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Original Article

Treatment and outcomes in undifferentiated and dedifferentiated endometrial carcinoma

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ABSTRACT

Objective: Undifferentiated and dedifferentiated endometrial carcinoma is a rare type of uterine malignancy. This study assesses disease characteristics, treatment and survival outcomes in patients with undifferentiated and dedifferentiated endometrial carcinoma treated at BC Cancer.
Methods: All patients diagnosed with undifferentiated and dedifferentiated endometrial carcinoma between 2000 and 2019 at BC Cancer were reviewed centrally. Clinical, pathologic, treatment and outcomes were reviewed retrospectively. The Kaplan-Meier method was used to evaluate overall survival (OS) and disease-free survival (DFS). Multivariable analysis was performed using Cox regression analysis.
Results: Fifty-two patients were included, 33% had undifferentiated carcinoma and 67% dedifferentiated carcinoma. Sixty-nine percent of those who had mismatch repair (MMR) testing of their tumor had an abnormal profile. The 5-year DFS was 80% (95% confidence interval [CI]=71%–89%) for stage I/II, 29% (95% CI=28%–40%) for stage III and 10% (95% CI 1%–19%) for stage IV. The 5-year OS was 84% (95% CI=75%–92%) for stage I/II, 38% (95% CI=26%–50%) for stage III and 12% (95% CI=1%–24%) for stage IV. Multivariate analysis showed that receiving adjuvant chemotherapy, adjuvant radiotherapy, lower stage and better Eastern Cooperative Group performance status were associated with improved DFS ($p<0.05$).
Conclusion: Patients with stage I/II undifferentiated and dedifferentiated endometrial carcinoma had excellent survival outcomes, those with stage III/IV had worse outcomes, similar to previously reported. Adjuvant chemotherapy and radiotherapy were associated with improved DFS. MMR testing should be performed for these patients due to the high incidence of abnormal profiles.

Keywords: Cancer; Neoplasm; Uterus

Synopsis

Patients with early stage I and II undifferentiated and dedifferentiated endometrial carcinoma had excellent survival outcomes. Adjuvant chemotherapy and radiotherapy was associated with improved disease-free survival. 70% of patients who had mismatch repair protein testing of their tumor had an abnormal profile.

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
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INTRODUCTION

The most common gynecologic malignancy is endometrial cancer and the majority of tumors (80%) are classified as endometrioid adenocarcinoma [1]. A rare type of endometrial cancer is undifferentiated carcinoma; which is defined as a malignant epithelial neoplasm with no overt cell lineage differentiation [1,2]. Previous studies have reported that 1%–2% of all endometrial cancers are undifferentiated [3,4]. However, they may be under recognized as they can be difficult to distinguish from other high-grade tumors such as grade 3 endometrioid adenocarcinoma, carcinosarcoma and high-grade sarcoma and the incidence may be as high as 9% [3,4]. Undifferentiated carcinoma is associated with poorer survival outcomes relative to high-grade endometrioid adenocarcinoma [1]. It can be often found admixed with differentiated tumor, typically a low-grade endometrioid carcinoma, and this is referred to as “dedifferentiated” endometrioid carcinoma [1,5].

Undifferentiated carcinomas have an aggressive clinical course; with previously published studies showing a high risk of locoregional and distant relapse compared to differentiated carcinomas [1,2,6,7]. Therefore, recognition and distinction of undifferentiated and dedifferentiated carcinoma is important for accurate prognostication [1,8]. More recently, genomic inactivation resulting in loss of expression of core switch/sucrose non-fermentable (SWI/SNF) complex proteins have been identified as key molecular alteration underlying dedifferentiation to undifferentiated carcinoma and loss of expression of these core SWI/SNF protein(s) appear to be reliable diagnostic feature that can aid in the identification of these aggressive tumors [5]. Given the rarity of this tumor, there is a lack of published literature regarding the disease characteristics, management and survival outcomes for this rare but more aggressive subtype of endometrial carcinoma. Additionally, most previously published studies have focused on pathological and immunohistochemical characteristics of these rare tumors [3,9,10].

Therefore, the purpose of our study was to evaluate the clinical aspects of undifferentiated and dedifferentiated endometrial carcinoma, specifically assessing disease characteristics, treatment and survival outcomes in patients treated at our institution.

