REDELVE INTERNATIONAL PUBLICATIONS

Advances in Obstetrics and Gynaecology
Volume 2019, Issue 01
Review Article: RD-OBG-10003

Endometrioid Uterine Cancer Apparently Confined to the Corpus. A Review Suggesting Overtreatment

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Citation: *Jonathan C (2019)* Endometrioid uterine cancer apparently confined to the corpus. A review suggesting overtreatment. *Advances in obstetrics and Gynaecology | ReDelve: RD-OBG-10003.*

Received Date: *17 April 2019;* ***Acceptance Date:*** *23 April 2019;* ***Published Date:*** *01 May 2019*

Abstract

Uterine cancer in most countries is the most prevalent of the gynaecological cancers with predictions that the number of deaths from this disease will shortly surpass that of ovarian cancer. The majority of patients will have disease localised to the uterus and a lesser proportion with microscopic regional nodal spread. Overall survival is high at 81% and for those with disease confined to the uterus is extraordinarily high at 95% and even those with regional spread their survival remains very high at 70%. This review was undertaken to review the relevant high level evidence pertaining to uterine endometrioid endometrial cancer (Type 1 cancers), apparently confined to the uterine corpus.

Uterine cancer encompasses a variety of low risk (Type 1) and high risk (Type 2) histologies with different biologies, response to treatment and outcomes. The most common type is the endometroid variety (Type 1). The vast majority of published studies on uterine cancer includes all histologies (Types) which in hindsight has likely skewed and biased published results. The majority of endometrioid cancers present with disease strictly or apparently confined to the uterus. Assignment of "risk" to patients, may help clinicians better plan post-surgery treatment options. The definition of risk however varies considerably around the world. The surgical management of endometrioid uterine cancer is the removal of the uterus and attached adnexa. There is no evidence to support a survival advantage when surgery is undertaken by a subspecialist gynaecological oncologist compared to general gynaecologist. The role of surgical staging (primarily lymph node sampling) is debated with the literature indicating increased morbidity, and not supporting a survival advantage. Radiation therapy (either vaginal brachy therapy or external beam) has been recommended as adjuvant therapy and has been shown to provide improved local control but no survival impact and at the cost of additional toxicity. The role for adjuvant chemotherapy in high risk patients remains unclear.

Introduction

Uterine cancer in most countries is the most prevalent of the gynaecological cancers with predictions that the number of deaths from this disease will shortly surpass that of ovarian cancer. Despite uterine endometrioid cancer being the most common of all the gynaecologic malignancies, and not withstanding a plethora of published clinical trials, there remains

significant and diverse management views, not only locally within Units, but also nationally and internationally [1,2].

It is axiomatic that not all cancers are the same, with different biologizes, treatments and prognoses. Likewise not all uterine endometrial cancers are the same with very different biologies, spread patterns, response to treatment and outcome of the more common Type 1 endometrioid histological subtype compared to the poorer prognosis of the Type 2 uterine cancers, namely Uterine Papillary Serous Carcinoma (UPSC) Clear Cell Carcinoma (CCC), undifferentiated and carcinosarcoma [3,4]. Despite an inordinate volume of published research in uterine cancer, much of it is skewed and biased due to the combination of both risk types (all histologies), in particular the less favourable Type 2 cancers, trials and publications. In retrospect, combining all uterine cancer histological types has resulted in in significant bias when one attempts to ascertain the effects of treatments of the more common Type 1 endometrioid uterine cancer apparently confined to the uterus.

With the publication of the now renowned Laparoscopic Approach to Cervical Cancer (LACC) Trial [4], clinicians and scientists have been forced to review their practice, not just on cervical cancer but indeed in other tumour sites to confirm the strength of evidence supporting current clinical practice.

This review was undertaken to review the relevant high level evidence pertaining to uterine endometrioid endometrial cancer(Type 1 cancers), apparently confined to the uterine corpus. The aim was to assess the role of surgery and the benefit or lack there-of, of adjuvant radiation or chemotherapy.

