Gynecologic Cancer

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Contents

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Abstract

The management of gynecologic cancers has historically been guided by a clinically-oriented staging system, based largely on physical examination and standard imaging studies including CT of the abdomen and pelvis. This has more recently been supplemented by pre-treatment MRI and functional imaging, as well as imaging biomarkers. This chapter will focus on the most common gynecologic malignancies, discussing the clinical, pathological, and treatment-related factors that influence clinical outcome as well as the influence of biomarkers on prognosis.

1 Introduction

Gynecologic cancers are a diverse group of tumors which are characterized by an orderly pattern of loco-regional spread that is correlated with prognosis. This is reflected in the International Federation of Gynecology and Obstetrics (FIGO) staging system. In addition to the traditional staging system, biologic and molecular markers reflecting angiogenesis, hypoxia and tumor cell proliferation are emerging that correspond to treatment response and prognosis. However, their use in clinical decision-making remains limited. Imaging-based predictors are easier to utilize in clinical management, and show promise in predicting outcome and risk of failure both before and during therapy.

At present, in patients treated primarily with surgery, histopathologic factors can be highly predictive of treatment outcomes, and these variables can dictate the need for

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Table 1 FIGO and TNM staging of cervical cancer

FIGO	TNM	Description
–	TX	Primary tumor cannot be assessed
–	T0	No evidence of primary tumor
–[a]	Tis	Carcinoma in situ (pre-invasive carcinoma)
I	T1	Cervical carcinoma confined to uterus (extension to corpus should be disregarded)[a]
IA	T1a	Invasive carcinoma diagnosed only by microscopy (*all macroscopically visible lesions are stage IB/T1b tumors*). Stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less. Vascular space involvement, venous or lymphatic, does not affect classification
IA_1	$T1a_1$	Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
IA_2	$T1a_2$	Measured stromal invasion more than 3.0 mm and not more than 5.0 mm, with a horizontal spread 7.0 mm or less
IB	T1b	Clinically visible lesion confined to the cervix or microscopic lesion greater than IA_1/IA_2
IB_1	$T1b_1$	Clinically visible lesion 4.0 cm or less in greatest dimension
IB_2	$T1b_2$	Clinically visible lesion more than 4.0 cm in greatest dimension
II	T2	Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina
IIA	T2a	Tumor without parametrial invasion
IIA_1	$T2a_1$	Lesion 4.0 cm or less in greatest dimension
IIA_2	$T2a_2$	Lesion more than 4.0 cm in greatest dimension
IIB	T2b	Tumor with parametrial invasion
III	T3	Tumor extends to pelvic wall and/or involves lower third of vagina, and/or causes hydronephrosis or nonfunctioning kidney
IIIA	T3a	Tumor involves lower third of vagina, no extension to pelvic wall
IIIB	T3b	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney
IV	T4	Bladder and/or rectal invasion or distant spread
IVA	T4a	Tumor invades mucosa of bladder or rectum, and/or extends beyond true pelvis (bullous edema is not sufficient to classify a tumor as IVA)
IVB	T4b	Distant metastasis (including peritoneal spread, involvement of supraclavicular or mediastinal lymph nodes, lung, liver, or bone)
3/4	Nx	Regional lymph nodes cannot be assessed regional lymph node metastasis
3/4	N0	No regional lymph node metastasis
3/4	N1	Regional lymph node metastasis
3/4	M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)
3/4	M1	Distant metastasis (including peritoneal spread, involvement of supraclavicular or mediastinal lymph nodes, lung, liver, or bone)

[a] FIGO staging no longer includes stage 0 (Tis)
Source Edge et al. (2009)

adjuvant radiation therapy and/or chemotherapy. For example, histopathologic variables such as margin status, lymphovascular invasion, and positive lymph nodes are commonly factored into adjuvant therapy decisions (Sedlis et al. 1999; Peters et al. 2000). In the future, there may be a role for biomarkers in this regard. However, to date, there has not been substantial progress in the use of biomarkers for use in the post-operative setting.

2 Cancer of the Cervix

The prognosis and treatment outcome for patients with cervical cancerare largely determined by local tumor extent, tumor size and regional lymphatic spread, which follows predictable pathways along anatomic routes and lymph node echelons. In general, the extent of loco-regional spread will guide the selection of therapy—tumors confined to the cervix are managed primarily by surgical therapy, while those with extension to the parametrium, distal vagina or adjacent organs are treated by primary radiation and chemotherapy.

2.1 Staging

The loco-regional tumor extent is only partially reflected by the traditional FIGO staging system (Pecorelli 2009). The FIGO staging system (Table 1) relies on findings from clinical examination and invasive investigations, including cystoscopy and proctoscopy, with biopsy. It also allows the

use of radiographic information from plain X-ray films. However, information regarding lymph node involvement, a strong determinant of outcome, is not incorporated. In addition, findings from CT, MRI and functional imaging, namely PET-CT, are not utilized. This results in inherent limitations in assessing well validated prognostic factors, including tumor volume, involvement of adjacent structures, and parametrial extension, that are challenging to assess by palpation and visual inspection alone. In addition, the detection of regional lymph node spread and sites of distant metastatic disease, that can be detected with cross-sectional imaging, can be missed (Eifel 1994). Due to these inherent limitations, FIGO staging has been shown to result in under-staging of 20–60 % of cervical cancer patients, when compared with surgical staging (Averette et al. 1975). This explains why significant variations in treatment failure rates and survival are observed within each FIGO stage category (Eifel et al. 1994; Perez et al. 1992a).

Despite the fact that the FIGO staging system suffers from the aforementioned limitations, it remains the current standard of practice, and provides the major entrance criteria utilized in determining the eligibility of patients for cooperative group trials. Thus, most current cooperative group trials enroll patients across almost the entire FIGO stage spectrum, from stage IB2-IVA, and accession them to largely uniform treatment regimens. Of note, although cross-sectional imaging is not "permitted" to influence FIGO stage assignment, the use of CT, MRI and molecular imaging with fluorodeoxyglucose (^{18}F)FDG PET imaging is likely to result in "stage migration" by excluding patients with subtle imaging-based evidence of regional or distant metastatic involvement from cooperative group trials (Fig. 1). This will make any improvements of therapy with newer interventions difficult to compare to historic controls. However, the incorporation of functional imaging into future clinical trials will potentially enhance our ability to accurately stratify patients and tailor therapy to the "true" clinical stage (i.e. locally advanced vs. metastatic disease).

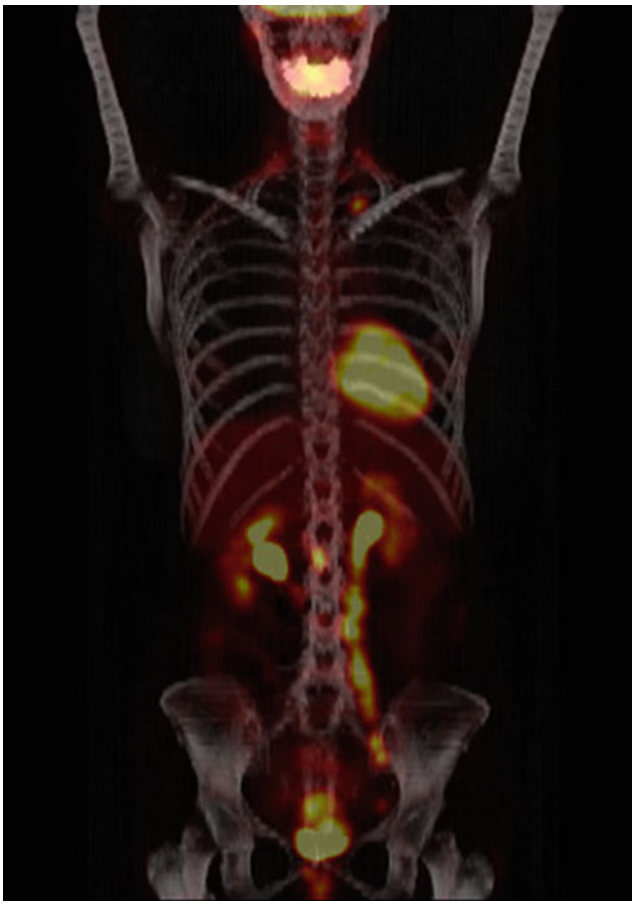

Fig. 1 PET-CT and Staging of Cervical Cancer: A 43 year old woman with invasive squamous cell carcinoma of the cervix underwent PET-CT revealing retroperitoneal and supraclavicular adenopathy, consistent with Stage IV disease

2.2 Clinical Factors

Eligibility for primary surgical therapy is determined by regional tumor extent to adjacent structures and significantly influences prognosis. Patients with stage I disease (tumor limited to the cervix) and selected patients with stage II disease (including patients with upper vaginal involvement), are candidates for radical hysterectomy. The overall survival of surgically treated patients with stage IB tumors ranges from 85 to 90 % (Morley and Seski 1976; Hopkins and Morley 1991; Landoni et al. 1997). However, large tumor size, deep cervical invasion, lymphovascular space invasion, as well as involved lymph nodes and parametrial involvement have been recognized as risk factors for pelvic recurrence after radical hysterectomy. Depending on the number and extent of these factors present, adjuvant therapy can improve outcomes, albeit at the cost of increased risk of toxicity from adjuvant radiation and/or chemotherapy (Sedlis et al. 1999; Peters et al. 2000; Rotman et al. 2006). Thus, if imaging modalities or other factors could identify the presence of these pathologic features during workup leading to upstaging, definitive radiation and chemotherapy could be considered instead of primary surgery, thus potentially reducing the morbidity of treatment.

2.2.1 Stage

In patients with cervical cancer treated with definitive radiation therapy, FIGO stage remains an important prognostic factor. Due to the relative rarity of cervical cancer in western nations, phase III cooperative group trials do not subclassify patients by stage, nor do they group patient cohorts as stages IB–II versus III–IVA for subgroup

Table 2 Tumor diameter versus disease free survival for stage IB cervical cancer

Size (cm)	NP	1	2	3	4	5	6	7	8	>8
Eifel et al. (1994) n = 1,526	94	87				86	72	69	64	47
Lowrey et al. (1992) n = 130	93				77		67			
Perez et al. (1992b) n = 384	90				65		~60			
Homesley et al. (1980) n = 45	95					67				

NP Not palpable

Table 3 Tumor diameter versus disease free survival for stage IIB cervical cancer

Size (cm)	NP	1	2	3	4	5	6	7	8	>8
Mendenhall et al. (1984) n = 83	–				84		66			
Lowrey et al. (1992) n = 130	100				85		61			

NP Not palpable

analyses, because analysis by individual stage categories would require unachievably large patient cohorts. Based on large single-institution series in which contemporary radiation techniques and concurrent chemotherapy were utilized, reported local control rates, disease free survival rates, and overall survival rates for patients with Stage IB–IIA and III–IVA are 87 and 79 %, 74 and 54 %, and 79 and 59 %, respectively (Whitney et al. 1999; Eifel et al. 2004; Rose et al. 2007).

2.2.2 Tumor Volume

In addition to FIGO stage, tumor size has profound prognostic significance (Eifel et al. 1994; Kovalic et al. 1991). In 1988 FIGO added tumor diameter as a stratifying factor for stage I disease, with tumors less than or greater than 4 cm classified as stage IB1 versus IB2 respectively. In the 2009 revision of the staging system, tumor size of greater or less than 4 cm was also incorporated into the stage IIB category (Pecorelli et al. 2009). Tables 2 and 3 shows the profound significance of tumor size, measured as largest or average palpated diameter, for local control and survival. Within the same stage category of IB, tumor size of <4 cm in diameter was associated with a disease-free survival of 87 %, compared to 72 % for 6 cm, 69 % for 7 cm, 64 % for 8 cm and 47 % for >8 cm tumors (Table 2). Similar relationship exists for tumor size and outcomes within the stage IIB category (Table 3) (Eifel et al. 1994; Hansgen and Dunst 1996; Hockel et al. 1996; Homesley et al. 1980; Lowrey et al. 1992; Perez et al. 1992b; Mendenhall et al. 1984).

2.2.3 Lymph Node Status

For any given FIGO stage, lymph node involvement reduces overall survival by approximately 50 % (Stehman et al. 1991). Furthermore, among patients with positive lymph nodes, prognosis declines with increasing extent of lymph node involvement (Macdonald et al. 2009; Hsu et al. 1972; Tsai et al. 1999; Takeda et al. 2002; Morice et al. 1999). In a pooled study by the Gynecologic Oncology Group (GOG), para-aortic involvement was associated with an 11-fold risk of recurrence and sixfold risk of death, and was also associated with extrapelvic failures (Berman et al. 1984). However, even with para-aortic lymph node involvement, survival in the range of 20–50 % has been reported for patients with locally advanced disease (Komaki et al. 1983; Rotman et al. 1994), justifying aggressive therapy for patients with regional lymphatic spread.

Although controversy exists whether surgical excision of suspicious lymph nodes improves outcomes, a large retrospective study of patients treated in the pre-chemo-radiation era showed among patients who underwent lymphadenectomy and postoperative radiation, patients with macroscopically involved lymph nodes had similar regional and distant tumor control as those with microscopic lymph node involvement, and significantly better than those patients with unresectable lymph nodes (Cosin et al. 1998). This supports the use of imaging for identification of involved nodes, thus allowing for a tumor directed combined modality approach. Increasing use of molecular imaging in cervix cancer will facilitate this approach and will also

likely lead to stage migration as lymph nodes with more subtle involvement can be identified and treated more aggressively.

2.3 Patient Factors

2.3.1 Hemoglobin

Over the past 50 years, numerous studies have provided indirect evidence that the effects of poor tumor blood supply have an adverse impact on radiation response. Early studies of morphologic parameters of angiogenesis, such as microvessel density, have been shown to correlate with radioresponsiveness and clinical outcome in cervical cancer (Awwad et al. 1986; Cooper et al. 1998). Cervical cancer patients with high inter-capillary distances locally within their tumors measured by colposcopy were found to have increased tumor recurrence rates after radiation therapy (Kolstad 1968).

Similarly cervical cancer patients with low hemoglobin levels have been reported to have higher recurrence rates after radiotherapy (Mendenhall et al. 1984; Bush et al. 1978; Evans and Bergsjo 1965; Diesche et al. 1983; Thomas 2001; Dunst et al. 2003). This supports the concept that poor "systemic" oxygenation is clinically significant for treatment outcome. Haensgen et al. analyzed hemoglobin levels of 70 patients, and reported survival was 27 % for patients with low hemoglobin (<11 g/dL), compared to 62 % in those with higher levels (Haensgen et al. 2001). Dunst et al. mirrored these results, showing overall survival of 64 and 32 %, respectively and local recurrence rates of 15 % versus 67 %, respectively (Dunst et al. 2003). Hemoglobin *during* the course of therapy, when the actual cytotoxic events occur, may also be relevant. Thomas et al. showed in 605 patients that the average weekly hemoglobin nadir <12 g/dL was associated with a higher incidence of local failure and metastases (Thomas 2001). In a recent study, weekly mean hemoglobin levels measured during the course of radiotherapy was more predictive of outcome than pre-therapy or nadir hemoglobin (Mayr et al. 2009). In all, the thresholds value for this effect of hemoglobin level appears to be in the range of 11–12 g/dL.

Although the impact of blood transfusion on outcome in patients treated with definitive radiation therapy remains controversial, the Canadian experience suggests that maintaining hemoglobin levels above 12 g/dL is associated with improved 5-year survival. Pre-treatment hemoglobin, which may not reflect the longitudinal status of hemoglobin levels, did not have any impact on outcome (Grogan et al. 1999). Interestingly, in one retrospective study of 204 patients at a single institution where departmental practice was to transfuse for hemoglobin <11 g/dL, it was noted that only 18.5 % of patients who received transfusion had a sustained response to transfusion, although outcomes for these patients were equivalent to those presenting with normal hemoglobin (Kapp et al. 2002). However, for patients who did not have a sustained response to blood transfusion, outcomes were significantly worse compared to those with response or with normal hemoglobin pre-therapy. While there was a therapeutic benefit to transfusion for those patients with sustained response, the low rate of response of 18.5 % was disappointing, and it was proposed that finding and treating the underlying cause of the anemia may be more beneficial.

2.4 Histologic Factors

2.4.1 Histology

Approximately 90 % of cervical cancers are squamous cell carcinomas. Squamous cell carcinomas arise from epithelial precursors, and can be classified into one of three cell types: large cell keratinizing, large cell nonkeratinizing, and small cell. Tumor grade is based on the degree of differentiation, and is reported as well, moderately, or poorly differentiated. Adenocarcinoma is the second most common, accounting for 10–15 % depending on region and age. More recently, the incidence of adenocarcinomas appears to be increasing, especially in younger patients (Liu et al. 2001; Smith et al. 2000). Adenocarcinomas arise from the mucus-secreting endocervical glands of the cervix or the cylindrical mucosa. The most common subtype of adenocarcinoma of the cervix is endometrioid adenocarcinoma, where cells have characteristic features of the endometrium and grading is based on the degree of gland formation. It is critical to differentiate this from primary endometrioid endometrial adenocarcinoma as recommended therapy would change, thus clinical presentation, such as absence or presence of an endometrial tumor with extension into the cervix, is incorporated to determine the true site of primary disease. The next most common subtype of adenocarcinoma is adenosquamous histology, comprising 21–30 % of adenocarcinomas (Farley et al. 2003; Kleine et al. 1989), and is characterized by epithelial cell cores mixed with glandular structures. Other histologies, such as clear cell, small cell carcinoma, basaloid carcinoma, lymphoma, and sarcomas occur, but are rare and have varying prognostic impact.

The prognosis of adenocarcinoma versus squamous cell histology is debated. While adenocarcinoma is associated with an increased risk of failure, particularly metastatic failure in some retrospective reports (Eifel et al. 1995; Huang et al. 2011, 2012), many show no significant impact on outcome between adenocarcinoma and squamous cell carcinoma (Shingleton et al. 1995; Look et al. 1996; Davidson et al. 1989). Interestingly, adenosquamous carcinoma may be associated with poorer recurrence free and overall survival (Farley et al. 2003; Look et al. 1996;

Lea et al. 2003; Grisaru et al. 2001; Galic et al. 2012). In all, the differences in outcomes among these studies may be in part due to regional variation in Human Papilloma Virus (HPV) genotype distribution, changes in etiology and incidence of histologic type, differences in treatment approach, and overall study sizes, making it difficult to draw any definitive conclusion about subtype implications in the absence of prospective data.

2.4.2 Histopathologic Risk Factors in Postoperative Patients

In surgically treated stage I-IIA patients, lymph node involvement, parametrial invasion and involved margins have long been recognized as *high risk factors* for local recurrence and death (Morrow 1980). In those with involved lymph nodes, number of involved nodes (<3 vs. >3), bilaterality, level (common iliac vs. pelvic) and size (micro- vs. macroscopic) impact outcome (van Bommel et al. 1987; Tanaka et al. 1984). Therefore, adjuvant therapy based on histopathologic risk factors is paramount because salvage therapy for recurrent cervical cancer after hysterectomy has dismal results with a 5–45 % survival (Thomas et al. 1993). Postoperative radiation has been the hallmark in adjuvant therapy.

Tumor size, depth of invasion and capillary-lymphatic space invasion have also been shown to impact prognosis in surgically treated stage I-IIA patients. However, until the completion of the phase III GOG 92 study, the impact of adjuvant therapy on survival was not well established. GOG 92 (Sedlis et al. 1999; Rotman et al. 2006) established a set of *intermediate risk factors* (commonly referred to as "Sedlis criteria") for poor outcome in stage IB patients treated with radical hysterectomy. Patients with two of the three features (capillary lymphatic space invasion, large clinical tumor diameter, or more than one-third cervical stromal invasion) were randomized to pelvic radiotherapy versus no further therapy (Table 4). At 10 years median follow-up, postoperative radiation reduced the risk of recurrence by 46 % (HR 0.54) with the greatest benefit in patients with a combination of *deep 1/3 invasion plus tumor size >4 cm* (HR 0.16) or *capillary lymphatic space invasion plus deep 1/3 invasion with any tumor size* (HR 0.53) (Rotman et al. 2006). There was no significant improvement in overall survival (Table 5). On subgroup analysis, proportionally greater improvement was noted among 44 patients with adenosquamous or adenocarcinoma, where adjuvant radiation therapy reduced the recurrence rate from 44 to 9 % (Rotman et al. 2006). A current GOG study is underway to evaluate whether postoperative radiation with concurrent chemotherapy can further improve upon this outcome.

Improvement of adjuvant therapy with the addition of concurrent chemotherapy to radiation has also been demonstrated for some select patients. The intergroup trial GOG 109 randomized stage IA2-IIA patients treated with radical hysterectomy and pelvic lymphadenectomy and high risk features, defined as positive pelvic lymph nodes and/or positive margins, and/or microscopic involvement of the parametrium, to pelvic radiotherapy versus pelvic radiotherapy with chemotherapy (cisplatin/5-FU for 4 cycles during and after radiation) (Peters et al. 2000). Addition of chemotherapy resulted in significant improvement of overall survival at 81 % versus 71 % (HR 1.96, p = 0.007). The greatest benefit was observed for patients with larger tumors and multiple involved lymph nodes, underscoring the importance of identification of involved lymph nodes in order to offer the optimal adjuvant therapy. Table 6 summarizes the results of five randomized trials that show improved survival with concurrent chemotherapy and radiotherapy (Peters et al. 2000; Whitney et al. 1999; Rose et al. 2007; Keys et al. 1999; Morris et al. 1999).

Table 4 Inclusion criteria for GOG 92: randomization to postoperative pelvic radiotherapy versus no further therapy in stage IB intermediate risk cervical cancer

LVSI	Depth of invasion	Tumor size (cm)
Positive	Deep 1/3	Any
Positive	Middle 1/3	≥2
Positive	Superficial 1/3	≥5
Negative	Deep or middle 1/3	≥4

Adapted from Sedlis et al. (1999). For inclusion into GOG 92, patients fit one of the above set of criteria. *LVSI* lymphovascular space invasion

Table 5 GOG 92 results: postoperative radiotherapy improves recurrence-free, but not overall survival, in intermediate risk stage IB cervix cancer

	RT (n = 137) (%)	Observation (n = 140) (%)	p value
Recurrences (all)	17.5	30.7	0.007
AC, AS	8.8	44.0	0.019[a]
Squamous cell	20.4	27.8	
Survival	80.3	71.4	n.s.

Adapted from Rotman et al. (2006)

[a] Adenocarcinoma and Adenosquamous histology had a statistically significant improvement in recurrence free survival with RT compared to other histologic subtypes treated with RT. *RT* radiotherapy, *AC* Adenocarcinoma, *AS* Adenosquamous carcinoma, *n.s.* not significant

2.4.3 Molecular Tumor Markers

2.4.3.1 HPV

HPV is found in an estimated 93–99.7 % of invasive cervical cancer (Bosch et al. 1995; Walboomers et al. 1999). Further, the prevalence of different genotypes varies in

Table 6 Estimates of the relative risk of death in five clinical trials of radiotherapy and concurrent chemotherapy

Study	FIGO stage	Control group	Comparison group	Relative risk of death	p value
Peters et al. (2000)	IB or IIA	RT	RT plus cisplatin and 5-FU	0.5	0.007
Whitney et al. (1999)	IIB–IVA	RT plus hydroxyurea	RT plus cisplatin and 5-FU	0.72	0.018
Rose et al. (2007)	IIB–IVA	RT plus hydroxyurea	RT plus weekly cisplatin RT plus cisplatin, 5-FU, hydroxyurea	0.61 0.58	<0.025 <0.025
Keys et al. (1999)	IB2	RT	RT plus weekly cisplatin	0.54	0.008
Morris et al. (1999)	IB–IVA	Extended field RT	RT plus cisplatin and 5-FU	0.52	0.004

RT radiotherapy, *5-FU* 5-fluorouracil

cellular histology. HPV16 is identified in the majority of squamous cell carcinomas, and HPV18 is the predominant genotype in adenocarcinomas and adenosquamous carcinomas (Bosch et al. 1995). HPV may be a prognostic indicator for outcomes. Several studies have shown HPV18 and HPV16 is associated with more advanced cervical cancers at presentation and poorer outcomes (Schwartz et al. 2001; Pilch et al. 2001; Burger et al. 1996). Further, HPV18 has been associated with increased radioresistance and increased recurrence rates compared to other HPV genotypes in patients receiving only radiation therapy (Wang et al. 2010). However, HPV18 has subsequently been shown to be predictive of improved disease specific survival when concurrent chemotherapy and radiotherapy was used in place of radiotherapy alone (Wang et al. 2012). The clinical utility of this association is an area of active investigation.

