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Why mismatch repair testing in endometrial carcinoma is needed in Canada
A GOC Position Statement

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Preamble

1. To perform immunohistochemistry (IHC) for mismatch repair (MMR) proteins in all endometrial carcinoma as a screening tool for Lynch Syndrome
2. To support access to immunotherapy treatment for patients with MMR deficient, metastatic/ recurrent endometrial carcinoma

GOC's Position

It is GOC's position that routine IHC for MMR status in endometrial carcinomas is recommended, both as a screening tool for Lynch Syndrome and to identify women who may benefit from immune checkpoint inhibitor (ICI) therapy. IHC for MMR status has proven to be a cost-effective strategy, and identifies many more individuals with Lynch Syndrome compared to traditional family history-based criteria. As a result, many more individuals will have the opportunity to undergo cancer-preventing interventions, which will reduce the burden of cancer and associated treatment costs incurred in our population. IHC for MMR status also serves as a diagnostic companion to identify women eligible for immune checkpoint inhibitor (ICI) therapy. ICIs are effective for the management of metastatic/recurrent endometrial carcinoma harboring MMR deficiency and should be made available to patients either as standard of care or through clinical trials.

Background

This year in Canada, approximately 7500 women will be diagnosed with endometrial cancer. This is the most common gynecologic cancer, and the 4th most common cancer diagnosed in Canadian women[1].

It is estimated that up to 5% of unselected women with endometrial carcinoma have a hereditary predisposition, known as Lynch Syndrome (previously Hereditary Non-polyposis Colorectal Cancer)[2,3], which is characterized by an inherited mutation in one of the DNA mismatch repair (MMR) genes. Identification of these women with Lynch Syndrome is critical because: (1) they may still be at high risk of developing colorectal cancer[4]; and (2) their family members (children, siblings) have a 50% chance of carrying the same mutation, and they may benefit from risk-reducing interventions such as colorectal cancer screening, and hysterectomy with bilateral salpingo-oophorectomy[5].

Problem

Historically, individuals with possible Lynch Syndrome were identified on the basis of a personal and/or family history of cancer, such as Amsterdam II or Bethesda criteria[6], which would determine eligibility for genetic testing for a germline mutation in one of the MMR genes. Applying these criteria to women with endometrial carcinoma has been proven to be neither sensitive nor specific in identifying individuals with Lynch Syndrome. It is estimated that at least 50% of women with endometrial carcinoma who have Lynch Syndrome do not fulfill genetic testing criteria based on Amsterdam II criteria[2]. In the absence of any other testing or screening strategy, these women would have unrecognized genetic mutations that could be shared or passed onto subsequent generations, leaving many male and female relatives unknowingly vulnerable to developing colorectal and/or endometrial carcinoma.

It is now recognized that MMR genes produce corresponding MMR proteins that can be detected in endometrial carcinoma tissue using immunohistochemistry (IHC). The absence of MMR protein staining (MMR deficiency) indicates that there may be a corresponding MMR gene mutation, but this must be confirmed with genetic testing. IHC for MMR deficiency as a triage for confirmatory genetic testing has been shown to be the most sensitive strategy and cost-effective for identifying individuals with Lynch Syndrome [3,7]. It can efficiently select those who are most likely to carry a mutation in one of the MMR genes, while ruling out those who almost certainly do not have a mutation (if MMR proteins are present in the tumour tissue, there is no mutation in any of the MMR genes)[8]. As a result, many jurisdictions in North America have adopted systematic IHC testing for MMR in endometrial carcinoma.

Evolution of MMR testing in endometrial carcinoma

There are 4 genes that account for the majority of Lynch Syndrome (MLH1, PMS2, MSH2, MSH6). Up to 3% of Lynch Syndrome is attributed to mutations in the EPCAM gene[9]. The most common MMR protein deficiency is associated with MLH1, but in 90% of cases this deficiency can be attributed to a somatic or epigenetic event (hypermethylation of the MLH1 promoter), not an inherited germline mutation[8]. A secondary triage can be done at this point to determine the presence or absence of hypermethylation. If hypermethylation is confirmed, genetic testing is not required, because this result is due to an epigenetic event that is not inherited. However, if MLH1 is unmethylated, the patient should be referred for confirmatory genetic testing because she has a 36-46% chance of carrying a germline mutation in MLH1[8].