Materials and Methods

Two major medical electronic databases, MEDLINE-PubMed and Scopus, were searched for high level articles of patients with uterine cancer. Various combinations of the following key words were used to identify publications: cancer, uterine, endometrial, endometrioid, Type 1, Type 2, clear cell, uterine papillary serous cancer, carcinosarcoma, surgery, radiation and chemotherapy.

The inclusion criteria for citation selection were: peer reviewed English-language journals, articles published in the last 40 years, studies needed to be of a prospective nature or large national database review of cancer of the uterine corpus of endometrioid histology (Type 1 cancers) with disease confined to the uterus. The exclusion criteria were: non-English-language full text or studies that contained high risk or Type 2 histology, retrospective in nature.

Thus a number of well-known often quoted publications were excluded due to a combination of the factors noted above (Table 1).

Stage at Presentation

The vast majority (85%) of patients with endometrioid uterine cancer will present with disease confined to the uterus whilst a small proportion (10-15%) will have spread to the regional nodes with approximately half of these having microscopic disease only (i.e. disease apparently confined to the uterus). Thus, more than 90% of patients with endometrioid uterine cancer will have disease strictly or apparently confined to the uterus.

Whilst the overall relative 5-year survival for all patients is high at 81%, for those with disease confined to the uterus, the 5-year survival is an extraordinarily high at 95% and is still very high at 70% with regional nodal spread [1,2].

As the survival of patients with endometroid uterine cancer confined to the uterus is so high [1,2], very large numbers of patients are required in randomised studies to show a difference in treatment outcomes when disease is apparently confined to the corpus. A large number of well of published and often quoted studies are flawed due to this one minor but significant point as patient numbers in trials are boosted by the inclusion of high risk Type 2 histologies where recurrences are lower and survival rates are higher compared to the Type 1 endometrioid cancers (Table 1) [3].

Publication	Reason
PORTEC 3(40)	Includes UPSC & CCC
GOG 258(41)	Extrauterine disease and includes UPSC & CCC
GOG 249(42)	Includes UPSC & CCC
GOG 122(43)	Includes UPSC & CCC, stage III and IV, bulky residual disease
SEPAL (44)	Stage III & IV; Retrospective
NSGO-9501/EORTC 55991(45)	Includes UPSC and CCC
Kuoppala (46)	Includes UPSC and CCC
Humber (2007); Vale (2012) (47, 48)	Advanced, recurrent, metastatic disease
Morrow (1990) (7)	All histologies, adnexal metastases
LAP2(17, 49)	Includes anaplastic, CCC, mixed epithelial, serous carcinomas and sarcoma. Also includes Stage III & IV disease
FIRES (26)	Includes all histologies and Stage III and IV disease

Table 1: Publications excluded from inclusion in review.

Risk Assignment

Risk is assigned to patients with uterine cancer to attempt to quantify either their Low Risk (LR) or High Risk (HR) of Lymph Node Metastases (LNM), and/or recurrence, and/or need for adjuvant treatment and/or risk of death.

Risk assignment can be based on either (i) local hostile uterine factors at hysterectomy such as high grade, deep myoinvasion, lymph vascular space invasion (ii) based upon preoperative imaging indicating nodal, regional or distant spread or (iii) based upon findings derived from formal surgical staging, usually lymph node positivity. The definition of risk varies considerably throughout the world with no clearly agreed upon consensus (Tables 2-4).

Publication	Definition
Norwegian (Aalders 1980) (5)	Grade 1, 2
	Grade 3 with < 50% myoinvasion
United States of America (Creasman; GOG 33) (6, 7)	Grade1, no myoinvasion, no intraperitoneal spread
Sweden (22)	Stage IA-IB
	Grade 1-2

Table 2: Low risk.

The binary risk classification system of LR and HR tumours was originally and largely based

upon the Randomized Controlled Trial (RCT) from the Norwegian Radium Institute where investigators were able to define a group of patients at higher risk of recurrence (i.e.deeply invasive and, high grade tumours) compared to the general cohort, and were able to show that this higher risk group might benefit from adjuvant radiation therapy [6].

