Outcome and predictive factors in uterine carcinosarcoma using postoperative radiotherapy: a Rare Cancer Network study

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Abstract

Uterine carcinosarcomas (UCS) are rare tumors. Consensus regarding therapeutic management in non-metastatic disease is lacking. This study reports on outcome and predictive factors when using postoperative radiotherapy. We analyzed a retrospective analysis in 124 women treated between 1987-2007 in the framework of the Rare-Cancer-Network. Median follow-up was 27 months. Postoperative pelvic EBRT was administered in 105 women (85%) and 92 patients (74%) received exclusive or additional vaginal brachytherapy. Five-year overall survival (OS), disease-free survival (DFS), cancer specific survival (CSS) and locoregional control (LRC) were 51.6% (95% CI 35-73%), 53.7% (39-71%), 58.6% (38-74%) and 48% (38-67%). Multivariate analysis showed that external beam radiation therapy (EBRT) >50Gy was an independent prognostic factor for better OS (P=0.03), CSS (P=0.02) and LRC (P=0.01). Relative risks (RR) for better OS (P=0.02), DFS (P=0.04) and LRC (P=0.01) were significantly associated with younger age (≤60 years). Higher brachytherapy (BT)-dose (>9Gy) improved DFS (P=0.04) and LRC (P=0.008). We concluded that UCS has high systemic failure rate. Local relapse was reduced by a relative risk factor of over three in all stages of diseases when using higher doses for EBRT and brachytherapy. Postoperative RT was most effective in UCS stage I/II-diseases.

Introduction

Uterine carcinosarcoma (UCS) is a rare but aggressive tumor entity, comprising of both malignant epithelial and mesenchymal components, accounting for 1-2% of uterine cancers.[1] According to the NCCN guidelines UCS is no longer recognized as a sarcoma due to its probable epithelial origin.[2,3] Therefore it is included in the high-risk malignant endometrial tumors section. The disease affects primarily postmenopausal women after sixty years of age.[4] Potential risk factors include excess estrogen exposure in relation to obesity, diabetes and high-fat diet, nulliparity, prior pelvic radiotherapy and tamoxifen use.[2,5] Women present with non-specific symptoms including vaginal bleeding, pain and swelling of the lower abdomen. Reported five-year survival rates are between 30-40%.[6] About 35% of carcinosarcomas are not confined to the uterus at diagnosis with corresponding median survival of 21 months.[7] Diagnostic work-up includes ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI). There are no distinct radiological features that discriminate UCS from other uterine malignancies. UCS generally show FDG-uptake and FDG-PET may be used for diagnostic and staging purposes.[8] For patients without evidence of metastatic disease, the standard treatment includes total hysterectomy with bilateral salpingo-oophorectomy (BSO), pelvic and para-aortic lymphadenectomy, cytology of peritoneal washings, omentectomy and biopsies of the peritoneal surfaces. For women with extrauterine disease limited to the peritoneum surgical cytoreduction may be recommended.[2]

Optimal management remains unclear.[6] Early stage of disease has been identified as most relevant element for treatment outcome.[9]

The aim of this Rare Cancer Network (RCN) study was to assess UCS recurrence pattern according to stage and treatment in an effort to evaluate the role of radiation therapy and identify predictive factors in the non-metastatic disease.

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Materials and Methods

Data from 124 patients with UCS treated between 1987 and 2007 at eleven institutions from Australia, France, Israel, Switzerland and Turkey were collected. Each institution in their respective country obtained ethics approval. Patients who underwent hysterectomy with or without BSO were included. Besides observation, postoperative treatment consisted of, brachytherapy (BT), External beam radiation therapy (EBRT), and/or adjuvant chemotherapy (ChT). The choice of adjuvant therapy was based on physician preferences. Patients treated with palliative intent were excluded. As recommended by the FIGO committee on gynecologic oncology in 2009, UCS was staged as carcinoma of the endometrium.[3] The medical records of all patients with UCS were reviewed to identify patient and tumor characteristics, treatment details, and follow-up (FU).

