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Chapter 12

Management of Advanced Stage Endometrial Cancer

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Abstract

Endometrial cancer is frequently diagnosed at early stage with a good prognosis. However, about 30 percent of endometrial cancer is in advanced stage at presentation with obviously poor prognosis. In this chapter, histology, clinical /imaging diagnosis, and treatment of the advanced stage endometrial cancer will be reviewed. *Histology:* Type II tumors including Grade 3 endometrioid tumors as well as non-endometrioid histology are commonly related with advanced stage of endometrial cancer. The most common histological types of Stage IVb tumors were endometrioid adenocarcinoma, followed by serous adenocarcinoma and clear cell adenocarcinoma. Histological characteristics of advanced stage endometrial cancer will be reviewed. *Clinical and imaging diagnosis:* Pelvic or/and para-aortic lymph nodes and intra-abdominal organs/tissues are the common sites of metastasis of advanced stage endometrial cancer. Extra-abdominal metastasis, with or without intra-abdominal lesions beyond the pelvis, are also observed

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in some cases. The pattern of tumor progression of advanced stage endometrial cancer and clinical /imaging diagnosis of the disease will be reviewed. *Treatment: Surgery:* Patients with advanced stage endometrial cancer are treated with surgical cytoreduction, followed by chemotherapy, or radiation therapy, or both. Recent studies showed optimal cytoreduction is associated with a significant increase in survival. In order to evaluate the effectiveness of cytoreductive surgery in patients with advanced stage endometrial cancer, we searched the electronic database PubMed search for relevant, using the headings and keywords ‘’advanced endometrial cancer’’, ‘’cytoreductive surgery’’, and ‘’cytoreduction’’. There was a statistically significant positive correlation between maximal cytoreduction and median survival time. The complete surgery had significantly better median survival than optimal surgery with macroscopic residual tumor or suboptimal surgery. The total mortality rate was 3.1% calculated from 7 studies, and pulmonary embolism was the main reason for the surgery-associated death. An intraperitoneal spread of the tumor and/or the extensive surgical procedure on or near the intestine would cause bowel obstruction. Although postoperative adjuvant therapy varied in studies, chemotherapy especially platinum-based chemotherapy seemed to have better effect on survival. *Chemotherapy:* Chemotherapy with platinum-based combination regimen seems to have effect of survival. Taxane is also an active drug for endometrial cancer. Effective regimens for advanced stage/recurrent endometrial cancer will be reviewed. Recent studies demonstrated that treatment-free interval (TFI) of ≥ or <6 months was significantly associated with the response to second-line chemotherapy, progression-free survival and overall survival in advanced stage/recurrent endometrial cancer.

1. Introduction

Endometrial cancer is the most common gynecologic cancer in the USA. The American Cancer Society has estimated that 43,470 women were diagnosed with endometrial cancer in 2010, and 7,950 women died from it that year [1]. The age-adjusted death rate is 4.1 per 100,000 women per year, which is significantly lower than for other gynecologic cancers. In Japan, 10,815 women were diagnosed with the disease in 2008 (the age-adjusted incidence rate is 16.5 per 100,000 women per year) [2], and 2092 women died from it in 2012 (the age-adjusted death rate is 12.5 per 100,000 women per year) [3]. The reason for this is that most women with endometrial cancer are diagnosed at an early stage and are treated by hysterectomy and surgical staging alone.

Patients with localized endometrial cancer represent 68% of all newly diagnosed cases and their 5-year relative survival rate is high (95.8%), whereas 8% of all cases are advanced, with distant metastasis at first diagnosis, and have only a 16.2% 5-year relative survival rate [4]. Patients with metastatic uterine disease respond poorly to current therapeutic regimens, and the optimal management in these women is not yet well established. The National Cancer Institute has treatment options for stage IV endometrial cancer, which include radiation therapy for bulky pelvic diseases and hormone therapy for distant metastases, and may include systemic chemotherapy, although no standard regimen is yet established. The role of cytoreductive surgery in advanced endometrial cancer is still somewhat controversial, but available data suggests that optimal surgical cytoreduction of the tumor and its metastases are associated with an improved survival. In this chapter, the role of such cytoreductive surgery in advanced endometrial cancer is reviewed.

Adriamycin and platinum have long played a key role in the treatment for advanced and recurrent endometrial cancer. Recently, an anti-tumor effect of taxane was shown for many kinds of solid cancers, and it was introduced for treatment of endometrial cancer. In this chapter, we review the results from comparative studies of chemotherapy for endometrial cancers with tumors measurable by imaging devices. In addition, we discuss the association of the efficacy of second line chemotherapy, and the treatment free interval (TFI) after first line chemotherapy, of current the gold standard regimens containing taxane and platinum, which has been demonstrated for ovarian cancer cases.

2. Histologic Features of Endometrial Cancer

The most common histology of endometrial cancer is the endometrioid type. Based on clinicopathologic and molecular genetic features, endometrial cancer is divided into two categories, type I and type II. A typical characteristic of a type I tumor is of an endometrioid adenocarcinoma developing through endometrial hyperplasia due to unopposed estrogen. Type I tumors usually exhibit a low tumor grade, minimal myometrial invasion, and behave indolently.On the other hand, the type II serous carcinoma represents the most common form of endometrial cancer not related to estrogen stimulation [5]. Serous carcinoma, usually referred to as uterine papillary serous carcinoma (UPSC) accounts for only 3-11% of all cases of endometrial carcinoma, but the prognosis is relatively very poor because of its high frequency of extra-uterine and intraperitoneal metastasis, and its high recurrence risk [6]. The extra-uterine spread is reported to be as high as 30-50%, even when the primary disease appears to be limited to the endometrium [7]. UPSC behaves similarly to papillary serous adenocarcinoma of the ovary, with roughly 70% of patients found to have intraperitoneal spread at a stage of III-IV at diagnosis. A high recurrence risk is also characteristic of UPSC, with 83% of such recurrences associated with abdominopelvic failure and 34% with distant failure. These characteristics are why UPSC is responsible for 15-20% of all endometrial cancer-related deaths [8].

