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Improving survival after endometrial cancer: the big picture

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To improve survival in women with endometrial cancer, we need to look at the "big picture" beyond initial treatment. Although the majority of women will be diagnosed with early stage disease and are cured with surgery alone, there is a subgroup of women with advanced and high-risk early stage disease whose life expectancy may be prolonged with the addition of chemotherapy. Immunohistochemistry will help to identify those women with Lynch syndrome who will benefit from more frequent colorectal cancer surveillance and genetic counseling. If they happen to be diagnosed with colorectal cancer, this information has an important therapeutic implication. And finally, because the majority of women will survive their diagnosis of endometrial cancer, they remain at risk for breast and colorectal cancer, so these women should be counselled about screening for these cancers. These three interventions will contribute to improving the overall survival of women with endometrial cancer.

Keywords: Endometrial Neoplasms; Colorectal Neoplasms, Hereditary Nonpolyposis

INTRODUCTION

The majority of women with endometrial cancer are expected to survive their diagnosis with surgery alone. However, there are important considerations for maximizing survival in these women with endometrial cancer. Approximately 80% of them present with type 1 endometrial cancer, mediated by estrogen [1]. Many of these women have other co-morbidities including diabetes and obesity [2-9], which increase their risk of other health conditions, including other cancers [10]. Women with advanced stage disease have a survival benefit from chemotherapy [11], but women with high-risk early stage disease may also benefit from this treatment. Finally, a small proportion of women with endometrial cancer have Lynch syndrome. Improving the detection rate of Lynch syndrome among these women increases the probability of reducing their subsequent colorectal cancer risk and prolonging their life expectancy.

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CHEMOTHERAPY FOR ENDOMETRIAL CANCER

There has long been controversy about the role of systematic lymphadenectomy in early apparent endometrial cancer. Nearly 30 years ago, the Gynecologic Oncology Group (GOG) published a surgical-pathologic staging study demonstrating the association between tumour grade, depth of myometrial invasion, and pelvic lymphadenopathy [12]. As a result, lymphadenectomy became widely adopted into clinical practice before its effectiveness was proven in prospective trials. Although there are now two prospective randomized trials that have not been able to demonstrate a survival benefit from lymphadenectomy [13,14], there are still many strong advocates for routine lymphadenectomy during surgery for endometrial cancer to: (1) remove occult metastatic disease that would be missed with hysterectomy alone, and (2) identify patients with metastatic disease who would benefit from adjuvant chemotherapy. However, the vast majority of women with

endometrial cancer do not have metastatic nodal disease [15], and chemotherapy may benefit some of these women without nodal disease as well. In fact, of the four major treatment modalities in addition to hysterectomy for endometrial cancer (lymphadenectomy, radiotherapy, chemotherapy, and hormonal therapy), only chemotherapy has been shown to improve survival in the context of a prospective randomized trial, in both advanced and high-risk early stage disease [11,16,17]. Therefore to improve outcomes in endometrial cancer, we should focus on risk factors that have the highest association with recurrence and mortality, and treatment that will mitigate these adverse outcomes for women with these risk factors.

It may be intuitive that pelvic nodal status is strongly associated with recurrence and mortality, but this is not necessarily true. Gynecologic Oncology Group (GOG)-99 was the first trial to demonstrate that negative nodes in fully-staged endometrial cancer patients were not always associated with a good prognosis [18]. Those with high-intermediate risk (HIR) disease (combination of risk factors including grade 2 or 3 tumor, deep myometrial invasion, lymphovascular space invasion+, age greater than 70) who did not receive adjuvant radiotherapy, had recurrence and mortality rates of 27% and 26%, respectively. Even among those with HIR disease who received adjuvant pelvic radiotherapy, recurrence and mortality rates were still high at 13% and 12%, respectively. A large Canadian population-based study by Kwon et al. [19] demonstrated that the only risk factors significantly associated with mortality were age, grade, depth of myometrial invasion, and cervical stromal involvement, while nodal status was not independently associated (hazard ratio [HR], 1.39; 95% confidence interval [CI], 0.89 to 2.18). Similarly, Nugent et al. [20] also demonstrated that the only risk factors significantly associated with survival were age and depth of myometrial invasion, while nodal status was not significant. In the Canadian study, women who were node-negative and two or three high-risk factors (therefore truly stage I or II) had a worse 5-year survival (55%) than those who were node-positive and had only one high-risk factor (therefore truly stage IIIC, with a grade 3 tumour or deep myometrial invasion, but not both risk factors), with a 5-year survival of 75% [19]. These studies indicate that even if patients are fully staged and proven to be node-negative, they do not necessarily have a good outcome, particularly if they have high-risk factors such as older age, grade 3 tumor, and deep myometrial invasion. This underscores the need for additional treatment (beyond lymphadenectomy) to improve their outcomes.

