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ORIGINAL ARTICLE

Neoadjuvant chemotherapy in patients with advanced endometrial cancer

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Abstract

Objectives Neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) is a treatment strategy for ovarian cancer patients with unresectable disease or poor performance status (PS). This strategy has been used in the treatment of advanced endometrial cancer and a survival benefit has been shown in patients who are subsequently able to undergo interval cytoreduction. This study sought to review our single institution experience with NACT for advanced endometrial cancer.

Methods We conducted a retrospective review of all patients who received NACT for advanced endometrial cancer at two institutions in New York City between 2002 and 2016.

Results We identified 39 patients (median age 61, range 35–89). The histologic subtype distribution was: serous (44%), endometrioid (28%), carcinosarcoma (10%), clear cell (8%), mixed (8%), neuroendocrine (3%). Contraindications to primary surgery included: unresectable disease (72%), poor PS (15%), unresectable disease and poor PS (13%). Twenty-three patients (59%) did not undergo IDS due to: progression of disease (70%), medical ineligibility (4%), unresectable disease (17%), lost to follow-up (4%), death (4%). Sixteen patients (41%) underwent IDS, 81% had an optimal cytoreduction. Disease status at NACT completion was: partial response (56%), stable disease (3%) and progression of disease (41%). There were no complete responses. Patients who responded to NACT had a significantly longer overall survival than those who did not (15 vs. 5 months. $P=0.015$). IDS was also associated with an improvement in overall survival versus no surgery (16 vs. 6 months, $P=0.04$).

Conclusions Unlike ovarian cancer, less than half of the patients undergoing NACT for endometrial cancer underwent IDS, none had a complete response, and 41% had disease progression during NACT. However, endometrial cancer patients who underwent IDS had a high rate of optimal cytoreduction. Both response to NACT and IDS were associated with improved survival.

Keywords Endometrial cancer · Neoadjuvant chemotherapy · Interval debulking

Introduction

Endometrial cancer is the most prevalent gynecologic cancer in the United States, with a lifetime incidence of 2.8% (based on 2012–2014 data [1]). Both the prevalence as well as the mortality from this cancer are thought to be increasing. The mainstay of treatment for advanced endometrial cancer is primary cytoreductive surgery. However, patients who are poor surgical candidates, either due to poor performance status or due to advanced or unresectable disease, are left with few treatment options.

European trials of neoadjuvant chemotherapy prior to debulking surgery in patients with advanced epithelial ovarian cancers have shown comparable overall and progression-free survival compared to primary debulking surgery [2, 3]. The EORTC-GCG/NCIC Clinical Trials Group Study also demonstrated lower rates of surgical morbidity and mortality in patients with bulky FIGO stage IIIc or IV disease who underwent neoadjuvant chemotherapy rather than primary debulking [4]. Because of its histologic resemblance to papillary serous ovarian cancers, including its tendency

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to present in advanced stages, uterine papillary serous carcinomas (UPSCs) have been traditionally treated with chemotherapy, based on data extrapolated from ovarian cancer and retrospective series [5]. Similarly, following the publication of GOG 122 [6], chemotherapy has become the standard of care in the treatment of patients with metastatic endometrioid endometrial cancer. However, the responsiveness to chemotherapy across these distinct cancer types is not the same.

There is a paucity of data in the literature describing the use of neoadjuvant chemotherapy in advanced endometrial cancer, particularly in endometrioid, clear cell and carcinosarcoma subtypes. The existing literature is predominantly relevant to patients with UPSC. In the only prospective study to date looking at neoadjuvant chemotherapy in endometrial cancer, 90% of the patients had serous histology [vii]. Similar to the data in ovarian cancer, high rates of optimal cytoreduction at interval surgery correlate with improved survival, however, the prognosis is poor with a median survival of only 23 months in the cohort of patients who were optimally debulked (92% of patients had no gross residual disease) [7].