Due to the characteristics of each histologic subtype, their distribution depends on the stage of the disease. According to the 2005 JSOG (Japan Society of Obstetrics and Gynecology) annual cancer registry report [9], the proportion of endometrioid adenocarcinoma decreased and that of non-endometrioid types, including UPSC, increased as the stage of the disease progressed (Table 1). Non-endometrioid types were observed in 240 (34%) of 699 advanced stage (stage III or IV) cases and in 316 (15%) of early stage (stage I or II) cases.

This difference was statistically significant (p <0.001). Eto et al. reported retrospective analysis of 248 patients of stage IVb endometrial cancer [10]. In their cases, the most common histological subtype was endometrioid (61%), however, there was a high frequency of poor histological factors, with endometrioid grade 3 (24%) or non-endometrioid histology (40%). Only 15% of patients were classified as endomtrioid grade 1. Moreover, there were high frequency of deep myometrial invasion (69%) and positive lymphovascular space invasion (LVSI) (70%).

3. Clinical and Imaging Diagnosis of Advanced Endometrial Cancer

3.1. Distribution of Metastatic Endometrial Disease

Proper imaging to search for metastatic lesions is essential for accurate clinical diagnosis of advanced endometrial cancer cases.

Table 1. Histologic subtypes on the stage of the disease

FIGO stage	endometrioid	non-endometrioid
I	1596 (86%)	270 (14%)
II	201 (81%)	46 (19%)
III	356 (69%)	159 (31%)
IV	103 (56%)	81 (44%)

Table 2. The sites of metastasis of endometrial cancer

	Total (n =413)		All Subtypes (n= 345)		UPSC alone (n= 68)		p value
Extra-pelvic	65/214	(30.4%)	50/183	(27.3%)	15/35	(48.4%)	0.02
Extra-abdomen	73/265	(27.5%)	68/234	(29.1%)	5/31	(16/1%)	0.01
Ovary	61/126	(48.4%)	48/89	(53.9%)	13/33	(39.4%)	N.S.
Cervix	41/87	(47.1%)	41/87	(47.1%)			
Vagina	12/152	(7.9%)	12/152	(7.9%)			
Retroperitoneal lymph node	78/222	(35.1%)	71/191	(37.2%)	7/31	(22.6%)	N.S.
Pelvic lymph node	37/136	(27.2%)	37/136	(27.2%)			
Paraaortic lymph node	48/136	(35.3%)	48/136	(35.3%)			
Peritonium	114/242	(47.1%)	106/205	(51.7%)	8/37	(21.6%)	0.0007
Omentum	139/273	(50.9%)	99/205	(48.3%)	40/68	(58.8%)	N.S.
Bladder	1/37	(2.7%)	1/37	(2.7%)			
Intestine	80/244	(32.8%)	53/176	(30.1%)	27/68	(39.7%)	N.S.
Liver	23/171	(13.5%)	21/140	(15.0%)	2/31	(6.5%)	N. S.
Spleen	8/111	(7.2%)	3/74	(4.1%)	5/37	(13.5%)	N.S.
Diaphragm	8/78	(10.3%)	3/41	(7.3%)	5/37	(13.5%)	N.S.
Lung	29/291	(10.0%)	28/260	(10.8%)	1/31	(3.2%)	N.S.
Pleural effusion	21/184	(11.4%)	19/153	(12.4%)	2/31	(6.5%)	N.S.
Other lymph node	27/231	(11/7%)	27/231	(11.7%)			
Bone	6/172	(3.5%)	6/172	(3.5%)			
Brain	3/143	(2.1%)	3/143	(2.1%)			
Other	1/41	(2.4%)	1/41	(2.4%)			

The sites of metastasis of endometrial cancer have been delineated in 10 studies, with results for 413 total patients, including 2 studies of UPSC only (Tables 2 and 3). The number of patients was small, especially in the UPSC group, thus the results differed among reports, as might be expected. Extra-pelvic metastasis, extra-abdominal metastasis, and metastasis to the peritoneum were all significantly less in the UPSC group. There was no statistical

difference in rates for other sites of metastasis. Twenty-seven cases had metastases to lymph nodes (not counting retroperitoneal lymph nodes); these included 9 with supraclavicular lymph node involvement and 9 inguinal lymph node cases; the 9 other cases of nodal disease were not precisely defined. There were 6 cases of UPSC metastasis to bone (3.5%), 3 cases of to the brain (2.1%), and 1 case of to the eye.

Table 3. Number and extent of regional involvement

	Frequency (%)	
	All types	UPSC
1 Region spread	16.9	3.2
2 Regions spread	23.1	22.6
3 Regions spread	27.7	25.8
≧4 Regions spread	32.3	48.4
	(Bristow, 2000)	(Bristow, 2001)

Ayhan et al. found that, upon multivariate analysis, an extra-abdominal metastasis was significantly negatively associated with survival, although Chi et al. [11] did not find a survival difference between patients with extra-abdominal versus intra-abdominal metastases, results which, combined, implies that at an advanced disease stage the volume of the metastatic mass is more important than its site [12].

As discussed in the section of uterine papillary serous carcinoma above, UPSC is more likely to have an intraperitoneal spread. Because of this, 50% of patients with UPSC are surgically staged higher at the time of laparotomy [6]. In a study by Memarzadeh et al., the preoperative endometrial sample was diagnostic for an endometrial adenocarcinoma in 94% of cases, but agreed with the specific diagnosis of UPSC in only 42% of cases, which makes seeing the intra-abdominal spread at the time of operation often unexpected [7].

