Management of Recurrent Endometrial Carcinoma

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Management of recurrent endometrial carcinoma has traditionally focused on providing targeted adjuvant therapy in select groups of patients based on their risk factors. Major progress has been made over the last two decades in identifying these clinical-pathological risk factors, which has led to the classification of patients into different risk groups. Patients with high-risk factors are generally treated with adjunctive radiation therapy immediately following surgery to minimize the incidence of recurrence. Those patients identified as low-risk generally receive no further treatment. Patients with intermediate-risk factors are individualized either to receive adjunctive therapy or not to receive further therapy based on institutional bias. Review of the literature suggests this traditional treatment strategy may reduce local recurrence, but fails to improve overall survival. Further studies to identify molecular based biomarkers may improve current classification of risk factors and the selection of patients for adjunctive therapy. Once the recurrence takes place, loco-regional disease can be treated with radiation therapy with reasonable success. Targeted radiotherapy and several cytotoxic chemotherapeutic agents are effective in the treatment of systemic recurrent disease. Hormonal therapy has also been demonstrated to be useful in selected group of patients for palliative purpose. The current areas of controversy and debate include the efficacy of adjunctive therapy, mode of therapy, timing of therapy, and issues related to surgical staging of patients as required by the current FIGO staging system. *(Chang Gung Med J 2004;27: 639-45)*

Key words: endometrial carcinoma, recurrence, adjunctive therapy, biomarkers, targeted treatment.

Endometrial cancer is the most common malignancy of the female genital tract. It was estimated that 39,300 new cases would be diagnosed and 6,600 patients would die from the disease in the United States in the year 2002.[1] The mortality rate from endometrial cancer has decreased progressively from the early 20th century and is currently less than half of what it was in 1940. The overall 5-year survival for all stages is 86%; patients with disease confined to the endometrium have 97% survival. The relatively high cure rate is largely due to their early presentation and effectiveness of primary surgery. Approximately 75% of patients with endometrial cancer are diagnosed with Stage 1 disease, and total hysterectomy with bilateral salpingo-oophorectomy has been shown to be an effective primary treatment in early stage disease.

Over the years, the strategy towards management of recurrent endometrial cancer has been directed at prevention of recurrence by identifying risk factors which predict the likelihood of recurrence. Based on these prognostic factors, patients are then classified as high-risk, intermediate-risk, or low-risk group after surgical staging. Patients with high-risk factors are generally treated with adjunctive radiation therapy immediately following surgery

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to minimize the risk of recurrence, whereas, those patients in low-risk group receive no further treatment. Patients with intermediate-risk factors are individualized either to receive adjunctive therapy or not to receive further therapy.

This approach of tailored adjunctive radiation therapy following initial surgical staging has been widely accepted as the standard of therapy without major controversy until recently. Over the last several years, however, some retrospective studies have questioned the necessity and effectiveness of this traditional therapeutic approach.[2-4]

Prevention of Recurrence

Identification of risk factors

The established clinical-pathological prognostic factors include age of patient, extent of clinical disease, histological grade of tumor, depth of myometrial invasion, lymphovascular space invasion, endocervical involvement, peritoneal cytology, adnexal metastasis, and lymph node status.[5] Non-endometrioid histologic subtypes, such as papillary serous and clear-cell histology, are also recognized as high risk factors due to their propensity in early extra-uterine spread.[6,7]

In 1975, the Gynecologic Oncology Group (GOG) sponsored a three-institution pilot study of surgical-pathological staging of early endometrial cancer. This landmark study documented that the risk of pelvic and para-aortic lymph node metastasis is closely associated with tumor grade, depth of myometrial invasion, and cervical extension.[8] The results of this study and subsequent confirmatory studies by other investigators led FIGO to change the staging system for endometrial cancer from universal clinical staging to a comprehensive surgical staging system in 1988.

Although the prognostic importance of lymph node metastasis is well established, the indication(s) for lymph node sampling and the extent of dissection remain controversial to this date. The issue of whether lymph node sampling is sufficient for staging purpose or if complete lymph node dissection is necessary is still a matter of debate.[9] Based on the anatomy of lymphatic drainage from the uterus, some investigators have advocated para-aortic lymph node dissection to be performed up to the level of renal vessels rather than to the level of inferior mesenteric vessels as is commonly practiced.[10] This lack of consensus regarding lymph node sampling and the fact that a significant number of patients with endometrial cancer is associated with massive obesity, making surgical approach difficult, it is estimated that less than 50% of cases with endometrial cancer world wide are surgically staged properly according to current FIGO criteria.