2.4.3.2 Angiogenesis

Angiogenesis-related molecular markers would be expected to be of great importance for radiation and chemotherapy because of the critical dependence of the cytotoxic effect on tumor microcirculation and oxygenation (Tannock 1972). It is postulated that poorly-perfused, hypoxic, endophytic tumors are associated with radio-resistance and resulting poor treatment outcome in cervical cancer. Angiogenic factors have been shown to correlate with tumor recurrence and survival in surgically treated patients (Cheng et al. 2000; Dellas et al. 1997; Dinh et al. 1996; Hawighorst et al. 1997; Lee et al. 2011; Mayr et al. 1999; Kainz et al. 1995; Obermair et al. 1998; Tjalma et al. 2000). Therefore, there has been increasing interest in molecular markers of angiogenesis and cytokines in cervical cancer. Cooper et al. (Cooper et al. 1998) reported that patients with high MVD had significantly poorer local control and survival. Although Gaffney et al. (2003) found increased VEGF and EGFR expression to be associated with poor survival, inconsistent results have been observed in regard to VEGF association with tumor progression, stage (Loncaster et al. 2000), histologic type (Cheng et al. 2000; Loncaster et al. 2000, 2002) and microvessel density (MVD) (Mayr et al. 1999; Hawighorst et al. 1998). High expression of another angiogenic marker, carbonic anhydrase IX (CA IX) correlates with poor survival (Loncaster et al. 2002). More recently the GOG evaluated a panel of angiogenesis markers including MVD, VEGF, CD31 (non-specific endothelial marker), TSP-1 (thrombospondin-1 an anti-angiogenesis factor), and CD105 (tumor-specific endothelial marker) and association with clinical outcome (Randall et al. 2009). Expression of each was determined in tumors from patients included in GOG 109, including stage IA2-IIA patients with positive lymph nodes, parametrial involvement, or positive surgical margins (Peters et al. 2000). Of these, only high expression CD31 was independently predictive of improved disease free and overall survival. Authors posit that this may be representative of CD31 as a surrogate marker for improved tumor flow and oxygenation, thus improving response to adjuvant therapy.

2.4.3.3 Alternate Candidate Molecules

There has been increasing interest in evaluation of molecular mechanisms of radiation response through candidate gene approach and microarray analysis. Studies in cervical cancer cell lines have found that genes related to angiogenesis, apoptosis and tumor cell invasion correlate with radio-resistance (Harima et al. 2004; Kitahara et al. 2002; Tewari et al. 2005; Wong et al. 2003). A pilot study of 12 patients in 2008 used microarray analysis and demonstrated immortalization upregulated protein (IMUP), IGF-2, and ARHD were associated with tumor recurrence in patients treated with radiation and concurrent chemotherapy (Klopp et al. 2008). Proteins that have been shown to correlate with clinical outcome include Ku80, GADD45 (Harima et al. 2003), bax, bcl-2 (Harima et al. 1998), intracellular adhesion molecule-3 (ICAM-3) (Chung et al. 2005), and hypoxia inducible factor (HIF)-1a (Bachtiary et al. 2003; Burri et al. 2003). However, to date, none of these molecular markers has been incorporated into clinical care.

2.5 Imaging Prognostic/Predictive Markers

2.5.1 Morphologic Imaging

Improvements in spatial and temporal resolution of cross-sectional imaging have broadened the capabilities of both anatomical and functional imaging in cervical cancer. Three-dimensional tumor volume can be quantified, and tumor extent and involvement of adjacent structures more accurately assessed than by clinical palpation (Hricak et al. 1988; Hricak 1991; Bhosale et al. 2010; Balleyguier et al. 2011). Higher temporal and spatial resolution also allows for functional imaging, such as dynamic contrast-enhanced (DCE) MRI and diffusion-weighted imaging, in addition to the morphologic/anatomical imaging. Beyond pre-therapy assessment, repeated imaging throughout the course of definitive chemoradiotherapy with an intact cervix provides longitudinal information on functional changes in response to ongoing therapy. Such on-therapy imaging shows promise for deriving imaging biomarkers to predict therapeutic response and disease outcome.

Tumor size in cervical cancer is best assessed with MRI (Bhosale et al. 2010; Balleyguier et al. 2011), which was demonstrated in imaging-histologic correlation studies (Burghardt et al. 1989; Greco et al. 1989). For on-therapy assessments, the velocity of tumor regression, assessed by 3D tumor volumetry (not diameter-based measurement) allows an indirect measure of therapy responsiveness (Mayr et al. 2006), which has been shown to be predictive of treatment outcome in cervical cancer patients treated with radiation/chemotherapy (Hatano et al. 1999; Mayr et al. 1996, 2010; Sethi et al. 2005; Lim et al. 2008). Using 3D volumetric measurements, Mayr et al. found that patients with <20 % of residual tumor volume at 40–50 Gy delivered over 4–5 weeks had excellent local control and disease free survival of 90.5 and 88.4 %, compared to 23.1 and 45.4 % in patients with slower tumor regression (Mayr et al. 1996). Similarly, Hatano et al. (1999) found 100 % local control in patients with rapid tumor volume regression to less than 30 % of the original volume at 30 Gy over 3 weeks. Further, the velocity of tumor shrinkage directly correlates with patients' risk for local failure and death of disease (Mayr et al. 2010). Such early predictive information, available *during* the ongoing therapy course, may open a window of opportunity to adapt and intensify therapy. For post-therapy assessment in the early follow-up period, complete resolution of the tumor 3–6 months after therapy is associated with better outcome (Hricak 1991; Flueckiger et al. 1992).

2.5.2 Functional Imaging

Among the functional imaging modalities, DCE MRI provides an in vivo imaging biomarker that indirectly reflects tumor perfusion and the delivery of oxygen and therapeutic agents to the tumor. Low perfusion, indicative of poor vascularity and oxygenation, before or early during the course of radiation therapy (at approximately 20 Gy, ~2 weeks), significantly predicts unfavorable local tumor control (73 % vs. 100 %, $p = 0.006$) and survival (47 % vs. 79 %, $p = 0.001$, respectively). The 2-week intra-treatment time point may be superior to the pre-therapy time point likely because the 2-week DCE MRI incorporates early therapy-specific information of responsiveness to the ongoing treatment (Yuh et al. 2009).

Diffusion-weighed imaging, which indirectly assesses tumor cellularity (Hamstra et al. 2008; Ross et al. 2003) provides another imaging biomarker in cervix cancer. The apparent diffusion coefficient (ADC) measures the magnitude of diffusion (of water molecules) within tissues. A low ADC value is indicative of increased tissue cellularity, and an increase in the ADC suggests cell death. Such an ADC increase can occur very early, within days of therapy start, prior to any morphologic changes (e.g. tumor volume) (Charles-Edwards and DeSouza 2006; Charles-Edwards et al. 2008; Chenevert et al. 2000). Early clinical experience shows that increase in ADC during ongoing radiation and chemotherapy correlates with improved tumor response (Harry et al. 2008; Naganawa et al. 2005; Liu et al. 2009). These studies suggest that both DCE-MRI and DW-MRI may have value as early imaging biomarkers of radioresponsiveness in cervical cancer.

In addition to being the most accurate assessment of lymph node involvement, FDG-PET/CT has also been used to assess the primary tumor during/after therapy. Persistent metabolic activity of the tumor 3 months after therapy has been correlated with poor outcome (Kidd et al. 2007). However, the optimal imaging timing for FDG-PET is a subject of active investigation.

3 Cancer of the Uterine Corpus

Endometrial cancer is the most common gynecologic malignancy in the United States. In 2013, 49,500 cases of endometrial cancer are expected, accounting for approximately 6 % of female malignancies, with approximately 8,200 deaths anticipated, accounting for 3 % of all female cancer deaths (Siegel et al. 2013). Mean age at diagnosis in the United States is approximately 62 years old, consistent with a disease largely occurring in postmenopausal women. SEER data show approximately 70 % of cases are diagnosed as localized disease, with an 81.5 % 5-year survival for all stages, and 95.3 % for localized disease (Howlader et al. 2013). Risk factors for endometrial cancer include diabetes, obesity, hyperestrogenic state, nulliparity, tamoxifen use, early menarche or late menopause, and anovulatory cycles (Brinton et al. 1992). Certain genetic diseases,

Table 7 FIGO and American Joint Committee on Cancer (AJCC 7th edition) TNM staging for endometrial cancer

FIGO staging (2008)	AJCC 7th edn (2009) TNM staging[a]			Description
Group	T	N	M	
IA	T1a	0	0	Limited to the endometrium or invades less than half of the myometrium
IB	T1b	0	0	Invades half or more of the myometrium
II	T2	0	0	Invades cervical stromal tissue but does not extend beyond the uterus
IIIA	T3a	0	0	Involves serosa and/or adnexa
IIIB	T3b	0	0	Vaginal involvement or parametrial involvement
IIIC1	T1–3	1	0	Metastasis to pelvic lymph nodes
IIIC2	T1–3	2	0	Metastasis to para-aortic lymph nodes
IVA	T4	Any	0	Invades bladder mucosa and/or bowel mucosa
IVB	Any	Any	1	Distant metastasis

Source Edge et al. (2009)

[a] Changes from the AJCC 6th edition and the previous FIGO staging recommendations (1988):
No longer includes uterine sarcoma (now staged with a new staging system)
Positive peritoneal cytology is no longer considered (previously was T3a/IIIA)
Involvement of the endocervical glands is not longer considered (previously was stage IIA)
Stages IA and IB combined (now: IA). IC moved to IB
Stage IIIC subdivided into IIIC1 and IIIC2

such as hereditary nonpolyposis colon cancer (HNPCC) or Lynch syndrome and Cowden disease, are associated with increased risk for endometrial cancer, with lifetime risks ranging from 10 to 60 % depending on disease and specific genetic mutation (Aarnio et al. 1995; Gustafson et al. 2007).

Most endometrial cancers are diagnosed during the workup of abnormal, or postmenopausal, vaginal bleeding. Pathologic diagnosis is essential, as both FIGO stage and FIGO histologic grade are prognostic for outcome and determine treatment. Thus, diagnosis is often made via endometrial biopsy or dilation and curettage for those patients in which endometrial biopsy is not possible or non-diagnostic. Endometrial cancers often arise within the endometrial layer, and spread by invasion into the myometrium. In more advanced disease, tumor can spread to the uterine serosa, adnexa, endocervical canal, peritoneal cavity, bowel, bladder, and other adjacent structures. Lymphatic drainage is to the pelvic lymph nodes (including the internal/external iliacs, common iliacs, obturator, presacral and parametrial), with direct spread to the para-aortic lymph nodes possible. FIGO staging requires surgical staging based on the at-risk areas of spread, therefore total hysterectomy and bilateral salpingo-oopherectomy, with or without lymph node dissection, is performed in most patients. Adjuvant therapy is then based on pathologic information that determines the stage and grade of each endometrial cancer, both of which are prognostic for patient outcome.

3.1 Staging

The gold standard for staging in endometrial cancer remains surgical staging as defined by FIGO (Creasman 2009), Table 7. Prior to the 1988 FIGO staging system, staging was clinical evaluation for tumor size, extent of disease (confined to uterus or pelvic extension), and bowel or bladder involvement. However, this was found to understage patients approximately 23 % of the time (Creasman et al. 1987). Therefore, FIGO staging was changed to incorporate surgical evaluation and subsequent pathologic information for staging which improved the prognostic accuracy of staging. Initially, myometrial invasion, cervical invasion (including endocervical glandular involvement), adnexal involvement, serosal involvement, positive peritoneal cytology, and lymph node status were factored into staging. On the last revision of the FIGO surgical staging for endometrial cancer (2009), peritoneal cytology and isolated endocervical glandular involvement have been removed from the criteria. Further, myometrial invasion, previously stratified into three levels of involvement, is now subdivided into only two categories; invasion of less than one-half or invasion of one-half or more of the myometrium. Lymph node positive disease is substratified to pelvic lymph node only, or para-aortic lymph node disease (IIIC1 vs. IIIC2). In summary, under 2009 FIGO staging, stage I disease now includes endometrial/myometrial only disease; stage II disease invades cervical stroma; stage III disease is a heterogenous group with IIIA including uterine serosa or adnexal involvement, IIIB involving the vagina, and IIIC1 versus IIIC2 denoting pelvic lymph node only versus any para-aortic lymph node positive disease; stage IV represents metastatic disease to other sites not included above.

Surgical staging at minimum is to include total hysterectomy and bilateral salpingo-oopherectomy (BSO). The role of extended surgical staging, with sampling and/or dissection of the pelvic and para-aortic lymph nodes, is

still debated. Given the significant prognostic importance of lymph node metastasis, many advocate for lymph node histologic evaluation, and some have suggested a possible therapeutic benefit to lymphadenectomy, although not been proven in a prospective manner. While older techniques for extended surgical staging required laparotomy, more modern techniques with laparoscopic assisted methods have yielded equivalent nodal yields with reduced morbidity for many experienced gynecologic oncologists (Eltabbakh 2002; Scribner et al. 2002). Given the fact that many women with endometrial cancer are elderly, obese, and have co-morbidities such as diabetes, hypertension, and coronary artery disease, concerns exist for increased risks of deep venous thrombosis, vascular injury, or pulmonary emboli in the postoperative setting. Further, extended surgical staging followed by adjuvant radiation therapy is reported by some to carry higher enteric morbidity than hysterectomy and radiation alone (Lewandowski et al. 1990). Thus, some point to the experience of PORTEC and ASTEC trials as data to support omission of routine lymphadenectomy in low and intermediate risk patients without clinical/palpable adenopathy. PORTEC-1 included intermediate risk stage I patients, all undergoing total hysterectomy and BSO without lymphadenectomy randomized to adjuvant radiotherapy versus observation with 80–85 % overall survival at 5 years (Creutzberg et al. 2000). In ASTEC, intermediate risk patients underwent total hysterectomy-BSO, pelvic washings, and para-aortic lymph node palpation and were randomized to lymphadenectomy or no further surgery, with no statistically significant difference on overall survival at 3 years (ASTEC study group et al. 2009). Conversely, several studies support the role of maximal surgical debulking and resection of gross nodal disease, with improvement in median survival in some cohorts from 8.8 to 37.5 months (Bristow et al. 2003; Chi et al. 1997; Lambrou et al. 2004).

Of note, the American College of Obstetricians Gynecologists (ACOG) recommends comprehensive surgical staging including total hysterectomy and BSO, pelvic washings, bilateral pelvic and paraaortic lymphadenectomy, and complete resection of all disease, with exceptions considered for young or perimenopausal women with grade 1 endometrioid adenocarcinoma associated with atypical endometrial hyperplasia and those at increased risk of morbidity/mortality secondary to comorbidities (American College of Obstetricians and Gynecologists 2005). Omental sampling is also often performed, especially in papillary serous and clear cell histology due to the risk of upper abdominal spread.

Table 8 GOG 33: Rate of pelvic lymph node metastasis based on extent of myometrial invasion and FIGO grade

	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)
Endometrium only	0	3	0
Inner 1/3 myometrial invasion	3	5	9
Middle 1/3 myometrial invasion	0	9	4
Deep 1/3 myometrial invasion	11	19	34

Adapted from Morrow et al. (1991). Rates of pelvic lymph node metastasis observed in 621 Stage I endometrial cancers treated primarily with surgery

3.2 Clinical Factors

3.2.1 Stage

Surgical stage continues to be one the most important clinical factors predictive of outcomes. The outcomes of 81,900 patients with endometrial cancer from 1988 to 2006 in a SEER database and a cohort of 1,268 patients from the MoMaTEC study were shown to verify the improved prognostic utility of the current 2009 FIGO staging in comparison to the FIGO 1988 staging schema (Lewin et al. 2010; Werner et al. 2012). Five year overall survival rates in early stage disease were 90–96 %, 78–87 %, and 74–80 %, respectively, for stage IA and IB and stage II. In locally advanced disease, 5-year overall survival was 48–56 %, 36–53 %, 57–60 %, and 49–53 % for stage IIIA (serosa/adnexa), IIIB (vaginal), IIIC1 (pelvic lymph node), and IIIC2 (para-aortic lymph node), respectively. Survival in stage IV disease ranged from 16 to 57 %.

3.2.2 Lymph Node Status

Lymph node status is incorporated in the staging classification above. A drop in 5-year overall survival from 74 to 96 % for stage I/II patients to 49–60 % for node positive patients is observed (Lewin et al. 2010; Werner et al. 2012). A variety of features are associated with increased risk for lymph node metastasis. The strong association of tumor grade, depth of myometrial invasion and pelvic lymph node involvement was first demonstrated in the results of GOG study 33 (Tables 8, 9) (Creasman et al. 1987). In this clinical-pathologic study, 621 stage I endometrial cancer patients, accrued from 1977 to 1983, prospectively underwent hysterectomy, selective pelvic and para-aortic lymph node dissection and peritoneal cytology. Increasing FIGO grade and increasing depth of invasion correlated with progressively higher probability of pelvic lymph node

Table 9 GOG 33: rate of para-aortic lymph node metastasis based on extent of myometrial invasion and FIGO grade

	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)
Endometrium only	0	3	0
Inner 1/3 myometrial invasion	1	4	4
Middle 1/3 myometrial invasion	5	0	0
Deep 1/3 myometrial invasion	6	14	23

Adapted from Morrow et al. (1991). Rates of para-aortic lymph node metastasis observed in 621 Stage I endometrial cancers treated primarily with surgery

involvement, ranging from less than 5 % in patients without myometrial invasion, to 34 % in those with both outer third myometrial invasion and FIGO grade 3 histology.

While node positive patients as a whole have poorer survival compared to stage I and II patients, it should be noted that the predictive outcome of node positive disease should be considered in the context of the extent of other extrauterine disease. Mariani et al. examined the outcomes of 51 patients with surgically staged IIIC disease. In this cohort, it was noted that the 5-year recurrence free survival (RFS) for node positive only disease was 68 %, but dropped to 25 % in patients with node positive disease in combination with other extrauterine disease such as adnexal, vaginal, serosal involvement or positive peritoneal cytology (Mariani et al. 2002a). While this study is limited in its correlation to today's practice as few patient received chemotherapy, this poorer outcome in "higher burden" disease suggests these patient may require a more aggressive treatment approach. The overall nodal disease burden, as described by absolute number of positive lymph nodes and ratio of positive nodes to total nodes on lympadenectomy has also been shown to be prognostic in some studies (Chan et al. 2007a). Five-year disease-specific survival for those with 1, 2–5, and >5 positive nodes were 68.1, 55.1, and 46.1 %, respectively ($p < 0.001$). Percentage of positive lymph nodes was also evaluated, with 5-year disease-specific survival of 77.3 to 60.7 to 40.9 % in those with ≤0, >10 to ≥50 %, and >50 % nodes involved, respectively. Both factors were independently prognostic on multivariate analysis.

3.2.3 Adnexal and Serosal Involvement

FIGO stage IIIA is defined by serosal and/or adnexal disease spread. Adnexal involvement is associated with poorer outcomes, but is highly correlated with other adverse features such as high tumor grade, other metastatic sites, and unfavorable histology. When considering adnexal involvement in the absence of other factors, outcomes are more favorable than for all stage IIIA patients taken as a whole, with 5-year disease-free survival ranging from 71 to 86 % (Connell et al. 1999; Greven et al. 1989). Serosal involvement is associated with high risk of distant failure, owing in part to its association with other risk factors such as other sites of metastatic disease and higher stage presentation (Greven et al. 1989; Ashman et al. 2001). Similar to adnexal involvement, however, isolated serosal involvement portends an improved prognosis over all patients with serosal involvement, with 5-year disease-free survival of 41.5 % versus 20 % (Ashman et al. 2001).

3.3 Patient Factors

3.3.1 Age

Age has long been considered a risk factor for development of endometrial cancer, as well as prognostic of outcomes. In general, endometrial cancer is a disease of postmenopausal women. Younger women who develop endometrial cancer tend to have improved survival, often with risk factors such as estrogen or other hormone related-disorders, including but not limited to, infertility, polycystic ovarian syndrome, ovarian dysfunction, anovulatory cycles, and obesity (Ota et al. 2005). Young patients tend to have low grade endometrioid histology, correlating to more favorable outcomes.

While many studies have shown advanced age to be an independent predictor of worse outcomes (Kosary 1994; Abeler and Kjorstad 1991; Irwin et al. 1998), many small studies have found this to not be a prognostic factor. Some of been concerned that patient comorbidities, potential de-escalation of therapy in the elderly, or narrow cohorts, or propensity for more advanced stage at diagnosis, or more aggressive histology at diagnosis, among a multitude of other confounding factors, may explain the apparent discrepancy. Regardless, age is still part of the risk stratification of patients for selection of adjuvant therapy as is discussed below.

3.3.2 Serum CA-125

CA-125 is a serum tumor marker that can readily be tested, commonly used to monitor ovarian cancer. The role of CA-125 in endometrial cancer has been proposed to be prognostic, with elevated preoperative CA-125 levels associated with increased risk of lymph node metastasis (Chung et al. 2006). Many suggest measurement of preoperative serum CA-125 given several studies suggestive of prognostic utility (Powell et al. 2005); although no change in therapy is offered based on this value. Some have also proposed an age stratified CA-125 cutoff to improve the predictive value of CA-125 levels, with higher cutoffs proposed in younger patients (Chao et al. 2013). The NCCN guidelines designate CA-125 as an optional test in both

workup and surveillance, while the American Society of Gynecologists Oncologists does not endorse the routine use of CA-125 during surveillance in the absence of clinical findings concerning for metastatic disease (Salani et al. 2011). Future studies regarding the use of CA-125 are warranted and will likely focus on its potential as a tool for prediction of extrauterine disease in early stage patients or its use during surveillance for early detection of disease recurrence and whether this translates to improved patient outcomes.

3.4 Histologic Factors

While tumor stage is the most important prognostic indicator, many of the other confirmed prognostic features relate to information from the histology of the tumor itself. Tumor cell type, grade of differentiation, and LVSI are significantly important, and assist with stratification of patients within surgical staging groups into risk categories. Thus, the results of each can have significant influence on the adjuvant therapy given, as patients with early stage, low risk histology may not require adjuvant therapy, the same stage patient with high risk histology or tumor grade may have poorer outcomes if adjuvant therapy is not offered.

3.4.1 Histology

Given that surgical staging predominates for endometrial cancer, characteristics found on pathologic evaluation are highly prognostic. Cell type and tumor grade are highly predictive of patient outcomes, and carry significant weight in determining if adjuvant therapy after hysterectomy should be offered. Additional information regarding myometrial invasion, cervical stromal invasion, lymphovascular invasion, and others have also been shown to be prognostic and are used to help stratify risk of recurrence in patients with early stage disease. The following section on histology relates to histologic factors studied largely in endometrioid adenocarcinomas. In general, non-endometrioid histologies such as papillary serous and clear cell adenocarcionoma are highly correlated with many of these adverse pathologic factors, thus are deemed high risk in even early stage disease, and are offered more aggressive adjuvant therapy.