Imaging devices, such as magnetic resonance imaging (MRI) and computed tomography (CT) are used to evaluate tumor progression. Accurate detection of extra-uterine lesions is very critical for the choice of the treatment for advanced endometrial cancer cases. The potential for an optimal resection is evaluated by preoperative imaging tests. Recently, metabolic imaging by positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) was introduced for imaging of various kinds of cancers. A previous study demonstrated that, compared to traditional MRI and CT, FDG-PET alone was only marginally superior; however, it was found that FDG-PET plus MRI or CT was significantly more accurate for detection of pelvic or extra-pelvic diseases (Table 4).

3.2. Chemotherapy for Advanced Endometrial Cancer

3.2.1. Transition of a Standard Regimen for Advanced / Recurrent Endometrial Cancer

A single agent chemotherapy of Adriamycin, epirubicin, cisplatin, cyclophosphamide, ifosphamide, carboplatin, paclitaxel, and decetaxel was shown to be effective for advanced /

recurrent diseases [13-25]. Among these drugs, adriamycin and platinum have been key drugs for the treatment of endometrial cancer, and AP therapy (Adriamycin plus cisplatin) has long been the gold standard (Table 5). Since Paclitaxel became available in the 1980s, it has been used for many cancers, including gynecologic malignancies. Regarding endometrial cancer, AT therapy (doxorubicin plus paclitaxel) showed a similar outcome to AP therapy, although G-CSF support was required because of AT's severe myelosuprression effect [26]. However, AP therapy has remained the standard regimen.

Table 4. Detection of pelvic or extra-pelvic diseases

	AUC	p-value
Pelvic metastasis		0.048
MRI and/or CT	0.868	
PET plus MRI and/or CT	0.944	
Extra-pelvic metastasis		0.010
MRI and/or CT	0.838	
PET plus MRI and/or CT	0.949	

Table 5. Results of comparison studies of chemotherapy regimens

Study	comparison	significant outcome
GOG 107	AP > A	PFS
EORTC	AP > A	response rate
GOG 163	AP = AT (+ G-CSF)	PFS・OS
GOG 177	AP < TAP (+G-CSF)	PFS・OS
JGOG 2041	DP = DC = TC	PFS
GOG 209	TAP = TC	PFS・OS

Fleming et al. showed that TAP therapy (AP plus paclitaxel) significantly improves PFS and OS compared to AP, but it did not replace AP as the standard regimen because of TAP's severe neurotoxicity.

In order to decrease side effects, platinum-based combination chemotherapies with paclitaxel became popular. Among these new regimens, TC (paclitaxel and carboplatin) became known as the "community standard" and it has been used frequently. In fact, TC therapy showed an efficacy similar to that of other regimens, such as taxane plus platinum, docetaxel plus cisplatin (DP), and docetaxel plus carboplatin (DC), as reported in the Japanese Gynecologic Oncology Group JGOG2041 study [27]. Recently, TC therapy was proven to be as active as TAP therapy, but with less toxicity [28]; thus, TC therapy could potentially become the standard regimen for advanced and recurrent endometrial cancer.

Hormone therapy is also used to treat endometrial cancer; however, its evidence level is lower than that of chemotherapy [29-36]

3.2.2. Treatment-Free Interval

The length of the treatment-free interval (TFI) before tumor recurrence/progression after a first line chemotherapy has been demonstrated to be a strong indicator of the likely response to the application of second-line chemotherapy for ovarian cancer. The response to the second-line chemotherapy is significantly related to the TFI after the original first-line platinum-based chemotherapy. The cases whose TFI was shorter than 6 months often had disease that was likely to be highly resistant to a second-line platinum-based chemotherapy; they are defined as resistant cases. Those patients with a TFI of 6-12 months still exhibited a relatively worse response to second-line chemotherapy using platinum than those with a TFI ≥12 months; these patients with a TFI of 6-12 months were considered to be partially sensitive cases. Patients with a TFI ≥ 12 months had a higher chance of responding well to a challenge with the platinum-based first-line treatment; these cases were defined as platinum-sensitive [37, 38].

A few studies analyzed whether the association of TFI and response to second-line chemotherapy was applicable to endometrial cancer. We have conducted a retrospective study of cases treated by a second-line chemotherapy containing tisane and platinum for advanced or recurrent diseases (after a first-line chemotherapy containing tisane and platinum). In our study, a TFI of ≥ or <6 months was demonstrated to be significantly associated with the response to second-line chemotherapy (p= 0.0026), progression-free survival (p= 0.0003) and overall survival (p= 0.025) [39]. Progression-free survival was shown to be significantly worse in those with TFIs of 6-12 months (median, 7 months) than those with TFIs of 12 or more months (median, 12 months) [40]. These results indicated that, in the same way as in ovarian cancer cases, TFI after a first-line chemotherapy was a strong indicator for the likely response to a second-line chemotherapy, and that the cases whose TFI < 6 months could be defined as resistant, those with a TFI of 6-12 months as partially sensitive, and those with TFI ≥ 12 months as sensitive. A recent, relatively large, study by Nagao et al. [41] confirmed this hypothesis. (Table 6)

4. Treatment

4.1. Surgical Treatment for Advanced Endometrial Cancer

4.1.1. Why Cytoreductive Surgery Is Discussed for Advanced Stage Endometrial Cancer?

The role of cytoreductive surgery for advanced endometrial cancer is still evolving; however, the survival benefits of an optimal cytoreduction for advanced ovarian cancer have been confirmed by multiple retrospective and prospective studies and optimal cytoreduction is still widely accepted as a standard of care [42].

In 1975, Griffiths et al. demonstrated a direct relationship between the post-surgical residual tumor diameter and the overall survival rate [43]. Since then, multiple retrospective studies have confirmed their observation. During the time when the importance of platinum-

based chemotherapy was first being recognized, Bristow et al. reported that maximal cytoreduction was still the most powerful determinant of cohort survival among patients with stage III or IV ovarian cancer [44, 45].

The survival benefit was greatest in those where the cytoreductive surgery was achieved most extensively; those who had microscopic residual disease fared better than those who had macroscopic residual disease, even if it was less than 1 cm.

