Identifying the proportion of high-risk endometrial cancers in NHS Grampian that would most benefit from somatic POLE (exonuclease domain of DNA polymerase-epsilon) mutation testing

Objectives

Molecular characteristics can be used for prognostic stratification of endometrial carcinomas. A histological high-risk subgroup may be considered for systemic adjuvant therapy; however, this includes a proportion of cases with somatic POLE mutation (6-12% of endometrial cancers) with more favourable prognosis, for which adjuvant chemotherapy does not confer benefit. The aim of this study was to determine what proportion of endometrial carcinomas in our Health Board cohort have high-risk histological characteristics and would require POLE testing to identify the subset which would derive most clinical benefit from POLE testing.

Introduction

Endometrial cancer is the sixth most commonly diagnosed cancer in women and the second most commonly diagnosed female genital organ cancer[1]. Currently endometrial carcinoma is diagnosed and subclassified on the basis of morphology using FIGO (The International Federation of Gynecology and Obstetrics) classification and according to Bokhman[2] split into two broad pathogenetic types1. Type I tumours consist of endometrioid endometrial carcinomas which are further sub-divided on morphology into grade 1, grade 2 and grade 3 endometroid endometrial carcinomas. Bokhmans second sub-division is of type II tumours which are non-endometroid and include serous carcinoma, clear cell carcinoma and carcinosarcoma. All type II tumours are regarded as FIGO grade 3 carcinomas.

The Cancer Genome Atlas (TCGA) integrated genomic and proteomic analysis of 373 endometrial cancers and this characterisation allowed identification of four new groups of endometrial carcinoma[3]. These subgroups, with their number distribution, is shown in figure 1. The significance of these new groups was shown by assessing progression free survival. The initial findings showing these survival differences is shown in figure 2. Further studies (such as PORTEC 3 study[4]) have shown these 4 subgroups have differing prognosis and response to treatment options and thus these subgroups are important for treatment decision making. The ProMisE study[5] has shown that effective use of immunohistochemistry (IHC) for p53 and mismatch repair proteins, alongside sequencing for polymerase-e (POLE) exonuclease domain mutations, allows accurate subclassification of endometrial carcinomas into these 4 groups.

In our Health Board we currently assess mismatch repair (MMR) protein expression and p53 status using immunohistochemistry on all our endometrial carcinomas. Across Scotland, we are hoping to add POLE mutation testing to this repertoire. We undertook this study as a scoping exercise, to determine the proportion of patients in our Health Board with 'high-risk and high-intermediate risk' endometrial cancers, to identify the cases for which POLE mutation testing would confer the most clinical benefit.

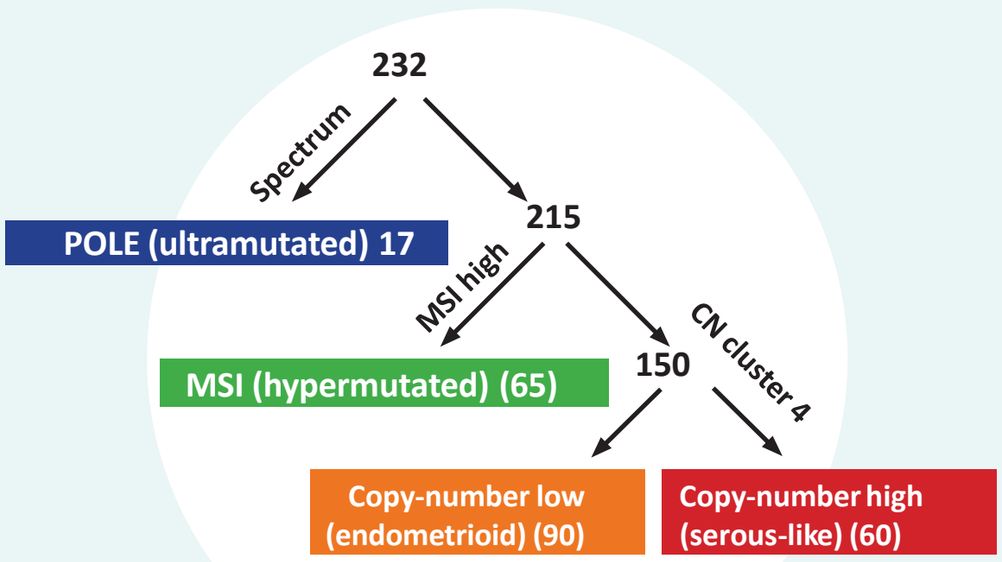

Figure 1. The new four groups of endometrial cancer as identified by The Cancer Atlas Genome project[1].

