Transworld Research Network
37/661 (2), Fort P.O.
Trivandrum-695 023
Kerala, India

Cytoreductive Surgery in Gynecologic Oncology: A Multidisciplinary Approach, 2010: 123-151
ISBN: 978-81-7895-484-4 Editor: Yusuf Yildirim

7. Cytoreductive surgery in endometrial cancer and uterine sarcomas

Stefanie M. Ueda and Robert E. Bristow
The Kelly Gynecologic Oncology Service, The Johns Hopkins Medical Institutions
Baltimore, MD, USA

Abstract. Optimal cytoreductive surgery has an emerging therapeutic role in the management of advanced and recurrent uterine carcinomas, especially if used in conjunction with adjuvant chemotherapy and/or radiation. Theoretically, successful tumor debulking can produce fractional log kill of malignant cells while sensitizing residual nodules to adjuvant therapies, expand tumor perfusion and drug delivery, and decrease the rate of somatic mutations associated with drug resistant phenotypes. Aggressive surgical interventions or salvage operations traditionally have been limited to women with only isolated pelvic disease or centralized, recurrent tumors. However, both extensive node resection as well as upper abdominal and omental assessment appear to benefit a subset of women with bulky metastases and high-risk histologies and perhaps more adequately detects and removes micrometastatic disease. As with epithelial ovarian cancers, more expansive and radical procedures therefore should be considered as treatment options for patients with even widespread or refractory uterine carcinomas, given the potential for improved clinical outcomes in these patients.

Introduction

Uterine corpus cancer is the most common gynecologic malignancy in the United States with over 40,000 women diagnosed annually. According to

Correspondence/Reprint request: Dr. Robert E. Bristow, The Kelly Gynecologic Oncology Service, The Johns Hopkins Medical Institutions, Baltimore, MD, USA. E-mail: rbristo1@jhmi.edu

American Cancer Society statistics, the number of deaths has dramatically risen despite a relatively stable number of new cases over the last 20 years, with only 3,000 deaths occurring in 1988 and 7,470 deaths expected in 2008. In the majority of cases, disease is confined to the uterus, but in approximately 20% of patients, tumor spreads to pelvic lymph nodes or more distant sites. The surgical management and treatment for early-stage endometrial cancer are fairly well-established, but patients with metastatic and recurrent disease continue to have low response rates to current therapeutic regimens, and optimal management of these patients remains ill-defined.

Advanced stage endometrial cancer, in particular, poses problems from a clinical standpoint because of historically poor outcomes and lack of consensus data for the most effective treatment programs. Patients with Stage III-IV disease, more specifically, account for over 50% of uterine cancer related deaths, with Stage IV disease being associated with five-year survival rates as low as 10–20% [1,2]. Radical surgery therefore has a promising role in the management of patients with locally or regionally advanced endometrial cancer, especially if utilized in combination with adjuvant radiation or chemotherapy.

Rationale for optimal cytoreductive surgery

The Gynecologic Oncology Group (GOG) defines optimal cytoreduction for endometrial cancer as resection of the maximal tumor mass to 1 cm or less. At present, no available technology exists that consistently allows clinicians to anticipate which patients have unresectable disease. The standard operation for women with advanced-stage endometrial cancer consists of removal of the uterus, ovaries, and tubes; pelvic and para-aortic lymphadenectomy; and if possible, resection of all visible tumor. Some physicians also advocate routine omental sampling and peritoneal staging biopsies to define extent of disease, particularly for endometrial cancer with a serous histological subtype. The specific surgical approach does vary across institutions, however, ranging from a simple extrafascial hysterectomy to more aggressive debulking procedures and lymphadenectomies based on intraoperative assessment of extra-pelvic and nodal metastases as well pre-operative tumor grading.

Similar to ovarian cancer, the survival benefit associated with successful surgical cytoreduction is thought to be a result of a number of hypothetical mechanisms [3-5]. In theory, successful tumor debulking can produce a three log kill of tumor cells, with smaller, better vascularized residual nodules being more vulnerable to chemotherapy. Resection of large volume disease further diminishes a tumor’s adverse metabolic effects, leading to better

patient performance status, expanded tumor perfusion and drug delivery, and decreased somatic mutations that often perpetuate drug resistance (Goldie-Coldman model). Given the high risk of recurrence in advanced stage endometrial cancer, a growing body of literature thus supports the concept of debulking surgery for metastatic disease to not only improve survival but also enhance the efficacy.

Role of lymphadenectomy

In 1988, the International Federation of Gynecology and Obstetrics (FIGO) changed the staging criteria for uterine corpus carcinoma from a clinical to surgical system. Surgical staging with pelvic and para-aortic lymphadenectomy specifically allows for the identification of patients with microscopic metastatic disease, presumably the group most likely to benefit from adjuvant treatment. Unfortunately, discrepancies between pre-operative histology, intra-operative assessment, and final pathology occasionally occur, and thus the extent of "adequate" lymph node sampling continues to be an area of controversy, with no agreement regarding the number of lymph nodes necessary for ideal evaluation.

Early GOG studies attempting to address this issue proposed only lymph node sampling from the external iliac, obturator, and hypogastric areas, finding that women with grade 1, superficially invasive cancers exhibited a 2–5% risk for nodal involvement [6]. A subsequent large series of 295 clinical Stage I patients with grade 2 or 3 carcinomas likewise revealed an 8% rate of retroperitoneal recurrences originating from sites thought to be "node negative" at the time of surgery [7]. This suggested that a failure to thoroughly assess pelvic and para-aortic nodes resulted in a small but real risk of undetected extrauterine metastasis in patients with supposed "low risk" endometrial cancer.

Later trials and retrospective reviews recommended retrieving a greater number of nodes from multiple sites. The rationale being that systematic lymphadenectomy in uterine cancer staging provided a more accurate assessment of neoplastic spread to permit better individualization of adjuvant therapy. This approach is generally organized into two parts: 1) a pelvic node dissection removing lymphatic tissue from the anterior and medial surfaces of the iliac vessels as well as from the obturator space superior to the obturator nerve and 2) a para-aortic node dissection removing precaval and lower aortic lymphatic tissue to the level of the inferior mesenteric artery. Reported rates of serious morbidity range from 6-19% [8].

Several studies further emphasized a therapeutic benefit to carrying out a systematic lymphadenectomy for endometrial cancer, particularly in cases of

high-grade disease [9,10]. For instance, among 509 women with apparent clinical Stage I/IIA disease, patients with poorly differentiated cancers undergoing more extensive lymphadenectomy (> 11 pelvic lymph nodes) had improved survival if no gross metastatic disease remained at the time of hysterectomy [8]. By comparison, the number of nodes obtained and the performance of selective para-aortic lymphadenectomy failed to predict either progression-free or overall survival among patients with grade 1 to 2 cancers in this analysis. These findings parallel those in other published series, which indicate no independent prognostic significance associated with histologically positive para-aortic nodes in the presence of positive pelvic nodes [11,12].

While the importance of systematic lymphadenectomy as a diagnostic tool in endometrial cancer is well accepted, the therapeutic relevance of a methodical para-aortic node assessment seems less clear. Although many gynecologists agree that patients with grade 1 endometrioid adenocarcinoma without myometrial invasion do not need complete lymphadenectomy, no standard method is described for determining which patients require an extensive para-aortic node dissection.

Given the low incidence of aortic node metastases in women with endometrial cancer that appears confined to the uterus (3%), some clinicians advocate limiting aortic lymphadenectomy to patients with high-risk features such as deep myometrial invasion (*i.e.* at least Stage IC) or grade 3 histology. Unfortunately, no risk factor profile reliably identifies all patients with aortic nodal spread, producing the debate surrounding the necessity for para-aortic lymphadenectomy in select patients. Reviewing the records of 137 high-risk (myometrial invasion >50%, palpable positive pelvic nodes, or positive adnexae) patients, Mariani *et al.* found that performance of para-aortic lymphadenectomy predicted longer progression free (OR = 0.25, p = 0.01) and overall survival (OR=0.23, p=0.006), with patients with para-aortic nodes not obtained showing a five-year progression-free survival and overall survival of 36 and 42%, in contrast to 76 and 77% for those with para-aortic nodes assessed (p = 0.02 and 0.05, respectively) [13]. Lymph node recurrences also arose in 37% of those without nodes procured but in no patients with nodes assessed (p = 0.01).

Recognition of pathologically positive lymph nodes by gross inspection alone therefore appears to be poor and not easily reproducible, with successful identification in only 39-61% of patients with clinically suspicious adenopathy [7,14-17]. In patients with microscopically positive pelvic nodes, the likelihood of involved para-aortics increases to 38-51% [6], and many investigators subsequently argue that complete para-aortic lymphadenectomy needs to be carried out in most patients to better identify those who require adjuvant chemoradiation and who might otherwise be underdiagnosed by pelvic node sampling alone. With such unreliable detection rates of extrauterine

disease by intraoperative palpation alone, the decision not to perform a complete node dissection as a part of routine surgical protocol ultimately may result in unrecognized macroscopic residual disease in patients thought to be optimally cytoreduced.

Resection of macroscopic nodal metastases

Several reports evaluating the efficacy of radiation therapy show that patients with Stage IIIC endometrial carcinoma initiating treatment with small-volume residual nodal disease experience superior local control and survival rates compared to patients with unresectable bulky adenopathy [11,16,18]. The potential benefit of more extensive lymphadenectomy thus includes the removal of occult small-volume disease undetectable by clinical inspection or palpation.

Amongst those patients with advanced uterine cancer, the advantage of debulking gross nodal metastasis has been validated by several studies. In a series of 96 patients with Stage IIIC disease examined by Havrilesky and colleagues, five-year disease-specific survival reached 63% in 45 patients with microscopic metastatic disease (Figure 1), in contrast to 50% in 44 patients with grossly positive nodes completely resected and 43% in 7 with residual macroscopic disease [19]. Among those with grossly involved lymph nodes, 86% underwent complete resection, and following multivariate analyses, gross nodal disease not debulked (HR=6.85, p=0.009) predicted greater death from disease.

