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Defining the survival benefit of adjuvant pelvic radiotherapy and chemotherapy versus chemotherapy alone in stages III-IVA endometrial carcinoma

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HIGHLIGHTS

- Stages III–IVA endometrioid patients had a 5% absolute 5-year survival increase with pelvic EBRT added to chemotherapy.
- Stages III–IVA non-endometrioid patients had a 9% absolute 5-year survival increase with pelvic EBRT added to chemotherapy.
- Within endometrioid patients, stage IIIC2 had a significant survival benefit with EBRT.
- Within non-endometrioid patients, stages IIIB–C had a significant survival benefit with EBRT.

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ABSTRACT

Objectives. To determine which patients with locoregionally advanced endometrial cancer may benefit from pelvic external beam radiotherapy (EBRT) in addition to chemotherapy compared to chemotherapy alone.

Methods. Patients with FIGO stages III–IVA endometrial carcinoma between 2004 and 2016 who underwent at least total hysterectomy and adjuvant multiagent chemotherapy were identified in the National Cancer Database. The primary outcome was overall survival according to receipt of pelvic EBRT, analyzed using the Kaplan-Meier method and Cox multivariable regression.

Results. In total, 13,270 patients were identified (62% pure endometrioid, 38% serous/clear cell or mixed histology; 22.6% stage IIIA, 4.7% stage IIIB, 71.2% stage IIIC, 1.5% stage IVA), of whom 40% received pelvic EBRT. In univariable analysis, EBRT was associated with absolute 5-year survival increases of 5% and 9% in the endometrioid and non-endometrioid cohorts, respectively ($P < 0.0001$). In multivariable analyses stratified by stage and histology, patients with a significant benefit from EBRT were stage IIIC (specifically IIIC2) endometrioid (adjusted hazard ratio [HR] 0.73, $P = 0.01$) and stages IIIB and IIIC non-endometrioid (adjusted HR 0.52, $P = 0.01$ and adjusted HR 0.79, $P < 0.0001$). The benefit of EBRT in node-positive patients persisted in those who underwent more extensive lymphadenectomy.

Conclusions. Stages III–IVA endometrial cancer comprised a heterogeneous population with respect to the added benefit of radiotherapy compared to chemotherapy alone. Patients with stage IIIC2 endometrioid and stages IIIB–C non-endometrioid cancer may be most likely to benefit from pelvic EBRT.

1. Introduction

In the United States, endometrial cancer is the most common gynecological malignancy [1]. While a minority of patients (5–10%) present with locoregionally advanced (stages III–IVA) disease, the survival outcomes for these patients is substantially worse compared to patients with earlier-stage disease [2]. Prior series have found high rates of distant recurrence after pelvic external beam radiotherapy (EBRT) alone; conversely, patients treated with chemotherapy alone have high rates of pelvic relapse [3–6]. These differing patterns of failure have prompted investigations evaluating combined modality treatment.

Previously, retrospective studies have reported a benefit for combined modality treatment compared to chemotherapy alone or EBRT alone [7–14]. Recent results from the PORTEC-3 trial demonstrated a significant failure-free survival benefit in stage III patients treated with chemoradiotherapy followed by additional chemotherapy compared

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to EBRT alone, which has firmly established the role of chemotherapy in this population [15]. However, results from GOG-258 did not find a significant benefit to combined modality treatment compared to chemotherapy alone, which has led to uncertainty as to which patients with locoregionally advanced disease, if any, should receive EBRT [16].

As the optimal postoperative approach to locoregionally advanced endometrial cancer remains controversial [17,18], we conducted a national cancer registry study of patients with stages III-IVA disease treated with adjuvant chemotherapy alone or chemotherapy with pelvic EBRT. We hypothesized that such patients may comprise a heterogeneous population, and that certain subgroups, as stratified by stage and/or histology, may be more likely to derive a survival benefit from the addition of EBRT to chemotherapy.

2. Methods and materials

2.1. Data source

The National Cancer Database (NCDB) is a registry sponsored by the American College of Surgeons and the American Cancer Society that captures 70% of all incident cancers in the United States. The NCDB was utilized given its large sample size, availability of chemotherapy and radiation therapy, and comprehensive pathological data. Reporting facilities are Commission on Cancer-accredited, required to have at least 90% patient follow-up over 5 years, and subject to periodic audits [19]. All data were de-identified. This study was deemed exempt by the university institutional review board. Our results have not been verified by the NCDB, and the NCDB is not responsible for the statistical validity of our conclusions.

2.2. Cohort inclusion and exclusion criteria

Adults with endometrial carcinoma of pure endometrioid, serous, clear cell, or mixed epithelial histology (histological codes 8380-8383, 8440, 8441, 8460, 8461, 8005, 8310, 8323, 8255) diagnosed 2004–2016 were identified in the NCDB. All patients had at least total hysterectomy within 6 months of diagnosis and available pathological tumor and nodal staging. Patients staged under the previous (FIGO 1988) system (i.e., prior to 2010) were converted to the modern (FIGO 2009) stage. Patients with stage IIIA disease according to the previous staging system solely for positive peritoneal cytology were excluded as their modern tumor stage could not be determined. Patients with stages III-IVA disease were selected. All patients received adjuvant multiagent (combination) chemotherapy and no preoperative chemotherapy or radiation. Patients missing follow-up or vital status data were excluded. Fig. 1 summarizes the cohort identification procedure.

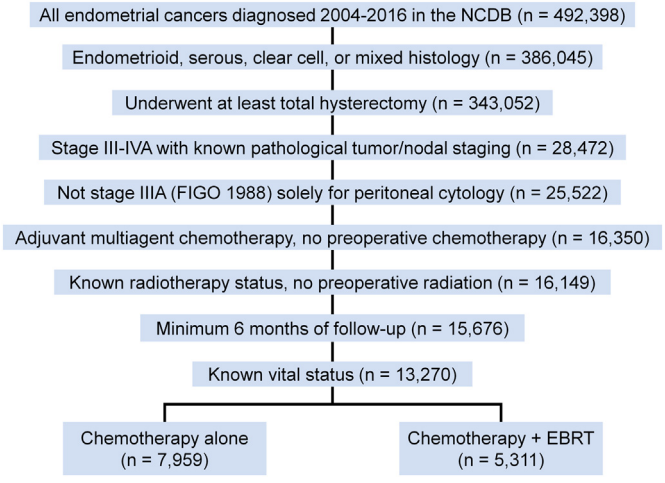

Fig. 1. Cohort identification algorithm. NCDB, National Cancer Database; EBRT, external beam radiation.