GOG122 was the first randomized clinical trial to demonstrate a survival benefit from adjuvant chemotherapy in advanced stage endometrial cancer [11]. Since then, other studies have demonstrated a survival benefit from chemotherapy in early stage high-risk disease [16,17]. The combined results of the NSGO (Nordic Society Gynecological Oncology)/EORTC (European Organisation for Research and Treatment of Cancer) and MaNGO (Mario Negri Gynecologic Oncology group) trials revealed a decrease in cancer-specific survival (HR, 0.55; 95% CI, 0.35 to 0.88) associated with adjuvant chemotherapy and radiation, compared to radiation alone, and a decrease in risk of relapse or death (HR, 0.63; 95% CI, 0.44 to 0.89) [16]. In the Japanese Gynecologic Oncology Group 2033 study, patients with HIR early stage disease who received chemotherapy had a significantly higher progression-free survival (PFS, 83.8% vs. 66.2%) and overall survival (OS, 89.7% vs. 73.7%) compared to those who received pelvic radiotherapy [17]. However, according to preliminary results from GOG-249, there was no difference in DFS or OS between pelvic radiotherapy and vaginal cuff brachytherapy followed by three cycles of chemotherapy [21]. This observation could be related to the heterogeneity of the patient population, as the trial included patients with stage I and II, endometrioid (71%), serous and clear cell histologic types. A population-based study from British Columbia demonstrated that three cycles of chemotherapy combined with radiotherapy was effective in reducing recurrence risk specifically among those with high-risk stage I or II endometrioid carcinoma (excluding serous and clear cell types) [22]. The 5-year PFS was 88.6% for these patients (compared to 61.3% for the historical comparison group, prior to using chemotherapy). However, with the same protocol, there was a 30% recurrence rate among those with stage IB serous carcinoma in this population, with the majority of these recurrences being distant [23], thereby raising the concern that three cycles of chemotherapy is insufficient for treatment of early stage serous carcinoma.

If women with two or more uterine risk factors are at risk of death regardless of nodal status, and chemotherapy improves survival, then by process of logic, it follows that chemotherapy should be offered to women with two or more risk factors, regardless of nodal status. However, it is well recognized that a small proportion of those with only one (or none) of the risk factors will have positive nodes. In the absence of lymphadenectomy, they would not be identified as such, and therefore would not have the benefit of receiving adjuvant chemotherapy. According to our population-based study in British Columbia, 9% of patients with intermediate risk disease (defined as having deep myometrial invasion, with a grade 1 or 2 tumour), and 2% of those with low-risk disease (less than 50% myometrial invasion, grade 1 or 2 tumour) will have positive nodes [24]. Assuming a 9% node-positivity rate

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among intermediate risk patients, the survival benefit from a combination of systematic lymphadenectomy and subsequent adjuvant chemotherapy is estimated to be only 1% [24], as these patients still appear to do reasonably well even without initial chemotherapy [19]. This raises questions about the utility of routine lymphadenectomy in endometrial cancer, particularly as the majority of women have low-intermediate risk disease.