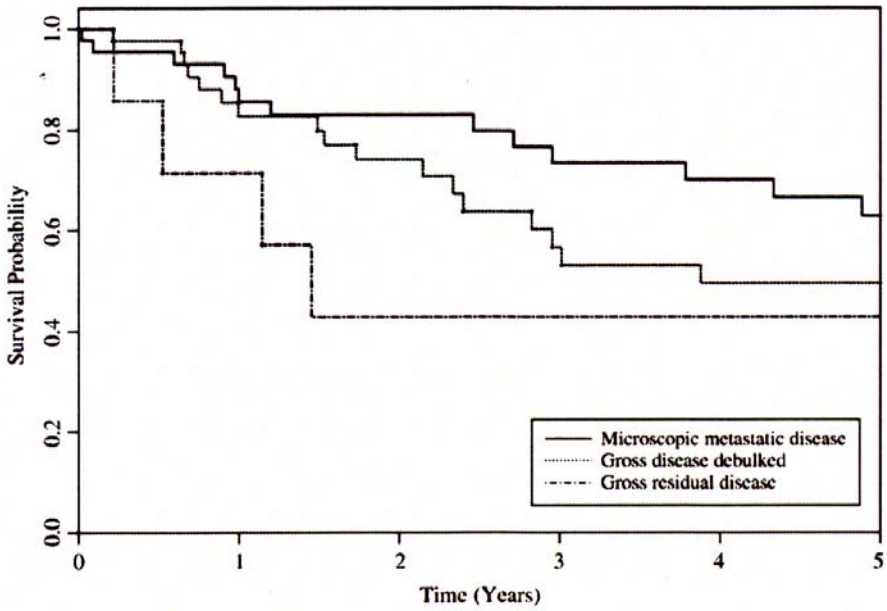

Figure 1. Disease-specific survival among patients with FIGO stage IIIC endometrial cancer stratified according to residual nodal disease, showing improved outcomes with increased resection of nodal metastases. Courtesy of Havrilesky L et al. Gynecol Oncol 2005;99(3):689.

Similarly, in a review of 41 surgically staged IIIC endometrial cancer patients who received postoperative whole pelvic radiation conducted by Bristow and coworkers, women with completely resected macroscopic lymphadenopathy exhibited a four-fold longer median survival compared to those left with residual nodal disease (37.5 vs. 8.8 months, p=0.006) [20]. Gross residual nodal disease again independently predicted disease specific survival (HR 7.96, 95% CI 2.54–24.97, p< 0. 001), and the authors advocated carrying out routine and systematic lymphadenectomy when feasible in patients with Stage IIIC endometrial carcinoma to ensure complete cytoreduction in patients with otherwise subclinical nodal disease.

A report by Lambrou *et al.* evaluating 66 patients with Stage III-IV disease undergoing primary surgery further revealed a higher likelihood of suboptimal debulking and tumor recurrence if bulky adenopathy was noted [21]. Of the six Stage IIIC patients with suboptimal cytoreduction, all demonstrated residual disease in the pelvic or para-aortic region. The presence of upper abdominal metastases, ascites, extra-pelvic disease (including upper abdomen, omentum, gastrointestinal tract other than rectosigmoid, and distant lymph nodes), and positive para-aortic lymph nodes were each significantly associated with suboptimal surgical cytoreduction. When feasible, removal of all grossly positive nodes in this setting led to a greater probability of achieving optimal cytoreduction and subsequent improved survival.

In one of the largest studies of over 12,000 patients utilizing the SEER database, Chan *et al.* subsequently proposed that a relationship existed between the number of lymph nodes resected and the survival of patients, but only in those patients with intermediate to high risk endometrioid uterine carcinomas [22]. These investigators stratified the total number of lymph nodes resected into three groups (≤ 10 nodes, 11–20 nodes, > 20 nodes) and concluded that disease specific survival increased in proportion to the number of nodes removed in intermediate and high risk patients, particularly in those with Stage IIIC-IV disease (Figure 2). In patients with intermediate to high risk disease (defined as Stage IB, grade3 and Stage IC-IV, all grades), a more extensive lymph node resection led to improved five-year survivals ranging from 75.3-86.8% (p<0.01), and in patients with Stage IIIC-IV, survival increased from 51-72% as an more nodes were removed (p<0.01).

A subsequent series of 63 Stage IIIC endometrial carcinoma patients also found that the number of positive pelvic lymph nodes predicted disease specific survival [23]. In this study, the performance of para-aortic lymphadenectomy significantly decreased recurrence risk and lengthened survival in patients with greater than 2 positive nodes beyond that seen with pelvic lymphadenectomy alone (p=0.011). The five-year disease-related survival was 19.4% in the pelvic node only group (n=12) but 59.6% in the

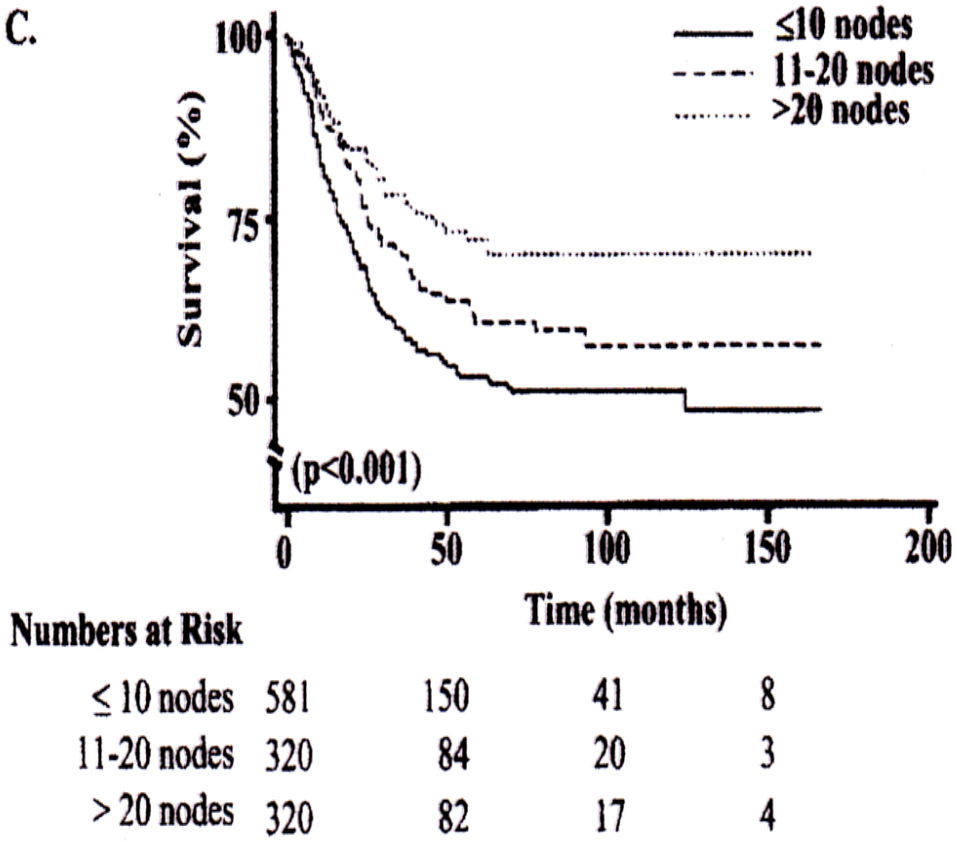

Figure 2. Disease specific survival increased in proportion to the number of nodes removed in intermediate and high risk but not low risk patients in Stage IIIC-IV patients. Courtesy of Chan J et al. Cancer 2006;107(8):1823.

pelvic and para-aortic group (n=21). Conversely for early stage disease at this same institution, para-aortic lymphadenectomy failed to yield superior outcomes, implying that extensive lymphadenectomy may only be of value in advanced disease.

Smaller, retrospective studies further support full lymphadenectomy for high risk serous cancers in order to guide need for adjuvant chemotherapy. Overall and progression-free survival significantly improves with pelvic lymph node counts ≥12 among women with high-risk histology ($p< 0.001$) but not among women with low-risk histology [24]. This increased survival potentially reflects a more rigorous evaluation to exclude lymph node metastases while removing histologically occult disease.

Consequently, although surgical treatment of endometrial cancer in the past has ranged from performing lymph node sampling only in high-risk patients to carrying out complete lymphadenectomies in all uterine cancer patients, systematic lymphadenectomy now appears to be the accepted standard in all but superficial grade I disease and appears to be especially

important in those patients with known bulky nodal metastases. Obtaining a greater number of nodes not only more adequately stages patients to detect and remove micrometastatic disease, but also is associated with prolonged survival in patients with Stage III-IV disease. It remains to be determined, however, if there exists an absolute number of nodes necessary to define a therapeutic lymphadenectomy. Nodal count as well as the comprehensiveness of pathologic analysis, surgical expertise, and anatomical variations probably all contribute to what constitutes an "adequate" nodal dissection, but clearly an appropriate assessment needs to be done intraoperatively to better direct adjuvant treatment.

Assessment of the omentum

The 1988 FIGO guidelines do not include omental evaluation as part of the surgical staging criteria for endometrial carcinoma, but omentectomy or omental biopsy is frequently performed in cases of serous histology because of the similar pattern of spread to ovarian cancer. Nonetheless, the rate of microscopic omental metastasis from uterine cancers only ranges from 3-8% [25], and the negative predictive value of a visually normal omentum at the time of surgery approaches 90% in women with serous cancers, suggesting that total omentectomy is not routinely indicated unless the omentum appears abnormal [26]. Despite these findings, omental biopsy or infracolic omentectomy is still commonly carried out as part of the staging procedure for serous uterine cancers, possibly because the associated morbidity is low.

Given the limited patient numbers and rarity of serous endometrial cancers in currently published studies, objective evidence determining whether routine omental sampling provides clinically useful staging information is difficult to attain. Jeffrey *et al.* first attempted to address this issue, reporting on 5 women who underwent omental evaluation at initial surgical exploration. Three women had gross omental involvement, and two had visually negative omentums that eventually were upstaged based on microscopic invasion. They concluded that total omentectomy should be included in the routine staging for uterine serous carcinoma [27]. In a series of 30 women with uterine serous carcinoma, Kato *et al.* further described 8 women who underwent either omental biopsy or omentectomy, with 88% of omental specimens containing malignant cells [28]. Their data, however, failed to answer the question of whether routine omentectomy should be performed, as omentums were not clearly delineated as being either grossly or microscopically involved with metastatic disease.

