Comparison of Chemotherapy vs Chemotherapy Plus Total Hysterectomy for Women With Uterine Cancer With Distant Organ Metastasis

Yuefeng Wang, MD, PhD; Todd Tillmanns, MD; Noam Vander Walde, MD; Bradley Somer, MD; Ari Vander Walde, MD; Lee Schwartzberg, MD; Matthew T. Ballo, MD

Introduction

Uterine cancer is the most common gynecologic cancer, and 9% of patients have metastatic disease at initial presentation.\(^1\) In addition to systemic therapy, total abdominal hysterectomy (TAH) with maximal cytoreduction has been shown to increase survival for patients with abdominal or pelvic metastases.\(^1-3\) However, to our knowledge, the role of TAH for uterine cancer with distant organ metastasis has not been established. In addition, there is growing evidence that definitive local therapies may increase survival for some types of metastatic cancers.\(^4-6\) In this cohort study, we evaluate the overall survival for patients with uterine cancer with distant organ metastasis treated with chemotherapy alone vs chemotherapy plus TAH.

Methods

This study was approved by the West Cancer Center and Research Institute institutional review board. All patient data were deidentified in the National Cancer Database (NCDB) and, therefore, informed consent was not required, in accordance with 45 CFR §46. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

The NCDB was used to identify patients with newly diagnosed uterine cancer with metastasis to the brain, lung, liver, bone, or distant lymph node. All patients received chemotherapy with or without TAH. Patients who received no treatments, definitive pelvic radiotherapy (dose $\geq$45 Gy), or those missing baseline variables were excluded (eFigure in the Supplement). Overall survival was analyzed using the Kaplan-Meier method, log-rank test, Cox proportional hazards models, landmark analysis, and propensity score–matched analyses. In all these analyses, 16 variables were used, including TAH, age, year of diagnosis, race, comorbidity score, grade, clinical T/N stage, facility type, insurance, histology, metastatic site, number of metastatic sites, hormone therapy, urban vs rural residence, education, and annual income. Race and ethnicity were analyzed in this study because they are associated with differences in cancer survival. Race and ethnicity reported in the NCDB were extracted from patients’ medical records. Subgroup survival analyses were done by age, comorbidity score, T/N stage, grade, histology, metastatic site, and number of sites. Statistical significance was calculated with 2-sided $\chi^2$ tests and was defined as $P < .05$. All statistical analyses were done using SAS statistical software version 9.4 (SAS Institute). This study was performed from January to June 2018.

Results

From 2010 to 2014, we identified 3197 patients (mean [SD] age, 61.9 [11.2] years; all women [100%]) with uterine cancer with distant organ metastasis in the NCDB. Most of these patients had lung metastasis (1544 patients), followed by liver metastasis (851 patients), lymph node metastasis (497 patients), bone metastasis (249 patients), and brain metastasis (56 patients). Among these patients, 1809 received chemotherapy alone and 1388 received chemotherapy plus TAH. At a median

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(interquartile range [IQR]) follow-up of 13.4 (1.9-54.9) months, TAH plus chemotherapy was associated with improved survival by both univariable (hazard ratio [HR], 0.57; 95% CI, 0.53-0.62) and multivariable (HR, 0.59; 95% CI, 0.54-0.65) analysis compared with chemotherapy alone (Figure and Table). Propensity score–matched analysis demonstrated superior survival (median [IQR], 19.8 [18.3-22.3] months vs 11.0 [10.0-12.2] months; HR, 0.59; 95% CI, 0.53-0.65) for TAH plus chemotherapy. Sequential landmark analysis demonstrated significant improvement in survival for long-term survivors at greater than or equal to 0.5 year (HR, 0.72; 95% CI, 0.51-1.02) or metastasis to brain (HR, 0.47; 95% CI, 0.07-3.16). Among surgical patients, 79% (1091 of 1388 patients) underwent TAH followed by chemotherapy and had significantly better survival than patients receiving chemotherapy alone (median [IQR] survival, 18.8 [17.0-20.4] months vs 10.3 [9.7-11.2] months) (Table). In the NCDB, we identified 228 patients who received definitive pelvic radiotherapy and 143 patients who underwent TAH and radiotherapy, in

Figure. Overall Survival Among Patients With Distant Metastatic Uterine Cancer Who Received Chemotherapy Alone vs Chemotherapy Plus Total Abdominal Hysterectomy (TAH)

Table. Survival Analysis for All Patients and Propensity Score–Matched Patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients, No.</th>
<th>Survival, median (95% CI), mo</th>
<th>2-y OS, mean (SD), %</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2-y OS, mean (SD), %</td>
<td>HR (95% CI)</td>
<td>P value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy alone</td>
<td>1809</td>
<td>26.8 (1.1)</td>
<td>1 [Reference]</td>
<td>NA</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>TAH plus chemotherapy</td>
<td>1388</td>
<td>44.1 (1.3)</td>
<td>0.57 (0.53-0.62)</td>
<td>&lt;.001</td>
<td>0.59 (0.54-0.65)</td>
</tr>
<tr>
<td>Chemotherapy followed by TAHb</td>
<td>297</td>
<td>52.0 (3.0)</td>
<td>0.47 (0.41-0.55)</td>
<td>&lt;.001</td>
<td>0.47 (0.40-0.55)</td>
</tr>
<tr>
<td>TAH followed by chemotherapyc</td>
<td>1091</td>
<td>41.9 (1.5)</td>
<td>0.61 (0.55-0.66)</td>
<td>&lt;.001</td>
<td>0.64 (0.58-0.70)</td>
</tr>
<tr>
<td>Definitive pelvic RT plus chemotherapy</td>
<td>228</td>
<td>42.9 (3.2)</td>
<td>0.56 (0.47-0.66)</td>
<td>&lt;.001</td>
<td>0.60 (0.51-0.71)</td>
</tr>
<tr>
<td>TAH with RT plus chemotherapy</td>
<td>143</td>
<td>68.0 (3.8)</td>
<td>0.29 (0.22-0.37)</td>
<td>&lt;.001</td>
<td>0.34 (0.26-0.44)</td>
</tr>
</tbody>
</table>