3.4.1.1 Histologic Type

The vast majority of endometrial cancers arise within the endometrial layer of the uterus, with subsequent growth and spread, usually into the myometrium, as it progresses. Adenocarcinoma accounts for the majority of endometrial cancer cases diagnosed. The most common histologic subtype is endometrioid histology, accounting for nearly 75–80 % of endometrial cancer cases. This is a gland forming variant of adenocarcinoma, often with appearance similar to that of the endometrium. Overall prognosis for low grade endometrioid adenocarcinoma is favorable. By some reports, approximately 25 % of adenocarcinomas can have squamous differentiation, where the grade of the glandular component is prognostic (Abeler and Kjorstad 1992). Villoglandular and mucinous adenocarcinomas are infrequently identified, with no significant effect on outcomes with villoglandular (Zaino et al. 1998a), and improved outcomes with mucinous features (Ross et al. 1983). Two less common, yet clinically significant subsets of adenocarcinoma, include papillary serous and clear cell adenocarcinoma, accounting for a majority of the remaining non-endometrioid cases. Papillary serous carcinomas histologically have a complex papillary architecture, resembling serous carcinoma of the ovary. Nuclear atypia is common, and psammoma bodies can be present. Clear cell carcinomas have 3 types of growth patterns, tubulocystic, papillary, or solid patterns, and are less likely to contain psammoma bodies. Any tumor that contains 10 % or more of either papillary serous or clear cell adenocarcinoma features are classified as mixed histology, although prognosis tends to correlate with the most advanced histology in the tumor.

Endometrial cancer is subdivided into type 1 or type 2 tumors; type 1 defined as low grade (FIGO grade 1 and 2) endometrioid tumors (nearly 80 % of adenocarcinoma), and type 2 encompassing FIGO grade 3 endometroid tumors, papillary serous, and clear cell adenocarcinomas. A different etiology of tumorigenesis has been proposed in these two subgroups. Type 1 tumors are generally associated with the classical risk factors for endometrial cancer including nulliparity, obesity, unopposed estrogen, early menarche/late menopause, tamoxifen therapy, among others. It has been proposed that elevated estrogenic state experienced in these situations can stimulate the endometrial layer, leading to hyperplasia, a likely precursor to endometrial cancer in some settings. Type 2 tumors, on the other hand, are not associated with hyperestrogenism or endometrial hyperplasia. Stage by stage, more aggressive histology is associated with poorer clinical outcomes (Boruta et al. 2004). As such, type 2 tumors are often included as a risk factor warranting intensification of adjuvant therapy as discussed below.

Uterine sarcomas (endometrial stromal sarcomas, leiomyosarcomas, and other mesenchymal tumors), and mixed epithelial and mesenchymal tumors (adenosarcomas and malignant mixed mullerian tumors), are much less common types of uterine cancer. As a group, they all confer very poor prognosis at diagnosis. They tend to be associated with higher stage at diagnosis, and dismal disease free and overall survival (Prat 2009; Callister et al. 2004). More aggressive therapy is generally favored in this group of patients given their significantly higher risk for failure and death, however given the relative rarity, poor response to

proposed interventions, and paucity of prospective data, there is no clearly defined guideline in management (Rauh-Hain and Del Carmen 2013; Kanthan and Senger 2011).

3.4.1.2 Tumor Grade

Across a multitude of studies, tumor grade has been shown to be strongly associated with prognosis, degree of myometrial invasion, and risk for lymph node metastasis. FIGO grading of endometrioid carcinomas incorporate the degree of gland formation and nuclear grade. The percent solid (nonglandular) growth is scored as increased solid growth is associated with more aggressive behavior. Grade 1 is defined as no more than 5 % solid growth, grade 2 with 6 to 50 percent solid growth, and grade 3 with more than 50 percent solid growth. If glandular grade is different from nuclear grade, nuclear grade predominates. Non-endometrioid tumors are graded by nuclear grade alone. Zaino et al. reported 5-year survival rates of 94 % for grade 1, 84 % for grade 2, and 72 % for grade 3 tumors (Zaino et al. 1998a). Given the significant prognostic feature of tumor grade, it is incorporated into risk stratification of patients within a given stage to help direct adjuvant therapy.

3.4.1.3 Myometrial Invasion

Degree of myometrial invasion has been shown to be an independent predictor for outcome in a multitude of studies (Creasman et al. 1987; Morrow et al. 1991). This has been validated since originally described and continues to be incorporated as part of the current FIGO staging. While risk factor groups have been described based on thirds of invasion, the most recent revision of FIGO staging has established 50 % as the cutoff between stage IA and stage IB endometrial cancer.

3.4.1.4 Cervical Stromal Invasion

Cervical stromal invasion is included in FIGO staging, given its prognostic significance in outcomes with reduced 5-year disease-free survival of 74–80 % for stage II disease compared to 90–96 % for stage IA. Previously, any cervical invasion was classified as stage II disease in the 1988 FIGO schema, with stage IIA defined as isolated endocervical epithelial involvement and stage IIB for deeper stromal invasion. However, several reports failed to demonstrate a difference in survival between the two groups (Orezzoli et al. 2009; Eltabbakh and Moore 1999). Thus, this subclassification was eliminated with the recent 2009 revision of FIGO staging and currently cervical *stromal* invasion only constitutes stage II disease. This has been shown to be independently prognostic for patient outcomes, with a 44 % increase in risk of progression or death and a 33 % increase in risk of death (Tewari et al. 2012).

3.4.1.5 Lymphovascular Space Invasion

Lymphovascular space invasion (LVSI) has been shown to be a predictor of risk of relapse and poorer survival, independent from tumor grade or depth of myometrial involvement (Morrow et al. 1991; Mariani et al. 2002b, c). LVSI has been shown to increase the rate of pelvic lymph node metastasis (Creasman et al. 1987). LVSI continues to be used as one of several histologic criteria for risk stratification for adjuvant therapy selection and clinical trial inclusion.

3.4.1.6 Peritoneal Cytology

In previous 1988 FIGO staging, the presence of malignant cells in peritoneal fluid was designated stage IIIA disease. However, multiple studies failed to show this as an independent prognostic factor (Hirai et al. 1989; Tebeu et al. 2004; Takeshima et al. 2001). The revised 2009 FIGO staging has eliminated positive peritoneal cytology as a factor in staging. However, recently Milgrom et al. showed that in stage III patients, positive peritoneal cytology was predictive of outcome and associated with distant relapse (Milgrom et al. 2013). This is consistent with the observation that positive peritoneal cytology, while not independently prognostic, may enhance the negative impact of other adverse factors (Takeshima et al. 2001). Peritoneal cytology is still obtained at most institutions during hysterectomy, as it may have some effect on adjuvant therapy selection, and is used as inclusion criteria of some ongoing phase III trials.

3.4.2 Implications of Postoperative Histology on Adjuvant Treatment

As previously discussed, multiple histologic and clinical factors have been found to be independently prognostic of clinical outcome. While some of these are directly used for staging, others are used for risk stratification to help predict a benefit from adjuvant therapy and aid in the selection of adjuvant therapy.

3.4.2.1 Risk Group Stratification in Early Stage Endometrial Cancer

Adjuvant therapy in endometrial cancer is dictated in large part by stage and risk factors within each stage. This is specifically true for early stage endometrial cancer where the extent and method of adjuvant radiotherapy has evolved.

Observation is reasonable for patients with stage IA, grade 1, favorable histology disease, otherwise deemed low risk. In patients with stage I disease, and any risk factor, including Grade 2–3 disease, LVSI, lower uterine segment involvement, deep myometrial invasion, or advanced age > 50–70, adjuvant therapy has traditionally been

considered. Previously, the GOG 33 data demonstrated advanced grade or deep myometrial invasion were risk factors for lymph node positive disease, which was associated with worse disease free survival. These risk factors had been employed to determine the need for postoperative pelvic radiation, but how to much weight to assign these risk factors has evolved.

The traditional indications for pelvic radiation in early stage disease have been challenged by the results of the Post-Operative Radiation Therapy in Endometrial Cancer (PORTEC) (Creutzberg et al. 2003, 2004) and GOG 99 (Keys et al. 2004) studies, resulting in identification of a new set of risk factors. This paradigm change has also been fueled by advances in surgical approach over the past 2 decades, with a more comprehensive degree of lymph node dissection, even in co-morbid patients. Based on both trials' results, a new high-intermediate risk group was defined by each cooperative group and a more multi-faceted algorithm was developed that incorporated grade, depth of myometrial invasion, LVSI, and age. PORTEC's and GOG 99's results are highly consistent showing an incidence of failure in the 30 % range for the GOG-defined high-intermediate-risk group and for the grade 3 group in PORTEC. The high-intermediate-risk group was defined by GOG as (1) grade 2–3 with deep third myometrial invasion and LVSI; or (2) age $>$ 50 and two of the risk factors in (1); or (3) age $>$ 70 and one of the risk factors in (1). The definition based on the PORTEC data is similar: $<$50 % myometrial invasion and grade 3 (any age); or $>$50 % invasion and grade 1–2 and age $>$ 60 years. However, the combination of $<$50 % myometrial invasion, grade 3 and LVSI is considered a high-risk feature by PORTEC-2 due to the significantly lower 5-year overall survival of 58 % observed in the PORTEC 1 study (Creutzberg et al. et al. 2004). These overall results are supported by a metaanalysis by Kong et al. (2007) of all four randomized trials (Creutzberg et al. 2000, 2004; Keys et al. 2004; Aalders et al. 1980) that shows adjuvant radiotherapy improved disease specific and overall survival for patients with grade 3 tumors and stage IB ($>$50 % invasion) disease. The failure pattern in the high-intermediate-risk group has been found to consist largely of vaginal recurrences, therefore, while the high risk patients are often recommended pelvic radiotherapy, high-intermediate risk group patients are often offered vaginal cuff brachytherapy and/or pelvic radiotherapy as vaginal recurrences are the most likely site of failure. This group has been studied by PORTEC-2, and vaginal cuff brachytherapy was found to be equivalent in preventing pelvic recurrence to whole pelvic radiation (Nout et al. 2010).

Adjuvant therapy for high risk disease is an area of active research as there is data to suggest intensifying therapy with chemotherapy is warranted, and currently practiced at many institutions. PORTEC-3 is currently enrolling patients with the high risk criteria and randomizing patients postoperatively to pelvic radiation or pelvic radiation with concurrent and post-radiation chemotherapy. Eligible patients include those with $<$50 % myometrial invasion plus grade 3 and LVSI; $>$50 % myometrial invasion with grade 3, or advanced endometrial cancer, including stage II–III disease, papillary serous or clear cell histologies. The results are eagerly anticipated.

3.4.2.2 Locally Advanced Endometrial Cancer

Stage III and IVA endometrial cancer is often described as locally advanced endometrial cancer. This group represents a heterogenous group of patients, with varying degrees of tumor burden and tumor histology, with the best adjuvant therapy not clearly defined. GOG 122 established a role for chemotherapy over whole abdominal radiation owing to improved disease free and overall survival of 38–50 %, and 42–55 %, respectively (Randall et al. 2006). More recently, Hogberg et al. compiled the data from two randomized European trials, NSGO-EC-9501/EORTC-55991 and MaNGO ILIADE-III, which randomized patients to adjuvant radiotherapy alone or sequential chemotherapy and radiation therapy. This indicated a significant improvement in 5-year progression-free survival from 69 to 78 %, with a trend for improved overall survival (Hogberg et al. 2010). The extent of radiotherapy, timing with chemotherapy, and patient selection is still an area of active study.

3.4.3 Molecular Markers

Molecular markers are an area of active interest. In most cases, markers are correlated with established prognostic indicators, such as tumor histology and grade. Some of the most studied factors are briefly reviewed. To date, the clinical utility of these markers is limited.

3.4.3.1 DNA Ploidy

DNA content, or more specifically, aneuploidy, has been studied by many groups. The frequency of aneuploidy has been shown to increase with increased tumor grade (Lundgren et al. 2002). Papillary serous carcinoma has been shown to exhibit aneuploidy, as well (Prat et al. 1994). Further, DNA aneuploidy has been shown to be an independent predictor for disease free survival (Zaino et al. 1998b; Nordstrom et al. 1996).

3.4.3.2 Microsatellite Instability

Microsatellite instability (MSI) is strongly associated with endometrial cancer in patient with HNPCC, occurring in nearly 75 % of such patients, and occurs in approximately 25–45 % of sporadic endometrial carcinomas. Microsatellites are short repeats of DNA that are integrated throughout the genome, and MSI is associated with deficits in DNA mismatch repair. In some studies, MSI is associated with

improved clinical outcome (Maxwell et al. 2001). However, there is discrepancy in the published literature, with several reports showing no correlation with clinical outcome (Zighelboim et al. 2007; Baldinu et al. 2002), while others have shown MSI to be an independent prognostic indicator for poorer survival (Mackay et al. 2010; Nout et al. 2012; Steinbakk et al. 2011). This disagreement may be related to sample size, cohort selection, different adjuvant therapies, confounding variables, or may indicate identification of the specific downstream genetic alterations is actually more relevant (Steinbakk et al. 2011).

3.4.3.3 Ki-67 Proliferation Index

Cellular proliferation is an area of interest in most cancer cell types. This has also been evaluated by many groups for endometrial cancer. Nuclear Ki-67 antigen is a marker of proliferating cells, and has been shown to be associated with histological grade and depth of myometrial invasion, as well as other risk factors (Kudela et al. 2012). High levels of Ki-67 expression have also been associated with increased risk of recurrence and poorer survival in some studies (Salvesen et al. 1998).

3.4.3.4 Oncogenes

HER2 and EGFR are both members of the ErbB/HER signaling family, a group of tyrosine kinase receptors critical in cellular proliferation and differentiation, and are implicated in tumorigenesis in many tumor models. HER2 expression was associated with higher tumor grade and depth of myometrial invasion but not independently prognostic for survival, whereas EGFR overexpression in endometrioid adenocarcinoma decreased survival from 89 to 69 % ($p < 0.04$), and in serous papillary and clear cell from 86 to 27 % ($p < 0.03$) (Khalifa et al. 1994; Konecny et al. 2009). There is continued interest in this pathway as inhibitors of EGFR and HER2 are actively used in other cancer treatment and exploitation of this pathway with these pharmaceuticals theoretically may improve patient outcomes.

P53 has been reported to be more highly expressed in type 2 tumors (Kudela et al. 2012). Not surprisingly, this has also been correlated with poorer patient outcomes (Mariani et al. 2000; Saffari et al. 2005; Silverman et al. 2000). Currently, clinical utility of this marker is uncertain as no targeted therapies are readily available.

The evaluation of PTEN as a prognostic factor is also controversial. PTEN is a tumor suppressor gene that down regulates the PI3-Kinase pathway, thus slowing down cellular proliferation. PTEN is mutated in approximately 20–80 % of endometrial cancers, but with less frequency in serous carcinoma. Results regarding the effect of PTEN on patient outcomes is mixed (Latta and Chapman 2002).

3.4.3.5 Cell Adhesion Molecules

Cell adhesion molecules have been widely studied in tumor biology, and are responsible in part for coordinating cell–cell interaction, cellular proliferation, and metastasis. E-cadherin is a cell membrane protein that complexes with cytoplasmic B-catenin regulating cellular adhesion and growth. The loss of E-cadherin expression results in release of B-catenin, which is then able to induce a subset of genes responsible for endothelial to mesenchymal transition which is one mechanism by which tumorigenesis and metastasis is thought to occur. Loss of E-cadherin expression is commonly seen in non-endometrioid endometrial carcinoma, but occasionally in endometrioid histology (Holcomb et al. 2002; Mell et al. 2004). Although in the same pathway, B-catenin has not been found to be independently prognostic of clinical outcomes (Nout et al. 2012; Singh et al. 2011).

3.4.3.6 Steroid Receptors

Expression of estrogen receptor (ER) and progesterone receptor (PR) has been extensively examined, given hormonally directed therapy is of particular interest in patients who may not be surgical candidates or have otherwise limited treatment options. Some studies indicate ER and PR expression are associated with less aggressive tumor behavior/grade (Ferrandina et al. 2005; Geisinger et al. 1986; Kadar et al. 1993; Jeon et al. 2006). While progestins are often used in relapsed or advanced disease, a recent metaanalysis indicates there is no data at present to support its use in primary disease (Martin-Hirsch et al. 2011); prospective evaluation of receptor expression and treatment response is warranted.

3.5 Imaging Prognostic Factors

FIGO staging for endometrial cancer by definition requires surgical staging. In the United States, a majority of centers include routine pelvic lymphadenectomy and para-aortic lymph node sampling at the time of hysterectomy. Morbidity is associated with such extended surgery, although has improved with advances in surgical technology. Further, the ASTEC trial, albeit with relatively limited follow-up, to date has not shown a survival benefit to lymphadenectomy in early stage disease (ASTEC study group et al. 2009). Thus, there is great interest in developing new ways to predict risk of lymph node involvement, and to identify those patients with acceptably low risk of involvement in order to identify patients where omission of lymphadenectomy is reasonable. While clinical exam prior to 1988 was shown to understage endometrial cancer in 13–22 % of patients, newer imaging technology is now available, and may be promising in identification of factors such as myometrial invasion, extrauterine involvement, as well as risk

of pelvic lymph node disease. These are briefly reviewed here.

3.5.1 Morphologic Imaging

Computed tomography (CT) has been used for preoperative assessment in endometrial cancer, but its role is with limitations. The ability of CT to delineate endometrial cancer in the uterus is relatively insensitive, especially for small endometrial cancers (i.e. stage IA), with overall sensitivity of 53 % (Grossman et al. 2008). Accuracy of CT for myometrial invasion has been reported to be 61 % with sensitivity of 40 % in one study comparing ultrasound, CT, and MRI for depth of myometrial invasion assessment (Kim et al. 1995). Multidetector CT has improved accuracy for depth of myometrial invasion and cervical involvement at 95 and 81 %, respectively (Tsili et al. 2008). The applicability of this modality is limited given this single experience in 16 patients, thus warrants further evaluation. Sensitivity and specificity of CT for lymph node involvement has been reported at 52 and 92 %, respectively (Connor et al. 2000). Chest CT can be considered in high risk patients, such as advanced stage or high grade tumors who are at increased risk for pulmonary metastasis.

The accuracy of ultrasound for myometrial invasion has been described by many groups. The accuracy of transvaginal ultrasound (TVUS) for predicting stage IA versus stage IB endometrial cancer reportedly ranges from 69 to 93 % (Kim et al. 1995; DelMaschio et al. 1993; Prompeler et al. 1994). High-frequency TVUS has been shown to have accuracy of 73 % for assessment of myometrial invasion (Arko and Takac 2000). The reported experience of ultrasonography to predict cervical involvement has also been limited, with only 7 of 10 patients with pathologic cervical involvement reported pretherapy to have involvement based on ultrasound (Akbayir et al. 2011; Szantho et al. 2001). The use of 3D ultrasonography with volume contrast imaging has also been described. Jantarasaengaram et al. reported accuracy of 92 % for predicting myometrial invasion and 90 % for cervical involvement (Jantarasaengaram et al. 2013). Sonohysterography, which involves intracavitary infusion of saline followed by evaluation with TVUS, has been employed in some settings, with accuracies of 84–89 % for assessing deep myometrial invasion (Chang et al. 2010; Valenzano et al. 2001; Dessole et al. 2006). The use of this modality is controversial, however, due to concern of tumor spillage into the peritoneal cavity with saline infusion, which has been documented by some investigators (Dessole et al. 2006; Alcazar et al. 2000).

The use of ultrasound has been compared to MRI in multiple investigations, and consistently has been found to be superior to ultrasound for evaluation of cervical involvement and depth of myometrial invasion (Kim et al. 1995; DelMaschio et al. 1993; Arko and Takac 2000; Antonsen et al. 2013a; Yamashita et al. 1993a). Further, contrast enhanced MRI, compared to unenhanced MRI, results in significantly improved accuracy, ranging from 85 to 92 % accuracy for depth of myometrial invasion versus 55–78 % for non-contrasted imaging (Kinkel et al. 1999; Ito et al. 1994; Saez et al. 2000; Sironi et al. 1992; Yamashita et al. 1993b; Sala et al. 2009). Accuracy rates for determination of cervical involvement range from 86 to 95 % (Manfredi et al. 2004; Takahashi et al. 1995; Nagar et al. 2006). The use of MRI for pelvic and para-aortic lymph node involvement is comparable to CT, with sensitivity and specificity reported at 44–66 % and 73–98 %, respectively. Thus, given MRI's superior assessment of depth of myometrial invasion and cervical involvement, it is generally preferred over CT and ultrasound for preoperative workup.

3.5.2 Functional Imaging

The use of PET/CT in endometrial cancer is an area of active investigation. A recent meta-analysis of 18F-FDG PET or PET/CT for identification of metastatic lymph nodes in endometrial cancer reported the pooled estimates for 243 patients, indicating sensitivity and specificity of 63 % (95 % CI, 48.7–75.7 %) and 94.7 % (95 % CI, 90.4–97.4 %), respectively (Chang et al. 2012). The relatively low sensitivity is uncertain, but may be related to low glucose metabolism in low grade lesions, as well as limited ability to detect subcentimeter metastases. Further, PET imaging is limited in ability to detect intraperitoneal tumor implants and parenchymal implants. Due to these limitations, CT and MRI are preferable for detection of extrauterine disease, although FDG-PET may be appropriate in patients with high grade tumor that is likely to be FDG avid (Lee et al. 2011).

The role for PET/CT for assessment of myometrial invasion and cervical invasion is uncertain. Antonsen et al. recently reported the results of 318 patients with endometrial cancer who preoperatively underwent 2D ultrasonography, MRI, and PET/CT imaging. Sensitivity, specificity, and accuracy for PET/CT for myometrial invasion were 93, 49, and 61 %, and 43, 94, and 83 %, respectively for cervical invasion, which were similar to MRI (Antonsen et al. 2013a).

SUVmax has been evaluated by some groups, with limited data suggesting SUVmax may be able to predict higher stage disease, higher grade tumors, risk of deeper myometrial invasion, and lymph node metastatic risk (Antonsen et al. 2013b; Nakamura et al. 2010). Other studies have indicated SUVmax can also predict for poor disease free survival (Kitajima et al. 2012) and overall survival (Nakamura et al. 2011, 2013).

Finally, 18F-FDG PET or PET/CT has also been used for detection of recurrent disease (Park et al. 2008; Belhocine et al. 2002; Chung et al. 2008; Kitajima et al. 2008).

Saga et al. assessed the use of 18F-FDG PET in 21 patients for detection of recurrence and evaluation of treatment response. Compared to conventional imaging and serum tumor markers, FDG-PET combined with CT or MRI was more accurate and had comparable or better sensitivity and specificity (Saga et al. 2003). Currently, the ACR guidelines indicate that FDG-PET is usually appropriate over MRI pelvis or CT pelvis if recurrence is suspected clinically (Lee et al. 2011).

4 Cancer of the Vulva

Vulvar cancer is a rare disease, accounting for only 5 % of malignancies of the female genital tract (Siegel et al. 2012). It is estimated that in 2013 there will be approximately 4,700 new cases and 900 deaths due to this disease in the United States (Siegel et al. 2012). The mean age at diagnosis for vulvar cancer is 65 years, and clinical risk factors for this disease include immunodeficiency, prior history of cervical cancer, cigarette smoking, vulvar dystrophy, vulvar or cervical intraepithelial neoplasia, and HPV infection (Ansink 1996; Madsen et al. 2008).

Vulvar cancer is a disease of the skin, arising from squamous epithelium, and tumor spread occurs primarily through the lymphatic system. The first station of nodal spread is the inguino-femoral lymph nodes, usually superficial first then deep, which then spreads in a predictable fashion to the pelvic lymph nodes in more advanced cases. Pelvic lymph node involvement without inguinal node involvement is rare (Krupp and Bohm 1978). Locally, vulvar cancer can invade adjacent structures including the vagina, bladder, anus and rectum. Given the propensity of this type of cancer to spread to adjacent structures and metastasize to lymph nodes, standard of care had previously been *en bloc* resection of the primary tumor with inguinofemoral lymph node dissection, resulting in significant risk of morbidity and psychosexual impact. However, the approach to treatment has evolved over the last several decades, with therapy ranging from wide local excision for small, superficial lesions, to definitive or neoadjuvant chemo-radiation which may reduce the extent of surgical resection required, versus pelvic exenteration in advanced disease.