Publication	Definition
PORTEC 1(23, 24)	Stage I, grade 1 with >50% invasion
	Grade 2 with any invasion
	Grade 3 with <50% invasion
	Assumption that endometrial cancer does not include UPSC or CCC. Not clear in manuscript
PORTEC 2(43, 44)	HIR defined as either (1) FIGO 1988 stage 1C (≥50% myometrial invasion) with age greater than 60 and grade 1 or 2; or (2) FIGO 1988 stage 1B (<50% myometrial invasion) with age greater than 60 and grade 3; or (3) FIGO 1988 stage 2A (endocervical glandular involvement, which is stage I in FIGO 2009) with any age, except for grade 3 with deep invasion.
GOG 99(29)	Defined IR as patients with any grade and any myo-invasion (node negative) (Keys 2004)
	Stage IB, IC, II (occult)
GOG 33(6, 7)	Grade 2-3; Inner mid invasion
Italian (19)	All stage I (except elderly & Gr1 <50% invasion)
Creutzberg (23, 24)	Grade 1, >50% invasion; Grade 2, any invasion or Grade 3, <50% invasion
ASTEC (45)	Stage IA and IB grade 3; IC all grades; papillary serous; or clear cell histology all stages and grades
Sweden (25)	Stage I; EAC; One of following: Grade 3, >50% MI, DNA aneuploidy, nuclear grade 1 & 2; negative nodes; negative cytology

Table 3: Intermediate Risk.

The Gynecologic Oncology Group (GOG) using surgical-pathological data derived from the study (GOG33) also defined risk groups, although somewhat different to that of the Norwegian classification, and in addition included an Intermediate Risk (IR) category [7].

Despite the GOG data being widely utilised, there are many concerns related to the conduct of this study and the strength of the data, and its relevance today. Recruitment commenced some 35 years ago, with little or no preoperative imaging. At surgical staging 22% of patients had disease outside the uterus. Furthermore the study included both Type 1 and Type 2 uterine cancers. Based upon this dubious data set, patients were classified for risk of nodal metastases into “low”, “high” and “intermediate” risk. Despite the inherent limitations of the study, the majority of subsequent GOG studies, indeed many gynaecologic oncologists world-wide have used this data and classification of risk seemingly unaware of the significant limitations noted above [8]. One could argue based upon the significant limitations of GOG33 that all GOG studies using this risk classification, be reviewed and re-evaluated.

GOG99 an RCT of External Beam Radiation Therapy (EBRT) in intermediate risk stage 1 and

2 corpus cancer patients used the original definition of risk defined by GOG33 (although Type 2 cancers were excluded). During conduct of the trial, it became apparent that the defined target population was at a lower risk of recurrence than previously determined and expected and the definition of risk in this trial was modified mid-trial accordingly. and thus, further classified IR patients into Low Intermediate Risk (LIR) and High Intermediate Risk (HIR). Despite this sub-classification of IR, in a practical sense gynaecological oncologists in the United States are electing to ignore the HIR classification and observing these patients as if they were LR, rather than offer them adjuvant treatment [9].

Publication	Definition
Norwegian (Aalders 1980) (5)	Grade 3 with > 50% myoinvasion
United States of America (Creasman; GOG 33(6)) (7)	Intraperitoneal disease
	Deep myoinvasion
United States of America (GOG 249) (36)	Stage I-IIA with HIR factors
	Age $\geq$ 70 with one risk factor
	Age $\geq$ 50 with 2 risk factors
	Age $\geq$ 18 with 3 risk factors
	Stage IIB occult
	Stage I-IIB (occult) with serous or CCC
	Risk Factors: G2 or 3; LVSI, outer 1/3 invasion
PORTEC 3(34)	Stage IAG3 endometrioid with LVSI
	Stage IBG3 endometrioid
	Stage II
	Stage IIIA, IIIB or IIIC
	Stage IA with invasion, IB, II or III serous or clear cell
Finland (Kuoppala) (30)	Stage IAG3
	Stage IBG3
	Stage IC-IIA Grade 1-3
EORTC/NSGO (39)	Surgical Stage I, II, IIIA (positive cytology only), IIIC (positive pelvic nodes only
	Serous or clear cell eligible
SEPAL (38)	Stage III and IV
Creutzberg (2004) (3)	Stage IC, grade 3
Maggi (2006) (31)	Stage IcG3, IIG3 with myometrial invasion >50%, & stage III