MATERIALS AND METHODS

1. Patient selection

Consecutive patients diagnosed with undifferentiated and dedifferentiated endometrial carcinoma between 2000 and 2019 at BC Cancer were included in this study. The tumor was classified as undifferentiated if the entire specimen consisted of undifferentiated carcinoma. The tumor was classified as dedifferentiated carcinoma if there was admixed differentiated carcinoma and undifferentiated carcinoma present in the specimen. Undifferentiated tumors were classified as per the criteria outlines by Silva et al. [3,6]; with total absence of glandular differentiation, patternless solid growth of tumor cells and minimal to absent neuroendocrine distribution. All pathology specimens were reviewed centrally at our institution by gynecologic subspecialty pathologist to confirm the diagnosis. Patients with other types of endometrial carcinoma were excluded from the study.

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2. Data abstraction

Patients were identified using the British Columbia Cancer Agency Information Systems database and the electronic medical charts were reviewed retrospectively. Demographic data were collected including age at diagnosis and Eastern Cooperative Oncology Group (ECOG) performance status at diagnosis. Pathology data including biopsy results, surgical pathology results, the International Federation of Gynecology and Obstetrics (FIGO) 2009 stage, cervix, fallopian tube, myometrial and lymph node involvement and lymphovascular space invasion (LVSI) were assessed. Treatment data including type of surgery (including extent of hysterectomy, lymph node sampling, washings, omentectomy), type of chemotherapy (agents, number of cycles), and type of radiation therapy (brachytherapy vs. external beam radiotherapy [EBRT], extent of fields) were abstracted from the chart. Immunohistochemical mismatch repair (MMR) protein profile and referral and results of hereditary counselling and testing were also documented when available. Follow-up data including date of last follow-up, date of death, and date of local, regional or distant recurrence were assessed.

3. Immunohistochemistry analysis for core SWI/SNF proteins

ARID1A, ARID1B, SMARCA4 and SMARCB1 immunohistochemistry was performed on tissue whole-sections as previously described [5]. The slides were incubated with antibodies to ARID1A (1:200, HPA005456; Sigma, Oakville, Canada), ARID1B (1:100, clone 2D2, H00057492-M01; Abnova, Taipei, Taiwan), SMARCA4 (1:25, clone EPNCIR111A, ab110641; Abcam, Toronto, Canada) and SMARCB1 (1:50, 25/BAF47, 612110; BD Biosciences, Mississauga, Canada); ARDIA, ARID1B and SMARCA4 were processed using Dako Omnis Autostainer (Dako Canada ULC, Mississauga, Canada) while SMARCB1 was processed using Ventana Benchmark XT (Ventana Medical Systems, Tucson, AZ, USA). For interpretation, only nuclear protein expression was assessed and the tumor was scored as showing intact expression if any tumor cell nuclei showed nuclear staining and deficient if all the tumor nuclei were unstained in the presence of internal positive control immunoreactivity (stromal endothelial cells and inflammatory cells).

4. Adjuvant treatment

According to BC Cancer treatment guidelines, patients with stage IA, myometrial invasion or higher were recommended to have 3–6 cycles of adjuvant carboplatin/paclitaxel chemotherapy delivered q3weekly. Contraindications to chemotherapy included ECOG performance status ≥3, pre-existing motor or sensory neuropathy greater than grade 2, AST or ALT greater than 10 times upper limit of normal, or total bilirubin >128 micromol/L. Patients with stage IA and superficial myometrial invasion without LVSI were recommended to have Ir-192 high dose rate vaginal vault brachytherapy, 2,100 cGy in 3 fractions delivered every other day at 5 mm depth, proximal 4 cm length. Patients with stage IB to IIIC2, or LVSI were recommended to have EBRT to the pelvis, 4,500 cGy in 25 fractions delivered daily Monday to Friday. Patients were treated using a 3-D conformal or volumetric mediated arc therapy technique, with or without a 300 cGy in one fraction vaginal vault brachytherapy boost. Patients with positive pelvic or para-aortic lymph nodes also received para-aortic radiotherapy. Gross residual primary or regional disease were given an external beam radiation boost to 10–15 Gy, delivered sequentially or as a simultaneously integrated boost. In general, patients were followed with history and physical examination for every 3 to 6 monthly for 5 years, routine imaging and investigations in the absence of clinical symptoms were not used.

