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Endometrial Cancer

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Introduction

Endometrial cancer is the fourth most common cancer in women with an estimated 46,470 new diagnoses and over 8000 deaths in 2011. Incidence of endometrial cancer is on the rise with a lifetime risk of approximately 3%. Most strikingly, 5-year survival is currently significantly worse than 30 years ago (84% survival in 2006 vs. 88% survival in 1975), making endometrial cancer only one of two cancers with increased mortality (1). This is stark in comparison to breast and prostate cancer, where 5 year survival has substantially improved to >90% for breast and 100% for prostate cancer. For patients with early stage disease, hysterectomy is considered curative. By contrast, advanced stage and high grade endometrial cancer is lethal. Certain risk factors have been well characterized, such as menopausal status, obesity, diabetes, hypertension and unopposed estrogen, though for some of these risk factors, such as obesity, the mechanisms by which this occurs are not completely understood (2). In this chapter, we describe the current practices for diagnosis and treatment of endometrial cancer and discuss emerging therapeutic strategies that are hoped to improve survival and reverse the alarming rising trend of this disease.

Diagnosis

Unlike breast and prostate cancer where screening tests are available to the general population, endometrial cancer is most commonly diagnosed at endometrial biopsy in symptomatic patients, i.e., after a postmenopausal patient reports vaginal bleeding. No generally applicable screening test is available. For patients who receive a pelvic ultrasound

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for another indication, an enlarged endometrial stripe or other intrauterine anomaly, such as a polyp, may prompt biopsy in the absence of vaginal bleeding. However, most experts agree that ultrasound is not recommended as a screening tool in asymptomatic patients.

Common non-cancerous histological findings include both simple and complex hyperplasia (both with and without atypia). If left untreated, the incidence of progression to endometrial cancer ranges from 1–29% of cases depending on the type of hyperplasia (simple vs. complex) and the degree of cytologic atypia (3). In addition to the risk of cancer progression with a diagnosis of endometrial hyperplasia made in the community setting, a recent study performed within the Gynecologic Oncology Group (GOG) demonstrated that a large percentage (42%) of patients with a biopsy diagnosis of atypical endometrial hyperplasia have a concurrent endometrial cancer at the time of hysterectomy (4). A similar study performed within an academic medical center examined the incidence of endometrial adenocarcinoma within hysterectomy specimens from patients with a pre-operative diagnosis of atypical hyperplasia. This study noted a slightly higher incidence (48%) of endometrial adenocarcinoma in patients with a pre-operative diagnosis of endometrial hyperplasia (5). This is in contrast to other smaller studies that reported rates of co-existence of endometrial hyperplasia and endometrial cancer as low as 10% of cases (6). These data suggest at a minimum close observation for women with atypical endometrial hyperplasia with strong consideration given to hysterectomy in women who have completed childbearing or who are not interested in reproduction and progestin therapy in women who wish to maintain fertility.

Staging

In 2009, the International Federation of Gynecology and Obstetrics (FIGO) revised the staging system for carcinomas of the vulva, cervix, and endometrium (7, 8). The primary changes made for endometrial cancer included the grouping of stages IA and IB together as stage IA with the loss of prior IC and the division of stage IIIC (metastasis to the pelvic and/or paraaortic lymph nodes) into stage IIIC1 (positive pelvic nodes) and IIIC2 (positive paraaortic lymph nodes). Specifically the old staging system defined stage IA as no invasion into the myometrium, stage IB as less than 50% invasion into the myometrium, and stage IC as equal to or greater than 50% invasion into the myometrium, whereas the new FIGO 2009 system defines stage IA as cancer confined to the uterus with less than 50% myometrial invasion, and stage IB as equal to or greater than 50% myometrial invasion, with both IA and IB including any tumor grade. This was modified after data from the FIGO Annual Report showed no difference in survival between previous stage IA grade 1 or 2 and stage IB grade 1 or 2 tumors (9). The other significant change involved patients with positive pelvic or paraaortic lymph nodes. Under the old FIGO guidelines, patients with positive pelvic and/or paraaortic lymph nodes were staged as IIIC, and under the new system patients with positive pelvic lymph nodes are separated from those with positive paraaortic +/- pelvic lymph nodes, stage IIIC1 and IIIC2, respectively. This change was made because many studies demonstrated worse survival for patients with positive paraaortic lymph nodes when compared to positive pelvic lymph nodes (10, 11).