Table 4: High Risk.

Due to the complexity and reproducibility of the IR, LIR, HIR classification systems, perhaps it is time to revert to the a-for-mentioned binary system of LR and HR rather than the complicated IR, LIR, HIR classification.

Surgery

The treatment of uterine cancer is the safe removal of the uterus, with minimal or no complications, without ongoing morbidity and good oncological outcomes. The achievement

of these goals is dependent upon several factors including experience of the surgeon, size of the uterus, patient related factors including obesity, cost and surgical waiting times. Initially abdominal hysterectomy but more recently a minimally invasive approach has become common (either standard laparoscopy or robotic). A limited number of prospective randomised studies attest to the feasibility, quality of life advantage, and oncological outcomes of such approaches in endometrioid cancer apparently confined to the uterine corpus [10-13].

A Dutch study confirmed benefits of Minimally Invasive Surgery (MIS) over open surgery, including less analgesia, shorter Length of Stay (LOS), earlier return to work, but with a longer operating time, similar complications but no overall difference in Quality of Life (QoL) [10].

The Australian Laparoscopic Approach to Carcinoma of the Endometrium (LACE) study, of which there have been a few publications has confirmed QoL, safety and outcomes of a MIS approach over laparotomy. Limitations of the study however, include variability in surgical staging between the MIS and open groups with similar intraoperative complications and fewer post op complications in the MIS group, shorter LOS with similar oncological outcomes. In comparison to all other studies, QoL was not measured between groups, rather compared to baseline scores. Whilst both MIS and laparotomy QoL scores were better than baseline, MIS had a greater improvement compared to baseline than laparotomy [11-13].

Two large meta-analyses of approximately 4000 patients each has shown that a MIS approach whilst resulting in more intraoperative complications, has fewer postoperative complications, longer operating time, lower blood loss, shorter LOS and similar oncological outcomes [14]. The Cochrane metanalysis has shown that MIS resulted in reduced operative morbidity, reduced blood loss and LOS, but no difference in severe postoperative morbidity, QoL and with similar oncological outcomes [15]. It needs to be remembered that the above 2 reviews are heavily influenced by the large American study comparing Laparoscopy With Laparotomy for Comprehensive Surgical Staging of Uterine Cancer (LAP2) study. Over half the patients in the reviews were from the LAP2 study**,** where patients with Type 2, high risk histologies were included and where disease was not apparently confined to the uterus [16,17].

Formal subspecialisation in Gynaecological Oncology commenced in the 1960's in the United States and thereafter around the globe. The impact of a Multidisciplinary Team (MDT) approach to management, enhanced surgical skills of gynaecological oncologists in performing lymph node dissection and cytoreductive surgery has had a significant impact on the outcome of patients with gynaecological cancer. However the data pertaining to the effect of subspecialisation on performing either an open or laparoscopic hysterectomy when compared to a general gynaecologist in endometrioid cancer apparently confined to the corpus is limited. Inferential data from the Dutch RCT indicates no difference in outcome [10].

In comparing traditional laparoscopy with robotic MIS, a metanalysis of 22 studies that included 4420 patients essentially confirmed equivalence between the 2 methods. Cost however was not included in this metanalysis [18].