Statistical analysis

Data were analyzed using χ^2 tests. Variables

significant in the univariate analysis were subsequently entered into a multivariate analysis (MVA) using the Cox proportional hazards ratio model. Disease-free survival (DFS), Cancer specific survival (CSS), locoregional control (LRC), and overall survival (OS) were calculated from the date of diagnosis to the date of progression, date of death, or date of last follow-up if the patient was alive. Time to any event was measured from the date of diagnosis. Kaplan-Meier curves were generated from the survival data. Statistical analysis was performed using SPSS software for Windows version 12.0 (SPSS, Chicago, IL, USA). A P-value of <0.05 was considered statistically significant for all tests.

Results

Patient demographics

Data from 124 patients with UCS were analyzed and summarized in Table 1.

Diagnostics, surgical treatment and pathologic findings

In 41 cases (33%), diagnosis was known due to biopsy or curettage. For the majority of patients (67%), UCS was diagnosed on the surgical specimen. The first-line treatment for all patients was total hysterectomy. With the exception of two, all patients underwent BSO. Lymph node sampling or pelvic lymph node dissection (PLND) was performed in 76 patients (61.3%), and lymph node metastases were found in 15 patients (13%). Surgical resection margins were positive in 12 patients (9.7%), of these five patients developed local recurrence in the later course of disease. For 20 patients operative margin status was unknown. Sixty-four patients (51.6%) had FIGO 2009[3] stage I, 17 (13.7%) stage II, 35 (28.2%) stage III, and four patients presented with stage IV disease (Table 1).

Postsurgical treatment

Thirteen patients (10.5%) received no postoperative RT (Table 1). EBRT was administered to 105 patients (84.7%). The mean total dose was 48.4 Gy (range, 9-59 Gy, median 50.4 Gy). In 104 patients (83.9%), EBRT included pelvic lymph node areas. In the one remaining case EBRT was limited to the tumor bed only. In 86 female patients (69.4%), EBRT was associated with BT at a mean dose of 16.1 Gy (range, 6-34 Gy, median 16.0 Gy). Six patients (4.8%) underwent postoperative vaginal cuff high-dose-rate (HDR) BT alone at total mean doses of 29.4 Gy (range 21-34 Gy) Gy. Twenty-five patients (20.2%) underwent adjuvant ChT mainly consisting of ifosfamide-based ChT.

Outcomes

The mean follow-up (FU) time was 40 months (range, 9-164 months, median 27 months). At the end of RT, 103 patients (83%) had no evidence of disease. Fourteen patients (11%) presented rapid systemic progression, and seven showed (6%) stable disease.

Seventy-six patients were alive at last FU, and 14 of them had relapsed. Forty-eight patients died: Seventeen due to UCS and 31 due to other reasons. Five-year OS, DFS and CSS rates for the entire cohort were 51.6% [95% confidence interval (CI) 35-67%], 53.7% (95% CI 39-71%) and 58.6% (95% CI 38-74%), respectively (Figure 1).

During FU, 20 patients (16.1%) relapsed both locally and systemically, 10 patients (8.1%) relapsed loco-regional, whereas 27 patients (21.7%) showed systemic relapse only. The median time to recurrence was 25 months (range, 2-159 months). Thirty-one patients had pelvic recurrence. The 5-year LRC rate was 48%. Ten patients had only loco-regional recurrence and none were retreated with RT. Metastatic disease occurred in 45 patients (36%). The metastatic sites were as follows: lung (31%), liver (15%), bones/ muscles (17%), peritoneum (29%) and brain (8%).