4.1 Staging

Prognostic factors for vulvar cancer include size and local extension of the primary tumor, as well as the degree of lymphatic involvement, as reflected in the most recent (2009) version of the FIGO staging system (Hacker 2009), Table 10. As with other gynecologic malignancies, the FIGO staging system is a clinicopathologic staging system and formal recommendations for the staging evaluation for vulvar cancer have not been established. The extent and size of the primary tumor is established by clinical examination, often by EUA, including colposcopy, excisional biopsy or FNA of clinically positive inguinal nodes, and/or cystoscopy and proctoscopy based on presentation in advanced disease. Clinical palpation alone does not have a high degree of specificity or sensitivity for inguino-femoral adenopathy (Homesley et al. 1993; Franklin 1972; Selman et al. 2005). Thus, imaging modalities such as MRI and PET/CT, as well as CT of the chest, abdomen, and pelvis are also typically employed, particularly to evaluate for lymph node involvement. Several studies have shown that MRI may be useful in evaluating the inguinofemoral lymph nodes (Singh et al. 2006; Sohaib et al. 2002). However, it is important to note that radiologic findings cannot be used as a substitute for pathologic assessment of the nodes.

The gold standard for pathologic assessment of the inguinofemoral lymph nodes is lymphadenectomy. However, this carries a significant risk for morbidity. Recently, studies have evaluated the utility of sentinel lymph node biopsy, rather than lymphadenctomy in select patients as this technique carries less morbidity (Hefler et al. 2008). Comparison of sentinel lymph node biopsy to lymphadenectomy in a phase II GOG study showed that a sentinel lymph node can be found in 92 % of patients, and is 92 % sensitive, with a false negative rate of 2 % in patients with tumor less than 4 cm in size (Levenback et al. 2012). Information from sentinel lymphadenectomy has not yet been incorporated into the staging system. However, data from the recent GROINSS-V study indicates that the disease burden identified in the sentinel node is a sensitive indicator of prognosis (Oonk et al. 2010).

4.2 Clinical Factors

Lymph node involvement and size and extent of primary tumor are the strongest prognostic indicators in vulvar cancer, thus the 2009 FIGO staging system incorporates both factors. In the past, wide local excision or en bloc resection with bilateral inguinofemoral lymph node dissection was the standard surgical approach. However, bilateral lymphadenectomy carries significant risk for morbidity, both in the short and long term due to wound complications, infection, and lymphedema. Therefore, efforts are made to identify a cohort of patients that may not require lymph node dissection, albeit with an abundance of caution. In early vulvar cancer, appropriate management of the lymph nodes is the single most important factor in decreasing mortality as recurrence in the undissected inguino-femoral lymph nodes results in higher mortality

Table 10 AJCC TNM and FIGO staging of vulvar cancer

TNM	FIGO	Description
Primary tumor (T)		
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis[a]		Carcinoma in situ
T1[a]	IA	Lesions 2 cm or less in size, confi ned to the vulva or perineum and with stromal invasion 1.0 mm or less[b]
T1[b]	IB	Lesions more than 2 cm in size *or* any size with stromal invasion more than 1.0 mm, confined to the vulva or perineum
T2[c]	II	Tumor of any size with extension to adjacent perineal structures (lower/distal third of urethra, lower/distal third vagina, anal involvement)
T3[d]	IVA	Tumor of any size with extension to any of the following: upper/ proximal two thirds of urethra, upper/proximal two thirds of vagina, bladder mucosa, rectal mucosa, or fixed to pelvic bone
Regional lymph nodes (N)[e]		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1[a]	IIIA	One lymph node metastasis each 5 mm or less
N1[b]	IIIB	One lymph node metastasis 5 mm or greater
N2[a]	IIIB	Three or more lymph node metastases each less than 5 mm
N2[b]	IIIB	Two or more lymph node metastases 5 mm or greater
N2[c]	IIIC	Lymph node metastasis with extracapsular spread
N3	IVA	Fixed or ulcerated regional lymph node metastasis
Distant metastasis (M)		
MX		Distant metastasis cannot be assessed
M0		No distant metastasis
M1	IVB	Distant metastasis (including pelvic lymph node metastasis)

Source Edge et al. (2009)

[a] FIGO no longer includes stage 0 (Tis)

[b] The depth of invasion is defined as the measurement of the tumor from the epithelial–stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion

[c] FIGO used the classification T2/T3. This is defined as T2 in TNM

[d] FIGO used the classification T4. This is defined as T3 in TNM

[e] An effort should be made to describe the site and laterality of lymph node metastasis

(Cormio et al. 2010). Tumor size and depth of invasion can help predict for risk of lymph node involvement, therefore, combined with clinical exam and imaging, the decision for surgical evaluation of lymph nodes is determined.

4.2.1 Stage

In the 1988 FIGO staging system, prognosis was well distributed among the stage categories with 89 % 5-year survival for stage I, 85 % for stage II, 74 % for stage III and 31 % for stage IV (Homesley et al. 1991). However stage III consisted of a heterogeneous group of patients, with survival ranging from 30 to 100 %. The current revised 2009 FIGO staging system improves upon the prior staging schema by including more detailed information regarding the extent of lymph node involvement by subdividing the category into Stage IIIA and IIIB based on size and number of lymph nodes, or extracapsular spread (Stage IIIC), all of which are reported to closely correlate with prognosis (Homesley et al. 1991; Hacker et al. 1983; Lataifeh et al. 2004; Origoni et al. 1992; Raspagliesi et al. 2006; Fons et al. 2009a; Woelber et al. 2009). Several recent studies have validated the prognostic utility of these expanded stage categories (Tan et al. 2012; Tabbaa et al. 2012).

4.2.2 Tumor Volume

While lymph node involvement is the most important outcome predictor in multivariate analysis, tumor size has been shown to be an independent prognostic factor for local recurrence (Rutledge et al. 1970). However, in several larger contemporary series, tumor size does not independently predict disease free and overall survival on multivariate analysis (Raspagliesi et al. 2006; Tantipalakorn et al. 2009), although associations between T-stage and local recurrence-free and disease-free survival are seen in univariate analysis in a large series of 215 patients with reported local recurrence-free survival and disease-free survival rates of 85 and 88 % in T1 lesions, 74 and 61 % in T2 and 69 % and 37 % for T3/4 tumors (Rouzier et al. 2002). Finally, tumor size

correlates closely with the probability of lymph node involvement, thereby likely conferring worse prognosis through its association with this unfavorable risk factor. The incidence of lymph node involvement is 5–8 % for tumors <1 cm and increases to 24 % for 1–2 cm, 31 % for 2–3 cm and 36 % for 3–5 cm tumors (Gonzalez Bosquet et al. 2003; Boyce et al. 1985).

4.3 Patient Factors

4.3.1 Age

While the mean age at diagnosis of vulvar cancer is 65, advanced age is a prognostic factor for increased risk of groin node metastasis and worse survival (Homesley et al. 1993; Sznurkowski et al. 2013; Blecharz et al. 2008; Ramanah et al. 2012). However, this variable has not been significant in some cohorts when adjusted for stage, lymph node status, and surgical therapy (Raspagliesi et al. 2006; Woelber et al. 2009; Burger et al. 1995).

4.3.2 Hemoglobin

As in many cancers, tumor hypoxia is thought to be one factor for poor prognosis. Vulvar cancer patients with anemia have been found to have higher incidence of inguinal lymph node metastasis (Stone et al. 2005; van de Nieuwenhof et al. 2010). On univariate analysis, Hefler et al. showed hemoglobin <12 g/dl resulted in shorter survival, similar to van de Nieuwenhof et al. that showed hemoglobin <11.3 g/dl was an independent predictor of poorer survival (van de Nieuwenhof et al. 2010; Hefler et al. 2000). Interestingly, this did not correlate with expression of hypoxia markers GLUT-1 nor CA-IX. Further evaluation of this variable has not been studied, therefore clinical utility is uncertain, as anemia may simply be a marker of poorer overall health.

4.4 Histologic Factors

4.4.1 Histology

Nearly 85–90 % of vulvar malignancies are squamous cell carcinoma. Melanoma is the second most common while other histologies such as basal cell carcinoma, Bartholin's gland adenocarcinoma, Merkel cell and sarcomas are more rare (Hunter 1975; Finan and Barre 2003; Sugiyama et al. 2007; Stang et al. 2005; Ragnarsson-Olding et al. 1993; Weinstock 1994). Squamous cell carcinoma are often classified into one of two types; classic, warty, Bowenoid type or keratinizing, differentiated, simplex type. Squamous cell carcinoma of the vulva often arise in the setting of premalignant conditions such as vulvar intraepithelial neoplasia (VIN) or other areas of chronic inflammation such as lichen sclerosis Bowen's disease, Paget's disease, and erythroplasia of Queyrat (Carlson et al. 1998; Kutlubay et al. 2013). A large subset of premalignant conditions, particularly usual type VIN, are associated with HPV infection and are more likely to be observed in young women or smokers and warty or basaloid type squamous cell tumors. Conversely, keratinizing type is more often reported in older women in the setting of chronic inflammation such as lichen sclerosis (Hildesheim et al. 1997; de Koning et al. 2008; Del Pino et al. 2013). This dichotomy is thought to be a result of two different tumorigenic mechanisms that can result in vulvar squamous cell carcinoma, HPV dependent or independent mechanisms. Several reports indicate patients with HPV positive tumors have better survival than those with HPV negative tumors (Lindell et al. 2010).

Data supporting prognostic implications of tumor grade or LVSI is varied. In multiple studies, higher tumor grade is associated with increased risk for lymph node metastasis and worse overall survival (Homesley et al. 1993; Sznurkowski et al. 2013; Podratz et al. 1983; Lavie et al. 1999). However, it was not a significant variable for survival according to Burger et al. or Lataifeh et al. (Lataifeh et al. 2004; Burger et al. 1995). LVSI is associated with increased risk of lymph node metastasis (Homesley et al. 1993; Husseinzadeh et al. 1990; Binder et al. 1990) and is significant for overall survival on univariate analysis (Lataifeh et al. 2004; Raspagliesi et al. 2006; Burger et al. 1995; Knopp et al. 2004; Paladini et al. 1994), but only retains significance on multivariate analysis in a select few reports (Raspagliesi et al. 2006; Knopp et al. 2004).

4.4.2 Depth of Invasion

Depth of tumor invasion, defined as the distance from the epithelial/stromal junction to the deepest point of invasion, correlates strongly with lymph node involvement. While the risk of lymph node involvement for tumors with < 1 mm invasion is essentially nil, it increases to 6 % for 1–2 mm depth of invasion, 8 % for 2–3 mm, 22 % for 3–4 mm, 25 % for 4–5 mm and 38 % for > 5 mm depth of invasion. Lymph node dissection is therefore recommended for tumors with a depth of invasion of >1 mm (Berek and Hacker 1989). Similar criteria should be applied for the decision of adjuvant radiation in un-dissected groins. Other investigators observed variable threshold level of 3 mm (Woelber et al. 2009) and 9 mm as predictors of relapse and survival (Nicoletto et al. 2010).

4.4.3 Surgical Margins

A clear association between surgical margins and local failure has been shown. Microscopic margins of <8 mm (in formalin fixed tissue) are associated with a local recurrence rate of 48 %, compared to no recurrences with wider

Table 11 The effect of positive lymph nodes on cancer specific survival

	Negative LN	1–2 + LN	3 + LN
Homesley et al. (1993)	91 %	75 %	36 %, [*5–6 LN:24 %, *7 LN: 0 %]
Hacker et al. (1983)	94 % (0–1 LN)	80 % (2 LN)	12 % ($\geq$ 3 LN)
Origoni et al. (1992)	–	55 % ($\leq$3 LN)	22 % (> 3 LN)
Chan et al. (2007b)	–	92 % ($\leq$2 LN)	30 % (> 2: LN)

LN lymph node

margins (Heaps et al. 1990). This correlation has been substantiated in a more recent study showing a 23 % incidence of local recurrence in patients with margin distance of < 8 mm, compared to no recurrences in those with >8 mm margins (Chan et al. 2007b). Adjuvant radiotherapy significantly reduces local recurrence rates for both close and positive margins and improved survival (Faul et al. 1997; Viswanathan et al. 2013).

4.4.4 Histopathologic Lymph Node Status

Lymph node status is the single most significant prognostic factor in vulvar cancer. Lymph node positivity has a profoundly adverse effect on treatment outcome, with survival declining from >90 % in patients with negative lymph nodes to as low as 30 % or less in those with involved lymph nodes (Homesley et al. 1993; Hacker et al. 1983; Origoni et al. 1992; Rutledge et al. 1970; Podratz et al. 1983; Chan et al. 2007b; Iversen et al. 1980).

Number and pathologic extent of the lymph node involvement are of paramount importance for prognosis (Table 11). Patients with involvement of one lymph node and small primary tumors tend to have a survival above 90 %, whereas survival is reduced below 35 % in those with 2 or more nodes (Homesley et al. 1991). In a large single institution study of 389 patients, nodal status was the most significant independent prognostic factor, followed by LVSI. Within the node-positive group, percentage of nodal replacement and extracapsular spread independently predicted outcome (Raspagliesi et al. 2006).

The prognostic significance of bilaterality of LN involvement has remained controversial, some suggesting that it influences outcome (Burger et al. 1995; Fons et al. 2009b), while others find no correlation when the number of lymph nodes is also considered (Hacker et al. 1983; Raspagliesi et al. 2006). Of note, the most recent revision of the FIGO staging has eliminated laterality of lymph node involvement in favor or number and size, and the presence or absence of extracapsular extension.

Recommendations regarding adjuvant therapy have been informed in part by GOG 37, in which 114 patients who underwent radical vulvectomy and bilateral inguinofemoral lymph node dissection, and with positive lymph nodes were randomized to adjuvant bilateral inguinal and pelvic radiation versus pelvic node dissection (Homesley et al. 1986). Patients with >2 involved inguinal nodes showed a significant benefit from adjuvant radiotherapy over surgery. The study was underpowered to draw clear conclusions on involvement of one or two lymph nodes. However, single-institution studies suggest that gross involvement of a single node also has a substantial recurrence risk, particularly if extranodal extension is present, and warrants consideration of adjuvant therapy (Origoni et al. 1992; Ansink et al. 1991).

4.4.5 Molecular Markers

4.4.5.1 DNA Ploidy

Aneuploidy has been reported to correlate with other poor prognostic factors, and has been reported to predict for worse outcome (Lerma et al. 1999; Mariani et al. 1998), although other studies have shown no significant relationship (Knopp et al. 2004; Dolan et al. 1993).

4.4.5.2 HPV Dependence and Independence

HPV positive tumors, which occurs more commonly in younger patients, may be associated with a better prognosis (Monk et al. 1995; Ansink et al. 1994). Given that vulvar cancer is thought to be driven by HPV-dependent and independent pathways, several groups have looked at associated markers. Basaloid and warty tumors, often considered HPV-dependent tumors, often express p16, and are p53 negative, whereas keratinized tumors, classically HPV-independent tumors, are p16 negative and p53 positive (Santos et al. 2004; Kruse et al. 2008). Investigators have also explored if markers of HPV infection, such as $p16^{INK4a}$, a protein that is increased due to HPV E7 oncogene activity, is prognostic in vulvar cancer. Knopp et al. and Tringler et al. showed high expression was associated with improved survival on univariate, but not multivariate analysis (Knopp et al. 2004; Tringler et al. 2007). The expression of p53 has also been associated with poorer overall survival in several studies (Hoffmann et al. 1999; Scheistroen et al. 1999; Kohlberger et al. 1995). Of note, in Scheistrøen et al., this was only found in stage III vulvar cancer, and not stage I and II disease. Kagie et al. and McConnell et al. did not find p53 overexpression to be a

significant prognostic indicator, but did note its presence in adjoining premalignant lesions, such as VIN, perhaps indicating it as a marker for malignant transformation from precursor lesions (Kagie et al. 1997; McConnell et al. 1997).

4.4.5.3 ErbB/HER Signaling Family

HER2 and EGFR expression have also been identified in a variety of small studies as prognostic indicators for clinical outcome. HER2 and EGFR overexpression has been identified in 47 and 67 % of vulvar cancers, respectively (Hantschmann et al. 2005; Johnson et al. 1997). Further, both HER2 and EGFR expression has been associated with increased risk for lymph node metastasis, while EGFR overexpression, in the absence of HPV infection, is associated with decreased survival (Johnson et al. 1997; Gordinier et al. 1997; Woelber et al. 2012; Growdon et al. 2008). Given that small molecule EGFR tyrosine kinase inhibitors and HER2 directed therapies are available, this may represent a cohort of patients that may benefit from targeted therapies in the future.

4.4.5.4 Angiogenic Factors

Increased VEGF expression is associated with increased microvessel density, and has been associated with poorer survival (Jach et al. 2011; Obermair et al. 1996). CA IX, often associated with hypoxia, is up-regulated in various solid tumors, including vulvar cancer. High intratumoral expression has been associated with unfavorable disease-free survival (Kock et al. 2011; Choschzick et al. 2010). Interestingly, higher serum CA IX preoperatively was also associated with unfavorable prognosis (HR 7.2 $p = 0.02$) (Kock et al. 2011). The clinical utility of such measurements is uncertain.

4.4.5.5 Microarray Identified Factors

Several groups have employed microarray techniques to try to identify prognostic markers, or therapeutic targets, in vulvar cancer (Kowalewska et al. 2012; Fons et al. 2007), some of which were significantly associated with worse disease free survival including cyclooxygenase 2 and Caspase 3, (Fons et al. 2007) and SFN, CA12 and JUP which are associated with increased nodal recurrence risk and earlier time to recurrence (Kowalewska et al. 2012). However, given the limited number of cases, and unknown mechanism of these markers, further studies will be needed in order to verify any prognostic or therapeutic potential.

4.5 Treatment Related Factors

Vulvar cancer is primarily surgically treated disease, while radiation therapy plays a major role in adjuvant therapy and in locally advanced unresectable disease. Over time, the surgical approach has become more tailored toward clinical stage at presentation, with wide local excision acceptable for stage IA lesions, and the use of sentinel lymph node biopsy instead of lymphadenectomy in lateralized, clinically negative, early stage patients at the time of primary treatment with vulvectomy result in reduced morbidity without compromise in local control (Levenback et al. 2012; Van der Zee et al. 2008).

The approach to locally advanced disease has also evolved. More recently, the use of neoadjuvant chemotherapy and/or radiation or definitive chemoradiotherapy have been investigated. Patients with locally advanced unresectable vulvar cancer treated on the GOG 101 and 205 studies received neoadjuvant concurrent radiation and chemotherapy prior to resection of residual disease (Moore et al. 2012; Montana et al. 2000). Response to neoadjuvant therapy was a powerful predictor of local control and survival. In GOG 205, among the patients who completed therapy, 64 % achieved a complete clinical response and 50 % of patients achieved a complete pathological response (Moore et al. 2012). Among those with pathological response, local control was 75 % (22/29), and 3 local failures were salvageable with surgical resection; thus 25/29 patients with complete pathologic response are disease free. Conversely, only 43 % (9/21) of patients with incomplete response survived. Among those who did not undergo resection of persistent tumor, none survived.

4.6 Imaging Prognostic Factors

As treatment of vulvar cancer has evolved from radical vulvectomy and bilateral inguino-femoral lymphadenectomy to a more tailored surgical and neoadjuvant chemoradiation approach, the accuracy of pre-treatment staging is increasingly important.

Imaging prognostic factors have not been clearly identified in vulvar cancer. However molecular imaging is emerging as a useful tool to identify lymph node involvement, location and extent. Given the rarity of vulvar cancer, diagnostic imaging utility is extrapolated from experience in cervical and anal cancer. In a small prospective study, PET/CT has been shown to have a sensitivity of 67 % and specificity of 95 % in indentifying lymph node involvement, and was particularly useful in detecting extranodal involvement (Cohn et al. 2002), which all constitute powerful prognostic factors. Thus patients may be triaged to more aggressive therapy based on the imaging findings, however at present, imaging cannot substitute for histologic information obtained with invasive lymph node evaluation.

MRI has also become common for evaluation of vulvar cancer at diagnosis. While early stage vulvar cancers can

often be staged on clinical exam, the extent of involvement of adjacent structures may be more difficult in locally advanced disease. MRI has been shown to be 70–85 % accurate with particular utility in defining the extent of invasion of adjacent structures and outlining tumor size, thus aiding in pretreatment surgical or radiotherapeutic planning (Kataoka et al. 2010; Sohaib et al. 2002).

5 Cancer of the Vagina

Primary vaginal cancer, defined as a lesion arising from the vagina, without involvement of the vulva or cervix, is a rare entity comprising only 1–2 % of gynecologic malignancies. The incidence of invasive vaginal cancer in the US has been reported at 0.69 per 100,000 women, with approximately 1,100 invasive cases annually. The median age at diagnosis is 68 years (Wu et al. 2008). Greater than 90 % are of squamous cell etiology. Risk factors for vaginal carcinoma include history of HPV infection, cervical intraepithelial neoplasia, prior hysterectomy, first intercourse before 17 years of age, five or more sexual partners, genital warts, chronic irritant vaginitis, and immunosuppression (Daling et al. 2002; Okagaki et al. 1983; Brinton et al. 1990; Bouma et al. 1994; Sillman et al. 1997).

Vaginal cancer is often found to be multifocal and often arises in the upper vagina. Tumor spread can be by local extension, lymphatic spread or hematogenous dissemination. Current FIGO staging is by clinical exam, chest and skeletal radiography. By definition, vaginal cancer cannot involve the vulva or cervix, therefore, multiple biopsies are performed to rule out involvement as this may change the diagnosis of the primary lesion. The lymphatic drainage of the vagina is very complex, with the upper vagina draining primarily via cervical lymphatics to the interiliac and parametrial nodes. The posterior vagina drains into the presacral, anorectal and inferior gluteal nodes, while the distal vagina drains in a vulvar pattern to the inguinal and femoral nodes, and subsequently to the pelvic nodes. Thus, all regional nodal stations are at risk for spread in vaginal carcinoma within the mid vagina, or tumors spanning several areas of the vagina.

Given the rarity of this disease, phase III trials have not been conducted, with guidelines drawn from retrospective studies and extrapolated from cervical and anal cancer experience given similarities in histology and preference for organ preservation. Similarly, prognostic and predictive factors are more challenging to elucidate in vaginal cancer due to limited data and relatively non-standardized treatment.

5.1 Staging

FIGO staging is the major prognostic indicator of disease outcome (2009). A thorough bimanual and rectovaginal exam is the most important tool for evaluation of local extent of disease, and often is carried out under anesthesia at which time biopsies can also be performed. Clinical exam focuses on differentiating vaginal wall only (stage I), extension to subvaginal tissue (stage II), or extension to the pelvic wall (stage III). In advanced disease, cystoscopy, proctoscopy, and IV pyelogram to rule out hydronephrosis may be indicated to rule out direct extension of tumor which would constitute stage IVA disease. Biopsies of the cervix or any other suspicious lesions should be performed to rule out cervical, urethral, or vulvar primaries, as these must be excluded for the diagnosis of vaginal cancer by FIGO criteria. Chest and skeletal radiography are also allowed. The results of biopsy or fine-needle aspiration of the inguinal/femoral or other nodes may be included in the clinical staging, although FIGO does not specify staging stratification for lymph node positive disease.

5.2 Clinical Prognostic Factors

5.2.1 Stage

Clinical stage is the major prognostic factor for overall survival. Most patients, except those with very limited involvement, are treated with primary radiation therapy. Based on NCDB data, one of the largest retrospective reviews of survival by stage, 5-year overall survival was 73 % for stage I, 58 % for stage II, and 36 % for stage III–IV (Creasman and Menck 1998). Similarly, in a SEER analysis by Shah et al., 5 year disease specific survival was 84 % for stage I tumors, 75 % for stage II tumors, and 57 % for stage III/IV (Shah et al. 2009).

5.2.2 Tumor Volume

Tumor size is an important predictor of outcome. In one of the largest series of patients treated with primary radiation, pelvic control was 85 % in tumors <4 cm versus 75 % in those >4 cm, and disease-specific survival was 82 and 60 % respectively (Frank et al. 2005). In a series of 301 patients by Chyle et al., lesions <5 cm maximum dimension had a 10-year local recurrence rate of 20 % compared to 40 % for >5 cm, which was significant on univariate analysis (Chyle et al. 1996). Perez et al. demonstrated tumor size was only predictive of pelvic control and disease free survival in stage II patients without parametrial involvement (Perez et al. 1999). Length of vaginal involvement has

been implicated as an adverse prognostic factor (Kirkbride et al. 1995), which may also be linked to tumor size.