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5. Statistical analysis

Kaplan-Meier analysis was used to calculate overall survival (OS) and disease-free survival (DFS). OS was calculated from the date of diagnosis to the date of death, with patients censored at the date of last follow-up. DFS was calculated from the date of diagnosis to the first of date of recurrence or date of death, with patients censored at the date of last follow-up without disease. The log rank (Mantel-Cox) test was used to perform pairwise comparison of OS and DFS for patients with stage 1/2 disease vs. stage 3 vs. stage 4. Two-sided p-values less than 0.05 were considered significant.

Cox regression multivariable analysis was used to assess variables associated with DFS and OS. Variables analyzed included: age (continuous), pathology (undifferentiated vs. dedifferentiated), ECOG performance status (0 vs. 1 vs. 2 vs. 3), stage (I/II vs. III vs. IV), adjuvant chemotherapy (yes/no), adjuvant radiotherapy (yes/no), SNI/SNF deficient (yes/no). Backward stepwise elimination was used for variable selection with 0.05 used as the level of statistical significance for variable retention. Statistical analysis was performed using the Statistical Package for the Social Sciences version 14.0 (IBM Corp., Armonk, NY, USA). This study was approved research ethics board of the University of British Columbia and BC Cancer (H19-00122), a waiver of consent was approved due to the retrospective nature of the study.

RESULTS

1. Patient, disease and treatment characteristics

Patient demographics and disease characteristics are shown in **Table 1**. There were 52 patients included in the study. The age ranges at diagnosis were as follows: 6% less than 40 years, 6% 41–50 years, 25% 51–60 years, 42% 61–70 years and 21% over 70 years. The majority of patients (77%) were ECOG performance status 0–1 at diagnosis.

Only 37% of patients were diagnosed with undifferentiated or dedifferentiated carcinoma at the time of endometrial biopsy. The 46 of 52 patients underwent surgery. The final surgical pathology showed that 33% had undifferentiated carcinoma and 67% dedifferentiated carcinoma. At diagnosis, almost half (46%) of patients had stage I, 8% stage II, 31% stage III and 15% stage IV disease. Over half (52%) had deep myometrial involvement and 10% had disease extension to serosa. Cervix involvement was seen in 19%, fallopian tube involvement in 14% and ovary involvement in 14%. Two thirds (66%) had LVSI, 17% positive pelvic lymph nodes and 9% positive para-aortic lymph nodes. Immunohistochemistry analysis for core SWI/SNF proteins (ARID1A, ARID1B, SMARCA4 and SMARCB1) was performed on 49 of 52 cases with available materials. The 34 tumors (69%) were core SWI/SNF-deficient, with 22 being ARID1A/ARID1B co-inactivated, 8 being SMARCA4-inactivated and 4 being SMARCB2-inactivated, while 15 tumors (31%) were core SWI/SNF-intact.

Treatment characteristics are outlined in **Table 2**. Most (73%) had total abdominal hysterectomy and bilateral salpingo-oophorectomy (BSO), 14% had laparoscopic assisted vaginal hysterectomy BSO and 2% radical hysterectomy BSO. Six patients did not have surgery due to presence of metastatic disease at the time of staging. Positive lymph nodes were seen in 21%, pelvic washings in 6% and omentum in 8%.

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Table 1. Patient and disease characteristics

Characteristic	No. (%) (n=52)
Age at diagnosis	
<40	3 (6)
41–50	3 (6)
51–60	13 (25)
61–70	22 (42)
>70	11 (21)
ECOG performance status	
0	26 (50)
1	14 (27)
2	6 (12)
3	6 (12)
Pathology: Endometrial biopsy	
No biopsy	1 (2)
Suspicious for adenocarcinoma	1 (2)
Grade 1	4 (8)
Grade 2	2 (4)
Grade 2/3	4 (8)
Grade 3	20 (38)
Carcinosarcoma	1 (2)
Dedifferentiated	5 (10)
Undifferentiated	14 (27)
Pathology: Definitive surgery	
Undifferentiated	17 (33)
Dedifferentiated	35 (67)
Stage at diagnosis	
IA	14 (27)
IB	10 (19)
II	4 (8)
IIIA	6 (12)
IIIB	1 (2)
IIIC	9 (17)
IV	8 (15)
Depth of invasion	
Endometrium only	3 (6)
Superficial myometrium	13 (25)
Deep myometrium	27 (52)
Serosa	5 (10)
Cervix involvement	10 (19)
Fallopian tube involvement	7 (14)
Ovary involvement	7 (14)
Lymphovascular space invasion	
None	17 (33)
Present	7 (14)
Focal	3 (6)
Extensive	20 (39)
Pelvic node involvement	9 (17)
Para-aortic node involvement	5 (9)
Genomic alterations	
Core SWI/SNF-intact	15 (28)
SMARCB1-deficient	4 (8)
SMARCA4-deficient	8 (15)
ARID1A/ARID1B co-deficient	22 (42)

Values are presented as number (%).
SWI/SNF = switch/sucrose non-fermentable.