Cirisano *et al.* later reviewed surgicopathologic characteristics in women with serous and clear cell carcinomas of the uterus in comparison to

endometrioid carcinomas and found that omental assessment was done more than twice as often in cases of uterine serous cancer [29]. In clinical stage I-II tumors, 21% of omental specimens from patients with uterine serous carcinoma also had evidence of microscopic omental metastases in contrast to only 3-9% of endometrioid specimens, with almost four times as many patients upstaged in serous cases following extensive operations that often incorporated omentectomy and pelvic and para-aortic lymphadenectomy [29].

In an analysis of 65 women, Geisler *et al.* likewise recommended surgical staging for uterine serous carcinomas to include at least partial omentectomy because of the propensity of this histologic subtype for extrauterine spread. Approximately 24% of patients exhibited microscopically positive omental or peritoneal biopsies despite negative lymph nodes, and nearly 40% of women with Stage IV disease were correctly diagnosed only after a staging operation similar to that employed for ovarian cancer was performed.

Faratian *et al.* correspondingly found omental involvement in 29% of 24 patient samples, and observed that women with a negative omental biopsy showed a significantly better progression free and overall survival than those with a positive biopsy. More notably, two recurrences (13%) occurred in biopsy positive omentums not removed by omentectomy, suggesting a potential therapeutic benefit following this procedure through increased abdominal tumor clearance [31].

Consequently, when the omentum is involved in uterine cancer, thereby upstaging the patient, the disease often is diagnosed by gross visualization. At minimum, sampling of the omentum does appear to assist in guiding management by excluding more advanced disease that definitively requires platinum therapy (Table 1). More radical resection, in contrast, should probably be reserved for bulkier disease that can be completely removed, as this possibly decreases tumor burden to sufficiently alter clinical outcome.

Table 1. Microscopic Omental Metastases in Uterine Serous Carcinomas.

Study	Total Number of Patients	Number of Omental Specimens	Visually Normal Omentums	% Subclinical Micrometastases
Gehrig *et a*l	65	52	34	6%
Jeffrey *et al*	15	5	2	100%
Kato *et al*	30	8	1	0%
Cirisano *et al*	53	19	19	21%
Geisler *et al*	67	65	42	24%
Faratian *et al*	59	24	21	29%

Primary cytoreduction surgery for advanced stage endometrial cancer

Surgical Stage III-IV endometrial cancer accounts for just 5-13% of all cases but is responsible for 23% of disease-related deaths. Five-year survival rates range from 10-25%, largely due to the lack of highly effective adjuvant treatment modalities [2,32]. Despite an overall poor prognosis, optimal cytoreductive surgery appears to lead to more favorable responses and improved clinical outcomes [33-35]. Surgery therefore has evolved as a cornerstone of treatment for most women with locally and regionally advanced endometrial cancer, but the appropriate extent of surgery in this setting and the utility of radical upper abdominal procedures in advanced disease are not clear. As with studies of surgery for ovarian cancer, the definition of what constitutes optimal debulking surgery, however, varies between investigators, and this makes it difficult to adequately compare results from different reports.

In one of the earliest reports addressing the issue of residual disease among women with advanced-stage endometrial cancer, Greer and Hamberger described a series of 31 women with Stage III-IV endometrial carcinomas. Ten patients with Stage IV disease undergoing surgical resection to $\leq$2 cm residual disease and postoperative radiation demonstrated 70% five-year survival, whereas all four patients with residual tumor greater than 2cm eventually died from their disease [35]. Martinez *et al.* similarly evaluated 25 Stage III/IV patients following cytoreductive surgery to $\leq$2 cm and whole abdomen radiation with nodal boost. Five-year relapse-free survival was 68%, but nearly one fourth of patients were left residual disease of up to 2 cm after their initial operation, mostly in the form of nodal disease [36].

Goff *et al.* later compared 29 patients with Stage IV disease who underwent cytoreductive surgery that left no "bulky" disease to 18 patients unable to undergo complete tumor reduction [34]. Median survival was 19 months in the surgically resectable group compared to 8 months in those who did not undergo surgery (p=0.0001), and by multivariate analysis, only successful cytoreduction was a significant prognostic variable.

Other publications have drawn more direct comparisons of optimal versus suboptimal cytoreduction in patients with Stage IV endometrial cancer. Chi *et al.*, for instance, evaluated cytoreductive surgery for 55 Stage IV endometrial cancer patients by dividing them into groups according to surgical outcome [33]. Histology included 33 (60%) endometrioid, 12 (22%) serous, and 3 (5%) adenosquamous. Patients with optimal cytoreduction ($\leq$2.0 cm residual disease) were found to have a median survival time of

31 months, in contrast to a median survival of 12 months for patients with suboptimal cytoreduction (>2.0 cm residual disease) and only 3 months for patients with unresectable carcinomatosis. Interestingly, the authors observed no significant difference in survival rates between those patients with small volume metastatic disease (≤2.0 cm) before surgery and those patients with initially large volume disease who successfully completed optimal cytoreduction. On multivariate analysis, extent of surgical cytoreduction seemed to be a notable prognosticator, suggesting that aggressive tumor reduction could potentially increase survival in even cases of advanced disease.

Bristow *et al.* subsequently assessed the role of optimal cytoreductive surgery in 65 patients with Stage IVB endometrial cancer, achieving optimal resection in 55% of cases [37]. Endometrioid histology accounted for 33.8% of patients, serous 32.3%, and mixed 16.9%. Patients undergoing optimal cytoreduction had a medial survival of 34.3 months compared to 11.0 months for those left with suboptimal residual disease (>1.0 cm). Among those optimally resected, patients with only microscopic residual disease survived longer than patients with optimal but macroscopic tumor residual (Figure 3), with lower residual disease, younger age, and better performance status independently predicting superior clinical outcome. The authors thus concluded that maximal cytoreduction at the time of primary surgery should be the goal in advanced uterine carcinomas because of the likely therapeutic benefit.

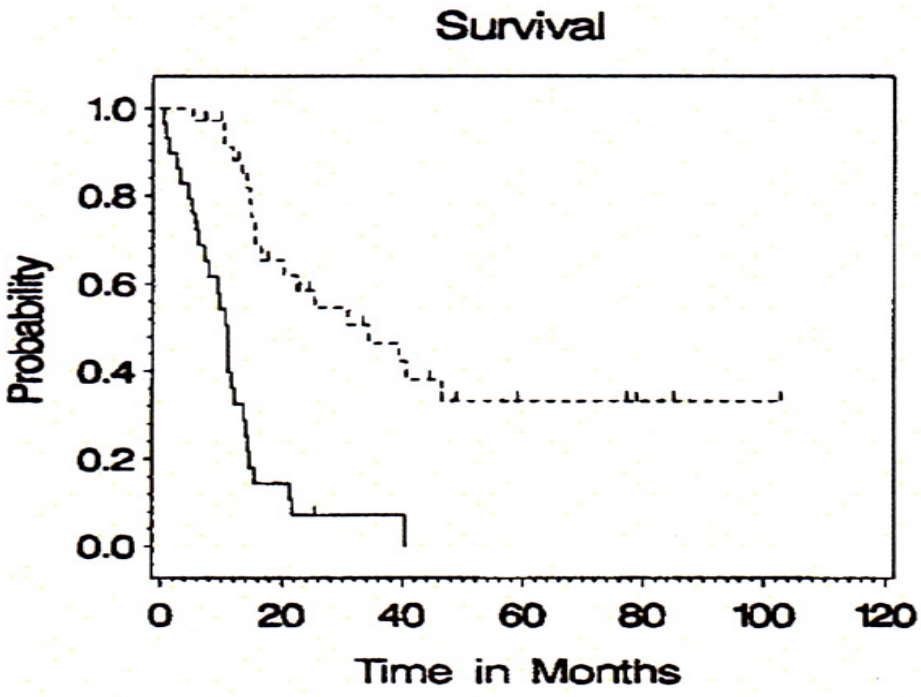

Figure 3. Stratification of overall survival in Stage IVB endometrial carcinomas by residual disease status (≤1 cm, n=36 or >1 cm, n=29). Courtesy of Bristow R et al. Gynecol Oncol 2000;78(2):85.

Ayhan *et al.* further evaluated 37 Stage IVB patients and found a median survival of 25 months for patients undergoing optimal cytoreduction (≤1.0 cm) compared to 10 months for the suboptimal group [38]. Patients left with no visible tumor exhibited a median survival of 48 months. Endometrioid subtype accounted for the majority of tumors. Operative morbidity appeared to be severe in approximately one-fourth of patients, though complicated by very small numbers. By univariate analysis, extra-abdominal metastases, suboptimal cytoreduction, visible tumor mass after cytoreduction, pelvic and para-aortic lymphatic metastases, and cervical extension predicted worse survival. On multivariate analysis, optimal cytoreduction, concomitant cisplatin radiotherapy, and extra-abdominal metastases associated with improved outcome.

Lambrou *et al.* most recently reported on 85 patients (66 Stage III and 19 Stage IV) with advanced endometrioid adenocarcinoma treated with primary surgery [21]. Overall survival proved lower and morbidity higher in patients suboptimally cytoreduced, with median survival measuring 6.7 months for patients with residual disease and 17.8 months for patients with optimal resection ($p = 0.001$).

In each of these studies, overall survival increased in women left with small volume disease after initial resection. As with ovarian cancer, surgical cytoreduction to no residual tumor should be the aim for patients with Stage III-IV uterine disease to maximize response to adjuvant therapies. Thus, more expansive preoperative assessment needs to be done to best predict which patients will be candidates for optimal surgical resection – patients in whom a reasonable attempt at primary surgical intervention may be more appropriate than chemotherapy or radiation.

