

HJOG 2022, 21 (4), 167-172 | DOI: 10.33574/HJOG.0515

# Laparoscopic surgery for clear cell endometrial carcinoma, is it a realistic approach?

Eleftherios Zachariou<sup>1</sup>, Vasilios Pergialiotis<sup>1</sup>, Evangelos Iliopoulos<sup>2</sup>, Dimitrios Haidopoulos<sup>1</sup>

<sup>1</sup>1<sup>st</sup> Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Alexandra Hospital, National and Kapodistrian University of Athens, Greece,

<sup>2</sup>General Maternal Hospital of Athens "Elena Venizelou", Athens, Greece

## Corresponding Author

Eleftherios Zachariou, 1<sup>st</sup> Department of Obstetrics and Gynecology, National and Kapodistrian University of Athens, Greece, e-mail: elefthzach@hotmail.com

## Abstract

Clear cell endometrial carcinoma is an aggressive form of endometrial cancer that has a poor prognosis for survival. Over the past ten years, laparoscopic surgery has replaced open surgery as the preferred method of treating early-stage endometrial cancer. However, its effect on the prognosis of patients with clear cell carcinoma is still unclear. In the current systematic review, we examined the information that was published in the following databases: Medline, Scopus, Clinicaltrials.gov, EMBASE, Cochrane Central Register of Controlled Trials, CENTRAL, and Google Scholar. Three studies were found to be significantly diverse; as a result, meta-analysis was not possible. Current research reveals that compared to traditional laparotomy, minimally invasive surgery does not significantly influence progression-free and overall survival rates; nevertheless, given the relative dearth of data, more research is required before the technique's safety can be determined.

**Key words:** Clear cell, endometrial cancer, laparoscopy, minimally invasive surgery

## Introduction

Endometrial cancer accounts for about 10.7% of malignancies in women in developed countries, with about 290,000 new cases and 750,000 deaths per year. The incidence of endometrial cancer has increased rapidly in recent years, and the 5-year average survival rate is about 81% in the United States of America and 80% in China.<sup>1</sup>

In 1983, Bokhman reported the hypothesis of

the existence of two different forms of endometrial cancer with different risk factors and prognosis. Morphologically, its classified into 2 main types. Type I, or endometrioid carcinoma, which is estrogen dependent and the most common (70-80%) and type II which is estrogen-independent. Type II is characterized by a worse prognosis as it occurs at a higher degree of differentiation, tends to infiltrate the myometrium at a higher frequency as well as

metastasizes and recurs. Typically type II is found in 38% in stage III or IV in FIGO with 5-year survival rate around 18-27%.

These high-risk histologic endometrioid carcinomas represent the 15-20% and more specifically include poorly differentiated endometrial carcinoma (PDEC),<sup>2</sup> uterine clear cell carcinoma (UCCC), uterine carcinosarcoma (UCS),<sup>5</sup> and uterine papillary serous carcinomas (UPCS). These types account for more than 50% of endometrial cancer mortality.<sup>3-5</sup>

Clear Cell Carcinoma (CCC) of the endometrium is an estrogen-independent type II endometrial cancer which accounts for <5% of endometrial cancer.<sup>6</sup> It was first described in 1967. Microscopically it is described as clear hobnail cells that appear clear because of glycogen. Biologically, CCCs have an increased propensity for lymphovascular invasion and intraperitoneal spread. It is estimated that roughly 45% on initial presentation of CCC have extrauterine metastases. Overall 5-year survival is 42-62% in the advanced stage compared to 68.8% when combining all uterine carcinoma regionally advanced.<sup>7</sup> The risk factors for CCC have not been validated. Some studies have shown higher incidence of CCC with age, obesity, hyperinsulinemia, African American race, and in nulliparous women.<sup>8,9</sup>

The above reasons, logically, create the need to improve survival rates as the high malignancy histological types have poor prognosis, high rates of metastases and are diagnosed at a high stage.<sup>10</sup> Although most studies have not observed any significant difference in complications and survival between open and minimally invasive surgery<sup>11</sup> in endometrial cancer, only a few studies have been conducted to study the surgical approach in high-risk endometrial cancer types due to the rarity of the disease.