Of the 61% of patients who received chemotherapy, the majority were treated with carboplatin/paclitaxel, except 2 patients who received carboplatin/doxorubicin. For 20 patients, chemotherapy was not given for the following reasons: not offered due to early stage (n=8), comorbidities/poor performance status postoperatively (n=6) and patient refusal (n=6).

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Table 2. Treatment characteristics

Characteristic	No. (%) (n=52)
Surgery	
TAH BSO	38 (73)
LAVH BSO	7 (14)
Radical hysterectomy BSO	1 (2)
None	6 (12)
Lymph node sampling	
Yes: Negative	20 (39)
Yes: Positive	11 (21)
Not performed	21 (40)
Washings	
Positive	3 (6)
Negative/Not performed	49 (94)
Omentectomy	
Positive	4 (8)
Negative/Not performed	48 (92)
Chemotherapy cycles	
None	20 (39)
1–2	5 (10)
3–4	20 (39)
5–6	6 (12)
Radiation	
None	23 (44)
Vaginal vault only	5 (10)
Pelvic EBRT only	17 (33)
Pelvic EBRT + Vaginal vault	3 (6)
Pelvic/Para EBRT	3 (6)
Pelvic/Para EBRT + Vaginal vault	1 (2)

BSO, bilateral salpingo-oophorectomy; EBRT, external beam radiotherapy; LAVH, laparoscopic assisted vaginal hysterectomy; TAH, total abdominal hysterectomy.

Over half (56%) received radiotherapy, with treatment volumes as follows: 10% vaginal vault brachytherapy only, 33% pelvic EBRT, 6% pelvic EBRT and vaginal vault brachytherapy, 6% pelvic/para-aortic EBRT and 2% pelvic/par-aortic EBRT and vaginal vault brachytherapy. For 24 patients, radiotherapy was not given for the following reasons: distant metastases or progression during chemotherapy (n=12), patient refusal (n=4), not offered due to early stage (n=3) and comorbidities/poor performance status (n=4).

2. MMR status

MMR protein status of the tumor was tested in 83% of cases. Of those tested, 30% had normal MMR status while the remaining 70% had MMR deficiency, as summarized in **Table 3**. MLH1 loss was the most common abnormality, and was observed in just over half of those tested (51%). For those with an abnormal MMR profile, 87% were referred for hereditary counselling referral. Of those referred, 76% did not have genetic testing: 16 patients had MLH1 promoter hypermethylation, 2 patients declined testing, 5 patients died before consultation. Of the 3 patients tested, 1 patient had normal testing results, 1 showed a MSH2 germline mutation, 2 were normal.

3. Disease outcomes

Median follow-up for all patients was 17.5 months (range: 0–138 months) and for living patients 49 months (range: 2–138 months). Disease outcomes are shown in **Table 4**. At initial staging, 15% were found to have distant metastases. Local relapse occurred in 15%, regional nodal relapse in 14% and distant relapse in 29%: 39% died of endometrial cancer and one patient (1%) died from other causes.

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Table 3. MMR status

Characteristic	No. (%)
Normal	13 (25)
Not tested	9 (17)
Loss MLH1	22 (42)
Loss MLH1/PSM2	3 (6)
Loss MSH2	2 (4)
Loss PSM2	2 (4)
Loss MSH6	1 (2)
MMR deficient patients referred for hereditary counselling	26 (87)
Results of hereditary counselling referral	
Testing done: Normal	2 (16)
Testing done: MSH2 germline rotation	1 (8)
No testing performed: MLH1 hypermethylation	16 (62)
Patient declined testing	2 (16)
Patient died before testing completed	5 (19)

MMR, mismatch repair.