5.2.3 Tumor Location

While location of the tumor is important, particularly in consideration of nodal regions at risk, the utility of location as a prognostic factor is unclear. Several studies have indicated better survival and decreased risk for recurrence for patients with tumors located in the proximal half compared to those of the entire vagina or distal portion (Chyle et al. 1996; Kucera and Vavra 1991; Urbanski et al. 1996; Ali et al. 1996). Lesions of the posterior vagina wall also have worse prognosis than other locations (Chyle et al. 1996; Dixit et al. 1993). Counter to these studies, however, Perez et al. did not show any prognostic value to tumor location in the posterior vaginal wall (Perez et al. 1988).

5.2.4 Lymph Node Status

Surgical series have reported rates of pathologic nodal involvement that range from 6 %-14 % for stage I disease and 26–32 % for stage II disease (Al-Kurdi and Monaghan 1981; Davis et al. 1991). Al-Kurdi and Monaghan noted that 12 % survived when pelvic or inguinal lymph nodes were involved as compared to 47 % survival in node negative patients. However, these are small studies, and given the fact FIGO staging does not include lymph node disease, it is difficult to assess its prognostic utility.

5.3 Histologic Factors

5.3.1 Histology

The majority of invasive vaginal cancers are squamous cell histology at >90 %. Approximately 5 % of primaries are adenocarcinoma, most commonly clear cell adenocarcinoma, and 3–5 % are malignant melanoma. Other less common histologies include sarcomas, lymphoma, leukemia, and neuroendocrine small cell.

Among the histopathologic factors, correlation between histologic tumor grade and outcome has been controversial although two studies have demonstrated increased rates of recurrence with higher tumor grade (Chyle et al. 1996; Vavra et al. 1991). Adenocarcinaomas appear to confer a less favorable prognosis than squamous cell carcinomas, particularly those unrelated to DES exposure (Frank et al. 2007). DES induced clear cell adenocarcinomas in younger women arising from in utero exposure have a generally better prognosis than squamous cell carcinoma, but are unlikely to be seen today, as the use of DES during pregnancy has been banned in 1975.

5.3.2 Molecular Markers

Squamous cell carcinoma of the vagina, much like other gynecologic malignancies, are associated with HPV-dependent and independent pathways. HPV-negative tumors tend to occur in older women, with classical keratinizing, verrucous features. HPV-positive tumors are associated with basaloid, non-keratinizing lesions, tend to occur in younger patients, and present with earlier stage disease (Daling et al. 2002; Larsson et al. 2013). Larsson et al. showed significantly improved 5 year overall survival in HPV-positive tumors compared to HPV-negative tumors at 51.1 and 10.7 %, respectively ($p = 0.0008$). Owing to the rarity of vaginal cancer, evaluation of other molecular markers has been limited.

5.4 Treatment Related Factors

Stage is an important determinant of therapy selection, as stage I patients and selected stage II patients may be amenable to surgical therapy alone, ranging from wide local excision to vaginectomy with reported survival rates of 90 % or greater (Creasman and Menck 1998). Some population based studies have also reported improved survival with surgery over radiotherapy for early stage disease of 90 % versus 38 %, but is likely confounded due to patient selection bias and the use of radiotherapy in patients deemed poor surgical candidates due to comorbid disease (Creasman and Menck 1998). Similar results were observed in a SEER analysis that identified an adjusted hazard ratio of 1.5 for increased mortality risk in stage I patients undergoing radiotherapy in place of definitive surgery (Shah et al. 2009).

Given that organ preservation is desirable if outcomes are equivalent to surgery, the utility of definitive radiotherapy has also been explored. Superficial stage I tumors can be treated with brachytherapy alone. However several investigators have observed higher local recurrence rates in stage I patients with infiltrating lesions or higher grade tumors, thus external beam radiation has been advocated in such patients (Nori et al. 1983; Leung 1993). Definitive radiotherapy for early stage disease has reported cause specific survival of 40–90 % for stage I and 35–78 % for stage II disease (Frank et al. 2005; Perez et al. 1999; Kucera and Vavra 1991; Urbanski et al. 1996; Kirkbride et al. 1995; de Crevoisier et al. 2007; Tran et al. 2007; Prempree and Amornmarn 1985; Pingley et al. 2000). In more advanced disease, the combination of external beam radiotherapy with brachytherapy has been shown to improve pelvic control and survival in stage II vaginal cancer (Pingley et al. 2000).

Locally advanced disease is often approached with external beam radiotherapy with or without chemotherapy, given to the extremely morbid exenteration that would be necessary to remove surgically.

Although the influence of tumor location within the vagina on prognosis has not been substantiated (Chyle et al. 1996; Perez et al. 1999; Kirkbride et al. 1995), tumor location has profound impact of radiation therapy planning, and treatment algorithms have been based on location and depth of invasion to optimize therapy and minimize toxicity. Following external beam therapy, upper vaginal and apical tumors are treated with intracavitary radiation, if their residual thickness is 5 mm but require more invasive interstitial therapy for thicker lesions. Anterior mid-vaginal lesions are treated with interstitial therapy, and posterior mid-vaginal lesions with a highly conformal or IMRT external beam boost due to the poor tolerance of interstitial therapy in the perirectal region. Confined distal vaginal lesions can be treated with interstitial brachytherapy, whereas massive lesions require external beam boost (Frank et al. 2005).

The role of addition of chemotherapy is still evolving. No randomized trials evaluating radiotherapy with or without chemotherapy have been performed, although chemotherapy is used concurrently in some settings given the experience of improved outcomes in locally advanced cervical cancer (Morris et al. 1999; Lanciano et al. 2005; Rose et al. 1999). Feasibility has been demonstrated in several small institutional studies. Concurrent 5-fluorouracil (5-FU) with bolus cisplatin or mitomycin C in patients with early stage disease resulted in 93 % cause specific survival at 5 years (Dalrymple et al. 2004). Five year cause specific survival of 50 % and pelvic control rate of 31 % were reported in 26 locally advanced patients treated with definitive radiotherapy and concurrent 5-FU and mitomycin C or single agent cisplatin (Kirkbride et al. 1995). A small series reporting outcomes for neoadjuvant paclitaxel and cisplatin prior to radical surgery in 11 stage II patients resulted in 27 % complete clinical response and 64 % partial clinical response with chemotherapy, and 18 % rate of disease recurrence at median follow up of 75 months (Benedetti Panici et al. 2008).

5.5 Imaging Prognostic Factors

Delineation of tumor size and degree of infiltration or spread is of critical importance, especially in the setting of definitive radiotherapy. Therefore, information obtained from radiographic workup guides treatment approach and delivery.

Given the inaccuracy of clinical palpation findings, MRI is a very useful tool for delineating extent of disease. MRI can be used in determining tumor thickness and paravaginal infiltration on T2-weighted imaging, identified as hyperintense lesions (Taylor et al. 2007). This is in line with the superior soft tissue resolution described with MRI from cervical cancer literature Bipat et al. 2003; Hricak et al. 2005. Visualization of the vaginal tumor may be improved with the instillation of vaginal gel or a dry vaginal tampon (Young et al. 2012).

Similar to its utility in cervical cancer, PET has shown high sensitivity in identifying inguinal or pelvic lymph node involvement in advanced vaginal cancer and by some reports is more accurate than CT scan (Lamoreaux et al. 2005). In practice, PET can be critical for defining target volumes for accurate external beam and brachytherapy planning. Taken together, MRI and/or PET imaging is often obtained to identify tumor size and predict lymph node involvement and MRI is often recommended in the setting of surveillance to distinguish between tumor recurrence or radiation change. These modalities appear more sensitive than CT alone, therefore 3D CT information is often used primarly for radiotherapy treatment planning.

6 Summary

Gynecologic malignancies are somewhat unique in regard to the methods of staging and treatment compared to more commonly encountered cancers such as lung, breast, or prostate. Clinical and surgical staging have long dominated how gynecologic cancers are evaluated and substratified. With the advent of new imaging modalities and molecular diagnostic abilities, more information is available prior to selection of therapy, and the prognostic utility of these factors is evolving. As more research focuses on validating prognostic utility of imaging, histopathologic characteristics, and molecular footprints, treatment approach will likely continue to evolve.

References

Aalders J, Abeler V, Kolstad P, Onsrud M (1980) Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. Obstet Gynecol 56(4):419–427

Aarnio M, Mecklin JP, Aaltonen LA, Nystrom-Lahti M, Jarvinen HJ (1995) Life-time risk of different cancers in hereditary non-polyposis colorectal cancer (HNPCC) syndrome. Int J Cancer 64(6):430–433

Abeler VM, Kjorstad KE (1991) Endometrial adenocarcinoma in Norway. A study of a total population. Cancer 67(12):3093–3103. Epub 1991/06/15

Abeler VM, Kjorstad KE (1992) Endometrial adenocarcinoma with squamous cell differentiation. Cancer 69(2):488–495

Akbayir O, Corbacioglu A, Numanoglu C, Guleroglu FY, Ulker V, Akyol A et al (2011) Preoperative assessment of myometrial and cervical invasion in endometrial carcinoma by transvaginal ultrasound. Gynecol Oncol 122(3):600–603 Epub 2011/06/28

Alcazar JL, Errasti T, Zornoza A (2000) Saline infusion sonohysterography in endometrial cancer: assessment of malignant cells dissemination risk. Acta Obstet Gynecol Scand 79(4):321–322

Ali MM, Huang DT, Goplerud DR, Howells R, Lu JD (1996) Radiation alone for carcinoma of the vagina: variation in response related to the location of the primary tumor. Cancer 77(9):1934–1939

Al-Kurdi M, Monaghan JM (1981) Thirty-two years experience in management of primary tumours of the vagina. Br J Obstet Gynaecol 88(11):1145–1150

American College of Obstetricians and Gynecologists. ACOG practice bulletin, clinical management guidelines for obstetrician-gynecologists, number 65, August 2005: management of endometrial cancer. Obstet Gynecol 106(2):413–425

Ansink A (1996) Vulvar squamous cell carcinoma. Semin Dermatol 15(1):51–59

Ansink AC vTH, Aartsen EJ, Heintz AP (1991) Outcome, complications and follow-up in surgically treated squamous cell carcinoma of the vulva 1956-1982. Eur J Obstet Gynecol Reprod Biol 42(2):137–143

Ansink ACKM, De Weger RA, Kleyne JA, Pijpers H, Van Tinteren H, De Kraker EW, Helmerhorst TJ, Heintz AP (1994) Human papillomavirus, lichen sclerosus, and squamous cell carcinoma of the vulva: detection and prognostic significance. Gynecol Oncol 52(2):180–184

Antonsen SL, Jensen LN, Loft A, Berthelsen AK, Costa J, Tabor A et al (2013a) MRI, PET/CT and ultrasound in the preoperative staging of endometrial cancer—a multicenter prospective comparative study. Gynecol Oncol 128(2):300–308 Epub 2012/12/04

Antonsen SL, Loft A, Fisker R, Nielsen AL, Andersen ES, Hogdall E et al (2013b) SUVmax of 18FDG PET/CT as a predictor of high-risk endometrial cancer patients. Gynecol Oncol 129(2):298–303

Arko D, Takac I (2000) High frequency transvaginal ultrasonography in preoperative assessment of myometrial invasion in endometrial cancer. J Ultrasound Med 19(9):639–643 Epub 2000/09/06

Ashman JB, Connell PP, Yamada D, Rotmensch J, Waggoner SE, Mundt AJ (2001) Outcome of endometrial carcinoma patients with involvement of the uterine serosa. Gynecol Oncol 82(2):338–343 Epub 2001/09/05

ASTEC study group, Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK (2009) Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet 373(9658):125–136

Averette HE, Ford JH Jr, Dudan RC, Girtanner RE, Hoskins WJ, Lutz MH (1975) Staging of cervical cancer. Clin Obstet Gynecol 18:215–232

Awwad HK, el Naggar M, Mocktar N, Barsoum M (1986) Intercapillary distance measurement as an indicator of hypoxia in carcinoma of the cervix uteri. Int J Radiat Oncol Biol Phys 12(8):1329–1333 Epub 1986/08/01

Bachtiary B, Schindl M, Pötter R, Dreier B, Knocke TH, Hainfellner JA, Horvat R, Birner P (2003) Overexpression of hypoxia-inducible factor 1alpha indicates diminished response to radiotherapy and unfavorable prognosis in patients receiving radical radiotherapy for cervical cancer. Clin Cancer Res 9(6):2234–2240

Baldinu P, Cossu A, Manca A, Satta MP, Pisano M, Casula M et al (2002) Microsatellite instability and mutation analysis of candidate genes in unselected Sardinian patients with endometrial carcinoma. Cancer 94(12):3157–3168 Epub 2002/07/13

Balleyguier C, Sala E, Da Cunha T, Bergman A, Brkljacic B, Danza F et al (2011) Staging of uterine cervical cancer with MRI: guidelines of the European Society of Urogenital Radiology. Eur Radiol 21(5):1102–1110 Epub 2010/11/11

Belhocine T, De Barsy C, Hustinx R, Willems-Foidart J (2002) Usefulness of (18)F-FDG PET in the post-therapy surveillance of endometrial carcinoma. Eur J Nucl Med Mol Imaging 29(9):1132–1139

Benedetti Panici P, Bellati F, Plotti F, Di Donato V, Antonilli M, Perniola G et al (2008) Neoadjuvant chemotherapy followed by radical surgery in patients affected by vaginal carcinoma. Gynecol Oncol 111(2):307–311. Epub 2008/08/19

Berek JS, Hacker NF (1989) Practical gynecologic oncology, 2nd edn. Williams & Wilkins, Philadelphia

Berman MLKH, Creasman W, DiSaia P, Bundy B, Blessing J (1984) Survival and patterns of recurrence in cervical cancer metastatic to periaortic lymph nodes (a Gynecologic Oncology Group study). Gynecol Oncol 19(1):8–16

Bhosale P, Peungjesada S, Devine C, Balachandran A, Iyer R (2010) Role of magnetic resonance imaging as an adjunct to clinical staging in cervical carcinoma. J Comput Assist Tomogr 34(6):855–864 Epub 2010/11/19

Binder SW, Huang I, Fu YS, Hacker NF, Berek JS (1990) Risk factors for the development of lymph node metastasis in vulvar squamous cell carcinoma. Gynecol Oncol 37(1):9–16

Bipat S, Glas AS, van der Velden J, Zwinderman AH, Bossuyt PM, Stoker J (2003) Computed tomography and magnetic resonance imaging in staging of uterine cervical carcinoma: a systematic review. Gynecol Oncol 91(1):59–66

Blecharz P, Karolewski K, Bieda T, Klimek M, Pudelek J, Kojs E et al (2008) Prognostic factors in patients with carcinoma of the vulva—our own experience and literature review. Eur J Gynaecol Oncol 29(3):260–263

Boruta DM 2nd, Gehrig PA, Groben PA, Bae-Jump V, Boggess JF, Fowler WC Jr et al (2004) Uterine serous and grade 3 endometrioid carcinomas: is there a survival difference? Cancer 101(10):2214–2221

Bosch FX, Manos MM, Munoz N, Sherman M, Jansen AM, Peto J et al (1995) Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International biological study on cervical cancer (IBSCC) Study Group. J Natl Cancer Inst 87(11):796–802. Epub 1995/06/07

Bouma J, Burger MP, Krans M, Hollema H, Pras E (1994) Squamous cell carcinoma of the vagina: a report of 32 cases. Int J Gynecol Cancer 4(6):389–394

Boyce J, Fruchter R, Kasambilides E, Nicastri AD, Sedlis A, Remy JC (1985) Prognostic factors in carcinoma of the vulva. Gynecol Oncol 20(3):364–377

Brinton LA, Nasca PC, Mallin K, Schairer C, Rosenthal J, Rothenberg R et al (1990) Case-control study of in situ and invasive carcinoma of the vagina. Gynecol Oncol 38(1):49–54

Brinton LA, Berman ML, Mortel R, Twiggs LB, Barrett RJ, Wilbanks GD et al (1992) Reproductive, menstrual, and medical risk factors for endometrial cancer: results from a case-control study. Am J Obstet Gynecol 167(5):1317–1325

Bristow RE, Zahurak ML, Alexander CJ, Zellars RC, Montz FJ (2003) FIGO stage IIIC endometrial carcinoma: resection of macroscopic nodal disease and other determinants of survival. Int J Gynecol Cancer 13(5):664–672

Burger MPHH, Emanuels AG, Krans M, Pras E, Bouma J (1995) The importance of the groin node status for the survival of T1 and T2 vulval carcinoma patients. Gynecol Oncol 57(3):327–334

Burger RA, Monk BJ, Kurosaki T, Anton-Culver H, Vasilev SA, Berman ML et al (1996) Human papillomavirus type 18: association with poor prognosis in early stage cervical cancer. J Natl Cancer Inst 88(19):1361–1368 Epub 1996/10/02

Burghardt E, Hofmann H, Ebner F et al (1989) Magnetic resonance imaging in cervical cancer: a basis for objective classification. Gynecol Oncol 33:61–67

Burri P, Djonov V, Aebersold DM, Lindel K, Studer U, Altermatt HJ, Mazzucchelli L, Greiner RH, Gruber G (2003) Significant correlation of hypoxia-inducible factor-1alpha with treatment outcome in cervical cancer treated with radical radiotherapy. Int J Radiat Oncol Biol Phys 56(2):494–501

Bush RS, Jenkin RDT, Allt WEC (1978) Definitive evidence for hypoxic cells influencing cure in cancer therapy. Br J Cancer 37(Suppl 3):302–306

Callister M, Ramondetta LM, Jhingran A, Burke TW, Eifel PJ (2004) Malignant mixed Mullerian tumors of the uterus: analysis of patterns of failure, prognostic factors, and treatment outcome. Int J Radiat Oncol Biol Phys 58(3):786–796

Carlson JA, Ambros R, Malfetano J, Ross J, Grabowski R, Lamb P et al (1998) Vulvar lichen sclerosus and squamous cell carcinoma: a cohort, case control, and investigational study with historical perspective; implications for chronic inflammation and sclerosis in the development of neoplasia. Hum Pathol 29(9):932–948

Chan JK, Kapp DS, Cheung MK, Osann K, Shin JY, Cohn D et al (2007a) The impact of the absolute number and ratio of positive lymph nodes on survival of endometrioid uterine cancer patients. Br J Cancer 97(5):605–611 Epub 2007/08/02

Chan JKSV, Pham H, Gu M, Rutgers J, Osann K, Cheung MK, Berman ML (2007b) PJ D. Margin distance and other clinicopathologic prognostic factors in vulvar carcinoma: a multivariate analysis. Gynecol Oncol 104(3):636–641

Chang SJ, Lee EJ, Kim WY, Yoo SC, Yoon JH, Chang KH et al (2010) Value of sonohysterography in preoperative assessment of myometrial invasion for patients with endometrial cancer. J Ultrasound Med 29(6):923–929

Chang MC, Chen JH, Liang JA, Yang KT, Cheng KY, Kao CH (2012) 18F-FDG PET or PET/CT for detection of metastatic lymph nodes in patients with endometrial cancer: a systematic review and meta-analysis. Eur J Radiol 81(11):3511–3517

Chao A, Tang YH, Lai CH, Chang CJ, Chang SC, Wu TI et al (2013) Potential of an age-stratified CA125 cut-off value to improve the prognostic classification of patients with endometrial cancer. Gynecol Oncol 129(3):500–504 Epub 2013/03/06

Charles-Edwards EM, DeSouza NM (2006) Diffusion-weighted magnetic resonance imaging and its application to cancer. Cancer Imaging 6:135–143

Charles-Edwards EMMC, Morgan VA, De Silva SS, McWhinney NA, Katesmark M, Attygalle AD, DeSouza NM (2008) Diffusion-weighted imaging in cervical cancer with an endovaginal technique: potential value for improving tumor detection in stage Ia and Ib1 disease. Radiology 249(2):541–550

Chenevert TLSL, Taylor JM, Robertson PL, Greenberg HS, Rehemtulla A, Ross BD (2000) Diffusion magnetic resonance imaging: an early surrogate marker of therapeutic efficacy in brain tumors. J Natl Cancer Inst 92(24):2029–2036

Cheng W, Chen C, Lee C (2000) Vascular endothelial growth factor and prognosis in cervical carcinoma. Obstet Gynecol 96:721–726

Chi DS, Welshinger M, Venkatraman ES, Barakat RR (1997) The role of surgical cytoreduction in Stage IV endometrial carcinoma. Gynecol Oncol 67(1):56–60

Choschzick M, Woelber L, Hess S, zu Eulenburg C, Schwarz J, Simon R et al (2010) Overexpression of carbonic anhydrase IX (CAIX) in vulvar cancer is associated with tumor progression and development of locoregional lymph node metastases. Virchows Arch 456(5):483–490

Chung YMKB, Park CS, Huh SJ, Kim J, Park JK, Cho SM, Kim BS, Kim JS, Yoo YD, Bae DS (2005) Increased expression of ICAM-3 is associated with radiation resistance in cervical cancer. Int J Cancer 117(2):194–201

Chung HH, Kim JW, Park NH, Song YS, Kang SB, Lee HP (2006) Use of preoperative serum CA-125 levels for prediction of lymph node metastasis and prognosis in endometrial cancer. Acta Obstet Gynecol Scand 85(12):1501–1505 Epub 2007/01/30

Chung HH, Kang WJ, Kim JW, Park NH, Song YS, Chung JK et al (2008) The clinical impact of [(18)F]FDG PET/CT for the management of recurrent endometrial cancer: correlation with clinical and histological findings. Eur J Nucl Med Mol Imaging 35(6):1081–1088

Chyle V, Zagars G, Wheeler JA, Wharton JT, Delclos L (1996) Definitive radiotherapy for carcinoma of the vagina: outcome and prognostic factors. Int J Radiat Oncol Biol Phys 35(5):191–905

Cohn DE, Dehdashti F, Gibb RK, Mutch DG, Rader JS, Siegel BA et al (2002) Prospective evaluation of positron emission tomography for the detection of groin node metastases from vulvar cancer. Gynecol Oncol 85(1):179–184

Connell PP, Rotmensch J, Waggoner S, Mundt AJ (1999) The significance of adnexal involvement in endometrial carcinoma. Gynecol Oncol 74(1):74–79 Epub 1999/07/01

Connor JP, Andrews JI, Anderson B, Buller RE (2000) Computed tomography in endometrial carcinoma. Obstet Gynecol 95(5): 692–696

Cooper RA, Wilks DP, Logue JP, Davidson SE, Hunter RD, Roberts SA et al (1998) High angiogenesis is associated with poor survival in carcinoma of the cervix treated with radiotherapy. Clin Can Res 4:2795–2800

Cormio G, Loizzi V, Carriero C, Cazzolla A, Putignano G, Selvaggi L (2010) Groin recurrence in carcinoma of the vulva: management and outcome. Eur J Cancer Care 19(3):302–307 Epub 2009/10/17

Cosin JAFJ, Chen MD, Paley PJ, Carson LF, Twiggs LB (1998) Pretreatment surgical staging of patients with cervical carcinoma: the case for lymph node debulking. Cancer 82(11):2241–2248

Creasman W (2009) Revised FIGO staging for carcinoma of the endometrium. Int J Gynaecol Obstet 105(2):109

Creasman WTPJ, Menck HR (1998) The National Cancer Data Base report on cancer of the vagina. Cancer 83(5):1033–1040

Creasman WTMC, Bundy BN et al (1987) Surgical pathologic spread patterns of endometrial cancer: a Gynecologic Oncology Group study. Cancer 60:2035–2041

Creutzberg CL vPW, Koper PC, Lybeert ML, Jobsen JJ, Wárlám-Rodenhuis CC, De Winter KA, Lutgens LC, van den Bergh AC, van de Steen-Banasik E, Beerman H, van Lent M (2000) Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet 355:1404–1411