Serous and clear cell carcinomas of the endometrium

Uterine serous carcinoma

Uterine serous carcinomas (USC) comprise 3-11% of all uterine cancers, but account for 15-25% of disease-related deaths and a notable proportion of advanced stage disease [39-41]. Paralleling ovarian cancer, USC demonstrates a propensity for more widespread disease and recurrence risk, with lymphovascular invasion and intraperitoneal dissemination seen more frequently in these tumors as compared to endometrioid uterine cancers (39, 42-43). As many as 69-87% of patients exhibiting extracorporeal disease at initial diagnosis [30,34,44]. Studies indicate that surgical staging for USC is critical (perhaps even more so than in endometrioid tumors), as these lesions often metastasize in the presence of minimal uterine disease.

Unlike endometrioid cancers, grade and depth of myometrial invasion of USC do not always predict extrauterine spread, as approximately 30-40% of patients with no obvious uterine invasion demonstrate advanced stage disease following comprehensive staging that includes omentectomy, peritoneal biopsies, and lymph node dissection [45,46]. Gehrig *et al.* observed in 69 patients that 67% of clinical Stage I USC cases with no myometrial invasion had distant disease at the time of surgical staging [47]. Moreover, in a meta-analysis by Dunton *et al.*, up to 63% of all USC patients stage higher surgically than clinically suspected [48]. Because of this discrepancy, many authors endorse complete surgical staging for patients with documented USC on preoperative biopsy [47].

Despite five-year survival rates as low as 5%, a growing body of literature also suggests a role for surgical cytoreduction in the management of Stage IV USC patients, given the potential survival advantage in several case series [42,49,50]. However, the rarity of these tumors again makes large, prospective studies difficult.

Bristow *et al.* initially reported on 31 patients who underwent primary cytoreductive surgery for Stage IV USC [49]. Optimal cytoreduction was defined as residual disease ≤1 cm, and 51.6% of patients successfully completed primary surgery with optimal disease status. The median survival time for those patients optimally resected was 26.2 months, compared with 9.6 months for patients left with suboptimal residual disease ($p < 0.001$). More specifically, the median survival time was 30.4 months in patients left with only microscopic residual disease, 20.5 months in patients with optimal but visible residual disease measuring ≤1 cm, and 9.6 months in patients with residual greater than 1 cm ($p=0.004$). The only significant predictor of suboptimal surgical outcome was the presence of disease in three or more anatomic regions. On multivariable analysis, the lone statistically significant predictor of extended overall survival was cytoreductive surgical outcome, but no single anatomic region appeared predictive of surgical outcome, pointing to the value of decreasing overall tumor burden rather than removing disease from a particular site.

Moller *et al.* presented a multi-institutional, retrospective review identifying 52 women with Stage IV USC [51]. Twenty-six patients underwent optimal debulking (≤1 cm residual) and 23 suboptimal. Although overall survival failed to correlate with the absolute size of residual disease (15 vs. 8 months, $p>0.05$), optimal cytoreduction combined with adjuvant platinum chemotherapy demonstrated a trend toward prolonged survival when compared to suboptimal cytoreduction combined with adjuvant therapy.

Memarzadeh *et al.* analyzed 43 women who underwent surgical cytoreduction for Stage III and IV disease [52]. The median survival for USC

patients in this series with microscopic residual disease significantly improved compared to those with macroscopic residual disease following primary surgical cytoreduction (43 vs. 10 months, $p<0.001$). Progression free survival for those left with microscopic disease also proved nearly 3 times longer than those with macroscopic residual disease (22 vs. 8 months, $p<0.0001$). Survival of patients with advanced UPSC correlated with the extent of residual tumor following primary surgical resection, and the presence of any measurable residual tumor dramatically decreased the median survival and the recurrence-free interval in these patients.

A large series described by Thomas *et al.* looked at 125 Stage IIIC–IV USC patients (Stage IIIC=12, Stage IV=58) [53]. Optimal cytoreduction was accomplished in 60% patients, with no visible residual disease in 37%. Median time to recurrence differed between those optimally resected and those suboptimally cytoreduced (9 months vs. 6 months, $p=0.04$). Women with no visible residual disease after cytoreduction, moreover, exhibited a longer median survival (51 months), in comparison to 14 months in those optimally cytoreduced albeit with residual disease and 12 months in those suboptimally cytoreduced (Figure 4). No decrease in survival rates occurred when radical procedures (*e.g.* splenectomy, diaphragmatic stripping, or bowel resection) needed to be done to completely remove all residual disease. Thus, in the context of resection of all macroscopic tumor, maximal surgical effort, including the use of extended procedures, enhanced clinical outcome.

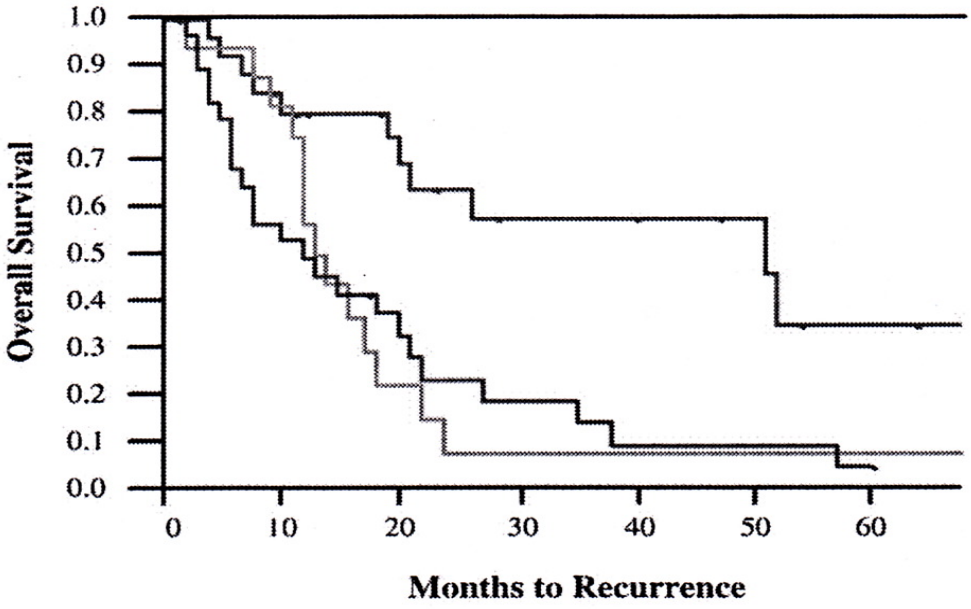

Figure 4. Kaplan-Meier plot for stage IIIC-IV patients with no residual (51 months), residual≤1cm (14 months), and residual>1 cm (12 months). Courtesy of Thomas M et al, Gynecol Oncol 2007;107(2):190.

The strongest predictor of overall survival for patients with advanced USC therefore seems to be the amount of residual disease left following primary resection, as over 80% of recurrences in these patients are associated with abdominopelvic failures and about one-third with distant metastases [48, 53]. Recommended management for this group of patients consequently should consist of optimal cytoreductive surgery to no residual tumor, including resection of disease in the upper abdomen, followed by platinum-based chemotherapy to maximally impact median and progression-free intervals.

Clear cell carcinoma

Uterine clear cell carcinomas similarly tend to spread to distant sites, accounting for 1–6% of endometrial cancers but linked to five-year prognoses as low as 20% in advanced disease [54]. Like serous carcinomas, occult extrauterine metastasis presents in 40% of patients with disease clinically confined to the uterus [29], and as with other non-endometrioid tumors, comprehensive surgical staging with systematic lymphadenectomy is generally advocated given the high risk of occult metastasis.

The relative rarity of clear cell carcinomas of the uterus, unfortunately, has compelled many investigators to combine examination of these tumors with uterine serous carcinomas. In one of the few multi-institution reviews focusing on uterine clear cell cancers conducted by Thomas *et al.*, 52% of 99 women were upstaged at the time of surgery, with 20% of women found to have lymphatic involvement after pathologic assessment [55]. No patient was upstaged solely on the basis of omentectomy or peritoneal biopsies. Cytoreduction to no visible disease was achieved in all Stage IIIC and nearly half of Stage IV patients. Women without visible residual disease had a significant improvement in median progression free survival (17 vs. 7 months, $p < 0.001$) and overall survival (40 vs. 18 months, $p = 0.02$) when compared to patients left with residual disease; this trend extended to Stage IV patients (Figure 5). Multivariate analysis identified only the absence of residual disease and adjuvant treatment with radiation or chemotherapy as independent predictors of local disease control.

Clear cell carcinomas of the uterus indeed display a propensity for metastatic disease at initial presentation, yet the relative rarity of clear cell tumors has necessitated that it be analyzed together with uterine serous cancers in many previous publications. Both variants have high rates of deep myometrial invasion and extensive lymphovascular space invasion at diagnosis, with increased rates of loco-regional recurrence and reduced overall survival seen in even early stage disease. As in other histologies, cytoreduction to no

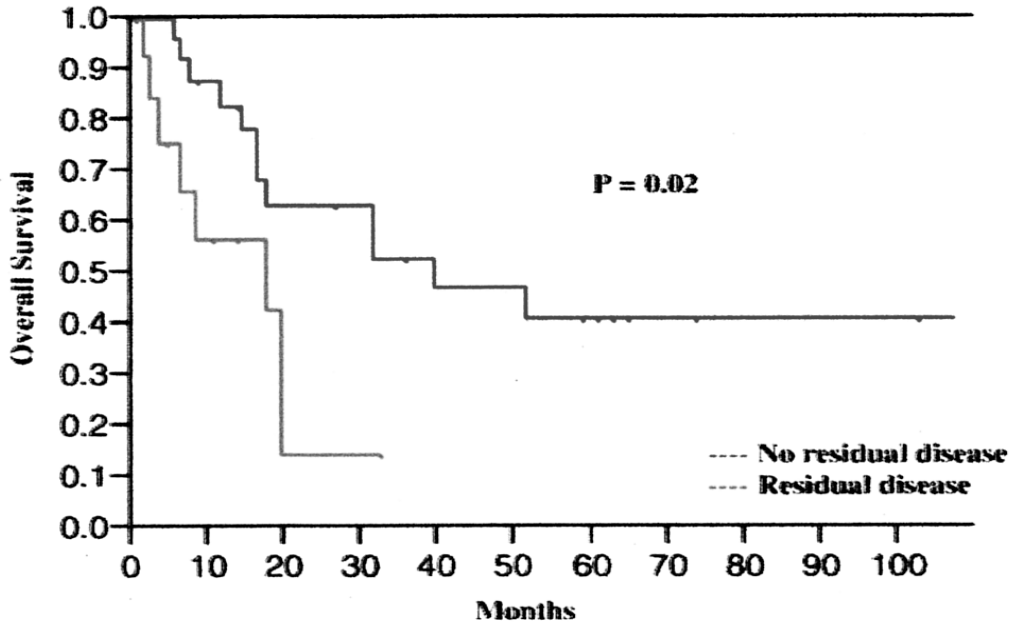

Figure 5. Longer median survival for Stage IIIC-IV patients with clear cell carcinoma left with no residual disease after primary surgery (40 vs. 18 months). Courtesy of Thomas M et al. Gynecol Oncol 2008;108(2):293.

visible tumor appears to be associated with better outcomes for patients with advanced uterine clear cell carcinomas. When feasible, an attempt at optimal resection consequently should be made in these cases, as a therapeutic benefit seems plausible based on the limited studies currently available.