To date, aggressive forms of cancer are rarely treated with laparoscopy. An exception to this obser-

vation is early stage type II endometrial carcinoma. Consensus regarding the prognostic effect of minimally invasive surgery in terms of disease free and overall survival has not been reached as the evidence in the literature remains scarce. In the present study we sought to gather the available data from the international literature in order to help evaluate the actual efficacy and safety of the procedure.

## Methods

### Study design

The present systematic review was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.<sup>12</sup> The study was based in aggregated data that have been already published in the international literature. Patient consent and institutional review board approval were not retrieved as they are not required in this type of studies.

### Types of studies and patients

Eligibility criteria for the inclusion of studies were predetermined. Randomized trials and observational studies (prospective and retrospective) that evaluated the presence of perineural invasion among patients that were surgical treated for cervical cancer were included in the present study. Studies that evaluated differences in survival rates of patients with clear cell endometrial carcinoma that were treated with minimally invasive surgery or laparotomy were considered eligible for inclusion. Studies were included irrespective of the stage of disease at initial diagnosis. Sub-analysis was initially designed in case of significant differences among studies in terms of the aforementioned variables.

### Information sources and search methods

Two authors (E.L. and M.N.) searched Medline (1966-2022), Scopus (2004-2022), Clinicaltrials.

gov (2008–2022), EMBASE (1980–2022), Cochrane Central Register of Controlled Trials CENTRAL (1999–2022) and Google Scholar (2004–2022) along with the reference lists of electronically retrieved full-text papers. The date of the last search was set at April 30<sup>th</sup>, 2022. The Rayyan web app was used for the screening process.<sup>13</sup> The search strategy included the text words “endometrial cancer; clear cell carcinoma; overall survival, progression free survival”.

Studies were selected in three consecutive stages. Following deduplication, the titles and abstracts of all electronic articles were independently screened by two authors (E.Z and V.P.) to assess their eligibility. The decision for inclusion of studies in the present meta-analysis was taken after retrieving and reviewing the full version of articles that were considered potentially eligible. Discrepancies that arose in this latter stage were resolved by consensus from all authors.

### **Predefined outcomes**

Outcome measures were predefined during the design of the present systematic review. Data extraction was performed using a modified data form that was based in Cochrane’s data collection form for intervention reviews for RCTs and non-RCTs.<sup>14</sup>

Differences in progression free and overall survival rates among women that were operated with minimally invasive surgery and those that were operated with traditional laparotomy were predefined as the outcomes of interest.

### **Assessment of risk of bias and quality of evidence**

The methodological quality of included randomized controlled trials was initially designed to be assessed by two independent reviewers (V.P. and N.T.) using the risk of bias 2 (RoB 2) tool. The qual-

ity of observational studies was evaluated with the Newcastle-Ottawa Scale (NOS), which evaluates the selection of the study groups, the comparability of the groups and the ascertainment of the exposure or outcome of interest.<sup>15</sup>

### **Results**

Overall, 3 studies were identified that reported survival outcomes of patients with type II (high grade) endometrial carcinoma subtypes.<sup>16–18</sup> One of those was specifically focused on survival rates of CC endometrial carcinoma patients.<sup>17</sup> The methodological quality of included studies was evaluated as high following estimation of the potential risk of bias with the Newcastle Ottawa tool.

Hu et al reviewed the largest series published to date that comprised 273 patients with a median follow up of 31 months and observed that the 3-year progression free survival rate did not differ among the two groups (HR, 1.06; 95% CI, 0.72–1.58;  $p=0.758$ ).<sup>17</sup> Similarly, overall survival rates were comparable among the two groups (HR, 1.06; 95% CI, 0.65–1.72;  $p=0.823$ ). Following subgroup analysis of patients with early-stage CC carcinoma the route of surgery also did not affect the outcome of surgery (aHR, 1.29; 95% CI, 0.78–2.12;  $p=0.321$  for overall survival and aHR, 1.11; 95% CI, 0.73–1.68;  $p=0.621$  for DFS).