Limitations of current surgical staging system notwithstanding, the current standard of treatment of endometrial cancer utilizes these known clinical-pathological prognostic factors in determining the necessity of adjunctive therapy following hysterectomy with bilateral salpingo-oophorectomy and staging procedure. Unfortunately, it has also been shown in multiple studies that significant fractions of patients at both ends of the prognostic spectrum respond to treatment in an unpredictable manner. The range of predicted outcome for patients in the intermediate-risk group is even broader. It is, therefore, reasonable to assume this heterogeneity in clinical outcome reflects some differences in underlying biologic characteristics of the tumors, which are not being recognized by current clinical-pathological criteria for prognostic classification. With advances in molecular biotechnology and an increased understanding of the molecular genetic basis of cancer in general, many investigators have, over the last 10 to 15 years, studied endometrial cancer in attempts to correlate specific molecular genetic based biologic markers with prognosis of endometrial cancer.

Cytogenetic studies have described gross chromosomal alteration in endometrial cancers. Aneuploidy occurs in 20% of cases and is associated with advanced stage, high grade, non-endometrioid histology, and poor survival rate.[11] Loss of heterozygosity in chromosome 17p and 10q have been correlated with mutational inactivation of TP53 and PTEN.[12,13] Overexpression and/or mutation of TP53 are reported to be associated with poor prognosis.[11,14] Mutation analysis of PTEN in endometrial cancer indicated that this gene is somatically inactivated in 30% to 50% of tumors.[15] Although the K-ras gene is observed in 10% to 30% of endometrial cancer, attempts to correlate the K-ras mutation with clinical outcomes have produced conflicting data.[16] Overexpression of the HER-2/neu oncogene is documented in only 10% to 15% of endometrial cancers, and seems to be confined to a subset of high-grade

and/or advanced stage tumors.[17] Correlation of HER-2/neu with clinical outcomes of the patients has been less conclusive. At present, investigations using molecular and genetic approaches to classify endometrial cancer have been proven unsatisfactory. Molecular markers studied so far are often not reproducible, and the molecular alterations often do not represent independent prognostic variables after accounting for well-established clinical-pathological prognostic factors.[18]

Adjunctive therapy to prevent recurrence

Total hysterectomy with bilateral salpingo-oophrectomy has been the cornerstone of treatment of endometrial cancer for many decades. Over the last two decades, adjunctive therapy has evolved from preoperative radiation for all patients to postoperative radiation for selected patients based on their prognostic risk factors. The role of adjunctive hormonal or chemotherapy is not well established. A recent report of patients treated with adjunctive chemotherapy alone without radiation indicated a substantial risk of pelvic recurrences.[19] An earlier, multi-institutional, prospective, randomized study compared Depo-Provera versus placebo as adjuvant therapy over a 14-week period. The primary therapy included treatment with surgery alone or surgery plus radiation. The study showed no survival benefit from hormonal therapy in the adjuvant setting.[20]

Adjuvant radiation can be delivered by external beam radiation to the pelvis, by brachytherapy to the vaginal cuff, or a combination of both. Treatment can also be directed to an extended field that includes both the pelvis and para-aortic region when extra-pelvic lymph node spread is suspected or confirmed. Whole abdominal radiation has also been utilized in some cases. When the pelvis is treated with external beam, 45 to 50 Gy is given to the whole pelvic region including pelvic side walls and the upper vagina. When vaginal brachytherapy is used, doses of radiation depend on dose rate, treatment volume, and whether it is combined with external-beam irradiation. External-beam radiation can be associated with severe chronic sequelae, such as bowel obstruction, fistula formation, or proctitis in 5% to 15% of patients. Serious complications from vaginal brachytherapy alone are rare.

Typically, patients with intermediate and high risk prognostic factors are treated immediately after surgery in the United States, even though the necessity and beneficial effects are still being debated. There are three prospective randomized studies reported so far and all three trials have documented a decrease in pelvic recurrence with no significant improvement in overall survival. Aalders et al. demonstrated that pelvic recurrence decreased from 15% to 5% for patients with deep myometrial invasion, when immediate postoperative pelvic radiation was given.[21] Roberts et al., in a GOG phase III study, reported 19 recurrences out of 202 patients not receiving postoperative pelvic radiation (9.4%), and only 1 recurrence in 188 patients receiving pelvic radiation (0.5%).[22] Crentzburg et al. recently reported that 14% of patients had loco-regional recurrence with no postoperative adjuvant treatment, compared with only 4% recurrence in patients who received pelvic radiation.[23] Currently, GOG is conducting a phase III prospective randomized study with adjuvant postoperative irradiation with or without Cisplatin/Taxol chemotherapy to test whether the addition of chemotherapy to radiation improves the relapse-free survival for patients with endometrial cancer (GOG 194).