2.3. Study variables, outcomes, and statistical analyses

Pelvic external beam radiotherapy (EBRT) was determined as receipt of EBRT to a regional dose of 40–50.4 Gy and treatment volume denoted as encompassing the pelvis or uterine bed. Brachytherapy boost was considered as a separate variable in the multivariable analyses. All other study variables were obtained directly from the NCDB and were selected based on clinical judgment of factors that may potentially influence overall survival, the decision to treat with radiation, and/or the efficacy of radiation. Baseline characteristics were compared using the chi-squared test or Wilcoxon rank-sum test.

The primary outcome was overall survival; the NCDB does not provide data related to relapse or recurrence. To address immortal time bias, all patients were required to have at least 6 months of follow-up. For univariable analyses, overall survival was estimated using the Kaplan-Meier method and compared using the log-rank test. For multivariable analyses, Cox regression was performed to incorporate and adjust for all study variables (listed in Tables 1–2), including age, comorbidity, race, and a variety of other patient, pathological, and surgical factors. MATLAB version R2018b (MathWorks, Inc.; Natick, MA, USA) was used for calculations. All tests were two-sided, and 0.05 was the threshold for statistical significance.

3. Results

In total, 13,270 patients were identified with stages III-IVA endometrial cancer (Fig. 1): 62% were pure endometrioid histology, and the remainder were serous/clear cell or mixed histology. Overall, 22.6% were stage IIIA, 4.7% were stage IIIB, 71.2% were stage IIIC, and 1.5% were stage IVA; 40% received pelvic external beam radiotherapy (EBRT). In patients who had at least 1 lymph node removed (96.7%), the median number of nodes dissected was 15. In patients known to have had at least 1 para-aortic lymph node removed (48.7%), the median number of para-aortic nodes dissected was 4. The median number of days from surgery to initiation of chemotherapy was 40 for both chemotherapy alone and chemotherapy with pelvic EBRT. Median follow-up was 3.7 years in living patients.

3.1. Endometrioid cohort

Table 1 displays baseline characteristics of the endometrioid cohort ($n = 8222$), of which 4676 (57%) received adjuvant chemotherapy alone, and 3546 (43%) received adjuvant chemotherapy with pelvic EBRT.

In univariable analysis, treatment with EBRT in addition to chemotherapy was associated with a 5% absolute increase in 5-year overall survival compared to adjuvant chemotherapy alone (77% vs 72%, $P < 0.0001$; Fig. 2A). Similarly, in multivariable analysis, EBRT had a modest but statistically significant survival benefit (adjusted HR for death: 0.86, 95% confidence interval [CI] 0.78–0.95, $P = 0.003$; Table 1). Other significant variables associated with increased survival were receipt of brachytherapy and higher number of lymph nodes removed, while variables associated with decreased survival included increasing age, stage, grade, and positive surgical margins (Table 1).

Interestingly, on subgroup analysis stratified by stage, there was substantial heterogeneity in the benefit of EBRT (Fig. 2B and Supplemental Table S1). EBRT was not associated with a significant survival advantage in patients with stages IIIA, IIIB, or IVA endometrioid carcinoma. The benefit of EBRT was only observed in stage IIIC, and specifically IIIC2 (adjusted HR 0.73, 95% CI 0.57–0.93, $P = 0.01$; Fig. 2B). Within stage IIIC2, the benefit of EBRT persisted in subgroup analysis of patients with >15 lymph nodes removed (adjusted HR 0.65, 95% CI 0.46–0.90, $P = 0.01$) or with at least 5 para-aortic nodes removed (adjusted HR 0.56, 95% CI 0.39–0.81, $P = 0.002$).

Table 1
Baseline characteristics and predictors of overall survival in the endometrioid cohort. EBRT, external beam radiotherapy; NOS, not otherwise specified; IQR, interquartile range; HR, hazard ratio; CI, confidence interval.

	Baseline characteristics			Cox regression	
	Chemo	Chemo and EBRT	*P*	Adjusted HR (95% CI)	*P*
Received EBRT					
No	4676 (100%)	0 (0%)	N/A	1	–
Yes	0 (0%)	3546 (100%)		0.86 (0.78–0.95)	0.003
Received brachytherapy					
No	3352 (72%)	2164 (61%)	<0.0001	1	–
Yes	1324 (28%)	1382 (39%)		0.79 (0.71–0.87)	<0.0001
Age	Median 60 (IQR 53–67)	Median 60 (IQR 54–67)	0.23	1.03 (1.03–1.04) per year	<0.0001
Facility type					
Non-academic	2524 (54%)	2204 (62%)	<0.0001	1	–
Academic	2152 (46%)	1342 (38%)		0.93 (0.84–1.02)	0.12
Geographic region					
Northeast	1072 (23%)	827 (23%)	0.002	1	–
South	1405 (30%)	934 (26%)		1.27 (1.11–1.46)	0.0004
East north central	909 (19%)	739 (21%)		1.16 (1.01–1.34)	0.042
West north central	514 (11%)	385 (11%)		1.30 (1.10–1.55)	0.002
Mountain/Pacific	776 (17%)	661 (19%)		1.21 (1.04–1.42)	0.015
Race					
White	4059 (87%)	3124 (88%)	0.08	1	–
Non-white	617 (13%)	422 (12%)		1.14 (1.00–1.31)	0.056
Insurance status					
Private	2483 (53%)	1975 (56%)	0.019	1	–
Other	2193 (47%)	1571 (44%)		1.25 (1.12–1.39)	<0.0001
Household income					
Above national median	2859 (61%)	2206 (62%)	0.32	1	–
Below national median	1817 (39%)	1340 (38%)		1.08 (0.98–1.19)	0.12
Charlson comorbidity score					
0 (no comorbidity)	3524 (75%)	2766 (78%)	0.0006	1	–
1 (mild)	914 (20%)	657 (19%)		1.13 (1.01–1.27)	0.038
≥2 (increased)	238 (5%)	123 (3%)		1.46 (1.20–1.77)	0.0002
Pathological tumor stage					
T1	1715 (37%)	1517 (43%)	<0.0001	1	–
T2	552 (12%)	485 (14%)		1.64 (1.41–1.90)	<0.0001
T3	2324 (50%)	1528 (43%)		2.19 (1.92–2.50)	<0.0001
T4	85 (2%)	16 (0%)		3.01 (2.10–4.31)	<0.0001
Pathological nodal stage					
N0	1576 (34%)	954 (27%)	<0.0001	1	–
N1 (pelvic)	1509 (32%)	1470 (41%)		1.87 (1.60–2.19)	<0.0001
N2 (para-aortic)	838 (18%)	612 (17%)		2.14 (1.80–2.56)	<0.0001
Node-positive, NOS	753 (16%)	510 (14%)		2.17 (1.80–2.62)	<0.0001
Grade					
1	898 (19%)	674 (19%)	0.004	1	–
2	1650 (35%)	1301 (37%)		1.51 (1.28–1.79)	<0.0001
3	1435 (31%)	974 (27%)		2.51 (2.13–2.97)	<0.0001
Unknown	693 (15%)	597 (17%)		1.84 (1.51–2.24)	<0.0001
Lymphovascular invasion					
Absent	1269 (27%)	934 (26%)	<0.0001	1	–
Present	1963 (42%)	1676 (47%)		1.41 (1.23–1.62)	<0.0001
Unknown	1444 (31%)	936 (26%)		0.98 (0.80–1.20)	0.82
Peritoneal cytology					
Negative	3783 (81%)	2940 (83%)	0.007	1	–
Positive	590 (13%)	432 (12%)		1.15 (1.00–1.33)	0.057
Unknown	303 (6%)	174 (5%)		1.03 (0.86–1.25)	0.72
Extent of lymphadenectomy					
None or unspecified	1260 (27%)	780 (22%)	<0.0001	1	–
Pelvic only	1274 (27%)	1049 (30%)		0.81 (0.65–1.01)	0.056
Pelvic and para-aortic	2142 (46%)	1717 (48%)		0.75 (0.60–0.93)	0.01
Lymph nodes removed					
<5 or unspecified	764 (16%)	492 (14%)	0.007	1	–
5–15	1779 (38%)	1413 (40%)		0.72 (0.63–0.82)	<0.0001
>15	2133 (46%)	1641 (46%)		0.64 (0.56–0.74)	<0.0001
Surgical margin status					
Negative	3776 (81%)	2941 (83%)	0.029	1	–
Positive	394 (8%)	252 (7%)		1.38 (1.19–1.59)	<0.0001
Unknown	506 (11%)	353 (10%)		1.13 (0.97–1.30)	0.11
Surgical approach					
Open or unknown	2876 (62%)	2139 (60%)	0.28	1	–
Laparoscopic	1800 (38%)	1407 (40%)		0.89 (0.80–1.01)	0.063