Table 6. Association of treatment-free interval and effectiveness of second-line chemotherapy containing taxane and platinum

Treatment free interval (TFI)	Sensitivity to second-line chemotherapy containing taxane and platinum
TFI < 6 months	sensitive
6 months ≤ TFI < 12 months	partially sensitive
TFI ≥ 12 months	sensitive

Thus, in the new millennium, the definition of postoperative tumor residuals has steadily progressed from so-called ‘optimal debulking’, with allowable small-volume tumor residuals, to the current allowance of only microscopic residuals, and ultra-radical cytoreductive surgery is now the goal with advanced ovarian cancer.

This trend for ever more radical surgical treatment of advanced ovarian cancer has raised the question of whether this same standard should be the goal with advanced endometrial cancer, and thus more attention is now being paid to cytoreductive surgery in this field.

4.1.2. Primary Cytoreductive Surgery for Advanced-Stage Endometrial Cancer

The first report which suggested a better outcome following cytoreduction for endometrial cancer was by Greer and Hamberger, in 1983 [46]. In their retrospective study, 31 women with intraperitoneal metastatic disease were reviewed. They were treated by whole-abdomen and pelvic boost-irradiation after their surgery. Twenty-seven patients with residual disease of 2 cm or less had an absolute 5-year survival rate of 63%, whereas the other 4 patients with residual diseases of greater than 2 cm had a 0% survival. In 1991, in their series of endometrial cancers, Dunton et al. found that patients who underwent tumor cytoreduction followed by a combination-chemotherapy of cisplatin, adriamycin and cyclophosphamide (CAP) had a substantially increased progression-free survival (PFS) rate [47]. Martinez et al. investigated 25 patients with stage III/IV endometrial cancer who underwent cytoreductive surgery (leaving less than 2 cm any residual disease) followed by whole abdominal radiation with nodal boost. They concluded that the size of the residual tumor was of prognostic value. These studies were originally designed to evaluate the effect of the radiation therapy, not the primary cytoreductive surgery. However, the results did suggest a correlation between the residual disease volume and the subsequent survival outcome [42] (Table 7).

Goff et al. reviewed 47 patients with stage IV disease in 1994 [48]. The median survival of 29 operative patients with no bulky disease left was 18 months, compared to 8 months for those who did not undergo surgery (p= 0.0001). Although the size of the residual disease was

not clearly specified, successful cytoreduction was the only statistically significant prognostic factor by multivariate analysis (p= 0.04).

The first study to rigorously examine the effect of surgical cytoreduction in stage IV disease was by Chi et al. [11]. They divided 55 patients into three groups: group I (n= 24) underwent optimal surgical cytoreduction to 2 cm or less; group II (n= 21) underwent suboptimal cytoreduction, with residual tumor greater than 2 cm; group III (n= 10) had unresectable disease and thus had no cytoreduction. The median survival rates for the three groups were 31 months for group I, 12 months for group II, and 3 months for group III (p <0.01). They also found, if an optimal cytoreduction was conducted, no statistically significant difference in survival between those who had a metastatic disease of 2 cm or less and those who initially had a metastatic disease greater than 2 cm. Their multivariate analysis found that only the surgical cytoreduction had prognostic significance for survival. In 2000, Bristow et al. analyzed 65 patients with stage IVb disease who underwent surgery as the primary therapy [49]. They defined optimal surgery more stringently, as having a residual tumor of less than 1 cm. The median survival of 36 patients who completed optimal surgery was 34 months, which was much longer than that of those who underwent suboptimal surgery (11 months) (p= 0.0001). Interestingly, among those with optimal surgery, patients with only microscopic residual disease survived significantly longer than patients with optimal surgery but retaining macroscopic tumor (41 vs. 15 months; p= 0.0001). On their multivariate analysis, residual disease, performance status and age were independent predictors of survival. They concluded that the volume of residual disease after cytoreductive surgery was still the strongest predictor of subsequent survival.

Performance status and younger age were found to contribute to having allowed both the extensive cytoreductive surgical efforts often required to produce an optimal surgical result and the subsequent intensive postoperative adjuvant therapy. Ayhan et al. also concluded, in a study of 37 patients with stage IVb endometrial cancer, that an optimal cytoreduction, again defined as residual disease of 1 cm or less, achieved a significant survival improvement [50]. The median survival of the suboptimally cytoreducted patients was 10 months, while that in the optimal cytoreduction group was 25 months (p= 0.001). In the optimal cytoreduction group, the median survival for 12 (55%) patients without visible tumor was 48 months, compared to 13 months in 10 (45%) patients with visible tumor. In a multivariate analysis, optimal cytoreduction concomitant with cisplatin-radiotherapy treatment, and extra-abdominal metastases were significant prognostic factors. Lambrou et al. analyzed 58 patients of stage IIIc and IV disease and found that 72% of the patients had optimal cytoreduction (defined by residual tumor of 2 cm or less) and these patients had longer overall survival compared with suboptimally cytoreducted patients (18 vs. 7 months, respectively; p= 0.001) [51]. In their study of for 67 patients, van Wijk et al. also reported a better prognosis for those receiving optimal cytoreduction, including those with stage IIIA disease. The 2-year and 5-year survival rates of optimal cytoreduction were 82.2% and 65.6%, respectively, compared with 50.8% and 40.6% for their suboptimal cytoreducted group [52].

Ueda et al. were the first to report that an aggressive cytoreductive surgery for stage IVb disease with extra-abdominal metastasis had a beneficial role. Out of their 30 patients, those who had optimal cytoreduction, with residual disease of 2 cm or less, had significantly better median survival, and this applied not only to those with intra-abdominal metastasis but also those with extra-abdominal masses [53].