In rare cases, there may be a high clinical suspicion for Lynch syndrome, based upon personal and family history, but MMR proteins are intact. Additional testing for microsatellite instability (MSI) should be performed, and the patient referred to a Hereditary Cancer Program. MSI-high status will identify a tumor as arising from MMR deficiency when the IHC studies are negative due a protein that is present, but non-functional.[10]

Of note, MMR IHC is a critical component of molecular classification of endometrial carcinomas and recommended to be integrated into standard pathologic practice in the recently released 5th Edition of the WHO classification of tumours of female reproductive organs.

Consequences of MMR testing in endometrial carcinoma

The most important reason for MMR testing in endometrial carcinoma is to cast a broad net in identifying those who are most likely to carry a germline mutation in one of the MMR genes, for future cancer prevention in these patients and their family members. There is uncertainty about the prognostic and predictive value of MMR status in endometrial carcinoma. MMR deficiency appears to be associated with higher response rates to adjuvant therapy (chemotherapy and/or radiotherapy) in non-endometrioid endometrial carcinoma[11], and adjuvant radiotherapy in Stage IB/II Grade 3 endometrioid endometrial carcinomas[12]. In contrast, higher recurrence rates have been observed in MMR deficient high-intermediate risk endometrioid endometrial carcinoma, compared to MMR proficient cases, despite similar adjuvant treatment[13]. As more centres acquire experience with MMR testing in endometrial carcinoma, the prognostic and predictive value with respect to conventional adjuvant therapy will likely become apparent. Finally, MMR testing may have an important role in determining eligibility for immune therapy, in particular with ICIs[14]. Over 50% of endometrial carcinoma with MMR deficiency have PD-L1 (programmed cell death ligand-1) expression.[15] Phase II studies have demonstrated encouraging response rates in advanced endometrial carcinoma to ICIs such as pembrolizumab[17], Lenvatinib plus pembrolizumab[16], dostarlimab[18] and Avelumab[20]. Across studies, approximately 50% of patients responded to ICIs, the median duration of response exceeds 12 months and complete responses are reported in up to 15% of cases, despite all patients having previously progressed on standard chemotherapy. Health Canada has approved pembrolizumab for women with metastatic/recurrent MMR deficient endometrial carcinoma who have no other available treatment options[19]. Further evaluation of PD-L1 inhibitors is ongoing or planned in early and advanced stage disease.

GOC Position and Conclusion

In summary, tumor testing immunohistochemistry (IHC) for MMR status in endometrial carcinoma is recommended as a screening tool for Lynch Syndrome. This has proven to be an effective and cost-effective testing strategy, and identifies many more individuals with Lynch Syndrome compared to traditional family history-based criteria. As a result, many more individuals will have the opportunity to undergo cancer-preventing interventions, which will reduce the burden of cancer and associated treatment costs incurred in our population. IHC for MMR also serves as a diagnostic companion for immune therapy with ICIs, which should be accessible to women with metastatic/recurrent, MMR deficient endometrial carcinoma.

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ABOUT GOC

The Society of Gynecologic Oncology of Canada is a non-profit organization consisting of physicians, nurses, scientists and other health care professionals specializing in gynecologic oncology. Its purpose is to improve the care of women with or at risk of gynecologic cancer by raising standards of practice, encouraging ongoing research, promoting innovation in prevention, care and discovery, and advancing awareness. GOC also seeks to disseminate knowledge to practitioners, patients and the general public on gynecologic cancer as well as cooperate with other organizations committed to women's health care, oncology, and related fields.