Creutzberg CL vPW, Koper PC, Lybeert ML, Jobsen JJ, Wárlám-Rodenhuis CC, De Winter KA, Lutgens LC, van den Bergh AC, van der Steen-Banasik E, Beerman H, van Lent M, PORTEC Study Group (2003) Survival after relapse in patients with endometrial cancer: results from a randomized trial. Gynecol Oncol 89(2):201–209

Creutzberg CL vPW, Wárlám-Rodenhuis CC, van den Bergh AC, de Winter KA, Koper PC, Lybeert ML, Slot A, Lutgens LC, Stenfert Kroese MC, Beerman H, van Lent M (2004) Postoperative Radiation Therapy in Endometrial Carcinoma Trial,. Outcome of high-risk stage IC, grade 3, compared with stage I endometrial carcinoma patients: the Postoperative Radiation Therapy in Endometrial Carcinoma Trial. J Clin Oncol 22(7):1234–1241

Current FIGO (2009) staging for cancer of the vagina, fallopian tube, ovary, and gestational trophoblastic neoplasia. Int J Gynaecol Obstet 105(1):3–4

Daling JR, Madeleine MM, Schwartz SM, Shera KA, Carter JJ, McKnight B et al (2002) A population-based study of squamous cell vaginal cancer: HPV and cofactors. Gynecol Oncol 84(2):263–270

Dalrymple JL, Russell AH, Lee SW, Scudder SA, Leiserowitz GS, Kinney WK et al (2004) Chemoradiation for primary invasive squamous carcinoma of the vagina. Int J Gynecol Cancer 14(1):110–117 Epub 2004/02/07

Davidson SE, Symonds RP, Lamont D, Watson ER (1989) Does adenocarcinoma of uterine cervix have a worse prognosis than squamous carcinoma when treated by radiotherapy? Gynecol Oncol 33(1):23–26 Epub 1989/04/01

Davis KP, Stanhope CR, Garton GR, Atkinson EJ, O'Brien PC (1991) Invasive vaginal carcinoma: analysis of early-stage disease. Gynecol Oncol 42(2):131–136

de Crevoisier R, Sanfilippo N, Gerbaulet A, Morice P, Pomel C, Castaigne D et al (2007) Exclusive radiotherapy for primary squamous cell carcinoma of the vagina. Radiother Oncol 85(3): 362–370 Epub 2007/10/30

de Koning MN, Quint WG, Pirog EC (2008) Prevalence of mucosal and cutaneous human papillomaviruses in different histologic subtypes of vulvar carcinoma. Mod Pathol 21(3):334–344

Del Pino M, Rodriguez-Carunchio L, Ordi J (2013) Pathways of vulvar intraepithelial neoplasia and squamous cell carcinoma. Histopathology 62(1):161–175

Dellas A, Moch H, Schultheiss E, Feichter G, Almendral AC, Gudat F et al (1997) Angiogenesis in cervical neoplasia: microvessel quantitation in precancerous lesions and invasive carcinomas with cliniciopathological correlations. Gynecol Oncol 67:27–33

DelMaschio A, Vanzulli A, Sironi S, Spagnolo D, Belloni C, Garancini P et al (1993) Estimating the depth of myometrial involvement by endometrial carcinoma: efficacy of transvaginal sonography vs MR imaging. Am J Roentgenol 160(3):533–538 Epub 1993/03/01

Dessole S, Rubattu G, Farina M, Capobianco G, Cherchi PL, Tanda F et al (2006) Risks and usefulness of sonohysterography in patients with endometrial carcinoma. Am J Obstet Gynecol 194(2):362–368

Diesche S, Anderson P, Sealy R (1983) Carcinoma of the cervix—anaemia, radiotherapy and hyperbaric oxygen. Br J Radiol 56:251–255

Dinh TV, Hannigan EV, Smith ER et al (1996) Tumor angiogenesis as a predictor of recurrence in stage Ib squamous cell carcinoma of the cervix. Obstet Gynecol 87(5, Part 1):751–754

Dixit S, Singhal S, Baboo HA (1993) Squamous cell carcinoma of the vagina: a review of 70 cases. Gynecol Oncol 48(1):80–87

Dolan JR, McCall AR, Gooneratne S, Walter S, Lansky DM (1993) DNA ploidy, proliferation index, grade, and stage as prognostic factors for vulvar squamous cell carcinomas. Gynecol Oncol 48(2):232–235

Dunst J, Kuhnt T, Strauss HG, Krause U, Pelz T, Koelbl H et al (2003) Anemia in cervical cancers: impact on survival, patterns of relapse, and association with hypoxia and angiogenesis. Int J Radiat Oncol Biol Phys 56(3):778–787

Edge SB, Byrd DR, Compton CC et al (eds) (2009) American Joint Committee on Cancer, American Cancer Society. AJCC Cancer Staging Manual, 7th ed. Springer, Berlin

Eifel PJ (1994) Problems with the clinical staging of carcinoma of the cervix. Semin Radiat Oncol 4:1–8

Eifel PJ, Morris M, Wharton JT, Oswald MJ (1994) The influence of tumor size and morphology on the outcome of patients with FIGO stage IB squamous cell carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys 29:9–16

Eifel PJ, Burke TW, Morris M, Smith TL (1995) Adenocarcinoma as an independent risk factor for disease recurrence in patients with stage IB cervical carcinoma. Gynecol Oncol 59(1):38–44 Epub 1995/10/01

Eifel PJ, Winter K, Morris M, Levenback C, Grigsby PW, Cooper J et al (2004) Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of radiation therapy oncology group trial (RTOG) 90-01. J Clin Oncol 22(5):872–880 Epub 2004/03/03

Eltabbakh GH (2002) Analysis of survival after laparoscopy in women with endometrial carcinoma. Cancer 95(9):1894–1901

Eltabbakh GH, Moore AD (1999) Survival of women with surgical stage II endometrial cancer. Gynecol Oncol 74(1):80–85

Evans J, Bergsjo P (1965) The influence of anemia and results of radiotherapy in carcinoma of the cervix. Radiology 48:709–717

Farley JH, Hickey KW, Carlson JW, Rose GS, Kost ER, Harrison TA (2003) Adenosquamous histology predicts a poor outcome for patients with advanced-stage, but not early-stage, cervical carcinoma. Cancer 97(9):2196–2202 Epub 2003/04/25

Faul CM, Mirmow D, Huang Q, Gerszten K, Day R, Jones MW (1997) Adjuvant radiation for vulvar carcinoma: improved local control. Int J Radiat Oncol Biol Phys 38(2):381–389 Epub 1997/05/01

Ferrandina G, Ranelletti FO, Gallotta V, Martinelli E, Zannoni GF, Gessi M et al (2005) Expression of cyclooxygenase-2 (COX-2), receptors for estrogen (ER), and progesterone (PR), p53, ki67, and neu protein in endometrial cancer. Gynecol Oncol 98(3):383–389 Epub 2005/06/28

Finan MA, Barre G (2003) Bartholin's gland carcinoma, malignant melanoma and other rare tumours of the vulva. Best Pract Res Clin Obstet Gynaecol 17(4):609–633

Flueckiger F, Ebner F, Poschauko H, Tamussino K, Einspieler R (1992) G. R. Cervical cancer: serial MR imaging before and after primary radiation therapy—a 2-year follow-up study. Radiology 184:89–93

Fons G, Burger MP, Ten Kate FJ, van der Velden J (2007) Identification of potential prognostic markers for vulvar cancer using immunohistochemical staining of tissue microarrays. Int J Gynecol Pathol 26(2):188–193

Fons G, Hyde SE, Buist MR, Schilthuis MS, Grant P, Burger MP et al (2009a) Prognostic value of bilateral positive nodes in squamous cell cancer of the vulva. Int J Gynecol Cancer 19(7):1276–1280

Fons G, Hyde S, Buist MR, Schilthuis MS, Grant P, Burger MP, van der Velden J (2009b) Prognostic value of bilateral positive nodes in squamous cell cancer of the vulva. Int J Gynecol Cancer 19(7):1276–1280

Frank SJJA, Levenback C, Eifel PJ (2005) Definitive radiation therapy for squamous cell carcinoma of the vagina. Int J Radiat Oncol Biol Phys 62(1):138–147

Frank SJDM, Jhingran A, Bodurka DC, Eifel PJ (2007) Primary adenocarcinoma of the vagina not associated with diethylstilbestrol (DES) exposure. Gynecol Oncol 105(2):470–474

Franklin EW 3rd (1972) Clinical staging of carcinoma of the vulva. Obstet Gynecol 40(3):277–286

Gaffney DK, Haslam D, Tsodikov A, Hammond E, Seaman J, Holden J et al (2003) Epidermal growth factor receptor (EGFR) and vascular andothelial factor receptor (VGEF) negatively affect overall survival in carcinoma of the cervix treated with radiotherapy. Int J Rad Oncol Biol Phys 56:922–928

Galic V, Herzog TJ, Lewin SN, Neugut AI, Burke WM, Lu YS et al (2012) Prognostic significance of adenocarcinoma histology in women with cervical cancer. Gynecol Oncol 125(2):287–291 Epub 2012/01/24

Geisinger KR, Marshall RB, Kute TE, Homesley HD (1986) Correlation of female sex steroid hormone receptors with histologic and ultrastructural differentiation in adenocarcinoma of the endometrium. Cancer 58(7):1506–1517 Epub 1986/10/01

Gonzalez Bosquet J, Kinney W, Russell AH, Gaffey TA, Magrina JF, Podratz KC (2003) Risk of occult inguinofemoral lymph node metastasis from squamous carcinoma of the vulva. Int J Radiat Oncol Biol Phys 57(2):419–424

Gordinier ME, Steinhoff MM, Hogan JW, Peipert JF, Gajewski WH, Falkenberry SS et al (1997) S-Phase fraction, p53, and HER-2/neu status as predictors of nodal metastasis in early vulvar cancer. Gynecol Oncol 67(2):200–202

Greco A, Mason P, Leung AWL, Dische S, McIndoe GA, Anderson MC (1989) Staging of carcinoma of the uterine cervix: MRI-surgical correlation. Clin Radiol 40(4):401–405. Epub July

Greven KM, Curran WJ Jr, Whittington R, Fanning J, Randall ME, Wilder J et al (1989) Analysis of failure patterns in stage III endometrial carcinoma and therapeutic implications. Int J Radiat Oncol Biol Phys 17(1):35–39 Epub 1989/07/01

Grisaru D, Covens A, Chapman B, Shaw P, Colgan T, Murphy J et al (2001) Does histology influence prognosis in patients with early-stage cervical carcinoma? Cancer 92(12):2999–3004 Epub 2001/12/26

Grogan M, Thomas GM, Melamed I, Wong FLW, Pearcey RG, Joseph PK et al (1999) The importance of hemoglobin levels during radiotherapy for carcinoma of the cervix. Cancer 86:1528–1536

Grossman J, Ricci ZJ, Rozenblit A, Freeman K, Mazzariol F, Stein MW (2008) Efficacy of contrast-enhanced CT in assessing the endometrium. Am J Roentgenol 191(3):664–669

Growdon WB, Boisvert SL, Akhavanfard S, Oliva E, Dias-Santagata DC, Kojiro S et al (2008) Decreased survival in EGFR gene amplified vulvar carcinoma. Gynecol Oncol 111(2):289–297

Gustafson S, Zbuk KM, Scacheri C, Eng C (2007) Cowden syndrome. Semin Oncol 34(5):428–434

Hacker NF (2009) Revised FIGO staging for carcinoma of the vulva. Int J Gynaecol Obstet 105(2):105–106

Hacker NF, Berek JS, Lagasse LD, Leuchter RS, Moore JG (1983) Management of regional lymph nodes and their prognostic influence in vulvar cancer. Obstet Gynecol 61(4):408–412

Haensgen G, Krause U, Becker A, Stadler P, Lautenschlaeger C, Wohlrab W, Rath FW, Molls M, Dunst J (2001) Tumor hypoxia, p53, and prognosis in cervical cancers. Int J Radiat Oncol Biol Phys 50(4):865–872

Hamstra DA, Rehemtulla A, Ross BD (2008) Diffusion magnetic resonance imaging: a biomarker for treatment response in oncology. J Clin Oncol 25:4104–4109

Hantschmann P, Jeschke U, Friese K (2005) TGF-alpha, c-erbB-2 expression and neoangiogenesis in vulvar squamous cell carcinoma. Anticancer Res 25(3A):1731–1737

Harima Y, Harima K, Shikata N, Oka A, Ohnishi T, Tanaka Y (1998) Bax and Bcl-2 expressions predict response to radiotherapy in human cervical cancer. J Cancer Res Clin Oncol 124(9):503–510

Harima Y, Sawada S, Miyazaki Y, Kin K, Ishihara H, Imamura M, Sougawa M, Shikata N, Ohnishi T (2003) Expression of Ku80 in cervical cancer correlates with response to radiotherapy and survival. Am J Clin Oncol 26(4):e80–e85

Harima Y, Togashi A, Horikoshi K (2004) Prediction of outcome of advanced cervical cancer to thermoradiotherapy according to expression profiles of 35 genes selected by cDNA microarray analysis. Int J Radiat Oncol Biol Phys 60:237–248

Harry VNSS, Gilbert FJ, Parkin DE (2008) Diffusion-weighted magnetic resonance imaging in the early detection of response to chemoradiation in cervical cancer. Gynecol Oncol 111:213–220

Hatano K, Sekiya Y, Araki H, Sakai M, Togawa T, Narita Y et al (1999) Evaluation of the therapeutic effect of radiotherapy on cervical cancer using magnetic resonance imaging. Int J Radiat Oncol Biol Phys 45:639–644

Hawighorst H, Knapstein PG, Weikel W, Knopp MV, Zuna I, Knof A et al (1997) Angiogenesis of uterine cervical carcinoma: characterization by pharmacokinetic magnetic resonance parameters and histological microvessel density with correlation to lymphatic involvement. Cancer Res 57:4777–4786

Hawighorst H, Weikel W, Knapstein PG et al (1998) Angiogenic activity of cervical carcinoma: assessment by functional magnetic resonance imaging-based parameters and a histomorphological approach in correlation with disease outcome. Clin Cancer Res 4(10):2305–2312

Heaps JM, Fu YS, Montz FJ, Hacker NF, Berek JS (1990) Surgical-pathologic variables predictive of local recurrence in squamous cell carcinoma of the vulva. Gynecol Oncol 38(3):309–314

Hefler L, Mayerhofer K, Leibman B, Obermair A, Reinthaller A, Kainz C et al (2000) Tumor anemia and thrombocytosis in patients with vulvar cancer. Tumour Biol 21(5):309–314

Hefler LA, Grimm C, Six L, Seebacher V, Polterauer S, Joura E et al (2008) Inguinal sentinel lymph node dissection vs. complete inguinal lymph node dissection in patients with vulvar cancer. Anticancer Res 28(1B):515–517. Epub 2008/04/04

Hildesheim A, Han CL, Brinton LA, Kurman RJ, Schiller JT (1997) Human papillomavirus type 16 and risk of preinvasive and invasive vulvar cancer: results from a seroepidemiological case-control study. Obstet Gynecol 90(5):748–754

Hirai Y, Fujimoto I, Yamauchi K, Hasumi K, Masubuchi K, Sano Y (1989) Peritoneal fluid cytology and prognosis in patients with endometrial carcinoma. Obstet Gynecol 73(3 Pt 1):335–338

Hansgen G hK, Dunst J (1996) Oxygen status of cervical cancer prior and during definitive radiotherapy: possible impact of pretreatment with INF-a-2a-Retinol acid on oxygenation (abstr). Int J Radiat Oncol Biol Phys 36(Suppl):324

Hockel M, Schlenger K, Aral B, Mitze M, Schaffer U (1996) P V. Association between tumor hypoxia and malignant progression in advanced cancer of the uterine cervix. Cancer Res 56:4509–4515

Hoffmann G, Casper F, Weikel W, Kummerle T, Pollow B, Schaffrath M et al (1999) Value of p53, urokinase plasminogen activator, PAI-1 and Ki-67 in vulvar carcinoma. Zentralbl Gynakol 121(10): 473–478. Untersuchungen zu p53, UPA, PAI-1 und Ki-67 beim Vulvakarzinom

Hogberg T, Signorelli M, de Oliveira CF, Fossati R, Lissoni AA, Sorbe B et al (2010) Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer—results from two randomised studies. Eur J Cancer 46(13):2422–2431

Holcomb K, Delatorre R, Pedemonte B, McLeod C, Anderson L, Chambers J (2002) E-cadherin expression in endometrioid, papillary serous, and clear cell carcinoma of the endometrium. Obstet Gynecol 100(6):1290–1295 Epub 2002/12/07

Homesley H, Raben M, Blake D (1980) Relationship of lesion size to survival in patients with stage IB squamous cell carcinoma of the cervix uteri treated by radiation therapy. Surg Gynecol Obstet 150:529–531

Homesley HD, Bundy BN, Sedlis A, Adcock L (1986) Radiation therapy versus pelvic node resection for carcinoma of the vulva with positive groin nodes. Obstet Gynecol 68(6):733–740 Epub 1986/12/01

Homesley HDBB, Sedlis A, Yordan E, Berek JS, Jahshan A, Mortel R (1991) Assessment of current International Federation of Gynecology and Obstetrics staging of vulvar carcinoma relative to prognostic factors for survival (a Gynecologic Oncology Group study). Am J Obstet Gynecol 164(4):997–1004

Homesley HD, Bundy BN, Sedlis A, Yordan E, Berek JS, Jahshan A et al (1993) Prognostic factors for groin node metastasis in squamous cell carcinoma of the vulva (a Gynecologic Oncology Group study). Gynecol Oncol 49(3):279–283

Hopkins MP, Morley GW (1991) Radical hysterectomy versus radiation therapy for stage IB squamous cell cancer of the cervix. Cancer 68(2):272–277 Epub 1991/07/15

Howlader N, Noone AM, Krapcho M, Garshell J, Neyman N, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds) (2013) SEER Cancer Statistics Review, 1975–2010. National Cancer Institute, Bethesda. http://seer.cancer.gov/csr/1975_2010. Accessed 13 April 2013, based on November 2 SEER data submission, posted to the SEER web site

Hricak H (1991) Cancer of the uterus: the value of MRI pre-and post-irradiation. Int J Rad Oncol Biol Phys 21:1089–1094

Hricak H, Lacey CG, Sandles LG, Chang YC, Winkler ML, Stern JL (1988) Invasive cervical carcinoma: comparison of MR imaging and surgical findings. Radiology 166:623–631

Hricak H, Gatsonis C, Chi DS, Amendola MA, Brandt K, Schwartz LH, Koelliker S, Siegelman ES, Brown JJ, McGhee RB Jr, Iyer R, Vitellas KM, Snyder B, Long HJ 3rd, Fiorica JV, Mitchell DG (2005) American College of Radiology Imaging Network 6651, Gynecologic Oncology Group 183,. Role of imaging in pretreatment evaluation of early invasive cervical cancer: results of the intergroup study American College of Radiology Imaging Network 6651-Gynecologic Oncology Group 183. J Clin Oncol 23(36):9329–9337

Hsu CT, Cheng YS, Su SC (1972) Prognosis of uterine cervical cancer with extensive lymph node metastases. Special emphasis on the value of pelvic lymphadenectomy in the surgical treatment of uterine cervical cancer. Am J Obstet Gynecol 114(7):954–962. Epub 1972/12/01

Huang YT, Wang CC, Tsai CS, Lai CH, Chang TC, Chou HH et al (2011) Long-term outcome and prognostic factors for adenocarcinoma/adenosquamous carcinoma of cervix after definitive radiotherapy. Int J Radiat Oncol Biol Phys 80(2):429–436 Epub 2010/06/15

Huang YT, Wang CC, Tsai CS, Lai CH, Chang TC, Chou HH et al (2012) Clinical behaviors and outcomes for adenocarcinoma or adenosquamous carcinoma of cervix treated by radical hysterectomy and adjuvant radiotherapy or chemoradiotherapy. Int J Radiat Oncol Biol Phys 84(2):420–427 Epub 2012/03/01

Hunter DJ (1975) Carcinoma of the vulva: a review of 361 patients. Gynecol Oncol 3(2):117–123

Husseinzadeh N, Wesseler T, Schneider D, Schellhas H, Nahhas W (1990) Prognostic factors and the significance of cytologic grading in invasive squamous cell carcinoma of the vulva: a clinicopathologic study. Gynecol Oncol 36(2):192–199

Irwin C, Levin W, Fyles A, Pintilie M, Manchul L, Kirkbride P (1998) The role of adjuvant radiotherapy in carcinoma of the endometrium-results in 550 patients with pathologic stage I disease. Gynecol Oncol 70(2):247–254 Epub 1998/09/19

Ito K, Matsumoto T, Nakada T, Nakanishi T, Fujita N, Yamashita H (1994) Assessing myometrial invasion by endometrial carcinoma with dynamic MRI. J Comput Assist Tomogr 18(1):77–86

Iversen T, Aalders J, Christensen A, Kolstad P (1980) Squamous cell carcinoma of the vulva: a review of 424 patients, 1956-1974. Gynecol Oncol 9(3):271–279

Jach R, Dyduch G, Radon-Pokracka M, Przybylska P, Mika M, Dulinska-Litewka J et al (2011) Expression of vascular endothelial growth factors VEGF- C and D, VEGFR-3, and comparison of lymphatic vessels density labeled with D2-40 antibodies as a prognostic factors in vulvar intraepithelial neoplasia (VIN) and invasive vulvar cancer. Neuro Endocrinol Lett 32(4):530–539

Jantarasaengaram S, Praditphol N, Tansathit T, Vipupinyo C, Vairojanavong K (2013) Three-dimensional ultrasound using volume contrast imaging (VCI) display for the preoperative assessment of myometrial invasion and cervical involvement in endometrial cancer. Ultrasound Obstet Gynecol. Epub 03 Sept 2013

Jeon YT, Park IA, Kim YB, Kim JW, Park NH, Kang SB et al (2006) Steroid receptor expressions in endometrial cancer: clinical significance and epidemiological implication. Cancer Lett 239(2):198–204 Epub 2005/09/20

Johnson GA, Mannel R, Khalifa M, Walker JL, Wren M, Min KW et al (1997) Epidermal growth factor receptor in vulvar malignancies and its relationship to metastasis and patient survival. Gynecol Oncol 65(3):425–429

Kadar N, Malfetano JH, Homesley HD (1993) Steroid receptor concentrations in endometrial carcinoma: effect on survival in surgically staged patients. Gynecol Oncol 50(3):281–286 Epub 1993/09/01

Kagie MJ, Kenter GG, Tollenaar RA, Hermans J, Trimbos JP, Fleuren GJ (1997) p53 protein overexpression, a frequent observation in squamous cell carcinoma of the vulva and in various synchronous vulvar epithelia, has no value as a prognostic parameter. Int J Gynecol Pathol 16(2):124–130

Kainz C, Speiser P, Wanner C (1995) Prognostic value of tumor microvessel density in cancer of the uterine cervix stage IB to IIB. Anticancer Res 15:1549–1551

Kanthan R, Senger JL (2011) Uterine carcinosarcomas (malignant mixed mullerian tumours): a review with special emphasis on the controversies in management. Obstet Gynecol Int 2011:470795

Kapp KS, Poschauko J, Geyer E, Berghold A, Oechs AC, Petru E et al (2002) Evaluation of the effect of routine packed red blood cell transfusion in anemic cervix cancer patients treated with radical radiotherapy. Int J Radiat Oncol Biol Phys 54(1):58–66 Epub 2002/08/17

Kataoka MY, Sala E, Baldwin P, Reinhold C, Farhadi A, Hudolin T et al (2010) The accuracy of magnetic resonance imaging in staging of vulvar cancer: a retrospective multi-centre study. Gynecol Oncol 117(1):82–87

Keys HM, Bundy BN, Stehman FB, Muderspach LI, Chafe WE, Suggs CL 3rd et al (1999) Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med 340(15):1154–1161 Epub 1999/04/15

Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, Bloss JD et al (2004) A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 92(3):744–751 Epub 2004/02/27