On univariate analysis, PLND showed a benefit for DFS, CSS and LRC (Table 2). EBRT and BT dose resulted in improved OS, DFS, CSS ad LRC. Early Stage I/II disease as well as younger age (<60 years) at diagnosis had significant beneficial effects on OS, DFS, CSS and LRC. However, CSS did not differ when comparing stage I/II with stage III/IV disease (Table 2). MVA showed that EBRT>50 Gy was an independent predictive factor for better OS (P=0.03), CSS (P=0.02) and LRC (P=0.01), reducing the relative risks (RR) by a factor of 3.6 for LRC. Patients with stage I/II compared to stage III/IV disease showed improved OS (P=0.03) and DFS (P=0.03). Early or advanced tumor stage did not cause different CSS, however. Age <60 years was predictive for better LRC (P=0.01), DFS (P=0.04) and OS (P=0.02). PLND also had a favorable impact on DFS (P=0.03). BT dose higher than 9 Gy signifi-

Table 1. Patient, tumor and treatment characteristics.

Characteristic	N=124
Age years, median (range)	66.5 (50-88)
Postmenopausal status	116 (94)
Symptoms at diagnosis	
Bleeding	102 (82)
Pain	18 (15)
Tamoxifen intake history	17 (14)
FIGO Stage (2009)	
IA	38 (30)
IB	26 (21)
II	17 (14)
All stage I/II	81 (65)
IIIA	17 (14)
IIIB	3 (2)
IIIC	15 (12)
IV	4 (3)
All stage III/IV	39 (32)
Unknown	4 (3)
Surgery	
Hysterectomy	124
Salpingo-oophorectomy	122 (98)
Pelvic nodal evaluation	76 (61)
Positive margin	12 (9) [20 pts without info concerning margins]
Radiation therapy	
No adjuvant RT	13 (10)
Adjuvant RT	111 (90)
EBRT only	19 (15)
EBRT+BT	86 (69)
BT only	6 (3)
Interruption >5 days	14 (11)
Mean EBRT dose (Gy)	48.4 (range, 9-59 Gy, median 50.4 Gy)
Mean BT dose (Gy)	16.1 (range, 6-34 Gy, median 16.0 Gy)
Adjuvant chemotherapy	25 (20)
Hormonal treatment	13 (10)

FIGO, International Federation of Gynecology and Obstetrics; RT, Radiation therapy; EBRT, External beam radiation therapy; BT, Brachytherapy; pts, Patients. Values are numbers (percentage) unless otherwise noted.

cantly ameliorated LRC (P=0.008) and DFS (P=0.04); no difference was detected for OS and CSS (Table 2).

None of the other analyzed variables, namely hormonal therapy, tamoxifen intake history, menopausal status, and operative margin status, had a significant influence on DFS, LRC, CSS or OS. It is of interest that 13.7% of patients included had a history of prior breast cancer and tamoxifen exposure.

Acute and late toxicity was scored according to the CTCAE v.3.0. Grade >1 acute toxicity was observed in 41 patients. Most of these complications were mild or moderate. Late toxicity was poorly documented.

Discussion

Surgery is the first treatment option for UCS providing effective disease control.[2,10] However, local recurrence rate for early stage disease yields between 40-60% showing the aggressive potential of the disease. Despite the risk for early metastases due to occult distant disease at time of diagnosis justifying the use of adjuvant systemic treatment,[4,11] better local tumor control is needed. The randomized trial (EORTC 55874) and several retrospective studies, showed that postoperative RT improves LRC (Table 3).[6,10,12-19] Reed and colleagues demonstrated in the EORTC 55874 study that for UCS stage I/II local relapse at any time was reduced by half using postoperative RT compared to observation.[12] Callister and colleagues confirmed in their retrospective study of 300 operable patients with stage I-III disease that pelvic RT increased the 5-year LCR from 28% to 48% compared to surgery alone, and time to any distant relapse was prolonged (17.3 *vs.* 7.0 months).[6] Sampath and colleagues showed in a retrospective analysis of 3650 patients (stage I/II/III: 49%), that postoperative RT conferred a 53% risk reduction in local failure at five years for all uterine sarcoma types compared to surgery. Brown and colleagues showed recently

Table 2. Analysis of predictive factors for overall survival, cancer-specific survival, disease-free survival and locoregional control.