Surgical procedure for endometrial cancer

Endometrial cancer is initially staged and treated at surgery. Standard treatment for this cancer in the United States consists of removal of the uterus, cervix, both fallopian tubes and ovaries, as well as selective pelvic and para-aortic lymphadenectomy.

Information regarding the need for lymph node dissection in all cases is difficult to decipher with data supporting both views. It appears that it is reasonable to determine the risk of nodal metastasis in order to assign patients to a low risk group and a high risk group. A

recent publication reporting the risk for lymph node metastasis in low versus high risk patients from a secondary analysis of GOG study LAP2 indicates only 0.8% of patients in the low risk group had nodal involvement (12). Thus, unnecessary lymphadenectomy may be avoidable in those patients with very low risk for nodal disease. Based upon data from Gynecologic Oncology Group (GOG) study 33, the two factors most important in determining lymph node involvement are depth of tumor invasion and tumor grade (13). Previous studies examining patients with early stage disease have demonstrated higher recurrence rates in patients with positive lymph nodes as well as decreased survival rates (14, 15). However, two large prospective studies that examined the value of lymph node dissection found no survival difference between groups who did or did not undergo lymphadenectomy. Yet, there were limitations to both of these studies, specifically the inclusion of postoperative therapy and the lack of complete pelvic and paraaortic lymph node dissection (16, 17).

The long-term risks of lymph node dissection are rather uncommon (18). Relatively recent data from the LAP2 trial has demonstrated the safe use of minimally invasive techniques for lymph node dissection when compared to an open procedure (19). Although the intraoperative complication rates were similar between these two groups, this study did not specifically examine the complication rates of lymph node dissection. A publication from the Mayo Clinic proposes the identification of a low risk subset of patients in which lymph node dissection can be avoided (20). No patients in this group had positive lymph nodes, thus demonstrating and confirming the belief that lymph node dissection may be best performed in patients with a high risk for nodal involvement.

For women who are not surgical candidates, primary radiation therapy (RT) may be recommended instead of surgery. As an alternative for younger women wishing to preserve fertility, progestin-containing intrauterine devices (IUDs) have been used with reasonable safety and efficacy (21, 22), though this has predominantly been performed in patients with grade 1 disease. However, one case of grade 2 has been reported to be successfully treated (21).

Risk stratification and adjuvant therapy

For those patients who have undergone an appropriate staging and treatment surgery, adjuvant RT (vaginal brachytherapy or external beam), chemotherapy or hormonal therapy may be recommended depending upon risk factors.

Patients are categorized based upon risk stratification in the post-operative period (23). Low and low-intermediate-risk patients may not require post-surgical therapy; however, molecular risk factors such as p53 mutations, etc. if known, may impact this decision. Given the potential side effects of adjuvant therapy, it is important to distinguish between patients who would benefit from adjuvant therapy and those who would be better served simply by close clinical follow up.

Those of high-intermediate-risk require post-surgical treatment with RT to reduce local recurrence based upon the fact that 75% of recurrences are in the pelvis. Currently, there is no well-established treatment protocol for patients with advanced-stage disease, although this is the subject of clinical trials. Patients at high risk require adjuvant treatment, which is most often RT for high risk cases confined to the uterus and chemotherapy for cases with extrauterine disease. Large prospective clinical trials have demonstrated that post-operative pelvic radiation therapy does decrease local recurrences, but has no overall impact on survival (23, 24).

Many clinicians had concerns regarding the side effects of whole pelvic radiation in treating patients with early stage endometrial cancer. Recent evidence from PORTEC-2 demonstrates that the use of vaginal brachytherapy is no worse than whole pelvic radiation therapy, and as a result of this trial many centers within the United States have shifted to the use of vaginal brachytherapy for their patients in whom adjuvant radiation therapy is warranted (25). Long-term follow up studies for PORTEC-1 and PORTEC-2 have demonstrated more urinary and bowel dysfunction for patients treated with whole pelvic radiation therapy (PORTEC-1) and, as expected, patients who received vaginal brachytherapy exhibited fewer adverse effects than those who received pelvic radiation (PORTEC-2) (26, 27).

