.30–3.87). CRT was not found to be superior to RT alone for grade 1–2 disease. CRT was found to be superior to RT alone, but not CT alone, in grade 3 subset. Based on the OS benefit, patients able to tolerate multimodality adjuvant treatment should be offered CRT; however, based on grade subset analysis, RT or CT alone may be non-inferior in respective groups (Binder et al., 2017).

A large national registry was used to determine OS of adjuvant CRT (receiving CT and RT either sequentially or concurrently) versus adjuvant monotherapy (CT alone or RT alone). Patients were excluded if they did not receive or complete adjuvant therapy, did not undergo surgery, received radiation to sites other than the pelvis, or expired < 3 months following surgery. A total of 21,027 patients (54.4% with monotherapy and 45.6% with CRT) were included. The use of CT increased throughout the study period while the use of RT monotherapy decreased. Median OS for CRT was 10.3 years compared with 6.2 years for monotherapy (multivariate HR for death = 0.61 (CI = 0.53–0.70). A propensity-matched analysis of 2,295 patients was performed and Cox proportional hazard models showed decreased risk of death for patients that received adjuvant chemotherapy and radiation in a matched cohort

Table 3
Outcome Data By Study.

			Recurrence Rate		Overall Survival (%)		Disease Free Survival (%)		Disease-Specific Survival (%)
Study	N		Pelvic	Extrapelvic	3-year	5-year	3-year	5-year	5-year
Mundt	30		23	40				34	56
Hicks	19	RT	9	27				27	
		RT + HT	0	100				0	
GOG 94	180	Endometrioid	16	46	35		35		
		Serous/CC	15	51	48		40		
Selman	31		29	42		40			52
Mundt	43		40	56	26				
Faught	20		20	5		70			
McMeekin	47		10	23	77	65			
Alvarez Secord	356	CT	13	41	33		19		
		RT	4	30	70		59		
		CRT	6	23	79		62		
Klopp	68	RT	12	32		73			78
		CT/HT	44	22		40			39
Brown	116	NAT				40			
		RT				58			
		CT				50			
		CRT				54			
Milgrom	40		6	25		85		79	
Binder	199							36	
Maggi	345	RT			78	69	69	63	
		CT			76	66	68	63	
GOG 122	388	WAI				42		38	
		CT				53		42	
GOG184	552		10	30			62–64		
PORTEC 3	295	RT	1	29		76		69	
		CRT	1	21		81		77	
RTOG9708	27		2	21		77+		72+	
GOG258	736	CRT	2*	27				59	
		CT	7*	21				58	

compared to those treated with adjuvant monotherapy (HR 0.61, 95%CI 0.53–0.69). Survival and multivariate analysis confirmed a significant survival benefit for CRT versus CT alone (Boothe et al., 2016).

Together, retrospective studies showed better local control suggested a possible survival benefit with multimodal therapy, however, may be histotype/grade and substage classification dependent.

4.2. Prospective studies

A phase II study of 46 patients with high grade stage IB-IIIC endometrioid endometrial carcinoma were treated with 45 Gy to the pelvis with cisplatin 50 mg/m2 on days 1 and 28, followed by vaginal brachytherapy 18–20 Gy. Patients then received four cycles of cisplatin 50 mg/m2 and paclitaxel 175 mg/m2 every 28 days. A subset of patients with stage III disease made up 61.4% (27/44) of the study population as well as the majority of recurrences. Pelvic and regional recurrence rates were each 2% (1/44), whereas distant recurrence rate was 18% (8/44). Overall, CRT provided excellent local control (Greven et al., 2006).

Maggi *et al* sought to directly compare RT to CT in patients with high-risk endometrial carcinoma (stage ICG3, IIG3 with > 50% myometrial invasion, and III). CT regimen was cyclophosphamide 600 mg/m^2, adriamycin 45 mg/m^2 and cisplatin 50 mg/m^2 q28 days for five cycles. RT consisted of 45–50 Gy. Patients with lymph node involvement were treated with extended field RT. About two-thirds of patients in each arm had stage III disease. There was no significant difference between RFS or OS in patients treated with RT or CT. Sixty of 166 patients (36%) randomized to RT recurred; 35 (21%) distant, 11 (7%) local, 9 (5%) concurrent local and distant. Among those randomized to CT, recurrences included 27 (16%) distant, 19 (11%) local, 8 (5%) concurrent local and distant. It was notable that local recurrences occurred in twice as many patients who received only CT, whereas distant recurrences were predominant in patients treated with only RT (Maggi et al., 2006).