Methods

Patients with a pathologic diagnosis of endometrial cancer, who received neoadjuvant chemotherapy at New York University Langone Medical Center and Bellevue Hospital between 2002 and 2016, were identified and their medical records were reviewed.

After IRB approval was obtained, a retrospective chart review was performed using electronic medical record systems. Data collected included baseline characteristics such as age at diagnosis, stage, tumor histologic subtype, medical comorbidities, surgical outcomes, treatment characteristics and oncologic outcomes. Specific outcomes included: response to chemotherapy (based on RECIST 1.1 criteria [8] or GCIG CA125 criteria), disease-free survival, whether or not patients underwent interval debulking surgery, as well as optimal versus suboptimal interval debulking procedure defined by residual disease < 1 cm.

Analysis

Descriptive statistics were used to analyze the data for this cohort. Baseline characteristics such as age were reported using central tendency, i.e., median. Other data were analyzed using percentages as compared to the entire group.

Kaplan–Meier survival curves were calculated for patients based on response to NACT (either partial or complete), as well as whether patients underwent IDS or not. The curves were compared using the Cox proportional hazards model. *P* values less than 0.05% were considered statistically significant.

Results

A total of 39 patients were identified between 2002 and 2016. Baseline characteristics are displayed in Table 1. The cohort had a median age of 61 years (range 35–89 years). The predominant histologic subtype was serous (44%), followed by endometrioid (28%), carcinosarcoma (10%), clear cell (8%), mixed (8%), and neuroendocrine (1%). The majority of tumors were considered Grade III by FIGO criteria (79%). 13% of tumors were FIGO Grade I or II, and 8% were of unknown FIGO grade. Contraindications to primary debulking surgery included: unresectable disease at presentation, 28 (72%); poor PS, 6 (15%); unresectable disease and poor PS, 5 (13%) (Fig. 1).

The majority of patients received a combination of carboplatin/paclitaxel (85%), while a small number of patients received single-agent carboplatin (10%), or paclitaxel (5%).

Four patients (20%) discontinued NACT due to progression of disease. There were no complete responses to NACT, 22 patients (56%) had a partial response (PR), 1 (3%) had stable disease (SD), 16 patients (41%) had progression of disease (PD). Patients who had a partial response to NACT were found to have a survival advantage over those who did not respond to NACT (15 months vs. 5 months, $P = 0.015$), which is demonstrated in Fig. 2.

Table 1 Demographics and baseline characteristics

Age	Median	Range
	61	(35–89)
Histology	N	Percent (%)
Serous	17	44
Endometrioid	11	28
Carcinosarcoma	4	10
Clear cell	3	8
Mixed	3	8
Neuroendocrine	1	3
FIGO grade		
I	2	5
II	3	8
III	31	79
Unknown	3	8
Contraindication to primary surgery		
Unresectable disease	28	72
Poor PS	6	15
Unresectable disease + poor PS	5	13