Salvage cytoreductive surgery for recurrent disease

Considering all patients with endometrial cancer, the risk of recurrence ranges from 7.7-63.3%, depending on the presence of specific prognostic factors [56,57]. Traditionally, surgical treatment of recurrent disease has been reserved only for patients presenting with a central pelvic recurrence recalcitrant to radiation therapy. In this scenario, exenterative procedures have been associated with long-term survival rates of 20-45%; yet, relatively few patients are candidates for this approach [58,59]. Although recent data support a positive correlation between survival and the successful surgical cytoreduction of advanced stage endometrial cancer, the role of non-exenterative cytoreductive surgery for recurrent disease has been less widely explored.

Central pelvic recurrence of endometrial cancer

For a select number of patients with a localized vaginal recurrence, radiation therapy can provide favorable long-term pelvic control and five-year

survival rates between 31% and 53% [60-62]. However, a significant proportion of patients will have already received pelvic irradiation to maximal doses and salvage chemotherapeutic regimens remain quite limited in this setting. In these patients, Barakat *et al.* proposed that the only potentially curative option was pelvic exenteration if the tumor was centrally recurrent. They identified a total of 44 patients in their review and, despite high operative morbidity, found that 9 patients (20%) achieved long-term survival of greater than 5 years [58].

Regional and distant recurrence of endometrial cancer

The subset of women with recurrent endometrial cancer that are candidates for pelvic exenteration is very specific. Unfortunately in the majority of patients, regional or distant disease is present at time of re-diagnosis, and treatment alternatives primarily consist of cytotoxic chemotherapy, hormonal treatment, or palliative radiation. The most effective chemotherapeutic agents for advanced or recurrent endometrial tumors include cisplatin, doxorubicin, paclitaxel, and topotecan. Although overall response rates range from 20-37%, stabilization of disease is generally of short duration [63-66]. Hormonal therapy with progestational agents, anti-estrogens, and gonadotropin-releasing analogs produce disappointing response rates ranging from 9-16%, with the likelihood of response correlating with the degree of tumor differentiation [67-70]. As these data indicate, alternative treatment strategies need to be developed to improve patient outcome for patients with recurrent endometrial cancer. Consequently, recent investigators have explored the role of surgical cytoreduction as a means of augmenting the durability of response to salvage therapies.

The first report of secondary cytoreductive surgery for recurrent endometrial cancer was described by Scarabelli *et al*. in 1998, which detailed a series of 20 patients [71]. Complete resection of all visible tumor was achieved in 65% of patients and was associated with significantly longer progression-free (9.1 months vs. 1.5 months, $p<0.05$) and overall survival (11.8 months vs. undefined, $p<0.01$) compared to patients left with residual disease. Several years later, Campagnutta and coworkers reported a larger series of 75 patients undergoing surgical treatment for recurrent disease [72]. Optimal resection to less than 1 cm was accomplished in nearly 75% of cases, and 64.0% of women underwent complete removal of all macroscopic tumor. The only clinical characteristic independently predictive of optimal resection seemed to be solitary rather than multiple sites of tumor recurrence. For all patients, the post-recurrence survival time measured a median of 19 months, with optimal secondary cytoreduction being associated with a median survival time of 53 months compared to just 9 months for patients left

with residual disease. On multivariate analysis, complete cytoreduction, the administration of post-operative chemotherapy, and central pelvic recurrence independently and significantly associated with a superior survival outcome. More recently, Awtrey and colleagues detailed their experience with 27 patients undergoing non-exenterative surgery for recurrent endometrial cancer [73]. Optimal cytoreduction (<2 cm residual disease) occurred in 67% of cases, and 56% of women were left with no gross residual disease. Patients optimally cytoreduced had a longer median survival time (43 months) compared to patients left with suboptimal residual disease (10 months, $p<0.05$). Following univariate analysis, the amount of residual disease proved to be the sole predictor of progression-free and overall survival.

Bristow *et al.* subsequently identified 61 patients with recurrent endometrial cancer, 35 of whom underwent salvage cytoreductive surgery [74]. Complete cytoreduction with no gross residual disease was achieved in nearly two-thirds of patients. Women undergoing complete salvage cytoreduction boasted a median post-recurrence survival time of 39 months, nearly three times longer than those with gross residual disease (13 months, $p=0.0005$). Following multivariate analysis, both successful surgical resection (HR=0.11) and residual tumor volume (HR=6.85) independently predicted post-recurrence survival (Figure 6).

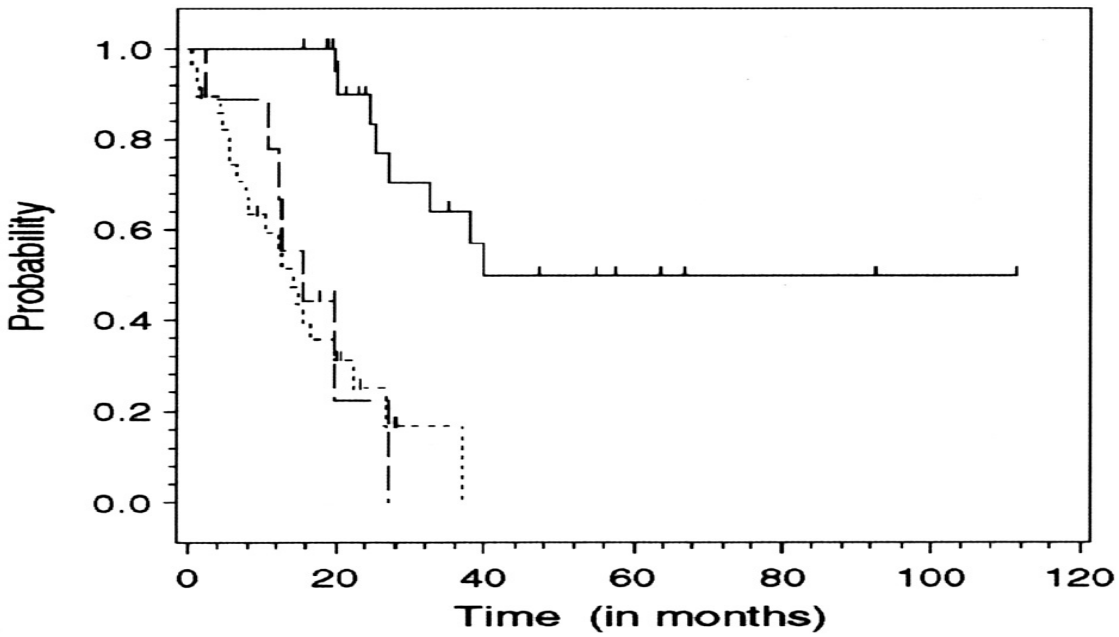

Figure 6. Overall survival in women with recurrent endometrial cancer classified by surgical status and residual disease with those patients with no gross residual tumor demonstrating better clinical outcomes. Courtesy of Bristow R et al. Gynecol Oncol 2006;103:281.

Although less clearly delineated than in primary debulking, salvage cytoreductive surgery appears justified in a specific subset of patients in whom prolonged post-recurrence survival can be attained. Theoretically, complete surgical resection of recurrent disease can augment chemotherapeutic response by reducing the kinetic and pharmacologic barriers to tumor cytotoxicity. The reported rates of surgical success thereby reflect both the use of discriminating patient selection criteria and recognizing those patients in whom secondary debulking provides an ensuing therapeutic advantage.

Uterine sarcoma

Primary cytoreductive surgery for advanced-stage uterine sarcomas

Although representing only 1% of uterine cancers, uterine sarcomas continue to be deadly. Five-year survival rates range from 25-75%, with recurrence of pelvic disease ranging from 14-64% [75-77]. Given the scarcity of good adjuvant therapies in uterine sarcomas, aggressive surgical cytoreduction at initial diagnosis offers one of the few treatment options that possibly prolongs survival.

While lymphadenectomy has not been shown to be therapeutically or prognostically helpful in uterine sarcomas [78], visualization and palpation of the peritoneal cavity are often recommended as sufficient for staging. Multiple studies have proposed that removal of the ovaries in premenopausal women may not be necessary either [79-81]. Berchuck *et al.*, for instance, evaluated 46 patients with uterine sarcomas and demonstrated parallel recurrence rates between 8 patients with ovarian preservation and the entire patient population [81]. Similarly, Gadducci *et al.* reported that preservation of the ovaries in apparent Stage I patients younger than age 50 did not affect recurrence rates [79]. Larson *et al.* further examined overall survival in premenopausal women with uterine sarcomas without controlling for stage or grade, showing no difference in overall survival between the 19 patients who underwent bilateral salpingo-oophorectomy and the 31 patients who maintained residual ovarian tissue postoperatively [80].

Surgery remains the treatment of choice for initial therapy in sarcomas, but the lack of efficacious adjuvant therapies in advanced stage disease ultimately leads to recurrence and poor overall survival. In a ten-year, single institution review of 27 patients with leiomyosarcoma, Dinh *et al.* concluded that patients with visible disease following primary surgery had a better overall outcome than patients who did not achieve surgical remission ($p < 0.0003$) [82]. Nearly 60% of patients presented with Stage IV disease, and

chemotherapeutic regimens (which often included doxorubicin and/or ifosfamide) appeared to be minimally effective. Adjuvant therapy after optimal cytoreduction failed to decrease the risk of recurrence, as 80% of treated patients developed progressive disease.