In GOG-122, 388 patients with stage III or IV EC were randomized to radiation (WAI,30 Gy in 20 fractions with pelvic boost to 45 Gy)or CT (doxorubicin 60 mg/m^2 and cisplatin 50 mg/m^2 q21 days for seven cycles followed by one cycle of cisplatin alone). Of 202 radiated patients, 54% had tumor recurrence limited to the pelvis (13%), abdomen (16%), and distant sites (22%), with the remainder unknown. In patients randomized to CT arm, 50% had tumor recurrence; sites of recurrence included pelvis (18%), abdomen (14%) and liver or distant (18%). Subgroup analysis of stage IIIC disease demonstrated a HR for death of 0.75 for CT compared with WAI (Randall et al., 1995). While this demonstrated survival benefit of CT alone versus radiation alone, the benefit of CRT remained unknown.

GOG-184 was a randomized phase III trial, planned to compare RFS in patients with stage III and IV EC after surgical debulking and volume directed radiation (50.4 Gy to pelvis, *para*-aortic lymph nodes treated to 43.5 Gy, optional intravaginal boost of 7 Gy HDR), treated with six cycles of cisplatin 50 mg/m^2 and doxorubicin 45 mg/m^2, with or without paclitaxel 160 mg/m^2. 486 of 552 (88%) of evaluable patients had stage III disease. Distant recurrence was diagnosed in 30% of patients and local–regional recurrence in 10% of patients, but no decreased risk of recurrence or death with the addition of paclitaxel. It demonstrated feasibility of CRT but did not define optimal therapy in stage III disease (Homesley et al., 2009).

PORTEC3 compared adjuvant CRT versus pelvic RT alone in "high-risk EC." This broad group (N = 660) included stage I, grade 3 endometrioid-type with deep myometrial invasion or lymphovascular space invasion (LVSI) or both, endometrioid-type stage II or III, or stage I to III with serous or clear cell histology. Patients were assigned to RT alone, 48.6 Gy, or RT plus two cycles of cisplatin 50 mg/m^2 during RT followed by four cycles of carboplatin AUC 5 and paclitaxel 175 mg/m^2. Isolated pelvic and vaginal recurrences were uncommon (1.2%). Distant recurrences occurred in 22% of patients with CRT and 29% of the RT group. With median follow up of 72 months, improved OS was observed ([HR] 0·70 [95% CI 0·51-0·97], p = 0·034) for CRT vs RT alone. RFS survival favored multimodality (HR ~ 0.7). In the subgroup of stage III (N = 295) and at a median FU of 72 months, the RFS and OS for stage III cancers was significant for CRT compared with RT with a HR 0.61 (CI 0.42–0.89) and HR 0.63 (CI 0.41–0.99), respectively (de Boer et al., 2018). This trial suggests that the addition of CT to RT improves failure rates and long-term survival outcomes for stage III ECs, as well as "high-risk" patients.

Subsequently, a comparison of CT and CRT on RFS was done in a phase III study (GOG-258). Patients (N = 736) were randomized to CT only (six cycles carboplatin AUC 6 and paclitaxel 175 mg/m^2), or CRT (Cisplatin 50 mg/m^2 days 1 and 29 with volume-directed EBRT 45 Gy with or without *para*-aortic boost and/or VB followed by four cycles of carboplatin AUC 5–6 and paclitaxel 175 mg/m^2). No significant difference was seen in five-year RFS (59% in the CRT group and 58% in the CT group; HR 0.9 (CI 0.74–1.10)). Analysis by surgical stage did not identify a subgroup that may benefit from addition of RT. Cumulative incidence of pelvic or *para*-aortic node recurrence was lower with CRT (11%) when compared with CT only (20%); HR 0.43 (CI 0.28–0.66). The cumulative incidence of distant recurrence was not significantly different between groups (27%vs 21%). CRT did not provide better RFS over CT alone for patients with stage III or IVA EC (Matei et al., 2019).