3.2. Non-endometrioid cohort

In the non-endometrioid cohort ($n = 5048$), 51.7% were serous, 9.2% were clear cell, and 39.1% were mixed histology. The majority of patients with mixed histology had >50% non-endometrioid/non-squamous histology (Supplemental Fig. S1). Table 2 displays baseline characteristics of the non-endometrioid cohort, of which 3283 (65%) received adjuvant chemotherapy

Table 2
Baseline characteristics and predictors of overall survival in the non-endometrioid cohort. EBRT, external beam radiotherapy; NOS, not otherwise specified; IQR, interquartile range; HR, hazard ratio; CI, confidence interval.

	Baseline characteristics			Cox regression	
	Chemo	Chemo and EBRT	*P*	Adjusted HR (95% CI)	*P*
Received EBRT					
No	3283 (100%)	0 (0%)	N/A	1	–
Yes	0 (0%)	1765 (100%)		0.80 (0.73–0.88)	<0.0001
Received brachytherapy					
No	2437 (74%)	1035 (59%)	<0.0001	1	–
Yes	846 (26%)	730 (41%)		0.89 (0.81–0.98)	0.02
Age	Median 66 (IQR 60–72)	Median 64 (IQR 59–70)	<0.0001	1.03 (1.02–1.03) per year	<0.0001
Facility type					
Non-academic	1611 (49%)	1080 (61%)	<0.0001	1	–
Academic	1672 (51%)	685 (39%)		1.00 (0.91–1.09)	0.98
Geographic region					
Northeast	861 (26%)	450 (25%)	<0.0001	1	–
South	1092 (33%)	518 (29%)		1.05 (0.93–1.18)	0.42
East north central	535 (16%)	381 (22%)		0.99 (0.87–1.14)	0.93
West north central	362 (11%)	127 (7%)		1.08 (0.92–1.27)	0.33
Mountain/Pacific	433 (13%)	289 (16%)		1.05 (0.91–1.22)	0.52
Race					
White	2491 (76%)	1388 (79%)	0.026	1	–
Non-white	792 (24%)	377 (21%)		1.14 (1.03–1.27)	0.011
Insurance status					
Private	1305 (40%)	793 (45%)	0.0004	1	–
Other	1978 (60%)	972 (55%)		1.05 (0.95–1.17)	0.33
Household income					
Above national median	1909 (58%)	1068 (61%)	0.1	1	–
Below national median	1374 (42%)	697 (39%)		1.09 (1.00–1.20)	0.051
Charlson comorbidity score					
0 (no comorbidity)	2407 (73%)	1326 (75%)	0.28	1	–
1 (mild)	711 (22%)	364 (21%)		1.09 (0.98–1.21)	0.12
≥2 (increased)	165 (5%)	75 (4%)		1.17 (0.97–1.42)	0.1
Pathological tumor stage					
T1	984 (30%)	662 (38%)	<0.0001	1	–
T2	465 (14%)	284 (16%)		1.67 (1.46–1.91)	<0.0001
T3	1754 (53%)	807 (46%)		1.71 (1.51–1.93)	<0.0001
T4	80 (2%)	12 (1%)		1.92 (1.40–2.64)	<0.0001
Pathological nodal stage					
N0	903 (28%)	373 (21%)	<0.0001	1	–
N1 (pelvic)	1017 (31%)	699 (40%)		1.65 (1.41–1.93)	<0.0001
N2 (para-aortic)	849 (26%)	452 (26%)		1.83 (1.55–2.16)	<0.0001
Node-positive, NOS	514 (16%)	241 (14%)		1.47 (1.23–1.77)	<0.0001
Histological category					
Serous	1787 (54%)	820 (46%)	<0.0001	1	–
Clear cell	311 (9%)	154 (9%)		1.01 (0.87–1.17)	0.88
Mixed histology	1185 (36%)	791 (45%)		0.73 (0.66–0.80)	<0.0001
Lymphovascular invasion					
Absent	739 (23%)	411 (23%)	0.01	1	–
Present	1626 (50%)	930 (53%)		1.39 (1.22–1.59)	<0.0001
Unknown	918 (28%)	424 (24%)		1.36 (1.12–1.65)	0.002
Peritoneal cytology					
Negative	2516 (77%)	1421 (81%)	0.001	1	–
Positive	607 (18%)	288 (16%)		1.34 (1.19–1.51)	<0.0001
Unknown	160 (5%)	56 (3%)		1.04 (0.84–1.29)	0.7
Extent of lymphadenectomy					
None or unspecified	839 (26%)	346 (20%)	<0.0001	1	–
Pelvic only	816 (25%)	444 (25%)		0.87 (0.70–1.08)	0.22
Pelvic and para-aortic	1628 (50%)	975 (55%)		0.85 (0.68–1.06)	0.14
Lymph nodes removed					
<5 or unspecified	566 (17%)	223 (13%)	<0.0001	1	–
5–15	1251 (38%)	714 (40%)		0.92 (0.81–1.04)	0.2
>15	1466 (45%)	828 (47%)		0.80 (0.70–0.91)	0.0008
Surgical margin status					
Negative	2574 (78%)	1412 (80%)	0.036	1	–
Positive	361 (11%)	154 (9%)		1.54 (1.35–1.75)	<0.0001
Unknown	348 (11%)	199 (11%)		0.99 (0.86–1.14)	0.9
Surgical approach					
Open or unknown	2089 (64%)	1074 (61%)	0.051	1	–
Laparoscopic	1194 (36%)	691 (39%)		0.95 (0.86–1.06)	0.36