A report by Giuntoli *et al.* of 208 women with uterine sarcomas mainly assessing the extent of surgical intervention found that initial surgery consisted of simple hysterectomy in 93% of patients [83]. Radical or modified radical hysterectomies were performed in 4% of patients, with 62% of women categorized as Stage I. Ovaries were preserved in 29 patients, and lymph nodes were evaluated in only 36 women. Multivariate analysis revealed that high grade, advanced stage, and oophorectomy were associated with significantly worse disease-specific survival (Figure 7). Consequently, tumor grade and stage (using modified criteria for endometrial cancer) appeared to be valid prognostic indicators for uterine sarcomas, and ovarian preservation seemed plausible in premenopausal patients with early-stage tumors, as the elimination of oophorectomy at therapy did not appear to significantly alter survival.

A subsequent retrospective review performed on 127 patients with histologically verified uterine sarcomas revealed that FIGO stage (p=0.025), depth of myometrial invasion (p=0.004), and complete cytoreduction (p=0.030) significantly lengthened the disease free survival [84]. Adjuvant therapy correspondingly played a limited role in patients with early-stage disease.

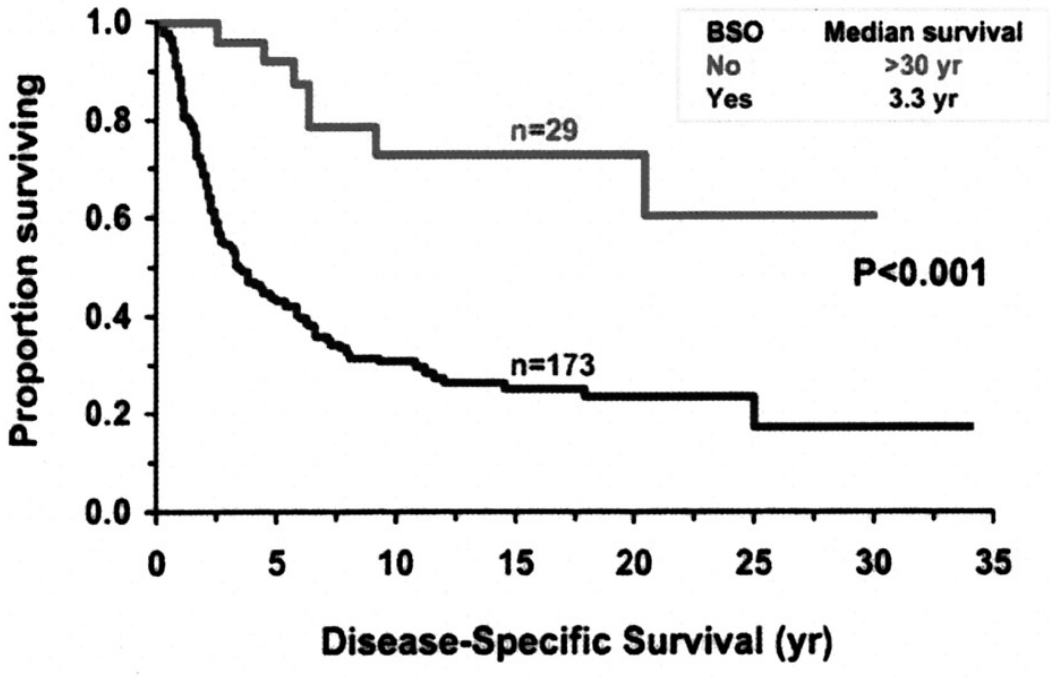

Figure 7. Kaplan-Meier analysis for unselected patients stratified by performance of oophorectomy. Courtesy of Giuntoli R et al. Gynecol Oncol 2003;89(3):460.

Unfortunately, up to 70% of patients with uterine leiomyosarcoma confined to the uterus and nearly all with extrauterine disease at diagnosis eventually recur, with median time to recurrence spanning 8-16 months [75,76,78,79,81]. Chemotherapy, radiation, and hormonal manipulation all have been advocated for the prevention of tumor recurrence, but all with moderate success. Unlike results seen epithelial histologic subtypes, adjuvant chemotherapy appears to be of minimal efficacy in uterine sarcomas, with various regimens recommended for advanced or recurrent disease showing disappointing response rates ranging from 19-30% [85-87]. In effect, while optimal cytoreductive surgery seems to play a role in improving clinical outcome in the primary setting, the ideal adjuvant treatment after surgical extirpation continues to be undefined.

Cytoreductive resection of recurrent uterine sarcomas

Several studies also have examined the feasibility of operative resection of metastatic disease in patients with recurrent uterine sarcomas. Surgery has been retrospectively shown to offer a survival advantage in patients with even pulmonary metastasis. Levenback *et al.* first described 45 patients with recurrent uterine sarcomas who had previously undergone hysterectomy at initial presentation. Among this carefully selected group of patients with isolated pulmonary metastases, surgical resection led to long-term survival in a substantial proportion of patients, with five-year survival rates of approximately 40% [88]. The absence of bilateral disease proved to be the only significant predictor of improved survival, while nodule size, use of adjuvant therapy, histologic type, and age did not influence clinical outcome.

The survival advantage observed following successful resection of thoracic disease is further seen in patients with extrapulmonary metastases. Leitao *et al.* examined the effects of secondary cytoreduction in 41 uterine sarcoma patients with both pulmonary and/or extrapulmonary recurrences, 12 of whom had thoracic procedures performed [89]. Following univariate analysis, time to recurrence of less than 12 months and optimal surgical resection predicted better outcome, with overall median survival for the entire group amounting to 3.9 years in comparison to 7-15 months for historical controls receiving chemotherapy alone.

Even in the presence of lung metastases, surgical excision of intra-abdominal metastases remains a viable option in light of the lack of response to other treatment modalities. Surgical excision has been tried, for instance, in cases of liver metastases with partial success. In a study of 26 patients by Lang *et al*., for example, prolonged survival was associated with removal of all metastatic foci, with 20% of patients surviving 5 years after surgery [90].

In one of the largest series to date, Giuntoli *et al.* identified 128 patients with recurrent uterine sarcomas [91]. Management of recurrent disease included secondary cytoreductive surgery in 63% of patients, chemotherapy in 55%, and radiation in 26%. Of the 80 patients undergoing secondary cytoreductive surgery, a complete resection with no residual disease was reported in 80%. In contrast to the survival benefit associated with successful secondary cytoreduction in ovarian cancer, however, median survival time in this study was only modestly improved (2.0 versus 1.1 years, $p<0.001$), with recurrence within 6 months of diagnosis indicating more aggressive disease often poorly responsive to secondary cytoreduction (Figure 8). Upon review, secondary cytoreductive surgery (HR=0.26) and prolonged time to recurrence (HR=0.58) independently predicted superior disease-specific survival, whereas neither chemotherapy nor radiation improved outcome in patients with recurrent disease.

By reducing tumor volume, optimal surgical resection of recurrent disease appears to be associated with extended post-recurrence survival in a select group of patients, although the modest magnitude of this benefit should be considered in selecting patients for surgical intervention. Patients presenting after a prolonged progression-free interval and preferably with an isolated site of recurrence appear to be the best candidates for attempted surgical resection.

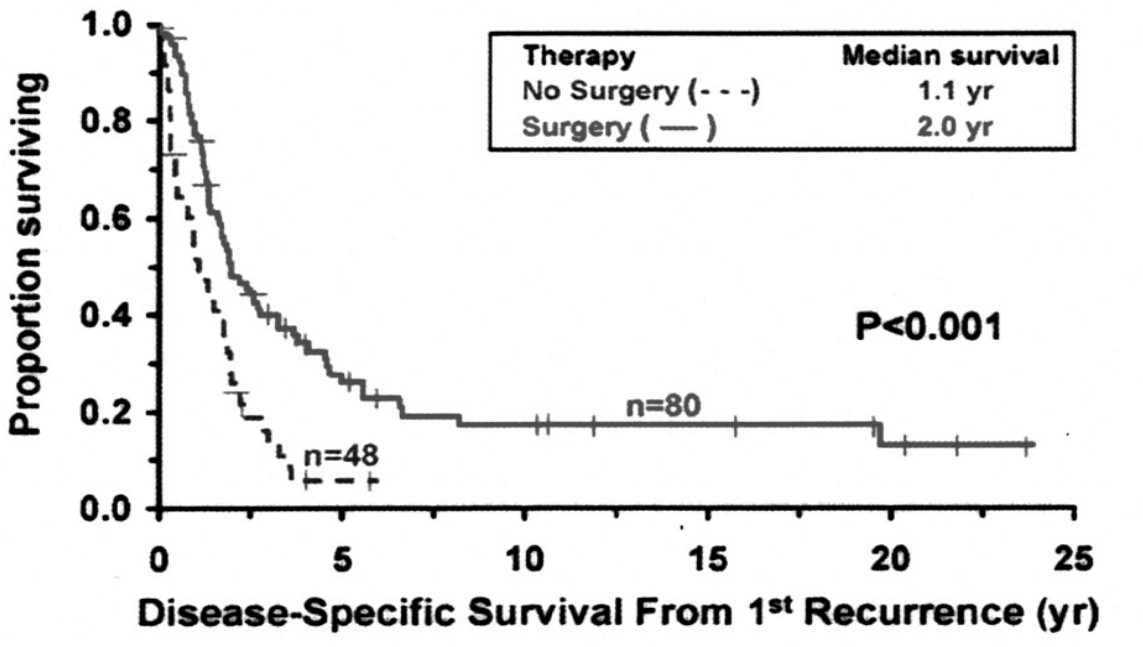

Figure 8. Secondary cytoreductive surgery led to significantly improved disease specific survival in patients with recurrent leiomyosarcomas. Courtesy of Giuntoli R et al. Gynecol Oncol 2007;106(1):82.

Surgical morbidity and postoperative complications

Inevitably, surgical and postoperative morbidity are key factors when considering cytoreductive surgery in patients with advanced or recurrent disease. Nevertheless, the value of radical pelvic and abdominal procedures in these patients needs to be balanced against the associated high morbidity and resulting quality of life for the individual woman.