5. Biomarkers and targeted therapy

5.1. Biological markers

Recent publications are defining molecular and genomic subgroups. Approaches using molecular signatures, such as gene expression profiling, are being examined to help predict patients at risk of metastases and may someday be a surrogate or adjunct to staging (Kang et al., 2018). Of course, we obviously still need clarity on the optimal adjuvant treatment. Ongoing work exploring molecular signatures to predict response to adjuvant therapy may someday provide further refinement to treatment algorithms (Mohammadi et al., 2020). And finally, molecular and biomarker features may define groups to target with novel therapies. For example, PORTEC-4a, is basing adjuvant therapy determinations almost solely on genomic categorizations and diminishing the reliance on traditional clinicopathologic features that have historically guided therapeutic selection in early stage ECs (Wortman et al., 2018).

5.2. Molecular typing

Two similar molecular characterization classifications have been published. The Cancer Genome Atlas (TCGA) Research Network performed an integrated genomic, transcriptomic and proteomic characterization of 373 ECs. Four distinct clusters were identified. 1) POLE ultra-mutated, 2) Copy number low-microsatellite stable 3) Microsatellite instability hypermutated, and 4) Copy number high, including high-grade cancers with frequent TP53 mutations. Similarly, the ProMisE molecular classification system has been validated with correlation of survival patterns and subtypes. The four categories, similar to above TCGA classification in order of best to worst prognosis include 1) POLE, 2) p53 wild type, 3) Mismatch Repair deficient (MMRd), and 4) p53 abnormal (p53abn) (Kommoss et al., 2018). This molecular classification has been shown to correlate with clinicopathologic factors, is reproducible and associated with clinical outcomes (Murali et al., 2018). p53abn cancers are associated with older patients, lower BMI, serous histology, high stage and grade, myometrial invasion, lymph node metastases and LVSI. MMRd ECs have the second worst survival and are associated with myometrial invasion and LVSI. Additionally, abnormal DNA ploidy has been associated with prognostic features and outcomes. Specifically, within the MMRd subset, abnormal DNA content was associated with worse OS & PFS (Proctor et al., 2017).

Given this evidence that molecular classification has prognostic value in high-risk EC, tissue samples from PORTEC3 were used to

evaluate the prognosis and impact of chemotherapy for each molecular subtype. Of the 410 EC available for classification 22.7% were p53abn, 12.4% were POLEmut, 33.4% were MMRd and 31.5% were no specific molecular profile. When evaluated by treatment type, p53abn EC had a significant benefit from CRT with an absolute difference of 22.4%. Exploratory subgroup analysis did not show benefit in stage III disease. Patients with POLEmut EC had 5-year PFS and OS of 100% with CRT and 96.6% with RT, though this difference was not statistically significant. Neither CRT or RT showed a statistically significant benefit in MMRd or no-specific molecular profile EC including in subgroup analysis by stage. Though there was not a benefit identified from the addition of CT to RT, this study was not powered to detect differences between molecular subtypes, subgroup analysis was small and testing for interaction between stage and adjuvant treatment was not significant. Further investigation with molecular classification should be continued to optimize adjuvant therapy (León-Castillo et al., 2020).

Soumerai *et al* published prospective molecular characterization of EC resulting in two-thirds of patients having at least one likely actionable alteration for which therapy was FDA approved or under clinical investigation and nearly one-third of patients were able to be enrolled in matched trials. Of enrolled patients, nearly half had clinical benefit (SoumeraiSoumerai et al., 2018). Molecular subtyping has been particularly fruitful for MMRd and POLE-mutant EC as these classifications have led to successful treatment with immune checkpoint inhibitors (ICIs) (Mehnert et al., 2016). Results of response of mismatch-repair deficient cancers to PD-1 blockade resulted in FDA approval of PD-1 inhibitors for MMRd solid tumors. (Proctor et al., 2017; Le et al., 2015).