In summary hysterectomy and bilateral salpingo-oophorectomy remains the cornerstone of treatment for apparent early endometrioid uterine cancer. There are pros and cons regarding the appropriate approach, needless to say in many countries the horse has bolted and MIS is the preferred option. There is no evidence to support a survival advantage as to whether a general gynaecologist or certified gynaecologic oncologist performs the hysterectomy in endometrioid carcinoma apparently confined to the uterine corpus.

Lymph Node Assessment

In its purest form, the treatment of any apparent early malignancy is to surgically remove the primary tumour. In cancer of the uterine corpus this involves a hysterectomy. Surgical staging involving Lymph Node Dissection (LND), peritoneal washings and omentectomy/biopsy has been advocated to "define the extent of disease" to better define treatment options and prognosis [19].

With enhanced preoperative imaging, patients with gross extrauterine spread can be largely identified (enlarged pelvic nodes, omental nodularity, peritoneal thickening) and form a high risk group of patients that should be considered in the surgical management of cancer "apparently confined" to the uterus. Greater than 90% of patients with endometrioid uterine cancer fall into this latter group of disease apparently confined to the corpus [1,2].

The role of LND remains controversial with no consistent evidence of a survival advantage for the procedure. There is clear evidence that operative morbidity is increased however. Mayo clinic data has shown that there is no survival advantage in performing a lymph node dissection in low risk patients [21]. Similarly the British ASTEC RCT and Italian RCT both in intermediate and high risk patients showed no survival benefit but with increased morbidity. The ASTEC group went on to conclude that "pelvic lymphadenectomy cannot be recommended as routine procedure for therapeutic purposes outside of clinical trials" [22,23]. A review of the Australian National Endometrial Cancer Study database in intermediate and high risk patients also showed no survival effect of LND but with greatly increased morbidity [13].

A recently published Cochrane review found no evidence that lymphadenectomy decreases risk of death or recurrence compared with no lymphadenectomy in women with presumed stage I disease, and is at the expense of increased surgical morbidity. Currently, there are no RCT's showing a positive impact of lymphadenectomy in patients with endometroid uterine cancer apparently confined to the corpus [24].

The role and outcome of Sentinel Node Dissection (SND) in uterine endometrioid adenocarcinoma of the uterus also remains unclear. The technique is reliable in most instances in detecting the sentinel (first draining node) [25]. Such nodes are often assessed for micro metastases using ultra staging and immunohistochemistry with no clear prognostic impact of detecting isolated tumour cells within the nodes. Evidence from the recently published Fluorescence Imaging for Robotic Endometrial Sentinel lymph node biopsy (FIRES) study is biased and confounded by the inclusion of high risk histologies and stage III and IV disease [26]. There are no RCT's in patients with endometrioid uterine cancer apparently confined to the corpus, indicating a survival advantage from SND.

In summary, LND including SND as a component of surgical staging of endometrioid uterine cancer apparently confined to the uterus does not appear to have a sound scientific basis as far as recurrence and Progression Free Survival (PFS) and Overall Survival (OS) is concerned.

Radiation Therapy

In 1980 investigators from the Norwegian Radium Institute published a landmark RCT of 540 patients with apparent Stage I endometrial cancer who underwent Total Hysterectomy Bilateral Salpingo-Oophorectomy (THBSO) and Vaginal Brachytherapy (VBT) and then randomised to either No Further Therapy (NFT) External Beam Radiation Therapy or (EBRT). Overall EBRT reduced local recurrences but did not provide an overall survival advantage. A more detailed analysis found patients with poorly differentiated tumours (grade 3) with greater than 50% myoinvasion might benefit from irradiation resulting in a reduced distant relapse rate and death

[6].

The (Danish Endometrial Cancer) (DEMCA) study group have published their nationwide uniform management guidelines and outcomes, confirming no advantage for radiation therapy in low risk patients with disease apparently confined to the corpus [27].

A Swedish RCT in low risk patients demonstrated no difference in vaginal recurrence rate and survival in patients given VBT after surgery compared to surgery alone [28].