Propensity score–matched patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients, No.</th>
<th>Survival, median (95% CI), mo</th>
<th>2-y OS, mean (SD), %</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2-y OS, mean (SD), %</td>
<td>HR (95% CI)</td>
<td>P value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Chemotherapy alone</td>
<td>1149</td>
<td>27.9 (1.3)</td>
<td>1 [Reference]</td>
<td>NA</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>TAH plus chemotherapy</td>
<td>1149</td>
<td>44.4 (1.6)</td>
<td>0.59 (0.54-0.65)</td>
<td>&lt;.001</td>
<td>0.59 (0.53-0.65)</td>
</tr>
<tr>
<td>Chemotherapy followed by TAHb</td>
<td>254</td>
<td>52.1 (3.3)</td>
<td>0.49 (0.41-0.58)</td>
<td>&lt;.001</td>
<td>0.45 (0.38-0.54)</td>
</tr>
<tr>
<td>TAH followed by chemotherapyc</td>
<td>895</td>
<td>42.2 (1.7)</td>
<td>0.63 (0.57-0.70)</td>
<td>&lt;.001</td>
<td>0.63 (0.57-0.70)</td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; NA, not applicable; OS, overall survival; RT, radiotherapy; TAH, total abdominal hysterectomy.

a Multivariable HRs are adjusted for the same factors analyzed in the primary analysis, as described in the Methods section.

b Sequence of treatments (chemotherapy and TAH) was determined by the number of days from diagnosis to initiation of treatments.

c Propensity analysis was done by 1-to-1-nearest-neighbor matching and the caliper width was 0.05 times the SD of the logit of the propensity score.
addition to chemotherapy (Table). Both groups of patients also had improved survival over chemotherapy alone (HR, 0.60; 95% CI, 0.51-0.71 and HR, 0.34; 95% CI, 0.26-0.44).

Discussion

Palliative TAH was included in the 2021 NCCN guideline for uterine cancer with distant organ metastasis. However, the role of TAH as a definitive treatment approach has not been established. To our knowledge, this analysis represents the largest reported cohort of patients with metastatic uterine cancer treated by local therapies.

To account for potential selection biases between responders and nonresponders (ie, immortal time bias), sequential landmark analysis demonstrated significant improvement in survival for long-term survivors, which suggests that the benefit of TAH in the study is not just associated with bias. In addition, by using the time of treatments initiation, we found that most (79%) surgical patients underwent TAH followed by chemotherapy and had significantly better survival than patients receiving chemotherapy alone, which helped to rule out the selection bias that TAH was only delivered to patients who had good response from neoadjuvant chemotherapy.

The median survival for patients with stage IVB uterine cancer receiving systemic therapy is less than 1 year. In this study, definitive local therapy (TAH) was associated with significantly improved survival compared with chemotherapy alone. We identified patients who received definitive pelvic radiotherapy and patients who underwent TAH and radiotherapy, in addition to chemotherapy, and both groups of patients also had improved survival over chemotherapy alone, which supports that definitive local therapies may benefit distant metastatic uterine cancer.

This study has several limitations. The information for number of metastatic lesions, specific chemotherapy agents, salvage therapies, performance status, and disease-specific survival is not available in the NCDB. Despite these limitations, the results in this analysis are intriguing.

In this cohort study, patients with newly diagnosed uterine cancer with distant organ metastasis receiving TAH plus chemotherapy lived substantially longer than patients receiving chemotherapy alone. Randomized clinical trials to evaluate the effect of TAH on distant metastatic uterine cancer appear to be warranted.

ARTICLE INFORMATION

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Author Contributions: Dr Wang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Wang, Tillmanns, A. VanderWalde, Ballo.

Acquisition, analysis, or interpretation of data: Wang, N. VanderWalde, Somer, Schwartzberg.

Drafting of the manuscript: Wang, Tillmanns, Ballo.

Critical revision of the manuscript for important intellectual content: Wang, N. VanderWalde, Somer, A. VanderWalde, Schwartzberg.

Statistical analysis: Wang.
Administrative, technical, or material support: Wang, A. VanderWalde.

Supervision: Tillmanns, N. VanderWalde, A. VanderWalde, Schwartzberg, Ballo.

Conflict of Interest Disclosures: Dr Tillmanns reported serving on the speaker bureau for Astra Zeneca and on the advisory board for EISAI during the conduct of the study. Dr A. VanderWalde reported serving as the Medical Director for Precision Oncology; serving as a consultant for Bristol-Myers Squibb, AstraZeneca, Caris Life Sciences Consulting, George Clinical Consulting, Compugen, Concerto Health, and Immunocore; and receiving research funding from Amgen and OneOncology. Dr Ballo reported serving as a consultant for Novocure. No other disclosures were reported.

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REFERENCES

SUPPLEMENT.

eFigure. CONSORT Diagram