5.3. Immune checkpoint inhibitors (ICIs)

Among gynecologic cancers, EC shows the highest expression of PD-1 (75%) and PD-L1 (25–100%) (Herzog et al., 2015). This suggests an important role of PD-1 and PD-L1 pathway and suggests potential therapeutic targets. POLE-mutant and MSI-H tumors are characterized by high numbers of tumor infiltrating lymphocytes and a high density of PD-1 and PD-L1, suggesting these are good candidates for immune checkpoint inhibitors (ICI) (Eggink et al., 2017). Data on clinical applications of ICI is limited. Le and colleagues published results of a phase II trial including a cohort of MMR-deficient cancers other than colorectal, including two EC patients, all treated with an anti-PD-1 agent and immune-related ORR and PFS were 71% and 67% respectively (Le et al., 2015). The KEYNOTE-028 trial, a phase 1b study, included 24 patients with advanced EC. Patients were treated with pembrolizumab 10 mg/kg every 2 weeks for 24 months or progression. Overall response rate (ORR) was 13%, including three patients with partial response and three with stable disease. PFS was 19% and OS 68.8% (Ott et al., 2017). Santin and colleagues reported two cases of recurrent EC refractory to surgery, chemotherapy and radiation with response to an anti-PD-1. Patients achieved a persistent partial response at seven and nine months from initiation of immunotherapy (Santin et al., 2016). Notably, the combination of lenvatinib (an oral multikinase inhibitor) and pembrolizumab was demonstrated to have an ORR of 38% in patients with advanced recurrent EC, regardless of PD-L1 status, leading to FDA approval of this combination (Makker et al., 2020). Additional studies with ICI are ongoing and may represent alternative or complimentary adjuvant therapy for advanced EC.

5.4. Other molecular targets

Dysregulation of *Her2/neu* has been identified in uterine serous carcinoma (USC). Fader et al conducted a phase II trial including 58 patients to quantify the benefit of the addition of trastuzumab to carboplatin-paclitaxel in women with stage III or IV or recurrent Her2/neu-positive UPS EC. In patients with stage III & IV disease undergoing primary treatment PFS was 17.9 months with the addition of trastuzumab versus 8.0 months in the control arm ($p = 0.13$, HR, 0.40; 90% CI 0.20–0.80), demonstrating a significant benefit in the upfront setting (Fader et al., 2018).

EC may have elevated or aberrant expression of a variety of other possible molecular targets including TSC2, CDK4, FRα, Her2/neu, as well as upregulation of the Ras/Raf/MAPK and PI3K/AKT/mTOR pathways. Studies targeting these proteins and pathways have demonstrated mixed response and are currently ongoing (Myers et al., 2016; Makker et al., 2017).

6. Discussion

In patients with stage IIIC EC, radiation therapy alone improves local control, but rates of distant failures remain frequent underscoring the need for effective adjuvant therapy. When considering survival rather than local control, the benefit of chemotherapy for patients with IIIC EC is evident from available trials; however, pelvic recurrences occurred with high frequency when patients received chemotherapy alone.

A generalization from these studies and stage III disease is that (1) radiation improves local control and (2) chemotherapy can improve overall survival. Several valid and unanswered questions remain. First, what is the role of local control in the absence of overall survival? Palliation and the prevention of morbidity associated with recurrence certainly is a valid concern; however, what is the comparative outcome of reserving palliative local treatment with recurrence versus prophylactic therapy? Second, have the trials to date been so heterogeneous in terms of staging, substaging, histology, and other factors that they lack the ability to apply the findings to the variety of patients seen within these broad groups? In other words, is there enough representation of substages to understand what to do with fully or incompletely staged FIGO III disease when the findings include only regional node positive status versus other stage III criteria?

CT alone appears to provide a survival benefit, as in GOG-122, but suboptimal local control. Retrospective data appear to show both improved local control and survival benefit with the addition of RT to CT. A retrospective study from Klopp, *et al* was the only retrospective study to demonstrate improved DSS and OS in patients who received multimodal therapy. However, a minority of patients in the systemic therapy only cohort had been treated with hormonal therapy, no CT, which may have negatively skewed these results. A multivariate analysis of a large national registry demonstrated an OS of adjuvant CRT versus adjuvant monotherapy in patients with IIIC EC, but biases may still exist.