With the adoption of extensive surgical staging, including controversial lymphadenectomy in recent years, some retrospective studies of patients with stage I disease with poor prognostic factors have shown excellent outcomes even without postoperative adjunctive pelvic radiation[2,4] or after treatment with vaginal brachytherapy alone.[24-27] Additional prospective randomized studies will be needed to determine which patients can be adequately treated with vaginal brachytherapy alone, and under what circumstances external-beam pelvic radiation is beneficial.

Patients found to have extra-uterine extension at the time of surgery can be treated with adjuvant extended-field radiation or whole abdominal radiation. Outcomes from such adjuvant treatment vary among published retrospective studies, likely due to the wide variability in patient populations studied. Axelrod et al. studied 77 patients with stage III/IV disease treated with whole abdominal radiation (GOG 94) and demonstrated a 5-year recurrence-free survival rate of 36%.[28] In a subsequent GOG study (GOG 122), the initial data comparing whole abdominal radiation versus chemotherapy alone appears to show better outcomes with chemotherapy than with

whole abdominal radiation. The final analysis of recurrence-free survival, however, is still underway.

Treatment of Recurrent Disease

Pattern of recurrence

Following total hysterectomy with bilateral salpingo-oophorectomy, surgical staging including lymph node sampling, and selective adjunctive radiotherapy, 15% to 20% of patients will eventually develop recurrent disease.[5,29] The vast majority of recurrences become clinically apparent within 3 years of primary therapy. The pattern of failure is strongly influenced by the use of postoperative adjunctive radiotherapy. In patients treated with primary surgery alone, isolated vaginal recurrence was most common,[30] whereas postoperative pelvic irradiation increased distant relapse.[21] Initial review of 304 clinical stage I patients treated with a combination of surgery and irradiation revealed a significant increase in the incidence of distant failure in patients with higher histologic grade of the tumor.[31] Subsequent update of 858 patients from the same institution with extensive multivariate analysis showed older age (>60), high histologic grade, positive peritoneal cytology, and extra-uterine disease were statistically associated with decreased distant control.[32] It is also interesting to note that in a retrospective review of 394 patients with FIGO stages I-III endometrial cancer, who were staged surgically prior to irradiation, those patients who failed locally had nearly a fourfold risk of failing distantly compared to those who remained locally controlled. Moreover, the earlier a local failure developed, the more likely it was to be associated with distant metastasis.[29]

The role of radiotherapy

Patients with recurrent endometrial cancer following hysterectomy can be successfully treated with aggressive radiotherapy consisting of external -beam radiation, vaginal brachytherapy, or a combination of both. Five year local control rate of 54%, disease specific survival of 51%, and overall survival of 44% has been reported in a group of patients with locoregional recurrence.[33] Patients who achieved control of vaginal recurrence had a 5-year disease specific survival of 74%, whereas those patients who did not have local control had only 23% survival. Age of patient, extension into the submucosal tissue the vagina, size of recurrence, time interval from hysterectomy, initial grade of tumor, location of recurrence, and radiation technique utilized, all had an impact on treatment outcome.

Retrospective anecdotal clinical observations have indicated that targeted radiotherapy with external-beam radiation and/or interstitial implant are effective in achieving tumor control for recurrent disease outside of the pelvis. Perhaps due to a wide variety of recurrence patterns, location of recurrence, size and number of recurrence, no meaningful survival data is available in the literature.

