Lynch Syndrome Associated Endometrial Carcinomas in Western Australia: Analysis of Four Years of Universal Screening by Mismatch Repair Protein Immunohistochemistry

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Introduction

Approximately 2% - 5% of endometrial carcinomas are associated with Lynch syndrome caused by germline variants in DNA mismatch repair (MMR) protein genes (MLH1, MSH2, MSH6 & PMS2) and germline deletions in the EPCAM gene that lead to epigenetic silencing of MSH2.[1]

Screening for Lynch syndrome in patients with endometrial carcinoma is essential because a Lynch syndrome diagnosis has implications for treatment, surveillance for other primary cancers, and reduction of cancer risk in affected family members.

Universal screening of endometrial tumours for Lynch syndrome using MMR protein immunohistochemistry has been shown to be cost effective in patients younger than 65 - 70 years and some guidelines recommend universal immunohistochemistry testing of tumours in all endometrial carcinoma patients regardless of age.

In January 2016, following publication of a report by Mills et al[2] that suggested a number of Lynch syndrome associated endometrial carcinomas may be missed using conventional clinical and histopathological screening parameters. Universal screening with MMR protein immunohistochemistry in tumours of all newly diagnosed endometrial carcinoma patients was introduced in Western Australia.

Universal testing of newly diagnosed endometrial carcinoma patients was facilitated by the centralisation of gynaecologic oncology, histopathology and genetic services.

Objectives

Our objective was to compare the proportion of Lynch syndrome associated endometrial carcinomas between 2016 – 2019 to a historical control (2015).

Secondary aims were to compare the number of cases appropriately referred for genetic assessment and to assess costs of universal testing by age group.

Methods

This was a retrospective cohort study performed at King Edward Memorial Hospital and St John of God Subiaco Hospital, Perth, Western Australia.

All newly diagnosed endometrial carcinomas from January 1st, 2015, to December 31st, 2019 were ascertained from the weekly outcome reports of the Western Australian gynaecologic oncology tumour board.

The following variables were extracted and entered into a de-identified Microsoft Excel spreadsheet: patient date of birth; age at endometrial carcinoma diagnosis; vital status; tumour MMR protein expression status (retained or lost) and if lost, the specific MMR protein deficiency; patients who were referred to a genetic clinic; and family history if recorded.

Tumours with combined loss of MLH1/PMS2 protein expression are routinely subject to methylation testing and the methylation status of these cases was also recorded; tumours with MLH1 methylation are very likely to be sporadic rather than related to Lynch syndrome. Patients with tumours showing isolated loss of PMS2 or MSH6, combined MSH2/6 loss, or loss of MLH1/PMS2 in the absence of MLH1 methylation should have been referred for genetic assessment. (Figure 1)

Results

Between 2016 and 2019, there were 1040 new endometrial carcinomas. Tumours of 883 (85%) patients underwent MMR protein immunohistochemistry compared to 117 of 199 patients (59%) in 2015 (Chi-square 73.14, p = 0.00). Of 883 tumours tested, 242 (27%) showed loss of MMR protein expression. In 2015, 30 (26%) tumours of 117 tested showed loss of MMR protein expression. During the four years of universal screening 13 of 883 patients screened (1.5%) were diagnosed with Lynch syndrome compared to 2 of 117 (1.7%) in 2015 (Fishers Exact 0.04, p = .69).

In 2015, 11 (37%) of 30 patients with loss of MMR protein expression, were not referred for genetic assessment compared to 36 (17%) of 209 patients in the universal screening group (Chi-square 6.28, p = 0.02).

No cases of Lynch syndrome were diagnosed in patients aged over 70 years. The annual incidence of endometrial carcinoma in Western Australia is approximately 268 cases[3] and the estimated laboratory cost of universal testing in the over 70 years age group in Western Australia is AU$15,034 (US$10,930).