Little data exists unfortunately regarding the true surgical morbidity associated with substantial cytoreductive procedures. Lambrou and coworkers first looked at the complexities of these complications in detail [21]. Even though the suboptimal and optimal groups in their review exhibited statistically similar radical debulking operations, the suboptimal group actually experienced increased morbidity thought secondary to inherent tumor biology rather than the type of surgical procedure performed. The proportion of patients with major postoperative complications (37.5% vs. 7.25%, p=0.005), unplanned postoperative ICU admissions (31.25% vs. 7.25%, p= 0.018), and length of hospital stay exceeding 15 days (31.25% vs. 4.35%, p= 0.005) proved to be much greater in patients left with residual disease. Specifically, the incidence of major adverse events including severe cardiopulmonary compromise, vascular embolus, fascial dehiscence, sepsis, bowel obstruction, and repeat laparotomy occurred significantly more in patients with suboptimal cytoreductive surgery (37.50% vs. 7.25%, p= 0.005), but the incidence of minor complications including febrile episodes, urinary and surgical site, simple pneumonia, and ileus, conversely, did not significantly differ between the two groups.

In advanced stage patients with only resection of nodal metastases, Havrilesky *et al.* similarly observed adverse events in 24% of patients [19]. Surgical complications included small bowel obstruction requiring surgery (3%), repeat laparatomy (3%), genitourinary obstruction (2%), wound dehiscence (1%), and lymphocyst requiring drainage (1%). Meanwhile, medical events included small bowel obstruction treated conservatively (3%), venous emboli (4%), cardiopulmonary compromise (5%), pneumonia (1%), and pyelonephritis (1%).

In their series, Bristow *et al.* likewise found excessive hemorrhage (>1 liter) in 11.4% of patients, with 28.6% of women requiring a blood transfusion [74]. No peri-operative deaths took place. Minor postoperative morbidity (*e.g.* adynamic ileus, urinary tract infection, superficial wound breakdown, pneumonia, deep vein thrombosis) occurred in nearly 30% of patients, while 5% of women experienced more life-threatening complications that included bacteremia, pulmonary emboli, and acute renal failure. The median length of hospitalization for all patients amounted to 6 days, ranging 1-21 days.

Cytoreductive surgery in women with either advanced or recurrent uterine cancer therefore demonstrates significant but acceptable risks that require thoughtful deliberation, given the potential therapeutic gains of these more expansive procedures. Before contemplating any surgical intervention, however, appropriate diagnostic evaluation, optimization of medical comorbidities, and thorough risk assessment should be undertaken prior to any tumor debulking operation in order to identify patients best suited to benefit in the long-term.

Conclusions and future directions

Certainly, women with metastatic, refractory, or chemoresistant uterine carcinomas need to be considered for primary and salvage cytoreductive procedures if deemed medically or technically possible. Only through maximal surgical efforts, in conjunction with the development of novel targeted based adjuvant drugs, will real therapeutic strides be made for these patients in whom prognosis continues to be abysmal.

References

1. Vardi J, Tadros G, et al. (1992). The value of exploratory laparotomy in patients with endometrial carcinoma according to the new International Federation of Gynecology and Obstetrics staging. *Obstet Gynecol* 80(2):204.
2. Wolfson A, Sightler S, et al. (1992). The prognostic significance of surgical staging for carcinoma of the endometrium. *Gynecol Oncol* 45(2):142.
3. Munkarah A, Levenback C, et al. (2001). Secondary cytoreductive surgery for localized intra-abdominal recurrences in epithelial ovarian cancer. *Gynecol Oncol* 81(2): 237.
4. Gadducci A, Iacconi P, et al. (2000). Complete salvage surgical cytoreduction improves further survival of patients with late recurrent ovarian cancer. *Gynecol Oncol* 79(3):344.
5. Eisenkop S, Friedman R, et al. (1995). Secondary cytoreductive surgery for recurrent ovarian cancer: a prospective study. *Cancer* 76(9):1606.
6. Creasman W, Morrow C, et al. (1987). Surgical pathologic spread patterns of endometrial cancer: a Gynecologic Oncology Group study. *Cancer* 60(8 Suppl): 2035.
7. Chuang L, Burke T, et al. (1995). Staging laparotomy for endometrial carcinoma: assessment of retroperitoneal lymph nodes. *Gynecol Oncol* 58(2):189.
8. Cragun J, Havrilesky L, et al. (2005). Retrospective analysis of selective lymphadenectomy in apparent early-stage endometrial cancer. *J Clin Oncol* 23(16): 3668.
9. Mohan D, Samuels M, et al. (1998). Long-term outcomes of therapeutic pelvic lymphadenectomy for stage I endometrial adenocarcinoma. *Gynecol Oncol* 70(2): 165.

10. Kilgore L, Patridge E, et al. (1995). Adenocarcinoma of the endometrium: survival comparisons of patients with and without pelvic lymph node sampling. *Gynecol Oncol* 56(1):29.
11. Rose R, Cha S, et al. (1992). Radiation therapy for surgically proven para-aortic node metastasis in endometrial carcinoma. *Int J Radiat Oncol Biol Phys* 24(2):229.
12. Potish R, Twiggs L, et al. (1985). Paraaortic lymph node radiotherapy in cancer of the uterine corpus. *Obstet Gynecol* 65(2):251.
13. Mariani A, Webb M, et al. (2000). Potential therapeutic role of para-aortic lymphadenectomy in node-positive endometrial cancer. *Gynecol Oncol* 76(3): 348.
14. McMeekin S, Lashbrook D, et al. (2001). Analysis of FIGO stage IIIC endometrial cancer patients. *Gynecol Oncol* 81(2): 273.
15. Hirahatake K, Hareyama H, et al. (1997). A clinical and pathologic study of para-aortic lymph node metastasis in endometrial carcinoma. *J Surg Oncol* 65(2): 82.
16. Corn B, Lanciano R, et al. (1992). Endometrial cancer with para-aortic adenopathy: patterns of failure and opportunities for cure. *Int J Radiat Oncol Biol Phys* 24(2): 223.
17. Boronow R, Morrow C, et al. (1984). Surgical staging in endometrial cancer: clinical-pathologic findings of a prospective study. *Obstet Gynecol* 63(6):825.
18. Hicks M, Piver M, et al. (1993). Survival in patients with paraaortic lymph node metastases from endometrial adenocarcinoma clinically limited to the uterus. *Int J Radiat Oncol Biol Phys* 26(4):607.
19. Havrilesky L, Cragun J, et al. (2005). Resection of lymph node metastases influences survival in stage IIIC endometrial cancer. *Gynecol Oncol* 99(3):689.
20. Bristow R, Zahurak M, et al. (2003). FIGO stage IIIC endometrial carcinoma: resection of macroscopic nodal disease and other determinants of survival. *Int J Gynecol Cancer* 13(5):664.
21. Lambrou N, Gomez-Marin O, et al. (2004). Optimal surgical cytoreduction in patients with stage III and stage IV endometrial carcinoma: a study of morbidity and survival. *Gynecol Oncol* 93: 653.
22. Chan J, Cheung M, et al. (2006). Therapeutic role of lymph node resection in endometrioid corpus cancer. *Cancer* 107(8):1823.
23. Fujimoto T, Nanjyo H, et al. (2007). Para-aortic lymphadenectomy may improve disease-related survival in patients with multipositive pelvic lymph node stage IIIc endometrial cancer. *Gynecol Oncol* 107(2): 253.
24. Lutman C, Havrilesky L, et al. (2006). Pelvic lymph node count is an important prognostic variable for FIGO stage I ad II endometrial carcinoma with high-risk histology. *Gynecol Oncol* 102:92.
25. Fujiwara H, Saga Y, et al. (2007). Omental metastases in clinical stage I endometrioid adenocarcinoma. *Int J Gynecol Cancer* 18(1):165.
26. Gehrig P, Van Le L, et al. (2003). The role of omentectomy during the surgical staging of uterine serous carcinoma. *Int J Gynecol Cancer* 13(2):212.
27. Jeffrey J, Krepart G, et al. (1986). Papillary serous adenocarcinoma of the endometrium. *Obstet Gynecol* 67(5):670.
28. Kato D, Ferry J, et al. (1995). Uterine papillary serous carcinoma (UPSC): a clinicopathologic study of 30 cases. *Gynecol Oncol* 59(3):384.