5-year outcome	OS 51.6% (95%CI 35-73%)	CSS 58.6% (95%CI 38-74%)	DFS 53.7% (95%CI 39-71%)	LRC 48.0% (95%CI 38-67%)
Multivariate analysis, P-value (RR)				
PLND	0.08 (1.9)	0.03 (2.6)	0.03 (2.3)	0.05 (2.0)
Dose EBRT >50 Gy	0.03 (2.5)	0.02 (2.2)	0.06 (1.8)	0.01 (3.6)
Dose BT ≤9Gy *vs.* ≥9Gy	0.1 (1.5)	0.08 (1.7)	0.04 (2.1)	0.008 (5.1)
FIGO stage I-II *vs.* III-IV	0.01 (3.3)	-	0.03 (2.4)	0.07 (1.7)
Age ≤60 *vs.* ≥ 60 years	0.02 (3.9)	0.05 (1.7)	0.04 (2.2)	0.01 (4.3)
Univariate analysis %, P value (95 CI)				
Chemotherapy	0.15 (24-79)	0.64 (33-81)	0.29 (38-70)	0.23 (34-71)
PLND	0.1 (36-73)	0.01 (31-77)	0.02 (33-72)	0.01 (26-63)
Dose Brachytherapy	0.01 (32-76)	0.04 (36-75)	<0.001 (36-71)	<0.001 (30-76)
Surgical resection margin	0.32 (27-84)	0.17 (30-76)	0.39 (37-74)	0.28 (36-69)
Pelvic lymph node RT	0.42 (37-76)	0.61 (30-69)	0.56 (37-70)	0.12 (29-72)
RT treatment interruption >5 days	0.45 (38-81)	0.72 (37-80)	0.68 (36-71)	0.22 (38-81)
EBRT	0.91 (38-74)	0.82 (34-76)	0.88 (38-73)	0.76 (23-73)
Premenopausal status	0.14 (29-74)	0.20 (26-77)	0.10 (37-70)	0.12 (34-71)
Dose postoperative RT	<0.001 (30-71)	0.009 (32-79)	<0.001 (34-62)	<0.001 (23-66)
Stage I/II *vs.* III/IV	0.04 (30-76)	0.05 (28-75)	0.04 (32-68)	0.04 (31-70)
Age at diagnosis	0.02 (33-74)	0.04 (27-78)	0.01 (36-63)	0.02 (34-67)

OS, overall survival; CSS, cancer-specific survival; DFS, disease-free survival; LRC, locoregional control; RR, relative risk; PLND, pelvic lymph node dissection; CI, confidence interval; Other abbreviations as in Table 1.