Table 1: Age distribution of mismatch repair (MMR) protein immunohistochemistry by group

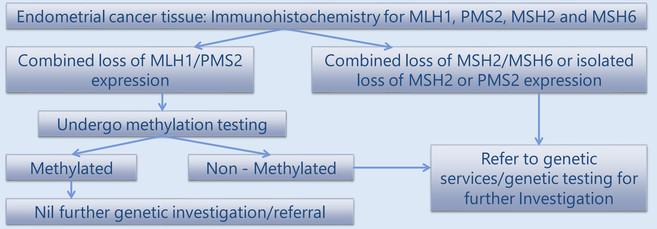
Group	Age Group (years)				
Universal screening 2016 – 2019	<60	60 - 64	65 – 69	70+	Total
Loss of MMR protein expression	98	20	48	76	242
Combined loss of MLH1/PMS2 methylation positive	42	18	43	63	166
Combined loss of MLH1/PMS2 methylation negative	8	1	2	5	16
Isolated loss of PMS2/MSH6/combined MSH2/MSH6	48	1	3	8	60
Normal MMR protein expression	214	129	100	198	641
Total	**312**	**149**	**148**	**274**	**883**
% of total with combined loss of MLH1/PMS2 expression	16%	12.7%	30.4%	24.8%	20.6%
Pre-universal screening 2015					
Loss of MMR protein expression	7	6	6	11	30
Combined loss of MLH1/PMS2 methylation positive	2	5	3	11	21
Combined loss of MLH1/PMS2 methylation negative	2	0	0	0	2
Isolated loss of PMS2/MSH6/combined MSH2/MSH6	3	1	3	0	7
Normal MMR protein expression	37	16	12	22	87
Total	**44**	**22**	**18**	**33**	**117**
% of total with combined loss of MLH1/PMS2 expression	9.0%	22.7%	16.7%	33.3%	19.7%

Table 2: Estimated laboratory costs of universal screening by age group based on an annual endometrial cancer incidence in Western Australia of 268 cases*

Estimate	Age Group (years)			
	<60	60-64	65-69	≥ 70
Percentage incidence in each age category in 2016 - 2019	35.6%	16.7%	16.7%	31.0%
Number of patients by age group (calculated by % above x total annual incidence of 268 cases)	95	45	45	83
% in age group with combined loss of MLH1/PMS2 2016 – 2019	16%	12.7%	30.4%	24.8%
Annual estimate of number of patients with combined loss of MLH1/PMS2 (calculated by estimated number of patients in age group x % with combined loss of MLH1/PMS2 loss 2016 - 2019)	15	6	14	21
Annual cost of IHC stains (all patients)	$8493	$4023	$4023	$7420
Annual cost of methylation testing	$5439	$2176	$5076	$7614
Total estimated laboratory costs by age group	$13932	$6467	$9730	$15034

* Estimates based on costs of $89.40 per case for immunohistochemistry and $362.59 for methylation testing. Excludes costs of pathologists, laboratory scientists, specimen transport, genetic counseling and germline testing. Department of Health. (2020). *Cancer incidence, mortality and survival in Western Australia, 2017*. Information and Performance Governance Directorate. Department of Health, Perth. Statistical Series Number 112

Figure 1: Universal screening of newly diagnosed endometrial cancers in Western Australia



Discussion

We did not observe an increase in the proportion of Lynch syndrome diagnoses in patients with endometrial carcinoma during the first four years of universal screening in Western Australia compared to the 12 months prior to its implementation. However, a post hoc power calculation showed that our study only had 4.4% power to detect a significant between-group difference, so it is possible that a type II error may have occurred (failing to detect a difference when one is present).

Although 'universal' screening should include all newly diagnosed endometrial carcinomas it was notable that 15% of tumours did not undergo MMR protein immunohistochemistry testing. Failure to screen cases was not associated with the year of endometrial carcinoma diagnosis as the proportion of untested tumours remained relatively constant throughout the period of the study (data not shown).

No patient older than 70 years was diagnosed with Lynch syndrome which is consistent with the findings of the Australasian Endometrial Cancer Study (ANECS) that showed a combination of MMR protein immunohistochemistry plus MLH1 methylation testing in women younger than 60 years of age at diagnosis provides the highest positive predictive value for the identification of Lynch syndrome variant carriers.[4]

Our findings suggest that universal screening in patients over age 70 could be omitted at a substantial cost saving. MMR protein immunohistochemistry is however advised in patients with a personal and/or family history suggestive of Lynch syndrome, or with advanced, metastatic or recurrent endometrial carcinoma as loss of MMR protein expression is associated with response to anti-PD-1 antibody immunotherapeutics.[5]

References

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