Fader et al evaluated patients with high-risk endometrial carcinomas and observed that patients with clear cell histology had a significant progression-free and overall survival benefit compared to patients with serous carcinoma and carcinosarcoma; however, they did not subgroup patients according to the route of surgery.<sup>16</sup>

Lastly, Han et al evaluated the impact of surgical approach on survival outcomes of high-risk endometrial carcinomas and observed that the laparoscopic route significantly decreased survival rates

of patients with type II endometrial carcinoma.<sup>18</sup> However, subgroup analysis according to the type of cancer did not significantly affected survival outcomes; although uterine clear cell carcinoma was associated with shorter survival rates compared to poorly differentiated adenocarcinoma in the whole series.

### Discussion

In the present systematic review, we observed that the available evidence concerning the impact of minimally invasive surgery on survival rates of patients with clear cell endometrial carcinoma is extremely limited and definitive data cannot be extracted as the series reported are particularly heterogeneous.

Traditionally clear cell carcinoma has been considered as an aggressive type of endometrial cancer; however, among type II endometrial carcinomas it is considered as less aggressive compared to carcinosarcoma and undifferentiated sarcoma. Stage seems to be the most important factor that affects survival rates<sup>19</sup> followed by age and extent of myometrial invasion<sup>7</sup> although other co-factors such as Ki-67 index and P53 expression have been also proposed as potential predictors of survival.<sup>20</sup>

Questioning of the actual benefit of minimally invasive surgery has started the last 2 years,<sup>21</sup> following the negative results of the LACC trial in cervical cancer.<sup>22</sup> A retrospective series that was based on 179 intermediate risk endometrial cancer patients suggested that progression free survival might be affected by the use of the robotic approach, compared to standard laparotomy (5-year disease free survival 91.8% vs 100%,  $p=.005$ ).<sup>23</sup> Taking this information into consideration one could assume that the the impact of minimally invasive surgery on aggressive subtypes of endometrial cancer could be detrimental.

### Implications for current clinical practice and future research

The findings of this review suggest that minimally invasive surgery may not affect survival rates of clear cell endometrial cancer patients; however, they cannot be considered definitive due to the paucity of evidence. Until further research becomes available, physicians should be cautious when retrieving patient consent and inform about the lack of substantial research in this field. Further studies are needed to clarify the impact of laparoscopy on patient survival when addressing clear cell endometrial carcinoma and subgroup analysis is essential to clarify whether patients with early-stage disease may benefit, or at least not be harmed, from the use of minimally invasive surgery.

### Disclosure

The authors report no conflict of interest.

### Funding

None to disclose for all authors.

### References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019 Jan;69(1):7-34.
2. Voss MA, Ganesan R, Ludeman L, McCarthy K, Gornall R, Schaller G, et al. Should grade 3 endometrioid endometrial carcinoma be considered a type 2 cancer-a clinical and pathological evaluation. *Gynecol Oncol*. 2012 Jan;124(1):15-20.
3. Vogel TJ, Knickerbocker A, Shah CA, Schiff MA, Isaacson C, Garcia RL, et al. An analysis of current treatment practice in uterine papillary serous and clear cell carcinoma at two high volume cancer centers. *J Gynecol Oncol*. 2015 Jan;26(1):25-31.
4. Versluis MA, de Jong RA, Plat A, Bosse T, Smit VT, Mackay H, et al. Prediction model for regional or distant recurrence in endometrial cancer based