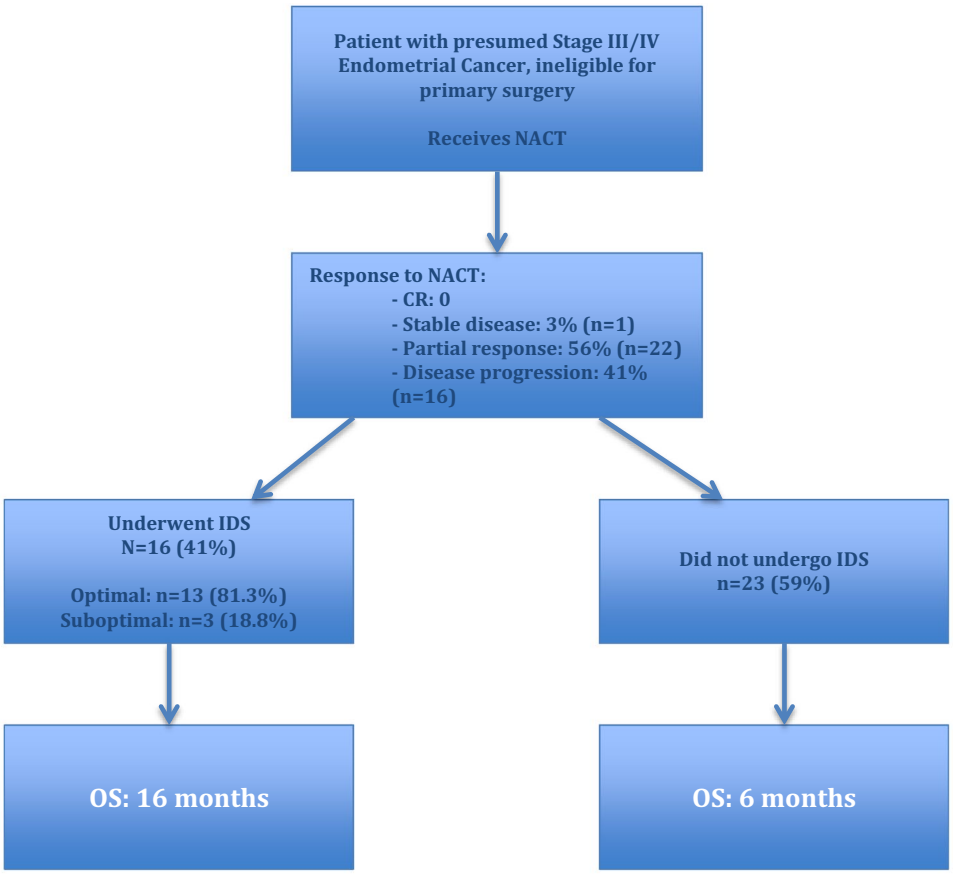

Fig. 1 Study cohort and outcomes

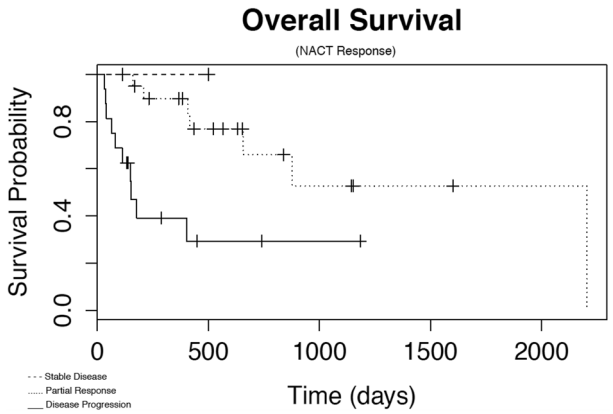

Fig. 2 Overall survival in patients who had a partial response to NACT versus those who did not respond to NACT

Twenty-three patients (59%) were unable to have an interval cytoreductive surgery (Table 2). 70% of these patients were ineligible for IDS due to disease progression, while 17% were lost to follow-up, 4% had persistent unresectable disease after NACT, and the remaining 4% died prior to IDS. Among those who were offered IDS, 81% had an optimal cytoreduction (< 1 cm residual disease). The ability to undergo IDS was associated with a significant improvement in survival compared to patients who did not undergo IDS (16 months vs. 6 months, $P = 0.037$) (Fig. 3).

Discussion

Patients with advanced endometrial cancer who are ineligible for upfront cytoreductive surgery have limited treatment options. For patients who present with unresectable disease, large disease burden and/or poor performance status, upfront surgery is often fraught with unacceptable morbidity and poor outcomes. Neoadjuvant chemotherapy versus best supportive care are both reasonable options in this setting. This treatment strategy of NACT followed by IDS is extrapolated from ovarian cancer data, in which non-inferiority of NACT/IDS compared with primary debulking surgery was established in EORTC-GCG/NCIC-CTG and CHORUS trials [9]. However, data on NACT in advanced endometrial cancer is based on retrospective data and case reports, and there is limited data to inform a preferred approach in this setting, especially in patients with non-UPSC histology.