The Post-Operative Radiation Therapy in Endometrial Cancer (PORTEC 1) study in intermediate risk patients confirmed that whilst EBRT reduced local recurrence, this was at the cost of increased complications and no survival impact and a long term increase in second cancers. The author elected to accept this study in the review as <1% patients had high risk histology [29,30].

The Swedish study in intermediate and high risk patients showed that EBRT was able to provide better local control compared to VBT but similar overall survival but with an increased adverse event and decreased QoL with EBRT [31,32].

The PORTEC 2 study in high intermediate risk patients comparing VBT with EBRT showed similar vaginal recurrence, increased pelvic recurrence and regional recurrence with VBT but no difference in survival and reduced complications with VBT and better QoL [33]. It has been argued that PORTEC 2 was likely underpowered in part due to the large proportion of low-risk, grade 1 tumours and the total number of events was small [34].

The often-quoted study GOG99 in intermediate and High Intermediate Risk (HIR) patients compare pelvic XRT to no further treatment after surgery. Patients with HIR risk factors were found to have increased recurrence rates and decreased survival if not offered EBRT [35]. However as stated above, one needs to view with caution the data and conclusions reached due to limitations and errors of inclusion relating back to GOG33 [8].

In a meta-analysis of 8 trials that evaluated EBRT, the risk of locoregional recurrence was reduced but EBRT did not have an effect on survival and at a cost of increased morbidity and reduced QoL [36].

In summary radiation therapy in apparent early endometroid cancer of the uterus will reduce local recurrence but likely not have an effect on overall survival in high risk patients. Low risk patients are not likely to derive a benefit from a survival perspective.

Chemotherapy

A large number of studies have examined the role of adjuvant chemotherapy with or without radiation in uterine cancer. Most of these studies have been in intermediate and high risk patients with disease NOT apparently confirmed to the uterus and often containing high risk histologies (clear cell, serous, carcinosarcoma) and are not included in this review (Table 1).

An Italian study comparing adjuvant chemotherapy with radiation therapy in high risk patients with endometrioid carcinoma showed a reduced local recurrence rate with radiation, lower distant recurrence rates with chemotherapy but no effect on survival [37].

A Japanese study of intermediate and high risk patients comparing radiation therapy with chemotherapy found similar Progression Free Survival (PFS) and Overall Survival (OS) however a subset analysis of high intermediate risk patients found better PFS and OS with chemotherapy compared to radiation therapy. However it is unclear if high risk histologies

were included in this study [38].

The Italian ILIADE-III study in high risk endometrioid cancer patients comparing chemotherapy with radiation again showed no overall survival benefit [39].

In summary the data for or against adjuvant chemotherapy in endometrioid adenocarcinoma apparently confined to the uterus is sparse with no apparent effect on survival except when subset analyses are undertaken. Most would agree that there is no role in low risk patients. There may be a role in high risk patients but the type of therapy, dosing, sequencing and survival effect remain to be clarified.

Conclusion

Based upon the data pertaining to endometrioid rather than all uterine cancer, one can make a number of conclusions supported by high level evidence. The majority of patients with endometrioid adenocarcinoma present with disease "strictly" or "apparently" confined to the uterus and have a very low recurrence rate and overall excellent survival. That comparative studies of endometrioid cancers require enormous numbers to show a difference between study groups. That risk assignment is variable across the world with no clear universal definitions. Risk assignment by the GOG is fundamentally flawed and all studies using their risk classification should be either viewed with caution or reanalysed. That hysterectomy is the treatment of endometrioid cancer and MIS has largely become the procedure of choice. There is no evidence to support an improved recurrence rate or survival when surgery is performed by a subspecialist gynaecological oncologist compared to general gynaecologist. There is no evidence that LND including SND provides a survival advantage and with no clear survival effect from either radiation therapy or chemotherapy, its role in patients with disease apparently confined to the uterus is not supported by data. Radiation therapy provides a benefit in local control terms but not survival and is at the expense of short term and long term morbidity. Finally, whilst promising, the evidence supporting the role of chemotherapy in patients with endometrioid cancer apparently confined to the corpus is limited.

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