- on classical pathological and immunological parameters. *Br J Cancer*. 2015 Sep 1;113(5):786-93.
5. Ji Q, Wang X, Jiang J, Chen L. Sentinel lymph node mapping in high-risk endometrial cancer: a systematic review and meta-analysis. *Gland Surg*. 2020 Dec;9(6):2091-105.
6. Monterossi G, Ghezzi F, Vizza E, Zannoni GF, Uccella S, Corrado G, et al. Minimally Invasive Approach in Type II Endometrial Cancer: Is It Wise and Safe? *J Minim Invasive Gynecol*. 2017 Mar-Apr;24(3):438-45.
7. Abdulfatah E, Sakr S, Thomas S, Al-Wahab Z, Mutch DG, Dowdy S, et al. Clear Cell Carcinoma of the Endometrium: Evaluation of Prognostic Parameters in a Multi-institutional Cohort of 165 Cases. *Int J Gynecol Cancer*. 2017 Oct;27(8):1714-21.
8. Setiawan VW, Yang HP, Pike MC, McCann SE, Yu H, Xiang YB, et al. Type I and II endometrial cancers: have they different risk factors? *J Clin Oncol*. 2013 Jul 10;31(20):2607-18.
9. Matthews RP, Hutchinson-Colas J, Maiman M, Fruchter RG, Gates EJ, Gibbon D, et al. Papillary serous and clear cell type lead to poor prognosis of endometrial carcinoma in black women. *Gynecol Oncol*. 1997 May;65(2):206-12.
10. de Boer SM, Powell ME, Mileschkin L, Katsaros D, Bessette P, Haie-Meder C, et al. 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*. 2018 Mar;19(3):295-309.
11. Bregar AJ, Melamed A, Diver E, Clemmer JT, Uppal S, Schorge JO, et al. Minimally Invasive Staging Surgery in Women with Early-Stage Endometrial Cancer: Analysis of the National Cancer Data Base. *Ann Surg Oncol*. 2017 Jun;24(6):1677-87.
12. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*. 2009 Oct;62(10):e1-34.
13. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev*. 2016 Dec 5;5(1):210.
14. Palas D, Ehlinger V, Alberge C, Truffert P, Kayem G, Goffinet F, et al. Efficacy of antenatal corticosteroids in preterm twins: the EPIPAGE-2 cohort study. *BJOG*. 2018 Aug;125(9):1164-70.
15. Wells GA, Wells G, Shea B, Shea B, O'Connell D, Peterson J, et al. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses. 2014; 2014.
16. Fader AN, Java J, Tenney M, Ricci S, Gunderson CC, Temkin SM, et al. Impact of histology and surgical approach on survival among women with early-stage, high-grade uterine cancer: An NRG Oncology/Gynecologic Oncology Group ancillary analysis. *Gynecologic oncology*. 2016;143(3):460-5.
17. Hu C, Mao X-G, Xu Y, Xu H, Liu Y. Oncological safety of laparoscopic surgery for women with apparent early-stage uterine clear cell carcinoma: a multicenter retrospective cohort study. *Journal of Minimally Invasive Gynecology*. 2022 2022/04/30/.
18. Han Z, Zheng Z, Tao K, Yu Y, Wu J, Tian X. The effect of surgical approach on the outcomes and prognosis of high-risk histologic endometrioid carcinomas. *Gland Surg*. 2021 Jan;10(1):355-63.
19. Loizzi V, Cicinelli E, Lepera A, Legge F, Memmola M, Chiarello G, et al. Prognostic factors in clear cell carcinoma of endometrium: analysis of 55 cases. *Acta Biomed*. 2022 Jan 19;92(6):e2021362.
20. Zhang Z, Gao P, Bao Z, Zeng L, Yao J, Chai D, et al. Clear Cell Carcinoma of the Endometrium: Evaluation of Prognostic Parameters in 27 Cases. *Frontiers in Oncology*. 2021 2021-December-02;11.
21. Leitao Jr MM. The aftershocks of the LACC earthquake.

- quake have begun: brace yourselves. International Journal of Gynecologic Cancer. 2020: ijgc-2019-001142.
22. Ramirez PT, Frumovitz M, Pareja R, Lopez A, Vieira M, Ribeiro R, et al. Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer. N Engl J Med. 2018 Nov 15;379(20):1895-904.
23. Song J, Le T, Hopkins L, Fung-Kee-Fung M, Lupe K, Gaudet M, et al. A comparison of disease recurrence between robotic versus laparotomy approach in patients with intermediate-risk endometrial cancer. International Journal of Gynecologic Cancer. 2020;30(2):160-6.
- Received 06-11-22*  
*Revised 23-11-22*  
*Accepted 03-12-22*