In a prospective study by Vandenput et al., where 90% of the cohort of 30 patients had UPSC, NACT was associated with decreased hospital stay and operating time[vi]. The data suggests, that similar to the data in ovarian cancer,

Table 2 Demographics of patients who underwent interval cytoreductive surgery

Age	Median	Range
	61	42–78
BMI	Median	Range
	28.9	21.8–49.3
Race/ethnicity	N	Percent
Caucasian	8	50
Hispanic	2	12.5
Black, non-Hispanic	5	31.3
PS		
0	8	50
1	2	43.8
Unknown	6	37.5
Tumor histology		
Serous	7	43.8
Clear cell	1	6.3
Endometrioid	4	15.4
Mixed	1	6.3
Carcinosarcoma	3	18.8
FIGO grade		
1	2	12.5
2	1	6.3
3	13	81.3
Presumed disease stage		
III/IV	15	93.8
I/II	1	6.30

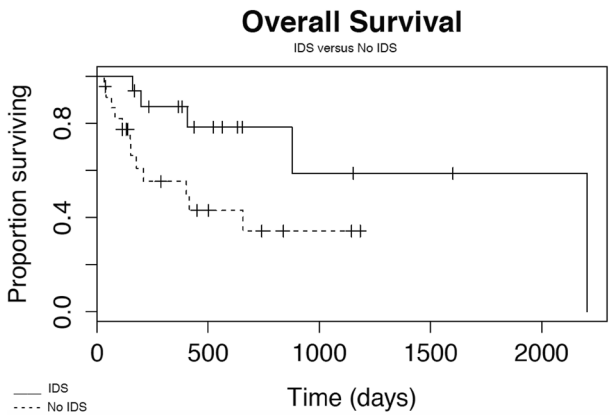

Fig. 3 Overall survival in patients who underwent IDS versus in those who did not undergo IDS

NACT in advanced endometrial cancer may improve the likelihood of an optimal cytoreduction, which correlates with improved survival. It may also allow a greater number of endometrial cancer patients with advanced disease or poor performance status to undergo IDS with lower surgical morbidity and mortality. These data are corroborated by a multi-institution retrospective study by Eto et al. of 426 patients with stage IVb endometrial carcinoma, 125 of whom received NACT. Among those who received NACT, 59 (47%) subsequently underwent surgery. The longest survival observed (21 months) was seen in patients who underwent primary cytoreductive surgery. Patients who underwent NACT followed by interval cytoreduction had a median OS of 12 months, whereas patients who received palliative chemotherapy had a median OS of 1 month, reflecting the distinct patient populations.

Here, we report data from a cohort of endometrial cancer patients who presented with unresectable disease, poor performance status or a combination of the two. Among this cohort, there were no complete responses and 41% of patients progressed during their NACT, the majority of which were comprised of taxanes and platinum therapy. This suggests that the extrapolation of ovarian cancer data to endometrial cancers of mixed histologic subtypes may be imprudent. While taxanes and platinum therapy have been the mainstay of treatment in advanced endometrial cancer, the addition of newer targeted and biologic agents such as bevacizumab and pembrolizumab may be beneficial for some patients [10].

In this cohort, less than half of patients (41%) ultimately underwent IDS. This roughly correlates to the response rate, 41% (0% complete response, 3% stable disease, 41% partial response), which is significantly lower than expected among patients with advanced ovarian cancer. The remainder of patients who did not undergo IDS may also be partially attributable to patients with persistent comorbidities precluding surgical management.

Of the patients who were offered IDS, 81% optimal cytoreduction rate. This strategy was associated with a 10-month survival benefit (16 vs. 6 months). We interpret this data to reflect a selected patient population of chemotherapy responsive patients who have a better prognosis relative to the remainder of the group and NACT has helped us identify and select these patients. The challenge remains, identifying patients and tumors that will respond to chemotherapy and selecting an effective regimen. Notably, 41% of patients had disease progression during the course of their neoadjuvant treatment, suggesting that the selection of NACT was not effective for close to half of this cohort. This is likely due to the heterogeneity of histologic subtypes in this study cohort, which may respond differently to NACT.