Table 7. Retrospective review of primary cytoreductive surgery for advanced-stage endometrial cancer

Author	Year	Total patients (n)	Median age	Non-endometrioid (%)	FIGO stage	Extra pelvic (%)	Etra abdomen (%)	Optimal definition (cm)	Optimal CR		Complete CR		Optimal median OS (months)	Complete median OS (months)	Suboptimal median OS (months)	p-value	Perioperative death (n)
									(n)	(%)	(n)	(%)					
Greer	1983	31	55	NA	III/IV	NA	NA	≦ 2	27	87	NA	NA	NA	NA	NA	NA	NA
Goff	1994	47	68*	40	IV	57	NA	no gross bulky mass	NA	NA	NA	NA	19	NA	8	0.0001	2
Chi	1997	55	67	40	IV	NA	33	≦ 2	24	44	10	18	31	NA	12	< 0.01	NA
Bristow	2000	65	65	66	IVB	25	14	≦ 1	36	55	26	40	34	40	11	0.0001	1
Ayhan	2002	37	62	22	IVB	NA	16	≦ 1	22	59	12	32	25	48	10	0.001	1
Lambrou	2004	85**	63	2.4	III/IV	20	NA	≦ 2	42**	72	NA	NA	18	NA	7	0.001	3
van Wijk	2006	67	63	15	III/IV	NA	NA	microscopic	50	75	NA	NA	66% 5-year survival	NA	41% 5-year survival	< 0.01	1
Ueda	2009	33	63	27	IVB	45	55	≦ 2	20	61	NA	NA	43	NA	6	0.0001	NA
Tanioka	2010	33***	62	41	IV	NA	44	≦ 1	23	69	NA	NA	26	NA	12	0.066	NA

* mean age.

** only analyzed of IIIC/IV (n=58).

*** including only operated for the initial treatment, 2 NAC.

Table 8. Retrospective review of primary cytoreductive surgery for advanced-stage uterine papillary serous cancer

Author	Year	Total patients (n)	Median age (yr)	Non-endometrioid (%)	FIGO stage	Extra pelvic (%)	Extra abdomen (%)	Optimal definition (cm)	Optimal CR		Complete CR		Optimal median OS (months)	Complete median OS (months)	Suboptimal median OS (months)	*p*-value	Perioperative death (n)
									(n)	(%)	(n)	(%)					
Bristow	2001	31	65	100	IV	48	16	≦ 1	16	52	6	19	26	30	10	< 0.001	1
Memarzadeh	2002	43	70	100	III/IV	37	0	microscopic	20	47	20	47	40	40	10	< 0.001	0
Moller	2004	52*	67	100	IV	NA	NA	≦ 1	26	50	NA	NA	15	NA	8	> 0.05	
Thomas	2007	70	68	100	IIIC/IV	NA	NA	≦ 1	42	70	26	37	20	51	12	0.02	NA
Gardner	2009	48**	69	100	IV	NA	NA	≦ 1	28**	58	NA	NA	51	NA	13	0.004	NA

* including 3 patients of biopsy alone.

** including 7 patients of NAC (total), 6 NAC in optimal CR.

Recently, Tanioka et al. operated on 31 patients with stage IV disease [54]. In their 28 patients in whom stage IV was diagnosed preoperatively, neither surgery as the primary therapy nor optimal cytoreduction was significantly related to overall survival. By their analysis, grade 1 or grade 2 endometrioid subtype, no or 1 site of extraperitoneal metastasis, and hormonal therapy were all found to be predictors of good outcomes, and they strongly raised the question of whether surgery is justified in all patients with stage IV disease. The reason why surgical cytoreduction is associated with survival benefit is not fully understood, but there are several speculations.

First, reduction in the tumor size would decrease adverse metabolic effects, leading to improved patient comfort and performance status. Second, tumor debulking can enhance perfusion and drug delivery. Third, decreasing the number of viable tumor cells would decrease the rate of somatic mutations that often perpetuate drug resistance [42]. Fourth, any positive immune response to the tumors would be less diluted or misdirected by excessive tumor mass.

In summary, to date, all but one study has concluded that cytoreductive surgery is beneficial for treatment of advanced endometrial cancer. The percentage of patients who could be successfully cytoreducted was between 44-72%, although the definition of optimal surgery has varied with time, from leaving residual tumor of 2 cm or less to now leaving no gross evidence of the disease (microscopic). The rate of complete optimal surgery, in other words 'microscopic 'or 'no gross evidence of disease' in these studies ranged from 18-75%. In six studies, the authors noted whether or not complete optimal surgery had a better prognosis than optimal surgery with macroscopic residual tumor or suboptimal surgery (Table 7). The complete surgery had significantly better median survival than the optimal surgery with macroscopic residual tumor or suboptimal surgery in five studies. This may be explained by the hypothesis that surgical cytoreduction makes patients' comfort and performance status improved by a decrease in adverse metabolic effects, and debulking enhances perfusion and drug delivery and decreases the rate of spontaneous mutations that can lead to drug resistance, as in ovarian cancer.

4.1.3. Primary Cytoreductive Surgery For Advanced-Stage Uterine Papillary Serous Cancer

The rarity of UPSC makes prospective studies with statistical significance highly difficult; however, there have been several retrospective studies which have suggested a role for surgical cytoreduction in the management of stage III-IV UPSC disease (Table 8).

In 2001, Bristow et al. was the first to evaluate the survival impact of cytoreduction, reporting on 31 patients with stage IV UPSC [6]. Optimal cytoreduction was defined as residual disease of 1 cm or less in maximal diameter. Optimal cytoreduction was conducted for 16 patients (51.6%) and they had a significantly better median survival than those with suboptimal cytoreduction (26.2 months and 9.6, months respectively; p <0.001). Furthermore, patients with microscopic residual tumors had a much longer median survival (30.4 months) than either patients with optimal surgery with macroscopic residual tumor (20.5 months) or those with suboptimally cytoreducted disease (p= 0.004). There was also an advantage for patients receiving a postoperative platinum-based chemotherapy. Upon multivariate analysis, the only statistically significant predictor of survival was the cytoreductive surgery. Later, Memarzadeh et al. retrospectively reviewed 43 patients with cytoreduction for stage III-IV UPSC [7]. Eight patients with stage IIIa were excluded from their analysis. Their definition of

optimal cytoreduction was surgery leaving only microscopic residual disease. The median survival of patients with microscopic residual disease was significantly improved compared to those with macroscopic residual disease (40 vs. 10 months, respectively; $p < 0.001$).