Khalifa MA, Mannel RS, Haraway SD, Walker J, Min KW (1994) Expression of EGFR, HER-2/neu, P53, and PCNA in endometrioid, serous papillary, and clear cell endometrial adenocarcinomas. Gynecol Oncol 53(1):84–92 Epub 1994/04/01

Kidd EASB, Dehdashti F, Grigsby PW (2007) The standardized uptake value for F-18 fluorodeoxyglucose is a sensitive predictive biomarker for cervical cancer treatment response and survival. Cancer 110(8):1738–1744

Kim SH, Kim HD, Song YS, Kang SB, Lee HP (1995) Detection of deep myometrial invasion in endometrial carcinoma: comparison of transvaginal ultrasound, CT, and MRI. J Comput Assist Tomogr 19(5):766–772 Epub 1995/09/01

Kinkel K, Kaji Y, Yu KK, Segal MR, Lu Y, Powell CB et al (1999) Radiologic staging in patients with endometrial cancer: a meta-analysis. Radiology 212(3):711–718

Kirkbride P, Fyles A, Rawlings GA, Manchul L, Levin W, Murphy KJ, Simm J (1995) Carcinoma of the vagina—experience at the Princess Margaret Hospital (1974–1989). Gynecol Oncol 56(3):435–443 Epub 1995/03/01

Kitahara O, Katagiri T, Tsunoda T (2002) Classification of sensitivity or resistance of cervical cancers to ionizing radiation according to expression profiles of 62 genes selected by cDNA microarrayanalysis. Neoplasia 4:295–303

Kitajima K, Murakami K, Yamasaki E, Hagiwara S, Fukasawa I, Inaba N et al (2008) Performance of FDG-PET/CT in the diagnosis of recurrent endometrial cancer. Ann Nucl Med 22(2):103–109

Kitajima K, Kita M, Suzuki K, Senda M, Nakamoto Y, Sugimura K (2012) Prognostic significance of SUVmax (maximum standardized uptake value) measured by [(1)(8)F]FDG PET/CT in endometrial cancer. Eur J Nucl Med Mol Imaging 39(5):840–845

Kleine W, Rau K, Schwoeorer D, Pfleiderer A (1989) Prognosis of the adenocarcinoma of the cervix uteri: a comparative study. Gynecol Oncol 35(2):145–149 Epub 1989/11/01

Klopp AH, Jingran A, Ramdas L (2008) Gene expression changes in cervical squamous cell carcinoma after initiation of chemoradiation and correlation with clnical outcome. Int J Radiat Oncol Biol Phys 71:226–236

Knopp S, Bjorge T, Nesland JM, Trope C, Scheistroen M, Holm R (2004) p16INK4a and p21Waf1/Cip1 expression correlates with clinical outcome in vulvar carcinomas. Gynecol Oncol 95(1):37–45

Kock L, Mahner S, Choschzick M, Eulenburg C, Milde-Langosch K, Schwarz J et al (2011) Serum carbonic anhydrase IX and its prognostic relevance in vulvar cancer. Int J Gynecol Cancer 21(1):141–148

Kohlberger P, Kainz C, Breitenecker G, Gitsch G, Sliutz G, Kolbl H et al (1995) Prognostic value of immunohistochemically detected p53 expression in vulvar carcinoma. Cancer 76(10):1786–1789

Kolstad P (1968) Intercapillary distance, oxygen tension and local recurrence in cervix cancer. Scand J Clin Lab Invest 106(Suppl): 145–157

Komaki R, Mattingly R, Hoffman RG, Barber SW, Satre R, Greenberg M (1983) Irradiation of para-aortic lymph node metastases from carcinoma of the cervix or endometrium. Preliminary results. Radiology 147(1):245–248

Konecny GE, Santos L, Winterhoff B, Hatmal M, Keeney GL, Mariani A et al (2009) HER2 gene amplification and EGFR expression in a large cohort of surgically staged patients with nonendometrioid (type II) endometrial cancer. Br J Cancer 100(1):89–95 Epub 2008/12/18

Kong A, Simera I, Collingwood M, Williams C, Kitchener H, Cochrane Gynaecological Cancer Group (2007) Adjuvant radiotherapy for stage I endometrial cancer: systematic review and meta-analysis. Ann Oncol 18(10):1595–1604

Kosary CL (1994) FIGO stage, histology, histologic grade, age and race as prognostic factors in determining survival for cancers of the female gynecological system: an analysis of 1973-87 SEER cases of cancers of the endometrium, cervix, ovary, vulva, and vagina. Semin Surg Oncol 10(1):31–46 Epub 1994/01/01

Kovalic JJ, Perez CA, Grigsby PW et al (1991) The effect of volume of disease in patients with carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys 21:905–910

Kowalewska M, Radziszewski J, Goryca K, Bujko M, Oczko-Wojciechowska M, Jarzab M et al (2012) Estimation of groin recurrence risk in patients with squamous cell vulvar carcinoma by the assessment of marker gene expression in the lymph nodes. BMC Cancer 12:223

Krupp PJ, Bohm JW (1978) Lymph gland metastases in invasive squamous cell cancer of the vulva. Am J Obstet Gynecol 130(8):943–952

Kruse AJ, Bottenberg MJ, Tosserams J, Slangen B, van Marion AM, van Trappen PO (2008) The absence of high-risk HPV combined with specific p53 and p16INK4a expression patterns points to the HPV-independent pathway as the causative agent for vulvar squamous cell carcinoma and its precursor simplex VIN in a young patient. Int J Gynecol Pathol 27(4):591–595

Kucera H, Vavra N (1991) Radiation management of primary carcinoma of the vagina: clinical and histopathological variables associated with survival. Gynecol Oncol 40(1):12–16

Kudela M, Pilka R, Lubusky M, Hejtmanek P, Dzubak P, Brychtova S (2012) Prognostic importance of selected molecular immunohistochemical markers and DNA ploidy in endometrial cancer. Eur J Gynaecol Oncol 33(2):159–163 Epub 2012/05/23

Kutlubay Z, Engin B, Zara T, Tuzun Y (2013) Anogenital malignancies and premalignancies: facts and controversies. Clin Dermatol 31(4):362–373

Lambrou NC, Gomez-Marin O, Mirhashemi R, Beach H, Salom E, Almeida-Parra Z 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(3):653–658

Lamoreaux WTGP, Dehdashti F, Zoberi I, Powell MA, Gibb RK, Rader JS, Mutch DG, Siegel BA (2005) FDG-PET evaluation of vaginal carcinoma. Int J Radiat Oncol Biol Phys 62(3):733–737

Lanciano R, Calkins A, Bundy BN, Parham G, Lucci JA 3rd, Moore DH et al (2005) Randomized comparison of weekly cisplatin or protracted venous infusion of fluorouracil in combination with pelvic radiation in advanced cervix cancer: a gynecologic oncology group study. J Clin Oncol 23(33):8289–8295

Landoni F, Maneo A, Colombo A, Placa F, Milani R, Perego P et al (1997) Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. Lancet 350(9077):535–540 Epub 1997/08/23

Larsson GL, Helenius G, Andersson S, Sorbe B, Karlsson MG (2013) Prognostic impact of human papilloma virus (HPV) genotyping and HPV-16 subtyping in vaginal carcinoma. Gynecol Oncol 129(2):406–411

Lataifeh I, Nascimento MC, Nicklin JL, Perrin LC, Crandon AJ, Obermair A (2004) Patterns of recurrence and disease-free survival in advanced squamous cell carcinoma of the vulva. Gynecol Oncol 95(3):701–705

Latta E, Chapman WB (2002) PTEN mutations and evolving concepts in endometrial neoplasia. Curr Opin Obstet Gynecol 14(1):59–65 Epub 2002/01/22

Lavie O, Comerci G, Daras V, Bolger BS, Lopes A, Monaghan JM (1999) Thrombocytosis in women with vulvar carcinoma. Gynecol Oncol 72(1):82–86

Lea JS, Coleman RL, Garner EO, Duska LR, Miller DS, Schorge JO (2003) Adenosquamous histology predicts poor outcome in low-risk stage IB1 cervical adenocarcinoma. Gynecol Oncol 91(3):558–562 Epub 2003/12/17

Lee JH DT, Andreotti RF, Cardenes HR, Dejesus Allison SO, Gaffney DK, Glanc P, Horowitz NS, Jhingran A, Lee SI, Puthawala AA, Royal HD, Scoutt LM, Small W Jr, Varia MA, Zelop CM (2011) Expert panel on women's imaging and radiation oncology-gynecology. ACR appropriateness Criteria® pretreatment evaluation and follow-up of endometrial cancer of the uterus. Ultrasound Q 27(2):139–145

Lerma E, Matias-Guiu X, Lee SJ, Prat J (1999) Squamous cell carcinoma of the vulva: study of ploidy, HPV, p53, and pRb. Int J Gynecol Pathol 18(3):191–197

Leung SSM (1993) Radical radiation therapy for carcinoma of the vagina—impact of treatment modalities on outcome: Peter MacCallum Cancer Institute experience 1970-1990. Int J Radiat Oncol Biol Phys 25(3):413–418

Levenback CF, Ali S, Coleman RL, Gold MA, Fowler JM, Judson PL et al (2012) Lymphatic mapping and sentinel lymph node biopsy in women with squamous cell carcinoma of the vulva: A Gynecologic Oncology Group Study. J Clin Oncol 30:3786–3791 Epub 04 July 2012

Lewandowski G, Torrisi J, Potkul RK, Holloway RW, Popescu G, Whitfield G et al (1990) Hysterectomy with extended surgical staging and radiotherapy versus hysterectomy alone and radiotherapy in stage I endometrial cancer: a comparison of complication rates. Gynecol Oncol 36(3):401–404

Lewin SN, Herzog TJ, Barrena Medel NI, Deutsch I, Burke WM, Sun X et al (2010) Comparative performance of the 2009 international Federation of gynecology and obstetrics' staging system for uterine corpus cancer. Obstet Gynecol 116(5):1141–1149. Epub 2010/10/23

Lim K, Chan P, Dinniwell R, Fyles A, Haider M, Cho YB, Jaffray D, Manchul L, Levin W, Hill RP, Milosevic M (2008) Cervical cancer regression measured using weekly magnetic resonance imaging during fractionated radiotherapy: radiobiologic modeling and correlation with tumor hypoxia. Int J Radiat Oncol Biol Phys 70(1):126–133

Lindell G, Nasman A, Jonsson C, Ehrsson RJ, Jacobsson H, Danielsson KG et al (2010) Presence of human papillomavirus (HPV) in vulvar squamous cell carcinoma (VSCC) and sentinel node. Gynecol Oncol 117(2):312–316

Liu S, Semenciw R, Mao Y (2001) Cervical cancer: the increasing incidence of adenocarcinoma and adenosquamous carcinoma in younger women. CMAJ 164(8):1151–1152 Epub 2001/05/08

Liu Y, Bai R, Sun H, Liu H, Zhao X, Li Y (2009) Diffusion-weighted imaging in predicting and monitoring the response of uterine cervical cancer to combined chemoradiation. Clin Radiol 64:1067–1074

Loncaster JA, Cooper RA, Logue JP, Davidson SE, Hunter RD, West CM (2000) Vascular endothelial growth factor (VEGF) expression is a prognostic factor for radiotherapy outcome in advanced carcinoma of the cervix. Br J Cancer 83:620–625

Loncaster JA, Carrington BM, Sykes JR, Jones AP, Todd SM, Cooper R et al (2002) Prediction of radiotherapy outcome using dynamic contrast enhanced MRI of carcinoma of the cervix. Int J Rad Oncol Biol Phys 54:759–767

Look KY, Brunetto VL, Clarke-Pearson DL, Averette HE, Major FJ, Alvarez RD et al (1996) An analysis of cell type in patients with surgically staged stage IB carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecol Oncol 63(3):304–311 Epub 1996/12/01

Lowrey GC, Mendenhall MW, Million RR (1992) Stage IB or IIA-B carcinoma of the intact uterine cervix treated with irradiation: a multivariate analysis. Int J Radiat Oncol Biol Phys 24:205–210

Lundgren C, Auer G, Frankendal B, Moberger B, Nilsson B, Nordstrom B (2002) Nuclear DNA content, proliferative activity, and p53 expression related to clinical and histopathologic features in endometrial carcinoma. Int J Gynecol Cancer 12(1):110–118

Macdonald OK, Chen J, Dodson M, Lee CM, Gaffney DK (2009) Prognostic significance of histology and positive lymph node involvement following radical hysterectomy in carcinoma of the cervix. Am J Clin Oncol 32(4):411–416 Epub 2009/05/20

Mackay HJ, Gallinger S, Tsao MS, McLachlin CM, Tu D, Keiser K et al (2010) Prognostic value of microsatellite instability (MSI) and PTEN expression in women with endometrial cancer: results from studies of the NCIC Clinical Trials Group (NCIC CTG). Eur J Cancer 46(8):1365–1373 Epub 2010/03/23

Madsen BS, Jensen HL, van den Brule AJ, Wohlfahrt J, Frisch M (2008) Risk factors for invasive squamous cell carcinoma of the vulva and vagina—population-based case-control study in Denmark. Int J Cancer 122(12):2827–2834

Manfredi R, Mirk P, Maresca G, Margariti PA, Testa A, Zannoni GF et al (2004) Local-regional staging of endometrial carcinoma: role of MR imaging in surgical planning. Radiology 231(2):372–378

Mariani L, Conti L, Atlante G, Sciarretta F, Pozzi M, Vercillo M, Francavilla V, De Franceschi L, Rossi S, Sindico R, Atlante M, Gandolfo GM (1998) Vulvar squamous carcinoma: prognostic role of DNA content. Gynecol Oncol 71(2):159–164

Mariani A, Sebo TJ, Katzmann JA, Keeney GL, Roche PC, Lesnick TG et al (2000) Pretreatment assessment of prognostic indicators in endometrial cancer. Am J Obstet Gynecol 182(6):1535–1544 Epub 2000/06/28

Mariani A, Webb MJ, Keeney GL, Haddock MG, Aletti G, Podratz KC (2002a) Stage IIIC endometrioid corpus cancer includes distinct subgroups. Gynecol Oncol 87(1):112–117 Epub 2002/12/07

Mariani A, Webb MJ, Keeney GL, Aletti G, Podratz KC (2002b) Predictors of lymphatic failure in endometrial cancer. Gynecol Oncol 84(3):437–442

Mariani A, Webb MJ, Keeney GL, Aletti G, Podratz KC (2002c) Assessment of prognostic factors in stage IIIA endometrial cancer. Gynecol Oncol 86(1):38–44

Martin-Hirsch PP, Bryant A, Keep SL, Kitchener HC, Lilford R (2011) Adjuvant progestagens for endometrial cancer. Cochrane Database Syst Rev 6:CD001040. Epub 2011/06/17

Maxwell GL, Risinger JI, Alvarez AA, Barrett JC, Berchuck A (2001) Favorable survival associated with microsatellite instability in endometrioid endometrial cancers. Obstet Gynecol 97(3):417–422 Epub 2001/03/10

Mayr A, Wang JZ, D Z, Montebello JF, Grecula JC, Lo SS et al (2009) Synergistic effects of hemoglobin and tumor perfusion on tumor control and survival in cervical cancer. Int J Radiat Oncol Biol Phys 74(5):1513–1521

Mayr NA, Magnotta VA, Ehrhardt JC, Wheeler JA, Sorosky JI, Wen BC et al (1996) Usefulness of tumor volumetry by magnetic resonance imaging in assessing response to radiation therapy in carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys 35(5):915–924

Mayr NA, Hawighorst H, Yuh WTC, Essig M, Magnotta VA, Knopp MV (1999) MR microcirculation in cervical cancer: correlations with histomorphological tumor markers and clinical outcome. J Magn Reson Imaging 10:267–276

Mayr NA, Yuh WTC, Taoka T, Wang JZ, Wu DH, Montebello JF et al (2006) Serial therapy-induced changes in tumor shape in cervical cancer and their impact on assessing tumor volume and treatment response. Am J Roentgenol 187:65–72

Mayr NA, Wang JZ, Lo SS, Zhang D, Grecula JC, Lu L et al (2010) Translating response during therapy into ultimate treatment outcome: a personalized 4-dimensional MRI tumor volumetric regression approach in cervical cancer. Int J Radiat Oncol Biol Phys 76:719–727 (23 July 2009, Epub ahead of print)

McConnell DT, Miller ID, Parkin DE, Murray GI (1997) p53 protein expression in a population-based series of primary vulval squamous cell carcinoma and immediate adjacent field change. Gynecol Oncol 67(3):248–254

Mell LK, Meyer JJ, Tretiakova M, Khramtsov A, Gong C, Yamada SD et al (2004) Prognostic significance of E-cadherin protein expression in pathological stage I-III endometrial cancer. Clin Cancer Res 10(16):5546–5553 Epub 2004/08/26

Mendenhall WM, Thar TL, Bova FJ, Marcus RB Jr, Morgan LS, Million RR (1984) Prognostic and treatment factors affecting pelvic control of stage IB and IIA-B carcinoma of the intact uterine cervix treated with radiation therapy alone. Cancer 53:2649–2654

Milgrom SA, Kollmeier MA, Abu-Rustum NR, Makker V, Gardner GJ, Barakat RR et al (2013) Positive peritoneal cytology is highly predictive of prognosis and relapse patterns in stage III (FIGO 2009) endometrial cancer. Gynecol Oncol 130(1):49–53

Monk BJBR, Lin F, Parham G, Vasilev SA, Wilczynski SP (1995) Prognostic significance of human papillomavirus DNA in vulvar carcinoma. Obstet Gynecol 85:709–715

Montana GS, Thomas GM, Moore DH, Saxer A, Mangan CE, Lentz SS et al (2000) Preoperative chemo-radiation for carcinoma of the vulva with N2/N3 nodes: a gynecologic oncology group study. Int J Radiat Oncol Biol Phys 48(4):1007–1013

Moore DH, Ali S, Koh WJ, Michael H, Barnes MN, McCourt CK et al (2012) A phase II trial of radiation therapy and weekly cisplatin chemotherapy for the treatment of locally-advanced squamous cell carcinoma of the vulva: a gynecologic oncology group study. Gynecol Oncol 124(3):529–533

Morice P, Castaigne D, Pautier P, Rey A, Haie-Meder C, Leblanc M et al (1999) Interest of pelvic and paraaortic lymphadenectomy in patients with stage IB and II cervical carcinoma. Gynecol Oncol 73(1):106–110 Epub 1999/03/30

Morley GW, Seski JC (1976) Radical pelvic surgery versus radiation therapy for stage I carcinoma of the cervix (exclusive of microinvasion). Am J Obstet Gynecol 126(7):785–798 Epub 1976/12/01

Morris M, Eifel PJ, Lu J, Grigsby PW, Levenback C, Stevens RE et al (1999) Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med 340:1137–1143

Morrow (1980) Is pelvic radiation beneficial in the postoperative management of stage Ib squamous cell carcinoma of the cervix with pelvic node metastasis treated by radical hysterectomy and pelvic lymphadenectomy? A report from the Presidential Panel at the 1979 Annual Meeting of the Society of Gynecologic Oncologists (1980) Gynecol Oncol 10(1):105–110

Morrow CP, Bundy BN, Kurman RJ, Creasman WT, Heller P, Homesley HD 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):55–65

Naganawa S, Sato C, Kumada H, Ishigaki T, Miura S, Takizawa O (2005). Apparent diffusion coefficient in cervical cancer of the uterus: comparison with the normal uterine cervix. Eur Radiol 15:71–78

Nagar H, Dobbs S, McClelland HR, Price J, McCluggage WG, Grey A (2006) The diagnostic accuracy of magnetic resonance imaging in detecting cervical involvement in endometrial cancer. Gynecol Oncol 103(2):431–434

Nakamura K, Kodama J, Okumura Y, Hongo A, Kanazawa S, Hiramatsu Y (2010) The SUVmax of 18F-FDG PET correlates with histological grade in endometrial cancer. Int J Gynecol Cancer 20(1):110–115

Nakamura K, Hongo A, Kodama J, Hiramatsu Y (2011) The measurement of SUVmax of the primary tumor is predictive of prognosis for patients with endometrial cancer. Gynecol Oncol 123(1):82–87

Nakamura K, Joja I, Fukushima C, Haruma T, Hayashi C, Kusumoto T et al (2013) The preoperative SUVmax is superior to ADCmin of the primary tumour as a predictor of disease recurrence and survival in patients with endometrial cancer. Eur J Nucl Med Mol Imaging 40(1):52–60

Nicoletto MO, Parenti A, Del Bianco P, Lombardi G, Pedrini L, Pizzi S, Carli P, Della Palma M, Pastorelli D, Corti L, Becagli L (2010) Vulvar cancer: prognostic factors. Anticancer Res 30(6):2311–2317

Nordstrom B, Strang P, Lindgren A, Bergstrom R, Tribukait B (1996) Carcinoma of the endometrium: do the nuclear grade and DNA ploidy provide more prognostic information than do the FIGO and WHO classifications? Int J Gynecol Pathol 15(3):191–201

Nori D, Hilaris B, Stanimir G, Lewis JL Jr (1983) Radiation therapy of primary vaginal carcinoma. Int J Radiat Oncol Biol Phys 9(10):1471–1475

Nout RA, Smit VT, Putter H, Jurgenliemk-Schulz IM, Jobsen JJ, Lutgens LC et al (2010) Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. Lancet 375(9717):816–823 Epub 2010/03/09

Nout RA, Bosse T, Creutzberg CL, Jurgenliemk-Schulz IM, Jobsen JJ, Lutgens LC et al (2012) Improved risk assessment of endometrial cancer by combined analysis of MSI, PI3 K-AKT, Wnt/beta-catenin and P53 pathway activation. Gynecol Oncol 126(3):466–473

Obermair A, Kohlberger P, Bancher-Todesca D, Tempfer C, Sliutz G, Leodolter S et al (1996) Influence of microvessel density and vascular permeability factor/vascular endothelial growth factor expression on prognosis in vulvar cancer. Gynecol Oncol 63(2):204–209

Obermair A, Wanner C, Bilgi S, Speiser P, Kaider A, Rheinthaller A et al (1998) Tumor angiogenesis in stage IB cervical cancer: correlaion of microvessel density with survival. Am J Obstet Gynecol 178:314–319

Okagaki T, Twiggs LB, Zachow KR, Clark BA, Ostrow RS, Faras AJ (1983) Identification of human papillomavirus DNA in cervical and vaginal intraepithelial neoplasia with molecularly cloned virus-specific DNA probes. Int J Gynecol Pathol 2(2):153–159

Oonk MH, van Hemel BM, Hollema H, de Hullu JA, Ansink AC, Vergote I et al (2010) Size of sentinel-node metastasis and chances of non-sentinel-node involvement and survival in early stage vulvar cancer: results from GROINSS-V, a multicentre observational study. Lancet Oncol 11(7):646–652

Orezzoli JP, Sioletic S, Olawaiye A, Oliva E, del Carmen MG (2009) Stage II endometrioid adenocarcinoma of the endometrium: clinical implications of cervical stromal invasion. Gynecol Oncol 113(3):316–323

Origoni M, Sideri M, Garsia S, Carinelli SG, Ferrari AG (1992) Prognostic value of pathological patterns of lymph node positivity in squamous cell carcinoma of the vulva stage III and IVA FIGO. Gynecol Oncol 45(3):313–316

Ota T, Yoshida M, Kimura M, Kinoshita K (2005) Clinicopathologic study of uterine endometrial carcinoma in young women aged 40 years and younger. Int J Gynecol Cancer 15(4):657–662 Epub 2005/07/15

Paladini D, Cross P, Lopes A, Monaghan JM (1994) Prognostic significance of lymph node variables in squamous cell carcinoma of the vulva. Cancer 74(9):2491–2496

Park JY, Kim EN, Kim DY, Kim JH, Kim YM, Kim YT et al (2008) Clinical impact of positron emission tomography or positron emission tomography/computed tomography in the posttherapy surveillance of endometrial carcinoma: evaluation of 88 patients. Int J Gynecol Cancer 18(6):1332–1338

Pecorelli S (2009) Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet 105(2): 103–104