Taken together, these results suggest that selection of NACT may require more tailoring in the case of advanced endometrial cancer. Identification of biomarkers, histology, or patient factors predictive of response to chemotherapy would allow stratification of non-responders to other treatments or best supportive care, thus reducing treatment-associated toxicity and improving the quality of life.

Despite this limitation, administration of NACT in patients who cannot undergo PDS is therefore an important strategy in chemotherapy-sensitive patients and improves their survival. Not surprisingly, given the decreased rates of sensitivity to chemotherapy observed in endometrial cancer compared to ovarian cancer, the expected response rates upwards of 70% seen in ovarian cancer were not observed in this cohort. In fact, the complete response (CR) rate was zero in our study.

These data highlight the need for tailored counseling and an adjustment of expectations prior to initiation of treatment in the endometrial cancer population. Despite the lower response rates, however, partial response to NACT was still an important marker of improved prognosis. Armed with the understanding that these patients may have improved overall survival, both physicians and patients may be more willing to risk additional morbidity for that benefit.

A larger prospective study of patients with unresectable endometrial cancer, particularly those with endometrioid and non-UPSC histology, is still needed to better understand these predictive factors and their impact on prognosis.

Compliance with ethical standards

Conflict of interest No funding was received for the execution of this work. None of the authors have any conflict of interest to declare.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study (retrospective chart review), formal consent is not required.

References

1. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J,Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds) SEER Cancer Statistics Review, 1975–2014. National Cancer Institute. Bethesda, MD. https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017
2. Vergote I, De Wever I, Tjalma W, Van Gramberen M, Decloedt J, Van Dam P (1998) Neoadjuvant chemotherapy or primary debulking surgery in advanced ovarian carcinoma: a retrospective analysis of 285 patients. Gynecol Oncol 71:431–436
3. Chambers JT, Chambers SK, Voynick IM, Schwartz PE (1990) Neoadjuvant chemotherapy in stage X ovarian carcinoma. Gynecol Oncol 37:327–331
4. Wright AA et al (2016) Neoadjuvant chemotherapy for newly diagnosed, advanced ovarian cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline. Gynecol Oncol 143(1):3–15
5. Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, Vergote I (2005) Endometrial cancer. Lancet 366:591–605
6. Homesley HD, Filiaci V, Gibbons SK et al (2009) A randomized phase III trial in advanced endometrial carcinoma of surgery and volume directed radiation followed by cisplatin and doxorubicin with or without paclitaxel: a Gynecologic Oncology Group Study. Gynecol Oncol 112(3):543–552
7. Vandenput I, Van Calster B, Capoen A et al (2009) Neoadjuvant chemotherapy followed by interval debulking surgery in patients with serous endometrial cancer with transperitoneal spread (stage IV): a new preferred treatment? Br J Cancer 101(2):244–249
8. Eisenhauer E, Verweji J (2009) Response assessment in solid tumours (RECIST): version 1. 1 and supporting papers. Eur J Cancer 45(2):225–310
9. Kehoe S, Hook J, Nankivell M, Jayson GC, Kitchener H, Lopes T, Luesley D, Perren T, Bannoo S, Mascarenhas M, Dobbs S, Essapen S, Twigg J, Herod J, McCluggage G, Parmar M, Swart AM (2015) Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. Lancet. https://doi.org/10.1016/s0140-6736(14)62223-6
10. Simpkins F, Drake R, Escobar PF, Nutter B, Rasool N, Rose PG (2015) A phase II trial of paclitaxel, carboplatin, and bevacizumab in advanced and recurrent endometrial carcinoma (EMCA). Gynecol Oncol 136(2):240–245. https://doi.org/10.1016/j.ygyno.2014.12.004