ENDOMETRIAL CANCER AND LYNCH SYNDROME

It is now well recognized that Lynch syndrome is characterized by a very high lifetime risk of endometrial cancer [25]. This cancer may be the sentinel cancer, which means that women are more likely to be diagnosed with endometrial cancer before colorectal cancer [26]. There are features of endometrial cancers that suggest Lynch syndrome, such as a lower age at diagnosis (majority under age 50), presence of tumor-infiltrating lymphocytes, dedifferentiation, and lower uterine segment origin [26-29]. However, these features are not specific for Lynch syndrome, and some tumors will exhibit none of these features. Relying on family history is also insufficient for identifying Lynch syndrome, as the sensitivity and specificity of Amsterdam II criteria are estimated around 50% [30,31]. A feasible, effective, and cost-effective approach to identify Lynch syndrome among these women is using immunohistochemistry (IHC) for the four most common mismatch repair proteins in their endometrial tumors [31,32]. In a cost-effectiveness analysis, Kwon et al. [33] demonstrated that universal IHC will identify more patients with Lynch syndrome, and therefore the average life expectancy among women with endometrial cancer who have their tumors screened by IHC will exceed that of women screened by Amsterdam II criteria. If a woman is proven to have Lynch syndrome, her risk of death can be reduced by more frequent colorectal cancer screening [34], but if she is diagnosed with this cancer, her risk of death can also be reduced by tailoring her treatment. There is a poorer response to 5-fluorouracil-based chemotherapy among individuals with Lynch syndrome [35,36], and therefore an alternative regimen would be chosen. Universal IHC screening has been implemented in the Vancouver Coastal Health authority region, as well as other jurisdictions around the world. Buchanan et al. [32] reported that among all endometrial tumors screened, 24% had abnormal IHC, of which 25% had abnormal MSH2/MSH6, while the remaining had abnormal MLH1/PMS2. Of those with abnormal MSH2/MSH6, the probability of a germline mutation is 43%, however among those with abnormal MLH1, the vast majority (over 90%) can be attributed to hypermethylation of the *MLH1* promoter, not a germline mutation [32]. The high positive predictive value of abnormal MSH2/MSH6 on IHC suggests that these patients should be offered genetic testing, regardless of family history. The low predictive value of abnormal MLH1 suggests that these tumors should be analysed further for hypermethylation, to identify those who are unlikely to have a mutation and do not need genetic testing.

In summary, it is important to identify Lynch syndrome among women with endometrial cancer for three reasons: (1) this will justify more frequent colorectal cancer surveillance, to avoid this cancer; (2) if diagnosed with colorectal cancer, there is an important therapeutic implication; and (3) their unaffected family members then have the opportunity to undergo genetic counseling and testing, and reduce their risks of colorectal and/or endometrial cancer(s). Ideally, identifying Lynch syndrome should occur before a woman is diagnosed with endometrial cancer. However, her endometrial cancer prognosis does not appear to be compromised as a result of the mutation [27], and subsequent colorectal cancer screening can contribute to prolonging her survival.

SCREENING FOR CANCERS AFTER ENDOMETRIAL CANCER

There are common risk factors for endometrial, breast, and colorectal cancer, including obesity and diabetes [2,37,38]. It is therefore no surprise that risks of breast and colorectal cancer are elevated among those already diagnosed with endometrial cancer [39,40]. A Canadian population-based study demonstrated 2- and 7-fold increased risks in breast and colorectal cancer, respectively, among those with endometrial cancer compared to those without this cancer [41]. In the same study, breast cancer screening rates were found to be reasonable among women diagnosed with endometrial cancer; however, colorectal cancer screening rates were low and comparable to those in the general population. Most women with endometrial cancer are seen in follow-up at least once after their diagnosis, and usually on a regular basis for up to 5 years. This follow-up visit represents an important opportunity for health care providers to discuss the risks of subsequent breast and colorectal cancer, and advise screening for these cancers.

To improve survival in women with endometrial cancer, we need to look at the "big picture" and think beyond treatment. Although the majority of women will be diagnosed with early stage disease and are cured with surgery alone, there is a subgroup of women with advanced and high-risk early stage disease whose life expectancy may be prolonged with

the addition of chemotherapy. IHC will help to identify those women with Lynch syndrome who will benefit by being able to undergo more frequent colorectal cancer surveillance, so that they don't die of advanced colorectal cancer. If they are diagnosed with colorectal cancer, this information has an important therapeutic implication. And finally, because the majority of women with endometrial cancer will survive this diagnosis, they remain at risk for breast and colorectal cancer, so these women should be counselled about screening for these cancers. These three interventions will contribute to improving the overall survival of women with endometrial cancer.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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