Moller et al. operated on 49 patients with stage IV UPSC. Optimal surgery was defined as leaving residual tumor of 1 cm or less [53]. They didn't find any advantage in median survival for optimal compared with suboptimal surgery (15 vs. 8 months, respectively; $p > 0.05$). They did, however, find that those receiving platinum-based adjuvant chemotherapy had a longer median survival than those who did not (21 vs. 2 months, respectively; $p < 0.0001$). In addition, an optimal cytoreduction combined with the adjuvant therapy gave a longer median survival than did a suboptimal cytoreduction with adjuvant therapy, but the difference did not achieve significance ($p > 0.05$) [55].

Thomas et al. conducted a retrospective review of 70 patients with stage IIIc-IV UPSC, which is the largest study of UPSC so far [8]. Their definition of optimal surgery was a residual tumor of 1 cm or less. In their study, 60% of patients were optimally cytoreducted, with 37% being 'complete', meaning optimally cytoreducted to the point of no visible residual disease. Those who were 'completely cytoreducted' had a significantly better median survival (51 months) compared to those optimally cytoreducted but with visual residual tumor (14 months), and those suboptimally cytoreducted (12 months) ($p = 0.002$). Having no residual tumor after cytoreduction also led to improved survival in those who received adjuvant chemotherapy compared to those with residual tumor who received adjuvant chemotherapy (52 vs. 16 months, respectively; $p < 0.001$). They concluded that cytoreduction to no gross residual disease, with the use of chemotherapy, was associated with a significant survival benefit.

Recently, Gardner et al. operated on 48 patients with stage IV UPSC. Optimal debulking to 1 cm or less residual disease was achieved in 28 of 48 (58.3%) patients [56]. Similarly to previous studies, there was a significantly improved median survival in those who had optimal surgery (50.6 months) compared with those who had suboptimal surgery (13.4 months) ($p = 0.004$). In multivariate analysis, optimal debulking surgery, platinum/taxane-based adjuvant treatment, and patient age were significantly associated disease-specific survival.

In summary, a majority (52-70%) of UPSC patients can be optimally cytoreducted, for which they receive the benefit of a better prognosis; however, an even more rigorous cytoreduction, resulting in no visible residual tumor, was associated with a much longer overall survival. These results are similar to the results for all the histological subtypes of advanced endometrial cancer discussed above. Although the number of studies of cytoreductive surgery for advanced UPSC was small, adjuvant chemotherapy was also found to be an important factor for survival benefit, especially with a platinum-based regimen. Taking into account that UPSC is more likely to have extra-uterine and intraperitoneal spread, it is reasonable to remove the upper abdominal as well as the extra-abdominal disease.

4.1.4. Surgical Procedure

There is as yet no commonly accepted standard procedure for the treatment of advanced stage endometrial cancer. The surgical procedure is varied according to the patient's performance status and the spread of the disease. However, in many of the previously discussed studies the standard operative procedure consisted of an abdominal total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and cytoreduction (Table 9).

Ayhan et al. were the first to report on 3 optimally cytoreducted patients with extra-abdominal metastasis; the first had supraclavicular lymph node metastasis, the second had lung metastasis, and the third had inguinal lymph node metastasis. All of these metastases were resected [50]. However, it was not mentioned whether or not these rigorous operations were associated with better prognosis.

Thomas et al. defined radical surgery as dissection of the diaphragm, bowel, and liver, or as extensive peritoneal stripping [8]. Of the 17 completely cytoreducted patients with stage IV UPSC, 6 had radical surgery and 11 did not.

Table 9. Surgical procedure performed for endometrial cancer with advanced-stage

	Total (n = 489)		All subtype (n = 363)		UPSC alone (n = 126)		p
	n	%	n	%	n	%	
TAH±BSO	433	88.5	327	90.1	106	84.1	
RH±BSO	29	5.9	18	5	11	8.7	
SCH±BSO	3	0.6	0	0	3	2.4	0.003
Exporatoly laparotomy	20	4.1	14	3.9	6	4.8	
Peritoneal lymph node resection	218	44.6	183	50.4	35	27.8	< 0.01
Peritoneal implants excision/albation	78	16	58	16	20	15.9	
Omentectomy	282	57.7	209	57.6	73	57.9	
Resection of intestine	75*	15.3	53*	14.6	22	17.5	0.02
Resection of uretter and bladder	1	0.2	1	0.3	0	0	
Resection of liver	3	0.6	3	0.8	0	0	
Splenectomy	4	0.8	2	0.6	2	1.6	
Resection of extra-abdominal lymph node	9	1.8	9	2.5	0	0	
Lung resection	3	0.6	3	0.8	0	0	

TAH: total abdominal hysterectomy, RH: radical hysterectomy (including modified radical hysterectomy), SCH: supracervical hysterectomy.

* including 2 patients who received a colostomy.

Survival at 3 years was no different in these two groups (56% vs. 58%, respectively; *p*= NS). This fact suggested that the tumor burden at the conclusion of the surgery is more important than the distribution of disease at presentation.

The beneficial effect of resecting extra-abdominal metastasis was first reported by Ueda et al. [53]. Debulking surgery was conducted in 15 out of 18 stage IVb patients with extra-abdominal metastasis. The optimal cytoreduction, defined as residual disease of 2 cm or less, was achieved in 10 patients (67%), and suboptimal cytoreduction was done in the other 5 patients (33%). Overall survival, as well as progression free survival, was significantly more favorable in optimal cytoreducted patients compared to those who were suboptimally cytoreducted. (OS; 57 vs. 6 months, PFS; 24 vs. 3 months, respectively, and *p*= 0.013, *p*= 0.016, respectively). Furthermore, there were no significant complications from the surgical removal of extra-abdominal metastasis, indicating that if surgery is attempted, then a maximum effort should be done to achieve optimal cytoreduction as long as the patient's condition allows.