The role of chemotherapy

A wide variety of chemotherapeutic agents have been studied in endometrial cancer over the years. Several agents, including Doxorubicin, Cisplatin, Paclitaxel, and Liposomal doxorubicin, have been shown to be active as single agents in phase II studies of endometrial cancer. To assess the effect of combination chemotherapy, GOG conducted a phase III randomized study of single agent Doxorubicin versus a combination of Doxorubicin plus Cisplatin in patients with primary Stage III, IV, and recurrent endometrial cancer (GOG 107). The study demonstrated advantages of the combination therapy over single agent with regard to response and, to a lessor extent, progression-free survival.[34] Subsequently, the group also demonstrated that there was no significant difference in response rate or survival between the two arms of a study looking at Doxorubicin plus Cisplatin versus Doxorubicin plus 24-hour Paclitaxel.[35]

In another GOG study, the three drug combination of Doxorubicin, Cisplatin, and Paclitaxel was found to produce an improvement in progression-free survival and a slight improvement in overall survival for patients with recurrent or metastatic endometrial cancer, compared with the two drug combination of Doxorubicin and Cisplatin.[36]

The role of hormonal therapy

Metastatic endometrial cancer can be effectively treated with progestational agents. Objective response to hydroxyprogesterone caproate was reported to be as high as 30% in early studies,[37,38] but later studies have reported substantially lower objective response rate of 10% to 15%.[39,40] Response rates

correlated statistically with histologic grade of tumor. Response rates ranged from 40% with grade 1 disease and 0% with Broder's grade 4 lesions.[40] The presence of progesterone receptors, which is closely correlated with histologic grade of the tumor, is also shown to have a strong statistical correlation with response rate.[41] Other factors, such as tumor volume and disease-free interval, have been shown to influence response rate, as well. In general, hormonal therapy of recurrent endometrial cancer is considered to be palliative in nature and the mean duration of response is about 10 to 12 months. After this time, the tumors tend to become resistant to continued progestational therapy. In this regard, a phase II GOG study demonstrated that sequential Megestrol Acetate and Tamoxifen Citrate are active in patients with recurrent and/or advanced endometrial cancer, and may offer a prolonged complete response interval (GOG 153).[42] This finding is consistent with laboratory studies indicating Tamoxifen exposure may up-regulate progesterone receptors in tumor cell culture.

Multimodality treatment of recurrent endometrial cancer

In an attempt to take advantage of beneficial effects from different treatment modalities and to improve survival, GOG is currently conducting a prospective randomized phase III study to compare treatment outcomes in patients with advanced endometrial cancer. Patients are treated with tumor-volume-directed irradiation followed by Cisplatin and Doxorubicin, or a three drug regimen consisting of Cisplatin, Doxorubicin and Paclitaxel chemotherapy (GOG 184). In another study, a crossover trial of chemotherapy versus hormonal therapy is underway to determine if combination Doxorubicin, Cisplatin and Paclitaxel chemotherapy improves progression-free survival and response, when compared to hormonal therapy alone (GOG 189).

Conclusion

In conclusion, significant progress has been made over the last two decades in our understanding of prognostic factors in endometrial cancer. However, the question of whether the selection of adjuvant therapy based on the universal adoption of surgical staging and subsequent risk stratification will translate into improved survival of patients or not remains to be answered. Three prospective randomized studies so far in patients with intermediate and/or high risk groups receiving immediate postoperative adjunctive radiation therapy have all demonstrated decreases in the incidence of local recurrence without impacting the overall survival of patients. In the absence of strong evidence-based proof that this traditional approach is beneficial to patients, the necessity of adjunctive radiation therapy will continue to be debated. If isolated vaginal or pelvic recurrence can be salvaged in a high percentage of patients and patients with distant metastasis or extrapelvic disease are likely to fail adjunctive therapy, it would be reasonable to withhold radiotherapy until recurrent disease become apparent clinically. On the other hand, if local recurrence increases the likelihood of distant dissemination, prevention of local recurrence by adjunctive therapy is clearly beneficial. Additional prospective randomized studies to explore these issues are needed urgently to resolve current controversies.

It is also evident that our current classification of prognostic risk factor is far from perfect. The state of knowledge indicates endometrial cancer associated with endometrioid histology, estrogen background, associated hyperplasia, low histologic grade, or young age, are associated with good prognosis. Molecular genetic studies of these tumors have shown that these tumors tend to be diploid, with low allelic imbalance, and are often associated with mutations of the PTEN and K-ras genes. Cancers with non-endometrioid histology, no estrogen related factors, no association with hyperplasia, of high histologic grade, or in patients of older age, are usually associated with poor prognosis. Tumors with poor prognosis are often found to be aneuploid, with high allelic imbalance and with alterations in TP53, Erb-2, and K-ras. It is hoped that further molecular genetic research of endometrial cancer will provide us with new insights into the fundamental biology of these tumors and lead us to new and better-defined prognostic tumor classification systems. Only then will we be able to apply this knowledge clinically to render more effective therapy and make improvements in the management of recurrent endometrial cancer.

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