alone, and 1765 (35%) received adjuvant chemotherapy with pelvic EBRT.

Survival was substantially lower in the non-endometrioid cohort compared to the endometrioid cohort. In univariable analysis, treatment with EBRT in addition to chemotherapy was associated with a 9% absolute increase in 5-year overall survival compared to adjuvant chemotherapy alone (57% vs 48%, $P < 0.0001$; Fig. 3A). In multivariable analysis, EBRT also had a significant survival benefit (adjusted HR

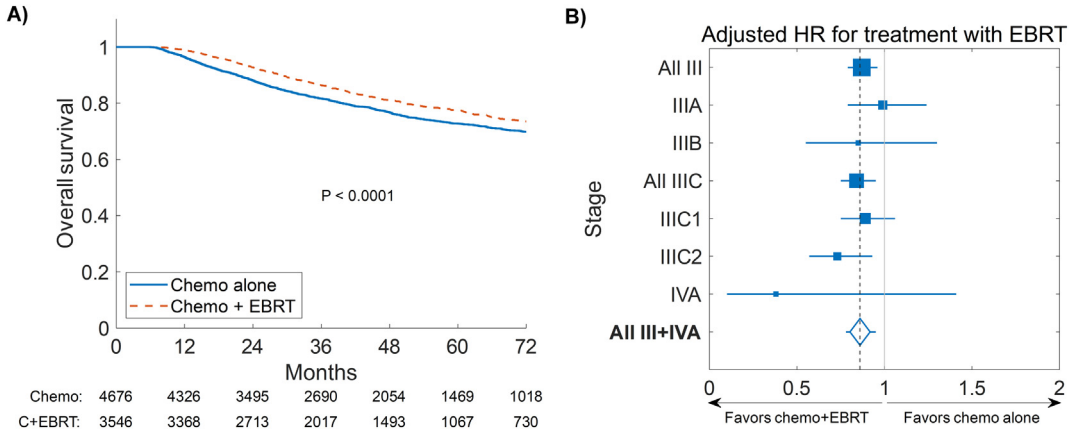

Fig. 2. Adjuvant external beam radiotherapy (EBRT) and chemotherapy versus chemotherapy alone in stages III–IVA endometrioid carcinoma. A) Overall survival according to receipt of EBRT. B) Forest plot of hazard ratios (HR) for treatment with EBRT according to disease stage. HRs were adjusted for the same variables as in Table 1. Sizes of the markers are proportional to relative sample sizes.

0.80, 95% CI 0.73–0.88, $P < 0.0001$). Significant variables associated with decreased survival included increasing age, stage, lymphovascular invasion, positive peritoneal cytology, and positive surgical margins (Table 2).

On subgroup analysis, stages IIIB and IIIC (including both IIIC1 and IIIC2), but not IIIA or IVA, had significantly improved survival with EBRT (Fig. 3B and Supplemental Table S2). Within stage IIIC1, the benefit of EBRT persisted in subgroup analysis of patients with >15 lymph nodes removed (adjusted HR 0.71, 95% CI 0.53–0.95, $P = 0.02$). Within stage IIIC2, the benefit of EBRT persisted in subgroup analysis of patients with >15 lymph nodes removed (adjusted HR 0.71, 95% CI 0.55–0.92, $P = 0.009$) or with at least 5 para-aortic nodes removed (adjusted HR 0.59, 95% CI 0.44–0.78, $P = 0.0003$).

3.3. Sequencing of chemotherapy and radiation

Across all patients treated with EBRT, radiation was initiated >14 days prior to chemotherapy in 8%, within 14 days of chemotherapy in 10%, and >14 days after chemotherapy in 82%. A significant benefit of EBRT persisted irrespective of whether EBRT or chemotherapy was administered first in stage IIIC2 endometrioid (adjusted HR 0.50, $P = 0.047$ and adjusted HR 0.75, $P = 0.032$, respectively) and in stage IIIC1 non-endometrioid patients (adjusted HR 0.64, $P = 0.033$ and adjusted HR 0.65, $P < 0.0001$, respectively) (Supplemental Table S3). The benefit of EBRT in stages IIIB and IIIC2 non-endometrioid patients was statistically significant only in women who received chemotherapy first, although relatively few patients received radiation first or concurrently with chemotherapy, resulting in more limited statistical power (Supplemental Table S3).

4. Discussion

In this national study of stages III-IVA endometrial carcinoma, the addition of pelvic external beam radiotherapy (EBRT) to chemotherapy was associated with a modest but significant survival benefit. Interestingly, when stratified by stage and histology, the benefit of EBRT was most evident in stage IIIC2 endometrioid and stages IIIB–C non-endometrioid patients. Previous studies indicated that removal of at least 11–20 lymph nodes [20] or >17 nodes [21] was associated with improved outcomes; in the current study, the median number of lymph nodes removed was 15. The survival benefit of EBRT in node-positive patients persisted in those with >15 lymph nodes removed or at least 5 para-aortic lymph nodes removed, suggesting that EBRT was not merely compensating for less comprehensive lymphadenectomy. Our findings show that locoregionally advanced endometrial cancer is a heterogeneous disease and help to define the subset of patients who may be most likely to benefit from the addition of EBRT to chemotherapy.