Obesity is clearly a risk factor for the development of endometrial cancer, but the mechanisms by which this occurs are not well understood (2). While production of estrone from the adipose tissue with local conversion to estradiol in the endometrium is one hypothesis, recent publications point to a genetic link between obesity and endometrial cancer. For example, an association between single nucleotide polymorphisms in genes related to obesity and endometrial cancer was recently made (28, 29). Much information remains to be understood about the relationship between obesity and endometrial cancer, and support for these efforts are being recognized by the National Cancer Institute (NCI) and other funding agencies, as is reflected by the NCI's recent request for applications directly related to obesity.

Chemotherapy

Chemotherapy is the treatment of choice for metastatic disease. The choice of the regimen has evolved over the past decade. The most active agents are anthracyclines, platinum compounds and taxanes. As single agents, these drugs result in a response rate greater than 20%. Single agent chemotherapy is an option for patients who are likely to have unacceptable side effects with multiple agents. However, for the majority of patients, multiple agents are used. Response rates for triple therapy with doxorubicin, cisplatin and paclitaxel were 57% in GOG 177; however, side effects were prominent (30). Phase II trials indicate that the double combination of cisplatin and paclitaxel results in a relatively high rate of response, and this regimen appears to be better tolerated (31–33). A comparison between the triple and double combination regimens with and without doxorubicin is currently underway in GOG 209, and the results are pending.

Molecular Therapies for Endometrial Cancer

We are in an age of renewed hope about cancer treatment with increasing numbers of available agents beyond standard chemotherapeutics (34–37). A plethora of new molecules which block important signaling and transcriptional/translational pathways in cancer cells are now in use, with many more in development. While molecular agents have been rapidly deployed to treat other types of malignancies, use in endometrial cancer seems to lag. Endometrial tumors are biologically highly diverse. To realize the benefit these newer drugs may provide, it is our challenge to match individual targeted agents with the tumors most likely to respond. This requires a more complete understanding of uterine carcinogenesis and the molecular events which allow malignant cells to escape normal growth controls. In addition, we must find creative ways to use targeted molecules not only individually, but together and/or with chemotherapy.

Overview of type I and II endometrial cancer

For simplicity, endometrial tumors have been divided into two main subtypes, I and II (38). Type I endometrial cancer is of endometrioid morphology; it occurs most often in obese

post-menopausal women and occasionally in anovulatory pre-menopausal women. Type I tumors are classically estrogen-related with relatively low grade features and carry a good prognosis. The lesions are commonly well-differentiated, preceded by endometrial hyperplasia, and comprise approximately 80% of sporadic tumors. On a molecular level, type I cancers are linked to mutations or down-regulation of *PTEN*, among other targets, leading to constitutive activation of Akt and mTOR (39–43). In comparison, type II tumors comprise a heterogeneous, poorly differentiated group of tumors of high grade endometrioid, serous papillary or clear cell morphology that primarily occurs in older post-menopausal women. Type II tumors may be estrogen independent, and they are often accompanied by surrounding endometrial atrophy. Type II cancers have been reported to be associated with abnormalities in *TP53*, *ErbB2*, and *P16*, where high immunostaining indicates mutated nonfunctional proteins (37, 42–47). These tumors are often locally advanced and/or metastatic, and they carry a very poor prognosis (48). For such lesions, survival is often less than six months despite aggressive chemotherapy and radiation.

From this discussion, it is clear that we are beginning to uncover the molecular differences between endometrial cancer subtypes, yet we have not adequately put these findings to use as it pertains to the choice of therapy. In actuality, endometrial tumors often display characteristics of both type I and II cancer in a single lesion. Thus, the challenge for the future will be to find ways to best incorporate targeted molecular therapies for patients with such heterogeneous tumors.

Central pathways controlling growth in the endometrium

Endometrial proliferation is controlled by steroid hormones in concert with a complex set of signaling pathways downstream of growth factors and their tyrosine kinase receptors. As shown in Figure 1, cross-talk between steroid hormone and growth factor signaling occurs and is critical for cellular function. The preeminent regulatory signaling pathway consists of two arms, RAS/RAF/MAPK and PTEN/PI3K/Akt/mTOR (Figure 1).