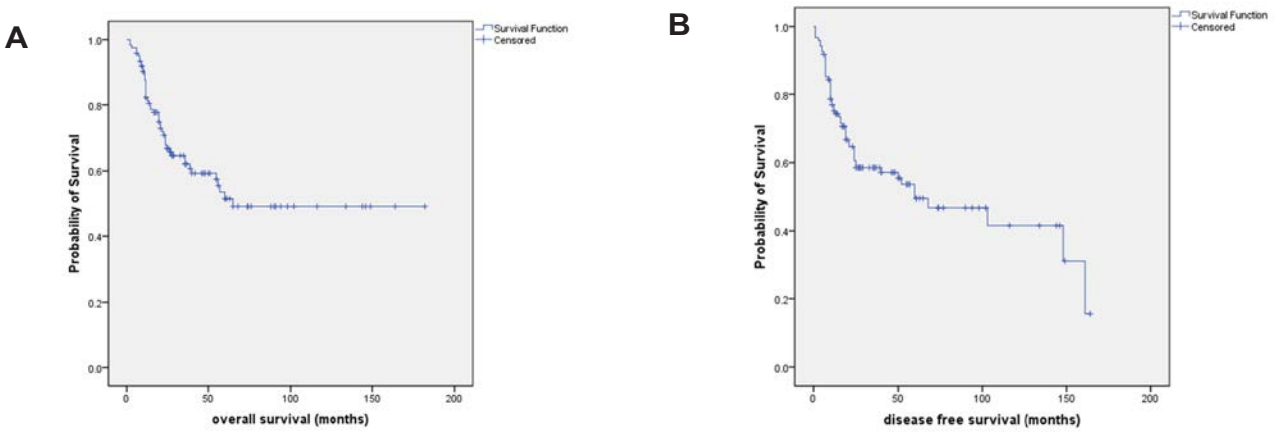

Figure 1. Five-year overall survival rates (A) and disease-free survival rates (B) in patients presenting with uterine carcinosarcoma.

Table 3. Selected studies reporting outcome and prognostic factors in uterine carcinosarcomas.

Author/ year	Year, n.	Median age, y	FIGO stage	Positive surgical margin	Median FU, months	LAD	Adjuvant treatment	OS	DFS	CSS	LRC	Outcome factors
Randomized prospective studies												
Reed 2008[12]	1988-2001, 92/224	59 whole study population	NR for subgroup UCS (98.2% of whole study population had stage I and II)	NR	81.6 (whole study population)	NR for subgroup UCS (74.1% of whole study population had no LAD)	Randomized: RT: 47 pts, No RT: 45 pts	5y: whole study population median survival time (y): RT: 8.53; No RT: 6.78; n.s.	5y: whole study population RT: 51%; No RT: 49%; n.s.	NR	5y: RT: 61%; No RT: 47%	NR
Wolfson 2007[11]	1993-2005, 206	68	I: 31%, II: 13%, III: 45%, IV: 12%	5.0% (gross residual disease)	5.3	NR RT	Randomized: (whole abdominial irradiation): 105 pts, No RT (but ChT): 101 pts	5y: RT: 35%; No RT: 45%; n.s.	5y: RT: 42%, No RT: 48%	NR	NR	NR
Retrospective studies												
Vongtama 1976[19]	1945-1972, 27/115	58 (mean) whole study population	I: 81%, II: 19%	NR	NR	NR	Sx: 10 pts; Sx + RT: 14 pts; RT alone: 3 pts	5y: Sx: 36%; Sx+RT: 57%; RT alone: 0%	NR	NR	NR	Adjuvant RT for OS
Major 1993[18]	1979-1988, 301/453	66	I: 59%, II: 21%, III: 9%, IV: 11%	NR	NR	95%	Sx: 182 pts; Sx + RT: 119 pts	NR	NR	NR	Crude rate, Sx: 43 pts, Rx+RT: 20 pts	Progression-free survival: Lymph adnexal involvement, histologic grade of sarcoma
Sartori 1997[30]	1980-1994, 118	67	I: 47%, II: 9%, III: 23.5%, IV: 18%, No Sx: 2.5%	NR	66	40%	FIGO stage I/II; Sx + RT: 28 pts; Sx: 33 pts; Sx + ChT: 5 pts	NR	5y: Sx+RT: 53%, Sx: 50%, n.s.	NR	At closure of study: 59%	Sx
Brown 2015[15]	2000-2013, 33	68	I: 97%, II: 3%	NR	24	Pelvis: 82%, para-aortic: 42%	BT: 100%; ChT: 55%	2y: 79%	66%	NR	81%	NR
Patel 2015[13]	1998-2010, 1581	<55: 12.7%, 55-64: 32%, 65-75: 30.8%, 75+: 24.5%	I: 86.7%, II: 13.3%	NR	NR	NR	Sx: 50.8%; Sx + EBRT±BT: 40.2%; Sx + BT alone: 9%	NR	NR	NR	NR	higher rates of OS and CSS: younger age at diagnosis, FIGO I (vs. II)
Harano 2015[14]	2007-2012, 486	65	I: 46%, II: 7%, III: 28%, IV: 19%	Residual tumor ≤1 cm: 87%, >1 cm: 11%, unknown: 2%	23.1	Pelvis: 56%, Para-aortic: 23%	Sx + ChT: 91%; Sx + RT: 2%; Sx + RT/ChT: 1%; Observation: 6%	5y: whole study population 53.6%; I: 69.9%, II: 64.4%, I II: 43.5%, IV: 25.3%	5y: whole study population 40.4%, I: 59.4%, II: 52.4%, III: 25.6%, IV: 12.3%	NR	NR	Poor prognosis: Stage, performance status, CA-125 level, Lymphovascular invasion, myometrial invasion, Good prognosis: pelvic LAD