Historically, adjuvant treatment for locoregionally advanced endometrial cancer involved EBRT [22], which resulted in excellent pelvic control rates of 89–96% [3–5,23–26]. Due to high rates of distant failure with EBRT alone, adjuvant chemotherapy has been used increasingly. RTOG 9708 was a single-arm phase II study of higher-risk endometrioid

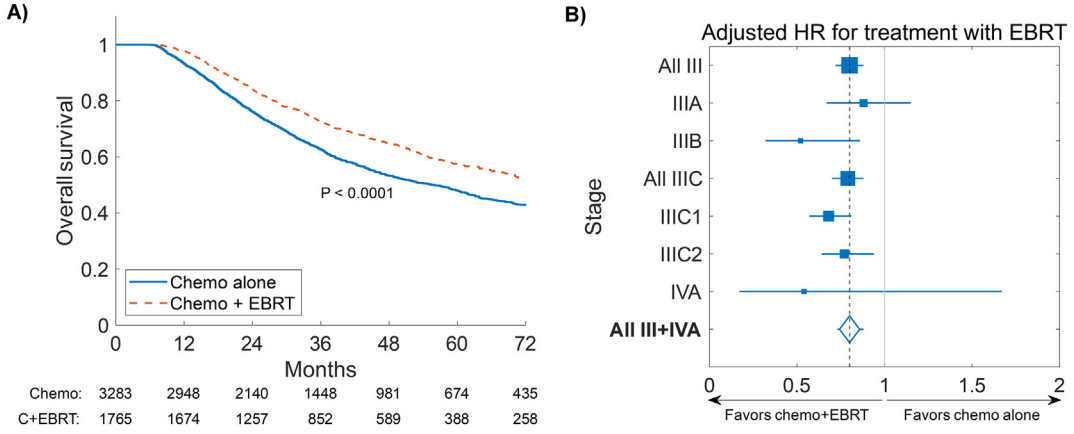

Fig. 3. Adjuvant external beam radiotherapy (EBRT) and chemotherapy versus chemotherapy alone in stages III–IVA non-endometrioid carcinoma. A) Overall survival according to receipt of EBRT. B) Forest plot of hazard ratios (HR) for treatment with EBRT according to disease stage. HRs were adjusted for the same variables as in Table 2. Sizes of the markers are proportional to relative sample sizes.

patients treated with adjuvant pelvic EBRT to 45 Gy with 2 cycles of concurrent cisplatin, followed by vaginal brachytherapy and 4 additional cycles of cisplatin/paclitaxel [27]. In stage III patients, the 4-year overall survival was 77%, similar to the 5-year overall survival of 77% in the endometrioid cohort treated with chemotherapy and EBRT in this study.

Several randomized trials compared EBRT alone versus chemotherapy alone. In GOG-122, patients with stages III-IVA endometrial carcinoma were treated with whole-abdominal irradiation (30 Gy in 20 fractions) plus 15 Gy pelvic boost or 7 cycles of doxorubicin/cisplatin followed by 1 cycle of cisplatin [28]. The radiotherapy arm had less pelvic recurrence (13% versus 18%) but more distant recurrence (22% versus 18%), and the chemotherapy arm had significantly increased progression-free and overall survival. Limitations of GOG-122 include its use of low radiotherapy dose per fraction, allowance of up to 2 cm residual gross disease, and omission of pelvic or para-aortic nodal assessment in 15% and 24% of patients, respectively. An Italian trial of stages I-II deeply-invasive grade 3 and stage III patients randomly assigned to EBRT (45–50 Gy) or 5 cycles of cyclophosphamide, doxorubicin, and cisplatin also reported increased distant failure in the EBRT arm and increased locoregional failure in the chemotherapy arm, without differences in progression-free or overall survival [29].

Given the different patterns of failure observed between EBRT and chemotherapy, subsequent trials investigated combined modality treatment. The landmark PORTEC-3 study included patients with higher-risk stage I endometrioid, stages II-III endometrioid, and stages I-III serous/clear cell cancers [15]. Treatment was pelvic EBRT alone (48.6 Gy) versus EBRT with 2 cycles of concurrent cisplatin followed by 4 cycles of carboplatin/paclitaxel. In the subgroup of stage III patients, 5-year failure-free survival was increased with chemoradiotherapy followed by chemotherapy compared to radiation alone (69% versus 58%), with a trend toward increased overall survival (79% versus 70%). Patients receiving chemotherapy experienced fewer pelvic (5% vs 9%) and distant recurrences (23% versus 30%). These results firmly established the benefit of the addition of chemotherapy to adjuvant radiotherapy in stage III patients.

The reciprocal question was tested in GOG-258, which included stages III-IVA (with up to 2 cm postoperative gross residual disease, as in GOG-122) and stages I–II serous/clear cell patients with positive peritoneal cytology [16]. Nearly all patients were stage III (97%), and the majority had endometrioid histology (approximately 80%). Treatment was 6 cycles of carboplatin/paclitaxel alone versus pelvic EBRT (45 Gy) with 2 cycles of concurrent cisplatin followed by 4 cycles of carboplatin/paclitaxel. Recently published findings from the study demonstrated that the chemoradiation arm had less vaginal (2% versus 7%) and pelvic/para-aortic relapses (11% versus 20%), but more distant failures (27% versus 21%) compared to chemotherapy alone, resulting in a non-significant improvement in relapse-free survival (HR 0.90, 95% CI 0.74–1.10). The endpoint of overall survival was not yet considered mature.

As relapse-free survival was not significantly different between combined modality therapy and chemotherapy alone, the results from GOG-258 have called into question the role of EBRT in locoregionally advanced endometrial cancer. The increased distant recurrence rate in the chemoradiation arm of GOG-258 may be due to less planned chemotherapy (4 versus 6 cycles of carboplatin/paclitaxel); the low dose of radiosensitizing cisplatin given concurrently with EBRT would not be expected to affect systemic control. A prior institutional series also reported more distant failures in patients who received RT and 3–4 cycles of chemotherapy versus 6 cycles of chemotherapy alone (20% versus 11%) [30]. Furthermore, fewer patients in the chemoradiotherapy arm completed full treatment (75% versus 85%), perhaps because acute toxicities of EBRT impaired delivery of subsequent chemotherapy. Another possibility is that the later initiation of full-dose systemic therapy in the EBRT arm led to a delay in the treatment of micrometastatic disease. Interestingly, a recent NCDB study found that patients receiving combined modality treatment had increased survival if chemotherapy was given prior to RT [7]. In our study, 82% of EBRT patients received chemotherapy first, indicating widespread use of a chemotherapy-first sequential (or possibly sandwich) approach.