Predominance of PI3K/Akt/mTOR signaling in endometrial cancer results from the fact that 30–50 percent of sporadic endometrial carcinomas carry somatically acquired inactivating mutations and/or deletions of the *PTEN* tumor suppressor gene (49, 50). A more recent study reports *PTEN* inactivation in up to 83% of endometrioid endometrial adenocarcinomas (41). *PTEN* is a dual specificity phosphatase that negatively regulates the PI3K/Akt signaling pathway. Mutations which activate PI3K also result in constitutive signaling through this pathway. Mammalian target of rapamycin (mTOR) is downstream of *PTEN* and both up- and downstream of Akt in signaling pathways. mTOR is a member of the phosphatidylinositol kinase-related kinases. Its catalytic activity is regulated by the mitogen activated phosphatidylinositol 3 kinase (PI3K)/Akt pathway. mTOR's principal downstream targets, p70S6 kinase and 4E-Binding Protein 1 (4E-BP1), control translation. Another of mTOR's targets, eukaryotic initiation factor 4e, induces transformation when overexpressed in experimental models (51).

Microsatellite instability (MSI), as well as mutations in K-ras, B-raf, FGFR2, PI3K, and beta-catenin, are other genetic alterations common in endometrioid endometrial cancer (37, 43, 52, 53). Activating K-ras and FGFR mutations result in high levels of activated MAPK, which phosphorylates pro-growth transcription factors such as ER and positively regulates beta-catenin activity. ER binds to the promoters of pro-growth genes, induces transcription and eventual enhancement of cellular proliferation. The importance of estrogen signaling unopposed by the differentiating effects of progesterone as a risk for endometrial cancer cannot be over-stated; this concept has been proven by over 50 years of research indicating that when women receive estrogen-only hormonal replacement therapy there is a resultant significant increase in the rate of endometrial cancer (54).

For patients with somatic mutations in the germline of the DNA mismatch repair gene, MMR, the disease is called hereditary nonpolyposis colorectal cancer or Lynch Syndrome. Mutations in MMR, which occur in endometrioid endometrial cancers, lead to microsatellite instability (MSI), and patients with Lynch syndrome are diagnosed with endometrial cancer approximated two decades younger than cases of sporadic cancer development (43).

Hormonal therapy – the first of the targeted agents

The uterine endometrium is exquisitely sensitive to hormonal stimulation. Estrogen enhances epithelial proliferation, and progesterone causes epithelial differentiation. In several recent reviews, the application of progestin therapy to endometrial cancer has been described (55–57). To achieve the anti-tumor effect, progestins are thought to induce differentiation of tumor cells as well as allow for activation of apoptotic pathways or block active cell division. Not surprisingly, prognosis and response to progestin therapy positively correlates with expression of PR. In patients with high PR expression, the overall response rate is 72% in patients compared to 12% in patients with tumors lacking PR (58). It is important to note, however, that patients that initially responded to progestin therapy frequently relapse. One potential reason for this lack of sustained benefit is because progestins promote downregulation of ER and PR (59, 60). It is thought that a pulse of estrogen can either upregulate both ER and PR (permitting more durable responses to progestin therapy), or recruit neoplastic cells into the cell cycle in a synchronous fashion, enhancing sensitivity to chemotherapy. Our group demonstrated, however, that re-expression of PRB in PR-negative endometrial cancer cells restores progestin control of cell growth (61). The addition of an estrogen-like molecule such as tamoxifen and the intermittent use of the progestin has been employed by the GOG in study 119 for the purpose of attempting to prevent the progestin-dependent down-regulation of PR (62). The response rate in advanced disease for this study was 33% and segregated with the expression of hormone receptors (63).

We now understand that one additional mechanism of PR down-regulation is epigenetic via promoter methylation, with one study documenting PRB promoter methylation in 75% of endometrial tumors (64). Towards developing an alternative treatment strategy, in preclinical studies DNA methyltransferase (DNMT) inhibitors have been explored as a novel approach to restore PR expression (65, 66). One group reported a decrease in proliferation of endometrial cancer cells in response to treatment with a DNMT inhibitor (65); however, no studies have been reported which examined progestin sensitivity after treatment with an epigenetic modulator in the clinical setting. We propose that the combination of progestin therapy with epigenetic modulators which enhance and maintain PR levels is an attractive regimen which offers the opportunity to enhance sensitivity to progestin therapy (55, 56). If hormonal and epigenetic combinations can be created which result in response rates which are the same or better than chemotherapy, but without the substantial side effects, older, frail patients would be particularly benefited.