To be continued on the next page

Table 3. Continued from previous page .

Author/ year	Year, n.	Median age, y	FIGO stage	Positive surgical margin	Median FU, months	LAD	Adjuvant treatment	OS	DFS	CSS	LRC	Outcome factors
												pelvic LAD
Livi 2003[17]	1974-2001, 42/141	56	NR for subgroup UCS. I: 50.5%, II: 9%, III: 22%, IV: 18.5%	NR	36	Not performed in any patient	Whole study population; Sx: 25.5%; Sx + RT: 52.5%	NR	5y: with stage I: Sx: 15%, Sx + ChT: 43%, Sx + RT: 70%, with stage III, Sx: 40%, Sx + RT + BT: 85.8%	5y: NR for UCS; whole study population 27.7%	3y: Sx: 38%; Sx + RT: 69%, Sx + RT + BT: 72%, Sx + ChT: 29%	Stage, histology, adjuvant RT >50 Gy (P=0.001)
Callister 2004[6]	1954-1998, 300	64	I: 64%, II: 21%, III: 10	NR	109	39%	Sx: 38%; Sx + RT: 53%; RT alone: 9%; Additional ChT: 16%	5y: 31%	NR	5y: 33%	5y: 62% pelvis control	Adjuvant RT
Denschlag 2007[29]	1989-2004, 36/94	60	I: 42%, II: 14%, III: 17%, IV: 6%	NR	48	74% whole study population	Sx + RT: 15 pts; Sx + RT + ChT: 13 pts	5y: 47%, whole study population	5y: 41%, whole study population	NR	NR	OS: Age, P=0.0015, adjuvant RT for UCS, P=0.003
Clayton Smith 2008[26]	1973-2003, 2461	70	I-IV	NR	47	NR	RT: 36%; Sx: 64%	5y: RT: 42.2%, Sx: 33.1%	5y: (Uterine specific survival), RT: 56.7%, Sx: 50.7%	NR	NR	Adjuvant RT
Ghaemmaghami 2008[16]	1999-2004, 17/57	50	NR for subgroup UCS, whole study population, I: 52.5%, II: 16%, III: 21%, IV: 10.5%	NR	19	UCS: 64%	UCS: Sx: 17 pts; Sx+ RT: 1 pt; (Sx + RT: whole study population: 14 pts)	5y: 52%, whole study population; UCS, 41%	NR	NR	5y: 75% whole study population	Stage, histology, grading, Local control: adjvant RT >50 Gy
Sorbe 2008[20]	1975-2003, 60/155	64.5 (mean) whole study population	NR for subgroup UCS, whole study population, I: 61%, II: 6%, III: 17%, IV: 15%	NR	160 whole study population	7.1.% whole study population	Stage I, II: 40 pts; Sx: 4 pts; Sx + RT: 36 pts	5y: NR for UCS; whole study population 42%	NR	NR	Crude rate Sx: 3 pts, Sx + RT: 28 pts	Tumor stage, histology, number of mitoses
Nemani 2008[27]	1988-2003, 1855	NR	I: 65%, II: 14%, III: 21%	NR	NR	57%	Sx: 939; Sx + RT: 653 pts	5y: no lymph node dissection ; Sx: 33%, Sx + RT: 36%	5y: improved with RT	NR	NR	Lymph node dissection
Sampath 2010[10]	1980-2005, 1877/3650	64	NR for subgroup UCS, I: 30%, II: 7%, III: 12%, IV: 13.5%, unknown: 37.5%	NR	59.3	Node positive: 7.9%; node negative: 51.6%, unknown; 40.5%	RT: 490 pts; No RT: 638 pts	5y: whole study population: 37%	NR	NR	5y: RT: 90%, No RT: 80%, P<0.001	Adjuvant RT
Zwahlen 2013	1987-2007, 124	66.5	I: 52%, II: 14%, III: 28%, IV: 3%	9.7%	40	61%	RT: 88%, ChT: 20%	5y: 51.7%	5y: 53.7.6%	5y: 58.6%	5y: 48%	adjuvant RT, FIGO stage I-II vs. III-IV, age (60 vs. > 60 years), LAD, higher BT dose