Lambrou et al. and Moller et al. compared the surgical procedure differences for both the optimally and the suboptimally cytoreducted groups [51, 55]. Lambrou et al., operating on stage III-IV endometrial cancers, found that a radical hysterectomy was conducted more often in the suboptimal group than in the optimal group (12.5% vs. 8.7%, respectively), and the occurrence of bowel resection and omentectomy had the same tendency [51]. Lymphadenectomy, however, was done more often in the optimal group (81.2%) than the suboptimal group (50.0%). Of the six, stage IIIc patients with suboptimal cytoreduction, all were left with residual disease in the pelvic or paraaortic region. Moller et al.'s study [55] focused only on treatment of stage IV UPSC patients. In contrast to the surgical procedure adopted by Lambrou et al. [51], a larger percentage of their patients underwent a modified radical hysterectomy in the optimal group compared to the suboptimal group (14% vs. 4%, respectively). Supracervical hysterectomy was done in 3 cases of the suboptimally cytoreducted group, whereas none of the optimal group had this performed. The optimal group was more likely to have a lymphadenectomy than the suboptimal group (53% vs. 15%, respectively; p= 0.008), as they did for an omentectomy (96% vs. 73%, respectively; p= 0.05). Bowel resection was performed slightly more often in the suboptimal group, but there was no significant difference [51, 55].

4.1.5. Morbidity and Mortality

It is not unusual that patients with an advanced stage of endometrial cancer are in poor condition at diagnosis, which makes the operation itself, and the postoperative management, more difficult. Understanding postoperative morbidity and mortality is essential when operating on patients with such poor conditions. Cumulatively, in 7 studies there were 11 perioperative deaths (occurring less than 30 days from operation) reported among 361 patients, giving a mortality rate was 3.1%. The cause of these deaths was pulmonary embolism in 4 cases, small bowel obstruction in 2 cases, cardiac arrest in 2 cases, multiple organ failure with severe acidosis with a small bowel incarceration in 1 case, respiratory compromise in 1 case, and 'cause unknown' in 1 case.

The postoperative complications are listed in Tables 10 and 11. Major complications occurred in 15.7% of cases and minor ones in 32%, which is somewhat tolerable. An intraperitoneal spread of the tumor and/or the extensive surgical procedure on or near the intestine caused bowel obstruction more often than other complications. Surgical site infection and venous thrombosis, including deep vein thrombosis and pulmonary embolism, were associated with the fact that patients of endometrial cancer are more likely to be obese.

Lambrou et al. analyzed the morbidity of optimally and suboptimally cytoreducted groups [51]. Interestingly enough, the percentage of major postoperative complications for suboptimal versus optimal cytoreduction, including severe pulmonary compromise, pulmonary embolus, fascial dehiscence, sepsis, bowel obstruction, and re-laparotomy is significantly different (37.5 % vs. 7.3%, p= 0.005), as is unplanned ICU admission (31.3% vs. 7.3%, p= 0.018) and the total length of hospital stay exceeding 15 days (31.3% vs. 4.4%, p= 0.005); these were all significantly associated with suboptimal cytoreductive surgery. Mean estimated blood loss was also significantly greater in the suboptimal group (722 vs. 533 ml, p= 0.023). The rates of intraoperative complications, minor postoperative complications, and mortality were not significantly different in the two groups. The authors led to conclude that the increase in morbidity in the suboptimal group was probably secondary to the biology of the disease rather than to the extent of surgery.

Moller et al. also compared morbidity in the suboptimal and optimal group. In their analysis, conversely, there was no significant difference in complication occurrence between the suboptimal and the optimal group (30.8% vs. 15.4%, respectively; p= 0.33), although a complication was more likely to occur in the suboptimal group [55]. In their study, 12 out of 52 patients with stage IV disease had serious postoperative complications. The suboptimal group had 8 cases of complications, including myocardial infarction, pulmonary embolus, CVA, gestational intestine bleeding, anastomotic GI leak, and complications of unknown reasons, whereas the optimal group had 4 complications including pneumonia, and one of unknown cause.

Table 10. Postoperative complications (1)

	n	%
Major complications	24	15.7
Minor complications	49	32.0

Analysis of 153 patients from 3 studies.

Table 11. Postoperative complications (2)

	n	%
Bowel obstruction (ileum)	9	3.9
Surgical site infection	8	3.5
Deep vein thrombosis	5*	2.2
Re-laparotomy	5	2.2
Urinary tract infection	4	1.7
Pulmonary embolism	3	1.3
Pneumonia	3	1.3
Lymphocyst	3	1.3
Myocardial infarction	2	0.9
Gastrointestinal bleed	2	0.9
Sepsis	1	0.4
Cerebrovascular accident	1	0.4
Anastamotic gastrointestinal leak	1	0.4
Atelectasis	1	0.4
Thrombophlebitis	1	0.4
Other	16	7

Includes 230 patients from 5 studies

* including 3 patients of VTE

These data suggest that the morbidity and mortality of cytoreductive surgery with stage IV disease seem to be acceptable. Aggressive surgical debulking may not be indicated for all patients; for example, it would not be indicated if the risk of perioperative morbidity is increased or if surgical complications would significantly delay the initiation of chemotherapy. Quality of life issues should also be strongly considered when surgery and postoperative therapy are planned.