Table 4. Disease and survival outcomes

Outcome	No. (%) (n=52)
Distant metastases at staging	8 (15)
Local relapse	8 (15)
Regional relapse	7 (14)
Distant relapse	15 (29)
Death from endometrial cancer	20 (39)
Death from other causes	1 (2)

DFS is shown in **Fig. 1A**. The 5-year DFS was 80% (85% confidence interval [CI]=71%–89%) for stage I/II, 29% (95% CI=18%–40%) for stage III and 10% (95% CI=1%–19%) for stage IV. Pairwise comparison showed a significant difference between stage I/II and III or IV ($p<0.05$). Multivariate analysis (MVA, **Table 5**) showed that receiving adjuvant radiotherapy, adjuvant chemotherapy, lower stage and better ECOG performance status were associated with improved DFS ($p<0.05$). Age, pathology (undifferentiated vs. dedifferentiated), and core SWI/SNF-deficiency were not associated with DFS ($p>0.05$).

The 5-year OS was 84% (95% CI=75%–92%) for stage I/II, 38% (95% CI=26%–50%) for stage III and 12% (95% CI=1%–24%) (**Fig. 1B**). Pairwise comparison showed a significant difference

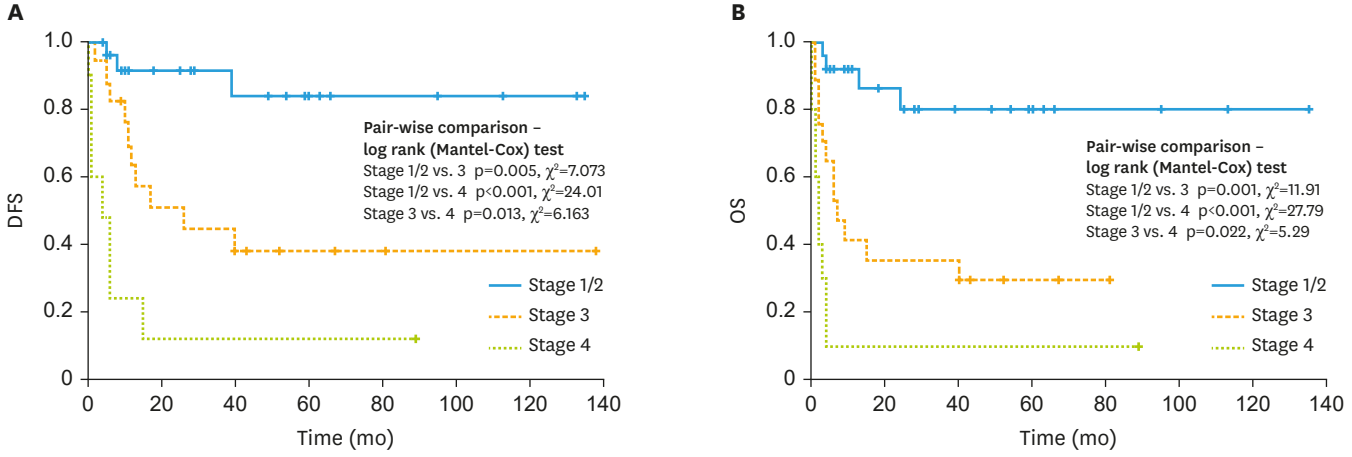

Fig. 1. Pair-wise comparison: log rank (Mantel-Cox) test. (A) DFS. Stage 1/2 vs. 3, p=0.005, χ^2=7.073; Stage 1/2 vs. 4, p<0.001, χ^2=24.01; Stage 3 vs. 4, p=0.013, χ^2=6.163. (B) OS. Stage 1/2 vs. 3, p=0.001, χ^2=11.91; Stage 1/2 vs. 4, p<0.001, χ^2=27.79; Stage 3 vs. 4, p=0.022, χ^2=5.29.
DFS, disease-free survival; OS, overall survival.

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Table 5. Multivariate analysis

Variable	p-value	HR	95% CI
DFS*			
Stage IV vs. III	0.18	0.41	0.11–1.53
Stage I/II vs. III	<0.001	0.07	0.018–0.28
ECOG 1 vs. 0	0.39	1.65	0.52–5.18
ECOG 2 vs. 0	0.001	14.72	2.88–75.35
ECOG 3 vs. 0	0.004	8.46	2.01–35.53
Chemo yes vs. no	0.02	0.27	0.10–0.78
Radiation yes vs. no	0.02	0.27	0.10–0.76
OS†			
Stage IV vs. III	0.02	3.34	1.24–9.05
Stage I/II vs. III	0.001	0.11	0.030–0.43
Chemo yes vs. no	0.001	0.21	0.082–0.54