FIGO, International Federation of Gynecology and Obstetrics; FU, follow up; LAD, lymphadenectomy; OS, overall survival; DFS, disease free survival; CSS, cause-specific survival; LRC, locoregional control; NR, not reported; ChT, Chemotherapy; HT, hormonal therapy; RT, radiotherapy; EBRT, External Beam RT; BT, Brachytherapy; Tx, Treatment; MT, metastases; Sx, surgery; BSO, bilateral salpingo-oophorectomy; pts, patients, n.s., not statistically significant; Numbers underlined represent UCS only; Other abbreviations as in Tables 1 and 2.

that even in UCS stage I/II relapse occurred in 33% after BT without external RT.[13] Node-negative patients receiving postoperative RT had significantly less local failures.[10] Better LRC comes at the cost of toxicity. In our study irradiated patients reported increased early toxicity (CTCAE Grade >1: 33%), but no severe late side effects were reported. However, late toxicity was only poorly documented in our trial. The EORTC 55874 study observed as well primarily increased early toxicity with low rate of late toxicity.[12] Sorbe and colleagues demonstrated increased early and 5-10% late side effects (bladder and intestine) when applying pelvic RT as reported in the PORTEC-1 trial.[20,21]

The role of dose escalation in UCS to ameliorate disease control is unclear. We showed that EBRT dose ≥50 Gy and BT dose ≥9 Gy improved LRC, CSS and OS in UCS (Table 2). In the EORTC 55874 randomized study, EBRT dose of 50.4 Gy improved local control. Some patients with stage I/II disease were escalated up to 65 Gy. It remains unanswered if local control improved.[12] A retrospective study by Livi and colleagues indicated that a dose ≥50 Gy reduced local recurrence. Yoney and colleagues observed in their retrospective study including 105 patients with uterine sarcoma (27.6% UCS) that postoperative RT >54 Gy improved OS.[22] Other groups observed similar correlations suggesting that UCS is a radiosensitive tumor and tumor response is dose dependent.[17,23] Importantly, local recurrence at three years was lowest for patients receiving EBRT and BT highlighting the importance of BT as a boost technique to escalate the dose without increasing toxicity rates.[17] If BT as a single postoperative treatment could compensate for the omission of EBRT remains to be tested.[20] Our data indicate that BT dose ≥9 Gy improves local control and DFS irrespective of EBRT (Table 2). However, there might be a bias that patients included with residual postoperative tumor or surgical resection margin positive disease, were treated with a higher BT dose. As UCS is staged as high-risk endometrial carcinoma and depending on risk factors combination of EBRT and BT remains standard to date.[2,3,17] However, postoperative BT correlates with increased toxicity in high-risk endometrial cancer.[24] Prospective studies evaluating dose escalation using modern RT techniques do not exist to date and the impact of higher dose on disease outcome is awaited. Combination of modern image-guided radiation techniques and CT or MR-guided brachytherapy should allow for safe dose escalation for better local control without increasing toxicity.[25]