Given the known relationship between unopposed estrogen stimulation and endometrial cancer risk, it is surprising that compared to progestin treatment, anti-estrogen therapy has been disappointing. Tamoxifen alone has limited activity in advanced disease with response rates of 10% in phase II studies (67). The study of both leuprolide, a gonadotrophin-releasing hormone agonist that results in profound hypoestrogenism (68), and fulvestrant (GOG188), the pure antiestrogen (69), failed to demonstrate sufficient clinical activity to support their widespread. Likewise, aromatase inhibitors do not demonstrate response rates as high as those obtained with progestins (70, 71). Thus, progestin therapy (at least as a component of the regimen) remains the preferred hormonal treatment for endometrial cancer.

Hormonal therapy compared to chemotherapy

Despite the relatively high response rates with combined chemotherapy, significant side effects are associated with chemotherapy. The negative effects of chemotherapy must be considered given that a majority of the patients with endometrial cancer are elderly and often have co-morbidities (i.e., obesity, diabetes, and cardiovascular disease). In addition, patients may have had previous radiation therapy. Only minor adverse effects have been associated with hormonal therapy (i.e., weight gain, edema, and thrombophlebitis), although there is an increased risk of thromboembolism. Thus, for older, frail patients, hormonal therapy is an option, particularly in cases where ER and PR expression are present. However, it is noted that patients without robust ER and PR expression may also respond (63).

Inhibitors of growth factors and growth factor receptor signaling

Our expanding knowledge of signaling pathways relating cell growth, cell cycle progression, and apoptosis has led to an improved understanding of the molecular events involved in carcinogenesis. Cancer cells require growth factors and their tyrosine kinase receptors to promote angiogenesis, proliferation, invasion, and metastasis. This sets the stage for expanded therapeutic options, which include blocking the growth factors or receptors with therapeutic inactivating antibodies or with tyrosine kinase inhibitors. For endometrial cancer, agents which block EGFR (gefitinib, GOG 229C; lapatinib, GOG 229D; erlotinib; cetuximab), HER-2 (lapatinib, GOG 229D), VEGF (bevacizumab, GOG 229E; VEGF-trap, GOG 229F), VEGFR (cediranib, GOG 229J), PDGFR (cediranib, GOG 229J), FGFR (brivanib, GOG 229 I and cediranib, GOG229 J) and mTOR (temsirolimus NCIC, temsirolimus, GOG 248) are under investigation.

In this decade, we have reached an important milestone with targeted inhibitors as single agents. mTOR inhibitors (temsirolimus and everolimus) and bevacizumab were the first molecular therapies other than progestins deemed to have notable clinical benefit in advanced endometrial cancer (72–74). The response rate for temsirolimus alone in patients with advanced chemo-naïve endometrial cancer was 26% (73). For bevacizumab, the response rate was modest (13.5%) in patients who recurred after chemotherapy and were treated on GOG 229E, yet 40.4% demonstrated progression-free survival beyond six months (72). Trials using tyrosine kinase inhibitors against angiogenic growth factor pathways (VEGFR, PDGFR, FGFR) have yet to be reported; yet, it is promising that these trials have achieved the preliminary level of activity required to initiate the second stage of patient accrual in a two-stage phase II design. Thus, it is anticipated that additional drugs with activity will be reported in the coming months. Inhibitors of EGFR and HER-2 have not been impressive thus far as single agents; erlotinib treatment resulted in only one partial response out of 27 cases (75). Nevertheless, a number of these trials are still ongoing.

Agents on the horizon

A number of agents are in preclinical testing using models of endometrial cancer. Some have shown remarkable activity alone, while others have been combined to achieve true therapeutic synergy. As a biomarker, high expression of the molecular target itself may or may not predict for response. For example, Her-2 amplification in breast cancer predicts for response to trastuzumab therapy, but the level of EGFR expression may not predict response to gefitinib in lung cancer where response has been reported to segregate with EGFR mutations. Similarly, VEGFA levels were not predictive of response to bevacizumab in colorectal cancer (76), but did positively correlate with response to bevacizumab in endometrial cancer as reported from GOG 229E (72). Regardless of whether the molecular target itself is predictive, we hypothesize that other downstream markers will be useful, and the molecular fingerprint of a responsive versus a resistant tumor can be derived. Further

research is urgently needed to explore the relationship between marker expression and outcome, the role of surrogate markers and the best use of accessible tissue.