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; DFS, disease-free survival; HR, hazard ratio; OS, overall survival; SWI/SNF, switch/sucrose non-fermentable.
*Age, pathology (undifferentiated vs. dedifferentiated), SWI/SNF-deficiency were not predictive for DFS on multivariate analysis (p>0.05).
†Age, pathology (undifferentiated vs. dedifferentiated), SWI/SNF-deficiency, ECOG, radiation treatment were not predictive of OS on multivariate analysis (p>0.05).

between stage I/II and III or IV (p<0.05). MVA showed that receiving adjuvant chemotherapy, and lower stage were associated with improved OS (p<0.05). Age, radiotherapy, pathology (undifferentiated vs. dedifferentiated), core SWI/SNF-deficiency status, and ECOG were not associated with OS (p>0.05).

The 5-year OS for the stage I/II patients treated with chemotherapy was 92% (95% CI=85%–99%) vs. 73% (95% CI=55%–90%) treated without chemotherapy (p=0.38). The 5-year OS for the stage III patients treated with chemotherapy was 50% (95% CI=36%–64%) vs. 0% (95% CI=0%) for the patients treated without chemotherapy (p=0.02). The 5-year OS for the stage IV patients treated with chemotherapy was 25% (95% CI=4%–46%) vs. 0% (95% CI=0%) for the patients treated without chemotherapy (p=0.03)

Of the 5 patients that received vaginal brachytherapy, no patients relapsed. Of the 23 patients who had EBRT, 1 patient (4%) had a vaginal relapse and 2 patients (8%) had nodal relapse. Of the 24 patients who had no radiation, 8 (33%) had a vaginal relapse and 1 (4%) had a nodal relapse.

DISCUSSION

This study is a retrospective review of undifferentiated and dedifferentiated carcinoma of the endometrium and is to our knowledge, the largest single institution study with central pathology review of this rare cancer. Our group had previously reported extremely poor outcomes associated with SWI/SNF deficiency and advanced stage disease [5]. However there was a limited number of these patients in this study, and therefore we were unable to find a statistically significant association between SWI/SNF status and survival outcome.

As expected, the survival outcomes for stage I and II undifferentiated and dedifferentiated carcinoma in our study (5-year OS, 84%) are slightly worse compared to the outcomes for stage I to II endometrial carcinoma of any histological subtype in randomized trials and database studies [11,12]. OS outcomes for stage III tumors in our study were worse at 38% vs. 47%–58% in the National Cancer Institute (NCI) database in Canada for all endometrial cancer subtypes and 50%–80% for grade 1–3 endometroid tumors in the National Cancer Database (NCDB)

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in the USA [13,14]. The 5-year OS survival for stage IV disease in our study was 11% also worse compared to database studies of differentiated tumors, with 15%–17% 5-year OS (95% CI=7%–33%) reported in the NCI database and 17% in the SEER database [14,15].

Reported survival outcomes in the literature for undifferentiated and dedifferentiated carcinoma have been mixed, however, most studies have also shown worse outcomes relative to differentiated tumors. The original study by Silva et al. [6] describing dedifferentiated carcinoma reported on 13 cases of dedifferentiated endometrial carcinoma of the endometrium at initial diagnosis. The crude survival was 46% (n=6/13) and of the surviving cases, 1 was a recent case, 4 were alive with progressive disease and only 1 patient had no evidence of disease at 104 months [6]. Of these cases, the majority of patients had stage III and IV (69%) at diagnosis, which could partially account for the poorer outcomes compared to our study [6]. The same authors also published outcomes of 16 cases of pure undifferentiated carcinoma; and reported a crude survival rate of 25% [4]. Of the 4 patients with stage I disease, 50% died of disease and 100% of the patient with stage II–IV tumors died of disease. Of 3 patients who did not have staging information available, 33% died of disease [4]. A study by Al-Hussaini et al. [9] of 17 patients with undifferentiated and dedifferentiated carcinoma reported on 6 patients with stage I/II disease, of these, 1 patient was alive, 2 were lost to follow-up and 3 died of disease (n=50%). A retrospective study from Turkey by Ureyen et al. [16] reported on a series of 18 patients with undifferentiated carcinoma; after a median of 66 months of follow-up, 33% had progressive disease and 16% died of disease. However, the largest previously published series of dedifferentiated and undifferentiated endometrial carcinomas by Tafe et al. [8] reported on 26 cases at Memorial Sloan Kettering and their results are similar to our study, with 72% of patients with stage I and II alive and 60% with stage III and IV, median follow-up was 20 months. Ganju et al. [17] reported on 24 cases and also had very similar results to our study, with 2 year OS of 93% and progression-free survival of 71%, with high usage of adjuvant chemotherapy and radiotherapy in their series. Most recently, a large NCDB study reported on outcomes of 3,313 patients with undifferentiated endometrial carcinoma. The 5-year OS was 75%, 59%, 44% and 22% for stage I–IV respectively, showing worse outcomes than in our study for stage I/II disease, but similar outcomes for stage III/IV disease. Central pathology review was not performed in this study; and dedifferentiated patients were not included [18].