29. Cirisano F, Robboy S, et al. (1999). Epidemiologic and surgicopathologic findings of papillary serous and clear cell endometrial cancers when compared to endometrioid carcinoma. *Gynecol Oncol* 74(3):385.
30. Geisler J, Geisler H, et al. (1999). What staging surgery should be performed on patients with uterine papillary serous carcinoma? *Gynecol Oncol* 74(3):465.
31. Faratian D, Stillie A, et al. (2006). A review of the pathology and management of uterine papillary serous carcinoma and correlation with outcome. *Int J Gynecol Cancer* 16(3):972.
32. Marino B, Burke T, et al. (1995). Staging laparotomy for endometrial carcinoma: assessment of peritoneal spread. *Gynecol Oncol* 56(1):34.
33. Chi D, Welshinger M, et al. (1997). The role of surgical cytoreduction in stage IV endometrial carcinoma. *Gynecol Oncol* 67(1):56.
34. Goff B, Goodman A, et al. (1994). Surgical stage IV endometrial carcinoma: a study of 47 cases. *Gynecol Oncol* 52(2): 237.
35. Greer B, Hamberger D. (1983). Treatment of intraperitoneal metastatic adenocarcinoma of the endometrium by the whole-abdomen moving strip technique and pelvic boost irradiation. *Gynecol Oncol* 16(3):365.
36. Martinez A, Podratz K, et al. (1988). Results of whole abdominopelvic irradiation with nodal boost for patient with endometrial cancer at high risk of failure in the peritoneal cavity: a prospective clinical trial at the Mayo Clinic. *Hematol Oncol Clin North Am* 2(3):431.
37. Bristow R, Zerbe M, et al. (2000). Stage IVB endometrial carcinoma: the role of cytoreductive surgery and determinants of survival. *Gynecol Oncol* 78(2):85.
38. Ayhan A, Taskiran C, et al. (2002). The influence of cytoreductive surgery on survival and morbidity in stage IVB endometrial cancer. *Int J Gynecol Cancer* 12(5):448.
39. Matthews R, Hutchinson-Cola J, et al. (1997). Papillary serous and clear cell type lead to poor prognosis of endometrial carcinoma in black women. *Gynecol Oncol* 65(2):206.
40. Rosenberg P, Blom R, et al. (1993). Death rate and recurrence pattern among 841 clinical stage I endometrial cancer patients with special reference to uterine papillary serous carcinoma. *Gynecol Oncol* 51(3):311.
41. Chambers J, Merino M, et al. (1987). Uterine papillary serous carcinoma. *Obstet Gynecol* 69(1):109.
42. Cirisano F, Robboy S, et al. (2000). The outcome of stage I-II clinically and surgically staged papillary serous and clear cell endometrioid cancers when compared with endometrioid carcinoma. *Gynecol Oncol* 77(1):55.
43. Nicklin J, Copeland, L. (1996). Endometrial papillary serous carcinoma: patterns of spread and treatment. *Clin Obstet Gynecol* 39(3):686.
44. O'Hanlan K, Levine P, et al. (1990). Virulence of papillary endometrial carcinoma. *Gynecol Oncol* 37(1):112.
45. Thomas M, Mariani A, et al. (2007). Role of systematic lymphadenectomy and adjuvant therapy in stage I uterine papillary serous carcinoma. *Gynecol Oncol* 107:186.
46. Slomovitz B, Burke T, et al. (2003). Uterine papillary serous carcinoma (UPSC): a single institution review of 129 cases. *Gynecol Oncol* 91(3):463.

47. Gehrig P, Groben P, et al. (2001). Noninvasive papillary serous carcinoma of the endometrium. *Obstet Gynecol* 97(1):153.
48. Dunton C, Balsara G, et al. (1991). Uterine papillary serous carcinoma: a review. *Obstet Gynecol Surv* 46(2):97.
49. Bristow R, Duska L, et al. (2001). The role of cytoreductive surgery in the management of stage IV uterine papillary serous carcinoma. *Gynecol Oncol* 81(1):92.
50. Carcangiu M, Chambers J. (1992). Uterine papillary serous carcinoma: a study on 109 cases with emphasis on the prognostic significance of associated endometrioid carcinoma, absence of invasion, and concomitant ovarian carcinoma. *Gynecol Oncol* 47(3):298.
51. Moller K., Gehrig P, et al. (2004). The role of optimal debulking in advanced stage serous carcinoma of the uterus. *Gynecol Oncol* 94(1):170.
52. Memarzadeh S, Holschneider C, et al. (2002). FIGO stage III and IV uterine papillary serous carcinoma: impact of residual disease on survival. *Int J Gynecol Cancer* 12(5):454.
53. Thomas M, Mariani A, et al. (2007). Role of cytoreduction in stage III and IV uterine papillary serous carcinoma. *Gynecol Oncol* 107(2):190.
54. Abeler V, Vergote I, et al. (1996). Clear cell carcinoma of the endometrium: prognosis and metastatic pattern. *Cancer* 78(8):1740.
55. Thomas M., Mariani A, et al. (2008). Surgical management and adjuvant therapy for patients with uterine clear cell carcinoma: a multi-institutional review. *Gynecol Oncol* 108(2):293.
56. Morrow C, Bundy B, et al. (1991). Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a gynecologic oncology group study. *Gynecol Oncol* 40(1): 55.
57. Aalders J, Abeler V, et al. (1984). Recurrent adenocarcinoma of the endometrium: a clinical and histopathological study of 379 patients. *Gynecol Oncol* 17(1):85.
58. Barakat R, Goldman N, et al. (1999). Pelvic exenteration for recurrent endometrial cancer. *Gynecol Oncol* 75:99.
59. Morris M, Alvarez R, et al. (1996). Treatment of recurrent adenocarcinoma of the endometrium with pelvic exenteration. *Gynecol Oncol* 60: 288.
60. Wylie J, Irwin C, et al. (2000). Results of radical radiotherapy for recurrent endometrial cancer. *Gynecol Oncol* 77(1):66.
61. Sears J, Greven K, et al. (1994). Prognostic factors and treatment outcome for patients with locally recurrent endometrial cancer. *Cancer* 74(4):1303.
62. Curran W, Whittington R, et al. (1988). Vaginal recurrence or endometrial carcinoma: the prognostic value of staging by a primary vaginal carcinoma system. *Int J Radiat Oncol Biol Phys* 15(4): 803.
63. Lincoln S, Blessing J, et al. (2003). Activity of paclitaxel as second-line chemotherapy in endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol* 88(3): 277.
64. Wadler S, Levy D, et al. (2003). Topotecan is an active agent in the first-line treatment of metastatic or recurrent endometrial carcinoma: Eastern Cooperative Oncology Group study E3E93. *J Clin Oncol* 21(11):2110.

65. Burke T, Munkarah A, et al. (1993). Treatment of advanced or recurrent endometrial carcinoma with single-agent carboplatin. *Gynecol Oncol* 51(3):397.
66. Thigpen J, Blessing J, et al. (1989). Phase II trial of cisplatin as first-line chemotherapy in patients with advance or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol* 33(1):68.
67. Thigpen T, Brady M, et al. (2001). Tamoxifen in the treatment of advanced or recurrent endometrial carcinoma: a gynecologic oncology group study. *J Clin Oncol* 19(2): 364.
68. Podratz K, O'Brien P, et al. (1985). Effects of progestational agents in treatment of endometrial carcinoma. *Obstet Gynecol* 66(1):106.
69. Quinn M, Cauchi M, et al. (1985). Endometrial carcinoma: steroid receptors and response to medroxyprogesterone acetate. *Gynecol Oncol* 21(3): 314.
70. Piver M, Barlow J, et al. (1980). Medroxyprogesterone acetate (Depo-Provera) vs. hydroxyprogesterone caproate (Delalutin) in women with metastatic endometrial carcinoma. *Cancer* 45(2):268.
71. Scarabelli C, Campagnutta E, et al. (1998). Maximal cytoreductive surgery as a reasonable therapeutic alternative for recurrent endometrial carcinoma. *Gynecol Oncol* 70(1):90.
72. Campagnutta E, Giorda G, et al. (2003). Surgical treatment of recurrent endometrial carcinoma. *Cancer* 100(1):89.
73. Awtrey C, Cadungog M, et al. (2006). Surgical resection of recurrent endometrial carcinoma. *Gynecol Oncol* 102(3):480.
74. Bristow R, Santillan A, et al. (2006). Salvage cytoreductive surgery for recurrent endometrial cancer. *Gynecol Oncol* 103:281.
75. Mayerhofer K, Obermair A, et al. (1999). Leiomyosarcoma of the uterus: a clinicopathologic multicenter study of 71 cases. *Gynecol Oncol* 74(2):196.
76. Major F, Blessing J, et al. (1993). Prognostic factors in early-stage uterine sarcoma: a Gynecologic Oncology Group study. *Cancer* 71(4 Suppl):1702.
77. Hannigan E, Gomez L. (1979). Uterine leiomyosarcoma. *Am J Obstet Gynecol* 134(5):557.
78. Goff B, Rice L, et al. (1993). Uterine leiomyosarcoma and endometrial stromal sarcoma lymph node metastases and sites of recurrence. *Gynecol Oncol* 50(1):105.
79. Gadducci A, Landoni F, et al. (1996). Uterine leiomyosarcoma: analysis of treatment failures and survival. *Gynecol Oncol* 62(1):25.
80. Larson B, Silfversward C, et al. (1990). Prognostic factors in uterine leiomyosarcoma: a clinical and histopathological study of 143 cases: the Radiumhemmet series 1936-1981. *Acta Oncol* 29(2):185.
81. Berchuck A, Rubin S, et al. (1988). Treatment of uterine leiomyosarcoma. *Obstet Gynecol* 71(6 Pt 1):845.
82. Dinh T, Oliva E, et al. (2004). The treatment of uterine leiomyosarcoma: results from a 10-year experience (1990-1999) at the Massachusetts General Hospital. *Gynecol Oncol* 92(2):648.
83. Giuntoli R, Metzinger D, et al. (2003). Retrospective review of 208 patients with leiomyosarcoma of the uterus: prognostic indicators, surgical management, and adjuvant therapy. *Gynecol Oncol* 89(3):460.

84. Park J, Kim D, et al. (2008). Prognostic factors and treatment outcomes of patients with uterine sarcoma: analysis of 127 patients at single institution, 1989-2007. *J Cancer Res Clin Oncol* 134(12):1277.
85. Omura G, Blessing J, et al. (1985). A randomized clinical trial of adjuvant adriamycin in uterine sarcomas: a Gynecologic Oncology Group study. *J Clin Oncol* 3(9):1240.
86. Sutton G, Blessing J, et al. (1996). Ifosfamide and doxorubicin in the treatment of advanced leiomyosarcomas of the uterus: a Gynecologic Oncology Group study. *Gynecol Oncol* 62(2):226.
87. Muss B, Bundy B, et al. (1985). Treatment of recurrent or advanced uterine sarcoma: a randomized trial of doxorubicin versus doxorubicin and cyclophosphamide (a phase III trial of the Gynecologic Oncology Group). *Cancer* 55(8):1648.
88. Levenback C, Rubin S, et al. (1992). Resection of pulmonary metastases from uterine sarcomas. *Gynecol Oncol* 45(2):202.
89. Leitao M, Brennan M, et al. (2002). Surgical resection of pulmonary and extrapulmonary recurrences of uterine leiomyosarcoma. *Gynecol Oncol* 87(3): 287.
90. Lang H, Nussbaum K, et al. (2000). Hepatic metastases from leiomyosarcoma: a single-center experience with 34 liver resections during a 15-year period. *Ann Surg* 231(4):500.
91. Giuntoli R, Garrett-Mayer E, et al. (2007). Secondary cytoreduction in the management of recurrent uterine leiomyosarcoma. *Gynecol Oncol* 106(1):82.