Furthermore, our finding of an adjusted HR of 0.86 for survival in the endometrioid cohort with receipt of EBRT is overall consistent with the HR of 0.90 for (relapse-free) survival reported in GOG-258. The relatively modest survival benefit of EBRT in this study was only apparent because of the large sample size afforded by the NCDB. Extrapolating from our results, a sample size of over 5500 patients would be needed to detect a significant benefit for EBRT (with 80% power and an alpha level of 0.05), which is 8-fold more than the approximately 700 patients treated in GOG-258. Moreover, we found that the benefit of EBRT for endometrioid histology was concentrated in stage IIIC, and specifically IIIC2. Given the adjusted HR of 0.73 in the stage IIIC2 endometrioid subgroup, at least 1100 stage IIIC2 patients would be needed to detect a significant difference with EBRT, which exceeds the total enrollment of GOG-258.

Interestingly, in a subgroup analysis stratified by stage, GOG-258 similarly found that stage IIIC2-IVA patients (who were nearly all stage IIIC2) had the largest magnitude of benefit from EBRT with a hazard ratio of 0.73 (closely matching our results), although it was not statistically significant (95% CI 0.48–1.10), perhaps because stage IIIC2 comprised only approximately 25% of the total patient population [16]. We observed a somewhat larger benefit for EBRT in non-endometrioid patients. GOG-258 likewise reported a larger magnitude of benefit from EBRT for serous and other non-endometrioid histology compared to endometrioid histology, but they comprised only approximately 20% of the patients in GOG-258, and this was also not statistically significant. While GOG-258 concluded that there was no significant heterogeneity of EBRT benefit across stage and histological subgroups, our analysis suggests that the trial was not adequately powered for those comparisons.

In the endometrioid cohort, we found that stage IIIC2 but not IIIC1 patients had a significant benefit from EBRT. Precise borders of the RT fields are not available in the patients who received pelvic EBRT in the NCDB. Prior studies in stage IIIC patients treated with pelvic EBRT have found that rates of para-aortic failure may be comparable to rates of distant failure, suggesting a potential role for extended-field RT [4,25,26,30]. As patients with a positive para-aortic node receiving EBRT are frequently treated with extended-field RT that includes the para-aortic chains [31], the survival benefit of EBRT in stage IIIC2 endometrioid patients may reflect a decreased risk of para-aortic relapse. By contrast, the para-aortic nodes are typically omitted in most patients with stage IIIC1 disease (unless there is a high common iliac node involved) to decrease toxicity, which may result in more para-aortic failures that diminish the benefit of EBRT. Another possibility to explain the greater benefit of EBRT in stage IIIC2 patients may be their higher likelihood of microscopic residual disease in the pelvis (e.g., in-transit lymphatic spread between the primary tumor and the para-aortic nodes) compared to IIIC1.

Stage IIIA (denoting serosal or adnexal involvement) did not benefit from EBRT, regardless of histology, even though they represented the second-largest subgroup (after stage IIIC). Such patients may be more likely to have occult disease extending to the peritoneal cavity, which would not be addressed by pelvic EBRT. Their lack of lymph node or vaginal/parametrial involvement may also indicate lower risk of residual pelvic-localized disease and hence lower potential for EBRT benefit. Overall, non-endometrioid patients derived more benefit from EBRT, which may be due to their increased risk of microscopic regional disease and worse outcomes compared to endometrioid patients. Previously, we did not find a survival benefit for EBRT in stage III serous/clear cell cancers in a SEER-Medicare analysis [1]. However, the prior study considered chemotherapy and EBRT as separate variables, rather than comparing chemotherapy alone versus chemotherapy with EBRT. Other differences from that study are the much larger sample size of the NCDB and its availability of more pathological data not available in SEER-Medicare.

Our results are also consistent with prior retrospective studies that suggested a benefit of combined modality treatment compared to chemotherapy alone or radiotherapy alone in patients with locoregionally advanced endometrial carcinoma [8–14]. However, previous studies did not stratify patients by stage and/or histology, and only one specifically compared chemotherapy with EBRT versus chemotherapy alone. Institutional series have described pelvic recurrence rates of 20–50% with chemotherapy alone [3–6], suggesting a role for EBRT to decrease regional relapse. In retrospective series of patients treated with pelvic EBRT (with or without chemotherapy), pelvic relapse rates were 5–10% [3–5,23–26], which was corroborated by the increased pelvic control rates in the radiotherapy-containing arms of GOG-122 and GOG-258. Taken together, our results and prior studies suggest that combined modality treatment with full-dose chemotherapy (perhaps initiated prior to RT) may lead to improved outcomes compared to chemotherapy alone, at least in a subset of stages III-IVA patients.

Our results should also be interpreted in the context of its limitations. Stage IVA had a small number of patients (approximately 100 for both endometrioid and non-endometrioid histology), with low utilization of EBRT (14–16%), which limited statistical power. As this study was retrospective, selection bias is possible, and the findings are primarily hypothesis-generating. Prospective validation is desirable in focused patient populations who are most likely to benefit from EBRT, although as noted above, the sample sizes required may not be logistically feasible. Additionally, the multivariable model adjusted for age and extent of comorbidity, among other factors; and a broad, non-specific selection bias in favor of EBRT would not likely produce the heterogeneity observed with regard to its survival benefit. Most patients in the study received chemotherapy first, and EBRT may be preferentially administered to patients without early clinical progression; however, the survival benefit of EBRT persisted in stage IIIC2 endometrioid and stage IIIC1 non-endometrioid patients regardless of chemotherapy and radiation sequencing. Other limitations are related to data unavailable in the NCDB, such as depth of myometrial invasion, relapses and recurrences, number of chemotherapy cycles, and specific agents and dosages (although all patients in this study received multiagent chemotherapy). It is not possible in the NCDB to distinguish between patients who received entirely sequential chemotherapy followed by radiation versus those who received radiation sandwiched between two periods of chemotherapy.

In summary, we showed that the addition of pelvic EBRT to multiagent chemotherapy in the adjuvant treatment of stages III-IVA endometrial cancer patients was associated with a modest but significant survival advantage. When stratified by stage and histology, patients with stage IIIC (specifically IIIC2) endometrioid and stages IIIB-C non-endometrioid cancer were most likely to benefit. The benefit of EBRT in node-positive patients persisted in those with >15 lymph nodes removed or at least 5 para-aortic nodes removed. These data demonstrate heterogeneity among patients with locoregionally advanced disease and highlight populations who may be most likely to benefit from combined modality treatment. Further research, ideally in a prospective setting, is warranted to confirm these findings.