In our study, MVA showed that better ECOG performance status was associated with improved DFS, similar to prior studies of differentiated endometrial cancer [19,20]. Similarly, receiving adjuvant carboplatin/paclitaxel was an independent predictor of both improved DFS and OS, which has also been shown in high-grade differentiated endometrial cancer [21]. Adjuvant radiotherapy predicted for improved DFS, but not OS, also similar to prior randomized studies, but given the relatively small sample size, a more detailed comparison based on the extent of field which was prescribed based on pathologic features (vaginal vault, pelvis, or pelvic and para-aortic fields) was not possible [11,12]. The increased use of adjuvant chemotherapy and radiotherapy relative to prior studies may also account for the improved survival outcomes in our study relative to some series [6,9]. In the NCDB study, adjuvant therapy was also associated with improvements in OS [18]. In our study, central pathology review was performed for the majority of cases at the time of referral, and the identification of undifferentiated carcinoma influenced treatment decision making regarding adjuvant therapies. Not surprisingly, stage III and IV were independent predictors of worse survival outcomes in our study relative to stage I and II; similar to other prior series of undifferentiated and dedifferentiated carcinoma [4,8,16]. We did not find that pure undifferentiated tumors

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had worse outcomes relative to dedifferentiated tumors on MVA, suggesting that outcomes are driven by the undifferentiated component [2,8]. However, we were unable to analyze based on percentage of dedifferentiation due to inconsistent reporting.

MMR protein testing was performed for 83% of specimens in our study and of those tested, 70% had an abnormal MMR profile. The most common abnormality was loss of MLH1. These results are very similar to Tafe et al. [8] who found that 47% of patients with undifferentiated endometrial carcinoma had loss of at least one MMR protein. Additionally, Al-Hussaini et al. [9] reported on 17 cases, of which 65% were MLH1/PMS2 deficient. Ramalingam et al. [10] found that MLH1 and PMS2 were lost in 50% of cases, and MSH2 and MSH6 were lost in 1 case (3%). Five patients were found to have MLH1 promoter methylation, which has also been shown in previous studies to be associated with undifferentiated carcinoma [22]. The majority of patients in our study with an abnormal MMR profile were referred to hereditary counselling; however, only a small proportion had genetic test results (n=3) at the time of analysis, with one patient found to have a germline MSH2 mutation consistent with Lynch syndrome. These results, together with previous studies, suggest that MMR protein testing should be performed in patients with undifferentiated and dedifferentiated carcinomas, given the high proportion of abnormal profiles, the potential risk of germline mutations associated with Lynch syndrome, and the therapeutic implications, particularly with immune checkpoint inhibitors in recurrent or metastatic disease [23].

Our study is limited by the retrospective study design. Additionally, although pathology was reviewed centrally, the proportion of dedifferentiation was not routinely assessed and not all patients had MMR profile testing. We are a referral center for oncologic treatment, and there may be a subset of patients with advanced stage disease not referred for treatment due to rapid disease course and/or co-morbidities. The strengths include that patients were treated based on our provincial guidelines and the large sample size of the study with central review, given the rarity of this tumor, and relative to other previously published studies of dedifferentiated and undifferentiated carcinoma.

In conclusion, in this study of clinical outcomes of undifferentiated and dedifferentiated endometrial carcinoma, patients with stage I and II had excellent survival outcomes. Patients with stage III and IV had worse outcomes, similar to previously reported in the published literature. Chemotherapy and radiotherapy were independently associated with improved DFS and the frequent use of adjuvant therapies in our study may have contributed to the improved outcomes when compared to the published literature. A large proportion of tumors that underwent MMR tested had an abnormal profile, suggesting that routine testing in patients with dedifferentiated and undifferentiated carcinomas should be performed.

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