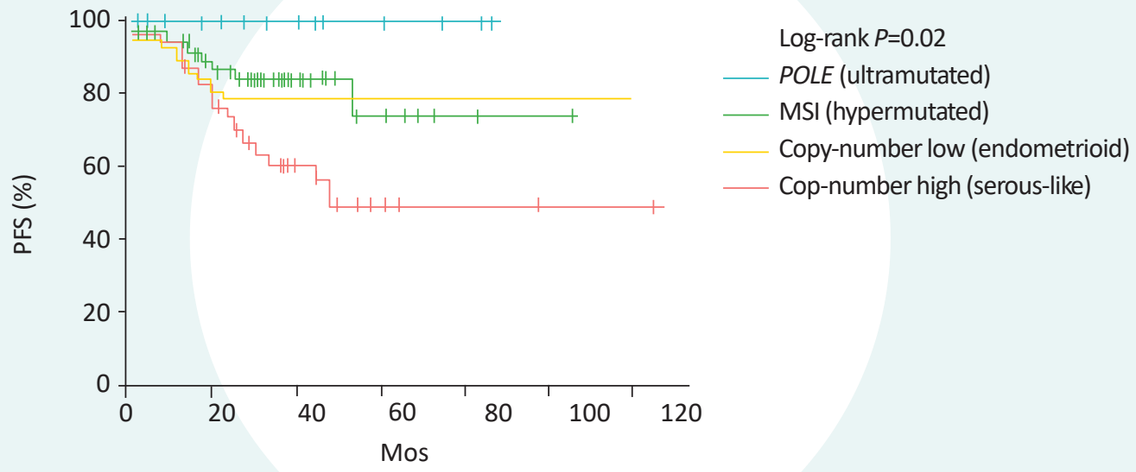

Figure 2. Results from The Cancer Atlas Genome project showing the four new endometrial cancer groups comparing progression free survival (PFS) against months (MOS) of patient follow up[1]

Material and methods

A retrospective analysis was undertaken of patients diagnosed with endometrial carcinoma resected in our department over 2 years (2019 and 2020). High-risk cases were defined as FIGO grade 3, at least FIGO stage 2, or carcinomas with extensive lymphovascular space invasion (LVSI).

Results

167 hysterectomies for endometrial carcinoma were undertaken in our Health Board over the 2 year study period. Table 1 shows the distribution of histological subtypes, FIGO staging and assessment for presence and extent of lymphovascular space invasion (LVSI). Extensive LVSI was defined as four or more foci of lymphovascular invasion.

Histological subtype	Total of subtype	Stage 1A	Stage 1B	Stage 2	Stage 3/4	No LVSI	Focal LVSI	Extensive LVSI
G1 endometroid	59	42	10	3	4	50	4	5
G2 endometroid	45	22	13	3	7	31	1	13
G3 endometroid	26	8	10	1	7	10	1	15
Serous carcinoma	15	7	3	1	4	9	1	5
Carcinosarcoma	10	2	3	2	3	1	1	8
Clear cell carcinoma	6	3	3	0	0	4	0	2

Table 1. The distribution of histological subtypes, FIGO staging and assessment for presence and extent of lymphvascular space invasion (LVSI) of all hysterectomy resections.

161 hysterectomies contained endometrial cancer of which 57 cases were FIGO grade 3, 17 cases grade 1 or 2 with FIGO stage 2 or above, and 11 stage 1 cases with extensive LVSI. In total, 85 histological high-risk cases were identified which would benefit from POLE mutation testing for therapeutic decision making, representing 52.8% of the endometrial cancer cases in our Health Board.

Conclusion

The addition of POLE mutation testing to our p53 and MMR protein immunohistochemistry panel, will improve the prognostic and therapeutic stratification of patients with endometrial cancer. Around half of our patients with endometrial cancer (52.8%) have high risk and high-intermediate risk histology and this represents the proportion of cases which, we deem, would most benefit from POLE testing. In the fullness of time, and as more information becomes available from future studies, we would hope to offer all patients with endometrial carcinoma, regardless of FIGO grade and stage, full tumour molecular subclassification to further refine prognostication and personalised treatment options.

References

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