Clinical benefit may also be achieved using a combinatorial strategy in which one agent improves the efficacy of another. For example, in a recent preclinical study from our group, combination of the mTOR inhibitor temsirolimus with either a dual PI3K/mTOR inhibitor BEZ235 or a “pure” PI3K inhibitor ZSTK474 resulted in synergistic cell death of endometrial cancer cells (77). For the BEZ235 and temsirolimus combination in particular, the synergy resulted from blockage of one arm of mTOR signaling, ribosomal 6S kinase, with temsirolimus, whereas BEZ235 inhibited the compensatory Akt activation that occurs in response to temsirolimus as well as a second arm of mTOR signaling, 4E-BP1. This study also identified the molecular fingerprint of cells most likely to respond to temsirolimus treatment alone: loss of PTEN and high basal Akt phosphorylation. However, all cells, regardless of PTEN and Akt phosphorylation status, responded to the BEZ235 and temsirolimus combination treatment.

Another area in which a combination approach may be beneficial is to improve sensitivity to chemotherapy. The first effort by the GOG to combine a molecular inhibitor (either temsirolimus or bevacizumab) with chemotherapy is GOG study 086-P, and the results have not been released. Another more recent GOG trial is studying how sensitivity to chemotherapy (docataxel and gemcitabine plus G-CSF) can be restored or increased with a molecular inhibitor, bevacizumab (GOG250). This strategy is being explored in many other types of solid tumors, and future endometrial cancer trials that pair other molecular inhibitors with chemotherapy are anticipated. These combination strategies will likely be based on results from preclinical experiments analogous to the temsirolimus and BEZ235 work from our group.

Combination of a molecular inhibitor, temsirolimus, with progestin is under study in GOG 248, though the results are not yet available. Given that progestin therapy is so safe for patients as compared to chemotherapy, we also propose that strategies to restore PR expression will expand the utility of progestin therapy. One approach is through use of DNMT inhibitors to reverse PR promoter methylation and thereby restore functional PR expression. However, cells may have other mechanisms in place to suppress PR expression, such as histone deacetylation, which also serves as a cellular cue to prevent PR transcription. In other tumors, combination of histone deacetylase (HDAC) inhibitors with DNMT inhibitors has been shown to produce synergistic effects, though the mechanisms are still being teased out.

Other possible inhibitors, including those of heat shock proteins, the proteasome, and PARP, and controllers of the mitotic machinery, such as polo-like kinase 1, are on the horizon and may be useful in many tumor types, including those of the endometrium. Application of molecular inhibitors in the treatment of solid tumors is still in its infancy as compared to other treatment modalities, and certain obstacles must be overcome to fully realize their potential. First, a better understanding of the types of tumors that are more likely to respond to each inhibitor is necessary. For example, PARP inhibitors may be more effective in type II tumors based on activity in p53-deficient mouse models of breast cancer (78). Furthermore, studies will need to determine if targeted agents provide benefit in the neoadjuvant setting, such as use of epigenetic modulators to restore PR expression. Finally, with respect to combination strategies, a careful analysis of the timing and sequence of administration must be undertaken.

Summary

Despite the questions and barriers, the incorporation of molecular therapy into treatment regimens in endometrial cancer is an exciting area of investigation with the potential to improve outcomes. Outside of the development of a reliable screening test for endometrial cancer, converting the disease to a chronic state and improving progression-free survival is our best hope to reverse the concerning trend of decreasing 5 year survival for this disease.

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Figure 1.

Critical pathways in endometrial cancer. Diagrammed are the major pathways in endometrial cancer that have been targeted with molecular agents to date. Mutations in key proteins that lead to dysregulation of function are indicated with an asterisk. Activating mutations include those in the tyrosine kinase receptor FGFR2, K-ras, B-raf, PI3K, and β -catenin. Inactivating mutations/deletions have been identified in the tumor suppressors PTEN and p53. Mutations in mismatch repair genes lead to microsatellite instability (MI).