Retrospective and prospective studies have demonstrated that multimodal adjuvant therapy is well tolerated and provides good locoregional control and benefit to overall survival. Milgrom *et al* demonstrated 5-year OS and DFS were 85% and 79% respectively in patients with IIIC EC treated with EBRT and sensitizing cisplatin and CT. However, there was no comparison to patients treated with chemotherapy alone. PORTEC3 demonstrated improved PFS and OS in patients treated with CRT compared with RT. RTOG 9708 demonstrated similar results when patients were treated with RT and sensitizing cisplatin followed by CT, however, there was no comparison to CT alone. GOG-258 was designed to address CRT to CT by direct comparison. No significant difference was seen in five-year RFS between groups. OS data are not mature.

Molecular subtyping for EC is increasing in frequency and applicability. Subtyping is not only prognostic but is now being used for therapeutic planning. MMRd and POLE-mutant EC have been successfully treated with ICI. EC with somatic TSC2 mutations have been associated with objective response to mTOR inhibition. Analysis by molecular subtype demonstrated p53abn EC benefiting from CRT, however this benefit was not seen in other molecular subtypes. Stage specific subgroup analysis did not show a significant difference between treatment regimens. Currently, molecular subtype for all patients in the clinical setting is not yet widespread, thus, limiting the applicability of treatment planning based on molecular subtype. As we further characterize actionable mutations there will be an increasing number of

targeted therapies available for treatment. Additionally, as molecular typing in the clinical setting becomes more widespread and further clinical trials are designed to include molecular subtypes, treatment recommendations based on this classification can be optimized.

Studies continue to demonstrate that in patients with stage IIIC EC, distant recurrences are frequent and ways to prevent these relapses are at the forefront of design of future clinical trials. The addition of CT has improved OS in patients with advanced EC. The continued use of pelvic RT has been shown to decrease risk of pelvic recurrence in most studies; however, this has not translated to improved survival and its use remains debated. While some earlier studies showed trends toward improved survival with multimodal adjuvant therapy, this was not borne out in a large randomized trial designed to evaluate the benefit of adding RT to CT.

The data seem to suggest that aside from the possibility of defining subgroups that may confer an OS from combined modality therapy, the future to improving survival lies in the exploration of better therapeutic regimens that will result from tailored biomarker-based therapy. This does not mean that the role of radiation, particularly in node positive stage III disease should not be further investigated. However, it should be noted that even this type of clinical investigation will be challenging as the type of surgical staging (i.e. full lymphadenectomy versus sentinel mapping) and the adjuncts of molecular profiles are applied. Furthermore, defining the individualized risk of distant and/or localized recurrences via better staging classification may not lead to better outcomes for most if the therapeutic options are not expanded. Further improvement in systemic therapy may be needed before an OS benefit could be appreciated from pelvic RT for node-positive EC. Another possibility is that variation of intrinsic radiosensitivity of disease limits the locoregional impact from radiotherapy in certain patients, whereas some may extract significant benefit. Perhaps this is where a novel application of a radiation sensitivity classifier may improve patient selection and outcomes. Further advances should result from personalized application of available therapies guided by predictive biomarkers.

In the meantime, we must treat patients who come to us with current, evidence-based practice. The authors feel that data support the use of systemic chemotherapy for stage IIIC EC, regardless of histology with consideration of the addition of trastuzumab for Her2/neu-positive USC. The use of radiation needs to be tailored to the patient. In terms of staged pelvic nodal disease positive patients, we support the recommendation of nodal directed radiation with or without vaginal brachytherapy. We generally include a vaginal brachytherapy boost for patients getting external beam RT in stage IIIC disease as well as those with cervical disease. It is important to be clear about the goals, limitations in our knowledge, the toxicities, and the alternative sequential strategies with each patient. The fact that we remain uncertain of the best treatment for Stage IIIC patients is a strong argument for future clinical trials.

CRediT authorship contribution statement

Andrea L. Buras: Writing - original draft. **Adrianne Mallen:** Writing - review & editing. **Robert Wenham:** Conceptualization, Writing - review & editing. **Michael Montejo:** Conceptualization, Writing - review & editing.

Declaration of Competing Interest

Dr. Wenham reports personal fees from Genentech, personal fees from Legend Therapeutics, personal fees from Regeneron, personal fees from GSK, personal fees from Clovis, personal fees from Astra Zeneca, personal fees from Tesaro, grants and personal fees from Merck, other from Marker Therpeutics, personal fees from Ovation Diagnostics, outside the submitted work. The remainder of the authors have no conflicts of interest to disclose.

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