The effect of postoperative RT on OS or CSS in UCS remains controversial. Neither the GOG 150 nor the EORTC 55874 randomized trial demonstrated improved OS or CSS using postoperative RT compared to adjuvant ChT or observation.[11,12] Sampath and colleagues reported a 5-year OS of 37% irrespective of using postoperative RT.[10] Callister and colleagues demonstrated that neither postoperative EBRT or BT nor adjuvant ChT significantly ameliorated 5-year OS of only 31%, similar CSS was 33% (Table 3). In contrast, our data showed that postoperative RT resulted in a five year OS of 51.6% (95% CI 35-73%) and CSS of 58.6% (95% CI 38-74%) offering one of the highest OS and CSS in literature to date. However, these findings should be read with caution due to small cohort size and potential selection bias for medically fitter patients undergoing RT.[26] A recently published large population-based database by Patel and colleagues showed that the type of radiotherapy was not associated with OS or CSS.[14]

The role of RT in the context of pelvic or para-aortic lymph node dissection with respect to OS is poorly studied. Using the Survey, Epidemiology and End Results data base, Nemani and colleagues demonstrated that lymph node dissection improved five year OS from 34% to 49% irrespective of RT.[27] Our data could not demonstrate better OS with PLND in combination with postoperative RT, however PLND predicted improved DFS and CSS (Table 2). This has been shown as well in the work from Harano and colleagues that PLND was associated with improved survival.[15] An important difference was that 61% of our patients underwent lymph node staging or lymphadenectomy reducing risk of occult lymph node disease. In the EORTC 55874 study only 25% of irradiated patients underwent node sampling, leaving a higher risk for residual disease in place.[12] Therefore selection bias operating and removing positive lymph nodes on more robust patients had to be considered that could explain our findings rather than a beneficial effect of pelvic RT.[28] Unfortunately, we were not able to differentiate locations of failure rate within the pelvis (tumor bed or lymph nodes). The role of routine lymphadenectomy is an ongoing debate for UCS and could not be answered in this study.[27,28]

Another focus of this work was to define predictive factors to determine effectiveness of postoperative RT in UCS. In our study stage I/II disease was predictive for improved DFS and OS indicating that early diagnosis and multimodality treatment improves outcome (Table 2). In contrast to the more favorable outcome of early stage disease, UCS stages III and IV diseases have a high potential of haematogenous spread most likely limiting the potential of postoperative RT to improve outcome. More effective systemic treatment regimens are needed to compensate for early metastases.[28] Other predictive factors identified that correlated with ameliorated OS or CSS were patient age <60 years, PLND and EBRT ≥50 Gy. BT dose was highly predictive for better local control, indicating the importance of a high dose to the vaginal vault to help to sterilize the tumor bed area.[21] Several retrospective studies confirmed that postoperative RT, higher dose, lymph node assessment, adnexal involvement, histologic grade, surgery and disease stage were relevant factors evaluating disease outcome and treatment response for either LRC or survival as summarized in Table 3.[6,10-20,27,29,30] Future trial design using RT for UCS should be guided by these findings to find the patient group that benefit most from intensified adjuvant treatment modalities.

This study has several limitations. This was a retrospective analysis with a pool of patients from different countries and treatment regimens with varied inherent selection bias toward treatment. The impact of adjuvant ChT on outcome in this disease could not be addressed in its full extent as treatment regimens were only partially reported. Similar long-term toxicities were not fully available. Despite these limitations we believe our study contributes to a better understanding of the role of postoperative RT in UCS.

Conclusions

Postoperative RT in our work had an impact on disease outcome. Despite the unfavorable prognosis of UCS, local relapse could be prevented by a relative risk factor of over three when using higher doses for EBRT as well as BT. Therefore use of postoperative RT should be considered as part of a multidisciplinary approach to therapy for early stage UCS. Image-guided radiation techniques for dose escalation without increasing toxicity should be used in future trials.

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