Pecorelli S, Zigliani L, Odicino F (2009) Revised FIGO staging for carcinoma of the cervix. Int J Gynaecol Obstet 105(2):107–108

Perez CA, Camel HM, Galakatos AE, Grigsby PW, Kuske RR, Buchsbaum G et al (1988) Definitive irradiation in carcinoma of the vagina: long-term evaluation of results. Int J Radiat Oncol Biol Phys 15(6):1283–1290

Perez CA, Grigsby P, Nene S et al (1992a) Effect of tumor size on the prognosis of carcinoma of the uterine cervix treated with irradiation alone. Cancer 69:2796–2806

Perez C, Grigsby P, Nene S et al (1992b) Effect of tumor size on the prognosis of carcinoma of the uterine cervix treated with irradiation alone. Cancer 69:2796–2806

Perez CAGP, Garipagaoglu M, Mutch DG, Lockett MA (1999) Factors affecting long-term outcome of irradiation in carcinoma of the vagina. Int J Radiat Oncol Biol Phys 44(1):37–45

Pilch H, Gunzel S, Schaffer U, Tanner B, Brockerhoff P, Maeurer M et al (2001) The presence of HPV DNA in cervical cancer: correlation with clinico-pathologic parameters and prognostic significance: 10 years experience at the Department of Obstetrics

and Gynecology of the Mainz University. Int J Gynecol Cancer 11(1):39–48 Epub 2001/04/04

Pingley S, Shrivastava SK, Sarin R, Agarwal JP, Laskar S, Deshpande DD et al (2000) Primary carcinoma of the vagina: Tata Memorial Hospital experience. Int J Radiat Oncol Biol Phys 46(1):101–108 Epub 2000/02/03

Podratz KCSR, Taylor WF, Williams TJ (1983) Carcinoma of the vulva: analysis of treatment and survival. Obstet Gynecol 61(1):63–74

Powell JL, Hill KA, Shiro BC, Diehl SJ, Gajewski WH (2005) Preoperative serum CA-125 levels in treating endometrial cancer. J Reprod Med 50(8):585–590 Epub 2005/10/14

Prat J (2009) FIGO staging for uterine sarcomas. Int J Gynaecol Obstet 104(3):177–178

Prat J, Oliva E, Lerma E, Vaquero M, Matias-Guiu X (1994) Uterine papillary serous adenocarcinoma. A 10-case study of p53 and c-erbB-2 expression and DNA content. Cancer 74(6):1778–1783

Prempree T, Amornmarn R (1985) Radiation treatment of primary carcinoma of the vagina. Patterns of failures after definitive therapy. Acta Radiologica Oncol 24(1):51–56. Epub 1985/01/01

Prompeler HJ, Madjar H, du Bois A, Lattermann U, Wilhelm C, Kommoss F et al (1994) Transvaginal sonography of myometrial invasion depth in endometrial cancer. Acta Obstet Gynecol Scand 73(4):343–346 Epub 1994/04/01

Peters WA r, Liu PY, Barrett RJ 2nd et al (2000) Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol18:1606–1613

Ragnarsson-Olding B, Johansson H, Rutqvist LE, Ringborg U (1993) Malignant melanoma of the vulva and vagina. Trends in incidence, age distribution, and long-term survival among 245 consecutive cases in Sweden 1960-1984. Cancer 71(5):1893–1897

Ramanah R, Lesieur B, Ballester M, Darai E, Rouzier R (2012) Trends in of late-stage squamous cell vulvar carcinomas: analysis of the surveillance, epidemiology, and end results (SEER) database. Int J Gynecol Cancer 22(5):854–859

Randall ME, Filiaci VL, Muss H, Spirtos NM, Mannel RS, Fowler J et al (2006) Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol 24(1):36–44

Randall LM, Monk BJ, Darcy KM, Tian C, Burger RA, Liao SY et al (2009) Markers of angiogenesis in high-risk, early-stage cervical cancer: a Gynecologic Oncology Group study. Gynecol Oncol 112(3):583–589 Epub 2008/12/27

Raspagliesi F, Hanozet F, Ditto A, Solima E, Zanaboni F, Vecchione F, Kusamura S (2006) Clinical and pathological prognostic factors in squamous cell carcinoma of the vulva. Gynecol Oncol 102(2):333–337

Rauh-Hain JA, Del Carmen MG (2013) Endometrial stromal sarcoma: a systematic review. Obstet Gynecol 122(3):676–683

Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA et al (1999) Concurrent Cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 340:1144–1153

Rose PGAS, Watkins E, Thigpen JT, Deppe G, Clarke-Pearson DL, Insalaco S (2007) Long-term follow-up of a randomized trial comparing concurrent single agent cisplatin, cisplatin-based combination chemotherapy, or hydroxyurea during pelvic irradiation for locally advanced cervical cancer: a Gynecologic Oncology Group Study. J Clin Oncol 25:2804–2810

Ross JC, Eifel PJ, Cox RS, Kempson RL, Hendrickson MR (1983) Primary mucinous adenocarcinoma of the endometrium. A clinicopathologic and histochemical study. Am J Surg Pathol 7(8):715–729

Ross BDMB, Lawrence TS, Mukherji SK, Gebarski SS, Quint DJ, Johnson TD, Junck L, Robertson PL, Muraszko KM, Dong Q, Meyer CR, Bland PH, McConville P, Geng H, Rehemtulla A, Chenevert TL (2003) Evaluation of cancer therapy using diffusion magnetic resonance imaging. Mol Cancer Ther 2(6):581–587

Rotman M, Aziz H, Eifel PJ (1994) Irradiation of pelvic and paraaortic nodes in carcinoma of the cervix. Semin Radiat Oncol 4(1):23–29

Rotman M, Sedlis A, Piedmonte MR, Bundy B, Lentz SS, Muderspach LI, Zaino RJ (2006) A phase III randomized trial of postoperative pelvic irradiation in Stage IB cervical carcinoma with poor prognostic features: follow-up of a gynecologic oncology group study. Int J Radiat Oncol Biol Phys 65(1):169–176

Rouzier R, Haddad B, Plantier F, Dubois P, Pelisse M, Paniel BJ (2002) Local relapse in patients treated for squamous cell vulvar carcinoma: incidence and prognostic value. Obstet Gynecol 100(6): 1159–1167

Rutledge F, Smith J, Franklin EW (1970) Carcinoma of the vulva. Am J Obstet Gynecol 106(8):1117–1130

Saez F, Urresola A, Larena JA, Martin JI, Pijuan JI, Schneider J et al (2000) Endometrial carcinoma: assessment of myometrial invasion with plain and gadolinium-enhanced MR imaging. J Magn Reson Imaging 12(3):460–466

Saffari B, Bernstein L, Hong DC, Sullivan-Halley J, Runnebaum IB, Grill HJ et al (2005) Association of p53 mutations and a codon 72 single nucleotide polymorphism with lower overall survival and responsiveness to adjuvant radiotherapy in endometrioid endometrial carcinomas. Int J Gynecol Cancer 15(5):952–963 Epub 2005/09/22

Saga T, Higashi T, Ishimori T, Mamede M, Nakamoto Y, Mukai T et al (2003) Clinical value of FDG-PET in the follow up of post-operative patients with endometrial cancer. Ann Nucl Med 17(3):197–203

Sala E, Crawford R, Senior E, Shaw A, Simcock B, Vrotsou K et al (2009) Added value of dynamic contrast-enhanced magnetic resonance imaging in predicting advanced stage disease in patients with endometrial carcinoma. Int J Gynecol Cancer 19(1):141–146

Salani R, Backes FJ, Fung MF, Holschneider CH, Parker LP, Bristow RE et al (2011) Posttreatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncologists recommendations. Am J Obstet Gynecol 204(6):466–478 Epub 2011/07/15

Salvesen HB, Iversen OE, Akslen LA (1998) Identification of high-risk patients by assessment of nuclear Ki-67 expression in a prospective study of endometrial carcinomas. Clin Cancer Res 4(11):2779–2785 Epub 1998/11/26

Santos M, Montagut C, Mellado B, Garcia A, Ramon y Cajal S, Cardesa A et al (2004) Immunohistochemical staining for p16 and p53 in premalignant and malignant epithelial lesions of the vulva. Int J Gynecol Pathol 23(3):206–214

Scheistroen M, Trope C, Pettersen EO, Nesland JM (1999) p53 protein expression in squamous cell carcinoma of the vulva. Cancer 85(5):1133–1138

Schwartz SM, Daling JR, Shera KA, Madeleine MM, McKnight B, Galloway DA et al (2001) Human papillomavirus and prognosis of invasive cervical cancer: a population-based study. J Clin Oncol 19(7):1906–1915 Epub 2001/04/03

Scribner DR Jr, Walker JL, Johnson GA, McMeekin DS, Gold MA, Mannel RS (2002) Laparoscopic pelvic and paraaortic lymph node dissection in the obese. Gynecol Oncol 84(3):426–430

Sedlis A, Bundy B, Rotman MZ, Lentz SS, Muderspach LI, Zaino RJ (1999) A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: A Gynecologic Oncology Group Study. Gynecol Oncol 73(2):177–183

Selman TJ, Luesley DM, Acheson N, Khan KS, Mann CH (2005) A systematic review of the accuracy of diagnostic tests for inguinal lymph node status in vulvar cancer. Gynecol Oncol 99(1):206–214
Sethi TK, Bhalla NK, Jena AN, Rawat S, Oberoi R (2005) Magnetic resonance imaging in carcinoma cervix—does it have a prognostic relevance. J Cancer Res Ther 1(2):103–107
Shah CA, Goff BA, Lowe K, Peters WA 3rd, Li CI (2009) Factors affecting risk of mortality in women with vaginal cancer. Obstet Gynecol 113(5):1038–1045
Shingleton HM, Bell MC, Fremgen A, Chmiel JS, Russell AH, Jones WB et al (1995) Is there really a difference in survival of women with squamous cell carcinoma, adenocarcinoma, and adenosquamous cell carcinoma of the cervix? Cancer 76(10 Suppl):1948–1955 Epub 1995/11/15
Siegel R, Naishadham D, Jemal A (2012) Cancer statistics, 2012. CA Cancer J Clin 62(1):10–29 Epub 2012/01/13
Siegel R, Naishadham D, Jemal A (2013) Cancer statistics, 2013. CA Cancer J Clin 63(1):11–30
Sillman FH, Fruchter RG, Chen YS, Camilien L, Sedlis A, McTigue E (1997) Vaginal intraepithelial neoplasia: risk factors for persistence, recurrence, and invasion and its management. Am J Obstet Gynecol 176(1 Pt 1):93–99
Silverman MB, Roche PC, Kho RM, Keeney GL, Li H, Podratz KC (2000) Molecular and cytokinetic pretreatment risk assessment in endometrial carcinoma. Gynecol Oncol 77(1):1–7 Epub 2000/03/31
Singh K, Orakwue CO, Honest H, Balogun M, Lopez C, Luesley DM (2006) Accuracy of magnetic resonance imaging of inguinofemoral lymph nodes in vulval cancer. Int J Gynecol Cancer 16(3):1179–1183 Epub 2006/06/29
Singh M, Darcy KM, Brady WE, Clubwala R, Weber Z, Rittenbach JV et al (2011) Cadherins, catenins and cell cycle regulators: impact on survival in a Gynecologic Oncology Group phase II endometrial cancer trial. Gynecol Oncol 123(2):320–328 Epub 2011/08/05
Sironi S, Colombo E, Villa G, Taccagni G, Belloni C, Garancini P et al (1992) Myometrial invasion by endometrial carcinoma: assessment with plain and gadolinium-enhanced MR imaging. Radiology 185(1):207–212
Smith HO, Tiffany MF, Qualls CR, Key CR (2000) The rising incidence of adenocarcinoma relative to squamous cell carcinoma of the uterine cervix in the United States—a 24-year population-based study. Gynecol Oncol 78(2):97–105 Epub 2000/08/06
Sohaib SA, Richards PS, Ind T, Jeyarajah AR, Shepherd JH, Jacobs IJ et al (2002) MR imaging of carcinoma of the vulva. Am J Roentgenol 178(2):373–377
Stang A, Streller B, Eisinger B, Jockel KH (2005) Population-based incidence rates of malignant melanoma of the vulva in Germany. Gynecol Oncol 96(1):216–221
Stehman FBBB, DiSaia PJ, Keys HM, Larson JE, Fowler WC (1991) Carcinoma of the cervix treated with radiation therapy. I. A multivariate analysis of prognostic variables in the Gynecologic Oncology Group. Cancer 67(11):2776–2785
Steinbakk A, Malpica A, Slewa A, Skaland I, Gudlaugsson E, Janssen EA et al (2011) Biomarkers and microsatellite instability analysis of curettings can predict the behavior of FIGO stage I endometrial endometrioid adenocarcinoma. Mod Pathol 24(9):1262–1271 Epub 2011/05/10
Stone JE, Parker R, Gilks CB, Stanbridge EJ, Liao SY, Aquino-Parsons C (2005) Intratumoral oxygenation of invasive squamous cell carcimoma of the vulva is not correlated with regional lymph node metastasis. Eur J Gynaecol Oncol 26(1):31–35
Sugiyama VE, Chan JK, Shin JY, Berek JS, Osann K, Kapp DS (2007) Vulvar melanoma: a multivariable analysis of 644 patients. Obstet Gynecol 110(2 Pt 1):296–301
Szantho A, Szabo I, Csapo ZS, Balega J, Demeter A, Papp Z (2001) Assessment of myometrial and cervical invasion of endometrial cancer by transvaginal sonography. Eur J Gynaecol Oncol 22(3):209–212 Epub 2001/08/15
Sznurkowski JJ, Milczek T, Emerich J (2013) Prognostic factors and a value of 2009 FIGO staging system in vulvar cancer. Arch Gynecol Obstet 287(6):1211–1218
Tabbaa ZM, Gonzalez J, Sznurkowski JJ, Weaver AL, Mariani A, Cliby WA (2012) Impact of the new FIGO 2009 staging classification for vulvar cancer on prognosis and stage distribution. Gynecol Oncol 127(1):147–152
Takahashi K, Yoshioka M, Kosuge H, Iizuka Y, Musha T, Yamauchi I et al (1995) The accuracy of computed tomography and magnetic resonance imaging in evaluating the extent of endometrial carcinoma. Nihon Sanka Fujinka Gakkai Zasshi. 47(7):647–654
Takeda N, Sakuragi N, Takeda M, Okamoto K, Kuwabara M, Negishi H et al (2002) Multivariate analysis of histopathologic prognostic factors for invasive cervical cancer treated with radical hysterectomy and systematic retroperitoneal lymphadenectomy. Acta Obstet Gynecol Scand 81(12):1144–1151 Epub 2003/01/10
Takeshima N, Nishida H, Tabata T, Hirai Y, Hasumi K (2001) Positive peritoneal cytology in endometrial cancer: enhancement of other prognostic indicators. Gynecol Oncol 82(3):470–473
Tan J, Chetty N, Kondalsamy-Chennakesavan S, Crandon A, Garrett A, Land R et al (2012) Validation of the FIGO 2009 staging system for carcinoma of the vulva. Int J Gynecol Cancer 22(3):498–502
Tanaka Y, Sawada S, Murata T (1984) Relationship between lymph node metastases and prognosis in patients irradiated postoperatively for carcinoma of the uterine cervix. Acta Radiologica Oncology 23(6):455–459
Tannock IF (1972) Oxygen diffusion and the distribution of cellular radiosensitivity in tumors. Br J Radiol 45:515–524
Tantipalakorn C, Robertson G, Marsden DE, Gebski V, Hacker NF (2009) Outcome and patterns of recurrence for FIGO stages I and II squamous cell vulvar cancer. Obstet Gynecol 113(4):895–907
Taylor MBDN, Davidson SE, Carrington BM (2007) Magnetic resonance imaging of primary vaginal carcinoma. Clin Radiol 62(6):549–555
Tebeu PM, Popowski Y, Verkooijen HM, Bouchardy C, Ludicke F, Usel M et al (2004) Positive peritoneal cytology in early-stage endometrial cancer does not influence prognosis. Br J Cancer 91(4):720–724
Tewari D, Monk BJ, Al-Ghazi MS (2005) Gene expression profiling of in vitro radiation resistance in cervical carcinoma: a feasibility study. Gynecol Oncol 99:84–91
Tewari KS, Filiaci VL, Spirtos NM, Mannel RS, Thigpen JT, Cibull ML et al (2012) Association of number of positive nodes and cervical stroma invasion with outcome of advanced endometrial cancer treated with chemotherapy or whole abdominal irradiation: a Gynecologic Oncology Group study. Gynecol Oncol 125(1):87–93
Thomas G (2001) The effect of hemoglobin level on radiotherapy outcomes: the Canadian experience. Semin Oncol 28(S8):60–65
Thomas GM, Dembo AJ, Myhr T, Black B, Pringle JF, Rawlings G (1993) Long-term results of concurrent radiation and chemotherapy for carcinoma of the cervix recurrent after surgery. Int J Gynecol Cancer 3(4):193–198
Tjalma W, Weyler J, Weyn B (2000) The association between vascular endothelial growth factor and, microvessel density and clinicopathologic features in invasive cervical cancer. Eur J Obstet Gynecol 92:251–257
Tran PT, Su Z, Lee P, Lavori P, Husain A, Teng N et al (2007) Prognostic factors for outcomes and complications for primary squamous cell carcinoma of the vagina treated with radiation. Gynecol Oncol 105(3):641–649 Epub 2007/03/17
Tringler B, Grimm C, Dudek G, Zeillinger R, Tempfer C, Speiser P et al (2007) p16INK4a expression in invasive vulvar squamous cell carcinoma. Appl Immunohistochem Mol Morphol 15(3):279–283

Tsai CS, Lai CH, Wang CC, Chang JT, Chang TC, Tseng CJ et al (1999) The prognostic factors for patients with early cervical cancer treated by radical hysterectomy and postoperative radiotherapy. Gynecol Oncol 75(3):328–333 Epub 1999/12/22

Tsili AC, Tsampoulas C, Dalkalitsis N, Stefanou D, Paraskevaidis E, Efremidis SC (2008) Local staging of endometrial carcinoma: role of multidetector CT. Eur Radiol 18(5):1043–1048

Urbanski K, Kojs Z, Reinfuss M, Fabisiak W (1996) Primary invasive vaginal carcinoma treated with radiotherapy: analysis of prognostic factors. Gynecol Oncol 60(1):16–21

Valenzano M, Podesta M, Giannesi A, Corticelli A, Nicoletti L, Costantini S (2001) The role of transvaginal ultrasound and sonohysterography in the diagnosis and staging of endometrial adenocarcinoma. Radiol Med 101(5):365–370. Ecografia transvaginale e isterosonografia nella diagnosi e nella stadiazione dell'adenocarcinoma dell'endometrio

van de Nieuwenhof HP, de Hullu JA, Kaanders JH, Bulten J, Massuger LF, van Kempen LC (2010) Hemoglobin level predicts outcome for vulvar cancer patients independent of GLUT-1 and CA-IX expression in tumor tissue. Virchows Arch 457(6):693–703

Van der Zee AG, Oonk MH, De Hullu JA, Ansink AC, Vergote I, Verheijen RH et al (2008) Sentinel node dissection is safe in the treatment of early-stage vulvar cancer. J Clin Oncol 26(6):884–889 Epub 2008/02/19

Vavra N, Seifert M, Kucera H, Weghaupt K (1991) Radiotherapy of primary vaginal carcinoma and effects of histological and clinical factors on the prognosis. Strahlenther Onkol 167(1):1–6

Viswanathan AN, Pinto AP, Schultz D, Berkowitz R, Crum CP (2013) Relationship of margin status and radiation dose to recurrence in post-operative vulvar carcinoma. Gynecol Oncol 130(3):545–549 Epub 2013/06/12

van Bommel PF vLA, Kock HC, Leers WH, Neijt JP (1987). A review of prognostic factors in early-stage carcinoma of the cervix (FIGO I B and II A) and implications for treatment strategy. Eur J Obstet Gynecol Reprod Biol 26(1):69–84

Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV et al (1999) Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 189(1):12–19 Epub 1999/08/19

Wang CC, Lai CH, Huang HJ, Chao A, Chang CJ, Chang TC et al (2010) Clinical effect of human papillomavirus genotypes in patients with cervical cancer undergoing primary radiotherapy. Int J Radiat Oncol Biol Phys 78(4):1111–1120 Epub 2010/03/17

Wang CC, Lai CH, Huang YT, Chao A, Chou HH, Hong JH (2012) HPV genotypes predict survival benefits from concurrent chemotherapy and radiation therapy in advanced squamous cell carcinoma of the cervix. Int J Radiat Oncol Biol Phys 84(4):e499–e506 Epub 2012/08/15

Weinstock MA (1994) Malignant melanoma of the vulva and vagina in the United States: patterns of incidence and population-based estimates of survival. Am J Obstet Gynecol 171(5):1225–1230

Werner HM, Trovik J, Marcickiewicz J, Tingulstad S, Staff AC, Amant F et al (2012) Revision of FIGO surgical staging in 2009 for endometrial cancer validates to improve risk stratification. Gynecol Oncol 125(1):103–108

Whitney CWSW, Bundy BN, Malfetano JH, Hannigan EV, Fowler WC Jr, Clarke-Pearson DL, Liao SY (1999) Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. J Clin Oncol 17:1339–1348

Woelber L, Mahner S, Voelker K, Eulenburg CZ, Gieseking F, Choschzick M, Jaenicke, F Schwarz J (2009) Clinicopathological prognostic factors and patterns of recurrence in vulvar cancer. Anticancer Res 29(2):545–552

Woelber L, Hess S, Bohlken H, Tennstedt P, Eulenburg C, Simon R et al (2012) EGFR gene copy number increase in vulvar carcinomas is linked with poor clinical outcome. J Clin Pathol 65(2):133–139

Wong YF, Selvanayagam ZE, Wei N (2003) Expression genomis of cervical cancer: molecular classification and predicton of radiotherapy response by DNA microarray. Clin Cancer Res 9:5486–5492

Wu X, Matanoski G, Chen VW, Saraiya M, Coughlin SS, King JB et al (2008) Descriptive epidemiology of vaginal cancer incidence and survival by race, ethnicity, and age in the United States. Cancer 113(10 Suppl):2873–2882

Yamashita Y, Mizutani H, Torashima M, Takahashi M, Miyazaki K, Okamura H et al (1993a) Assessment of myometrial invasion by endometrial carcinoma: transvaginal sonography vs contrast-enhanced MR imaging. Am J Roentgenol 161(3):595–599

Yamashita Y, Harada M, Sawada T, Takahashi M, Miyazaki K, Okamura H (1993b) Normal uterus and FIGO stage I endometrial carcinoma: dynamic gadolinium-enhanced MR imaging. Radiology 186(2):495–501

Young P, Daniel B, Sommer G, Kim B, Herfkens R (2012) Intravaginal gel for staging of female pelvic cancers—preliminary report of safety, distention, and gel-mucosal contrast during magnetic resonance examination. J Comput Assist Tomogr 36(2):253–256

Yuh WTC, Mayr NA, Jarjoura D, Wu DH, Grecula JC, Lo SS et al (2009) Predicting control of primary tumor and survival by DCE MRI during early therapy in cervical cancer. Invest Radiol 44:343–350

Zaino RJ, Kurman RJ, Brunetto VL, Morrow CP, Bentley RC, Cappellari JO et al (1998a) Villoglandular adenocarcinoma of the endometrium: a clinicopathologic study of 61 cases: a gynecologic oncology group study. Am J Surg Pathol 22(11):1379–1385

Zaino RJ, Davis AT, Ohlsson-Wilhelm BM, Brunetto VL (1998b) DNA content is an independent prognostic indicator in endometrial adenocarcinoma. A Gynecologic Oncology Group study. Int J Gynecol Pathol 17(4):312–319

Zighelboim I, Goodfellow PJ, Gao F, Gibb RK, Powell MA, Rader JS et al (2007) Microsatellite instability and epigenetic inactivation of MLH1 and outcome of patients with endometrial carcinomas of the endometrioid type. J Clin Oncol 25(15):2042–2048 Epub 2007/05/22