Table 12. Adjuvant therapy for advanced-stage endometrial cancer

	Total (n = 519)	All subtype (n = 363)	UPSC alone (n = 196)
no adjuvant therapy	32 (5.7%)	19 (5.2%)	13 (6.6%)
HT	62 (11.1%)	58* (16.0%)	4 (2.0%)
CT	271 (48.5%)	140* (38.6%)	131 (66.8%)
RT alone	145 (25.9%)	113 (31.1%)	32 (16.3%)
CT+HT	5 (0.9%)	5 (1.4%)	0 (0.0%)
CT+RT	45 (8.1%)	37 (10.2%)	8 (4.1%)

Analysis of 12 studies and 4 studies from UPSC.
HT: hormonal therapy.
CT: chemotherapy.
RT: radiation therapy.
* some cases are overlapping.

4.1.6. Postoperative Adjuvant Therapy

Like much else about advanced endometrial cancer, there has not yet been established a standard postoperative adjuvant therapy. Adjuvant therapy of postoperative stage IV patients can include chemotherapy, radiation therapy, hormone therapy, or any combination thereof. A collection of the published data is shown in Table 12. There was no adjuvant therapy given in 32 patients (5.7%), either because of their refusal for further treatment or because of their poor health condition. Chemotherapy was carried out in 271 patients (48.5%); 76% of them received platinum-based regimens, with available data which showed the precise regimens. In the 1990s and early 2000s, the main regimen was CAP, and in the later 2000s, a combination of carboplatin and paclitaxel was favored. Radiation therapy was carried out in 145 patients (25.9%), and a combination of chemotherapy and radiation therapy was given in 45 patients (8.1%). Radiation therapy included whole pelvis and whole abdominal radiation and vaginal brachytherapy, but the rate of each varied per study.

Goff et al. were the first to report on the effectiveness of adjuvant therapy [47]. In their study, CAP chemotherapy increased survival significantly on univariate analysis but not on multivariate analysis. Chi et al. also did not find any survival benefit of different adjuvant treatment regimens on multivariate analysis [11]. Bristow et al. showed adjuvant chemotherapy followed by radiation therapy was significantly associated with superior survival by univariate analysis, but this did not hold up under multivariate analysis [49]. Ayhan et al. found a significantly longer median survival in those who received cisplatin and radiation (54 months) compared with those who received only radiation therapy (15 months) or only chemotherapy (13 months) (p= 0.001), and this benefit was also indicated on multivariate analysis (50). Lambrou et al. did not find an association of survival benefit and

adjuvant therapy, but they found patients with suboptimal residual disease had an increased risk of death after adjusting for radiation, chemotherapy, and hormonal therapy (risk ratio = 3.6, p= 0.002) [51]. In findings limited to UPSC, Bristow et al. found postoperative platinum-based chemotherapy was associated with a median survival of 17.1 month, compared with 9.5 months without such therapy (p= 0.018) [6]. Among those who received platinum-based chemotherapy, the combination of platinum plus paclitaxel was associated with a median survival rate of 29.1 months, compared with 14.4 months for patients receiving platinum plus cyclophosphamide and/or doxorubicin, although this difference did not reach statistical significance (p= 0.054).

Moller et al. analyzed the effect of postoperative platinum-based chemotherapy. Those who received platinum-based chemotherapy (either a combination of paclitaxel and carboplatin (TC) or a combination of cisplatin, doxorubicin, and cyclophosphamide (CAP) had a longer median survival (21 months) compared with those who did not receive a platinum-based regimen (2 months) (p <0.0001) [55]. The median survival in the TC group was 24 months and that of CAP group was 13 months, which did not suggest statistical significance. Interestingly, this benefit from platinum-based chemotherapy was found regardless of the amount of residual disease. The authors recommend the inclusion of paclitaxel and a platinum agent in the treatment of women with uterine serous carcinoma. Thomas et al. found that chemotherapy was the most predictive of overall survival, as well as was complete cytoreductive surgery (HR= 0.56, p= 0.07) [8].

4.1.7. Limitations

In this chapter, we have reviewed the currently acceptable data for the role of cytoreductive surgery, but we must recognize that these data have some limitations. Firstly, the studies discussed are all retrospective and thus may have the potential selection bias inherent to most retrospective reviews. Secondly, the case numbers in each study are small because the majority of endometrial cancers are at an early stage at diagnosis. Thirdly, the definition of 'optimal' surgery has varied among these studies over time. Finally, adjuvant postoperative therapy is also varied in each study, and the variable treatment courses may have impacted survival outcomes. During the time from the first study in 1983 to the most current study in 2010, the regimens of chemotherapy in the gynecologic field have been changing, and this should be logically associated with better prognoses as advances progress.

Future Directions

Needless to say, prospective multi-institutional studies are needed to evaluate the size of the residual disease after debulking surgery has a benefit for survival in cases with an advanced stage of endometrial cancer, although it seems these studies will to be difficult to achieve, considering the increasing rarity of advanced-stage disease cases in developed countries. Thus, there must be cooperation among institutions to increase the number of patients enrolled in such a study.

The role of cytoreductive surgery in advanced endometrial cancer is only a stepping stone. Many more questions are waiting to be answered. Is there a role of neoadjuvant therapy, especially for those with massive dissemination of metastases? What is the most

effective postoperative therapy: radiation therapy, systemic chemotherapy as a single or combination regimen, or hormone therapy?

The surgical skills needed to operate on patients with advanced-stage cancer are still one of the most critical parameters in affecting the chances of patient survival. There is always going to be a need to cooperate with surgeons in other specialty fields. The success rates of cytoreductive surgery for advanced ovarian cancer varies widely depending on the level of extensive formal training that the surgeon has undergone (Barlin et al., 2009). We, as gynecologic oncologists, must improve our surgical skills so we can reduce the tumors in the patient as much as possible to achieve the ideal of 'complete cytoreductive surgery'.

As the standard chemotherapy, TC therapy will play an important role for advanced endometrial cancer cases. TFI after a first-line chemotherapy will predict response to a second-line chemotherapy. However, an effective regimen of second-line chemotherapy has not yet been established. This will remain a critical need for the treatment of advanced endometrial cancer.

Further research is needed to acquire more evidence for the role of cytoreductive surgery and effective chemotherapy in advanced endometrial cancer.

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