Author contributions

M.X.: conceptualization, data curation, formal analysis, investigation, methodology, writing (original draft, review and editing). D.P.E.: investigation, methodology, writing (review and editing). E.A.K.: conceptualization, investigation, methodology, project administration, supervision, writing (review and editing).

Declaration of Competing Interest

The authors declare no competing financial interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.06.020.

References

[1] M. Xiang, D.P. English, E.A. Kidd, National patterns of care and cancer-specific outcomes of adjuvant treatment in patients with serous and clear cell endometrial carcinoma, Gynecol. Oncol. 152 (2019) 599–604, https://doi.org/10.1016/j.ygyno.2018.12.007.

[2] S.N. Lewin, T.J. Herzog, N.I. Barrena Medel, I. Deutsch, W.M. Burke, X. Sun, J.D. Wright, Comparative performance of the 2009 International Federation of Gynecology and Obstetrics' staging system for uterine corpus cancer, Obstet. Gynecol. 116 (2010) 1141–1149, https://doi.org/10.1097/AOG.0b013e3181f39849.

[3] A. Schwandt, W.C. Chen, F. Martra, P. Zola, R. Debernardo, C.A. Kunos, Chemotherapy plus radiation in advanced-stage endometrial cancer, Int. J. Gynecol. Cancer Off. J. Int. Gynecol. Cancer Soc. 21 (2011) 1622–1627, https://doi.org/10.1097/IGC.0b013e31822b6594.

[4] A.H. Klopp, A. Jhingran, L. Ramondetta, K. Lu, D.M. Gershenson, P.J. Eifel, Node-positive adenocarcinoma of the endometrium: outcome and patterns of recurrence with and without external beam irradiation, Gynecol. Oncol. 115 (2009) 6–11, https://doi.org/10.1016/j.ygyno.2009.06.035.

[5] M. Matsuura, T. Suzuki, M. Morishita, R. Tanaka, E. Ito, T. Saito, Chemotherapy (CT) with radiotherapy versus CT alone for FIGO stage IIIc endometrial cancer, Eur. J. Gynaecol. Oncol. 30 (2009) 40–44.

[6] A.J. Mundt, R. McBride, J. Rotmensch, S.E. Waggoner, S.D. Yamada, P.P. Connell, Significant pelvic recurrence in high-risk pathologic stage I–IV endometrial carcinoma patients after adjuvant chemotherapy alone: implications for adjuvant radiation therapy, Int. J. Radiat. Oncol. Biol. Phys. 50 (2001) 1145–1153.

[7] C.R. Goodman, S. Hatoum, B.-L.L. Seagle, E.D. Donnelly, E.L. Barber, S. Shahabi, D.E. Matei, J.B. Strauss, Association of chemotherapy and radiotherapy sequence with overall survival in locoregionally advanced endometrial cancer, Gynecol. Oncol. 153 (2019) 41–48, https://doi.org/10.1016/j.ygyno.2019.01.007.

[8] D. Boothe, A. Orton, B. Odei, G. Stoddard, G. Suneja, M.M. Poppe, T.L. Werner, D.K. Gaffney, Chemoradiation versus chemotherapy or radiation alone in stage III endometrial cancer: patterns of care and impact on overall survival, Gynecol. Oncol. 141 (2016) 421–427, https://doi.org/10.1016/j.ygyno.2016.03.021.

[9] C. Marchetti, C. Pisano, G. Mangili, D. Lorusso, P.B. Panici, G. Silvestro, M. Candiani, S. Greggi, G. Perniola, M. Di Maio, S. Pignata, Use of adjuvant therapy in patients with FIGO stage III endometrial carcinoma: a multicenter retrospective study, Oncology 81 (2011) 104–112, https://doi.org/10.1159/000331677.

[10] S. Kuku, M. Williams, M. McCormack, Adjuvant therapy in stage III endometrial cancer: treatment outcomes and survival. A single-institution retrospective study, Int. J. Gynecol. Cancer Off. J. Int. Gynecol. Cancer Soc. 23 (2013) 1056–1064, https://doi.org/10.1097/IGC.0b013e3182978328.

[11] A.T. Wong, J. Rineer, Y.-C. Lee, D. Schwartz, J. Safdieh, J. Weiner, K. Choi, D. Schreiber, Utilization of adjuvant therapies and their impact on survival for women with stage IIIC endometrial adenocarcinoma, Gynecol. Oncol. 142 (2016) 514–519, https://doi.org/10.1016/j.ygyno.2016.07.091.

[12] P.S. Binder, L.M. Kuroki, P. Zhao, S. Cusworth, L.M. Divine, A.R. Hagemann, C.K. McCourt, P.H. Thaker, M.A. Powell, D.G. Mutch, L.S. Massad, Benefit of combination chemotherapy and radiation stratified by grade of stage IIIC endometrial cancer, Gynecol. Oncol. 147 (2017) 309–314, https://doi.org/10.1016/j.ygyno.2017.08.031.

[13] C.J. Wang, A. Christie, M.R. Folkert, X.J. Xie, K. Albuquerque, Value of combined adjuvant chemotherapy and radiation on survival for stage III uterine cancer: is less radiation equal to more? J. Gynecol. Oncol. 29 (2018), e49. https://doi.org/10.3802/jgo.2018.29.e49.

[14] N.H. Lester-Coll, H.S. Park, C.E. Rutter, C.D. Corso, M.R. Young, E.S. Ratner, B. Litkouhi, R.H. Decker, J.B. Yu, S. Damast, Who benefits from chemoradiation in stage III–IVA endometrial cancer? An analysis of the National Cancer Data Base, Gynecol. Oncol. 142 (2016) 54–61, https://doi.org/10.1016/j.ygyno.2016.04.544.

[15] S.M. de Boer, M.E. Powell, L. Mileshkin, D. Katsaros, P. Bessette, C. Haie-Meder, P.B. Ottevanger, J.A. Ledermann, P. Khaw, A. Colombo, A. Fyles, M.-H. Baron, I.M. Jürgenliemk-Schulz, H.C. Kitchener, H.W. Nijman, G. Wilson, S. Brooks, S. Carinelli, D. Provencher, C. Hanzen, L.C.H.W. Lutgens, V.T.H.B.M. Smit, N. Singh, V. Do, R. D'Amico, R.A. Nout, A. Feeney, K.W. Verhoeven-Adema, H. Putter, C.L. Creutzberg, M. McCormack, K. Whitmarsh, R. Allerton, D. Gregory, P. Symonds, P.J. Hoskin, M. Adusumalli, A. Anand, R. Wade, A. Stewart, W. Taylor, R.F.P.M. Kruitwagen, H. Hollema, E. Pras, A. Snyers, L. Stalpers, J.J. Jobsen, A. Slot, J.-W.M. Mens, T.C. Stam, B.V. Triest, E.M.V. der S.-Banasik, K.A.J.D. Winter, M.A. Quinn, I. Kolodziej, J. Pyman, C. Johnson, A. Capp, R. Fossati, S. Gribaudo, A.A. Lissoni, A. Ferrero, G. Artioli, C. Davidson, C.M. McLachlin, P. Ghatage, P.V.C. Rittenberg, L. Souhami, G. Thomas, P. Duvillard, D. Berton-Rigaud, N. Tubiana-Mathieu, Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial, Lancet Oncol. 19 (2018) 295–309, https://doi.org/10.1016/S1470-2045(18)30079-2.

[16] D. Matei, V. Filiaci, M.E. Randall, D. Mutch, M.M. Steinhoff, P.A. DiSilvestro, K.M. Moxley, Y.M. Kim, M.A. Powell, D.M. O'Malley, N.M. Spirtos, W. Small, K.S. Tewari, W.E. Richards, J. Nakayama, U.A. Matulonis, H.Q. Huang, D.S. Miller, Adjuvant chemotherapy plus radiation for locally advanced endometrial cancer, N. Engl. J. Med. 380 (2019) 2317–2326, https://doi.org/10.1056/NEJMoa1813181.

[17] M.E. Bernard, M.E. Randall, Point: should radiation therapy be routinely used in the adjuvant treatment of stage III endometrial cancer? Yes—radiation therapy improves local control and possibly survival for some patients, Oncol. Williston Park N. 32 (2018) 455–458.
[18] J.P. Diaz, Counterpoint: should radiation therapy be routinely used in the adjuvant treatment of stage III endometrial cancer? No—the literature does not support routine use of radiation therapy, Oncol. Williston Park N. 32 (2018) 455 (458–459, 462).
[19] D.J. Boffa, J.E. Rosen, K. Mallin, A. Loomis, G. Gay, B. Palis, K. Thoburn, D. Gress, D.P. McKellar, L.N. Shulman, M.A. Facktor, D.P. Winchester, Using the National Cancer Database for outcomes research: a review, JAMA Oncol 3 (2017) 1722–1728, https://doi.org/10.1001/jamaoncol.2016.6905.
[20] J.K. Chan, M.K. Cheung, W.K. Huh, K. Osann, A. Husain, N.N. Teng, D.S. Kapp, Therapeutic role of lymph node resection in endometrioid corpus cancer: a study of 12,333 patients, Cancer 107 (2006) 1823–1830, https://doi.org/10.1002/cncr.22185.
[21] I. Alagkiozidis, J. Weedon, A. Grossman, P. Wang, B. Mize, K. Wilson, T. Shah, K. Economos, G. Salame, O. Abulafia, Y.-C. Lee, Extent of lymph node dissection and overall survival in patients with uterine carcinosarcoma, papillary serous and endometrioid adenocarcinoma: a retrospective cohort study, Int. J. Surg. 24 (2015) 9–13, https://doi.org/10.1016/j.ijsu.2015.10.006.
[22] M. Cowan, J.B. Strauss, E.L. Barber, D. Matei, Updates on adjuvant chemotherapy and radiation therapy for endometrial cancer, Curr. Opin. Obstet. Gynecol. 31 (2019) 31–37, https://doi.org/10.1097/GCO.0000000000000506.
[23] G. Nelson, M. Randall, G. Sutton, D. Moore, J. Hurteau, K. Look, FIGO stage IIIC endometrial carcinoma with metastases confined to pelvic lymph nodes: analysis of treatment outcomes, prognostic variables, and failure patterns following adjuvant radiation therapy, Gynecol. Oncol. 75 (1999) 211–214, https://doi.org/10.1006/gyno.1999.5569.
[24] J.K. Lee, M. Mahan, R.K. Hanna, M.A. Elshaikh, Survival outcomes and patterns of failure in women with stage IIIC2 endometrial carcinoma, Eur. J. Obstet. Gynecol. Reprod. Biol. 216 (2017) 192–197, https://doi.org/10.1016/j.ejogrb.2017.08.001.
[25] L.J. Lee, A.N. Viswanathan, Combined chemotherapy and radiation improves survival for node-positive endometrial cancer, Gynecol. Oncol. 127 (2012) 32–37, https://doi.org/10.1016/j.ygyno.2012.06.026.
[26] L.J. Lee, P. Bu, C. Feltmate, A.N. Viswanathan, Adjuvant chemotherapy with external beamradiation therapy for high-grade, node-positive endometrial cancer, Int. J. Gynecol. Cancer Off. J. Int. Gynecol. Cancer Soc. 24 (2014) 1441–1448, https://doi.org/10.1097/IGC.0000000000000248.
[27] K. Greven, K. Winter, K. Underhill, J. Fontenesci, J. Cooper, T. Burke, Final analysis of RTOG 9708: adjuvant postoperative irradiation combined with cisplatin/paclitaxel chemotherapy following surgery for patients with high-risk endometrial cancer, Gynecol. Oncol. 103 (2006) 155–159, https://doi.org/10.1016/j.ygyno.2006.02.007.
[28] M.E. Randall, V.L. Filiaci, H. Muss, N.M. Spirtos, R.S. Mannel, J. Fowler, J.T. Thigpen, J.A. Benda, Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a gynecologic oncology group study, J. Clin. Oncol. 24 (2006) 36–44, https://doi.org/10.1200/JCO.2004.00.7617.
[29] R. Maggi, A. Lissoni, F. Spina, M. Melpignano, P. Zola, G. Favalli, A. Colombo, R. Fossati, Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: results of a randomised trial, Br. J. Cancer 95 (2006) 266–271, https://doi.org/10.1038/sj.bjc.6603279.
[30] A. Gadducci, S. Cosio, M.G. Fabrini, M.E. Guerrieri, C. Greco, A.R. Genazzani, Analysis of failures in patients with FIGO stage IIIc1-IIIc2 endometrial cancer, Anticancer Res. 32 (2012) 201–205.
[31] P. Kabolizadeh, S. Fulay, S. Beriwal, Are radiation therapy oncology group para-aortic contouring guidelines for pancreatic neoplasm applicable to other malignancies—assessment of nodal distribution in gynecological malignancies, Int. J. Radiat. Oncol. 87 (2013) 106–110, https://doi.org/10.1016/j.ijrobp.2013.05.034.