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Hormone receptor loss in endometrial carcinoma curettage predicts lymph node metastasis and poor outcome in prospective multicentre trial ☆

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KEYWORDS
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Abstract ***Background:*** Preoperative histologic examination of tumour tissue is essential when deciding if endometrial cancer surgery should include lymph node sampling. We wanted to investigate if biomarkers could improve prediction of lymph node metastasis and outcome.

Patients and methods: Curettage specimens from 832 endometrial carcinoma patients prospectively recruited from 10 centres in the MoMaTEC trial (Molecular Markers in Treatment of Endometrial Cancer) were investigated for hormone receptor and p53 status.

Results: Eighteen per cent of tumours were double negative for oestrogen- and progesterone receptors (ER/PR loss), 24% overexpressed p53. Pathologic expression of all markers correlated with nodal metastases, high FIGO (Federation International of Gynecology and

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Obstetrics) stage, non-endometrioid histology, high grade and poor prognosis (all $P < 0.001$). ER/PR loss independently predicted lymph node metastasis (odds ratios (OR) 2.0, 95% confidence interval (CI) 1.1–3.7) adjusted for preoperative curettage histology and predicted poor disease-specific survival adjusted for age, FIGO stage, histologic type, grade and myometrial infiltration (hazard ratio (HR) 2.3, 95% CI 1.4–3.9). For lymph node negative endometrioid tumours, ER/PR loss influenced survival independent of grade.

Conclusion: Double negative hormone receptor status in endometrial cancer curettage independently predicts lymph node metastasis and poor prognosis in a prospective multicentre setting. Implementing hormone receptor status to improve risk-stratification for selecting patients unlikely to benefit from lymphadenectomy seems justified.

1. Introduction

Endometrial cancer is the most common gynaecologic malignancy in industrialised countries. Fifteen to twenty per cent of patients with presumed localised disease at primary treatment recur.[1,2] Of all patients dying from this disease, one third was initially classified as low risk for recurrence.[3] Contrasting breast cancer,[4,5] improved knowledge of molecular alterations relevant for prognostication and targeting therapies in endometrial cancer[6,7] has not been systematically incorporated to tailor therapy.[8]

Metastatic lymph nodes detected as part of staging during primary surgery, identifies patients with poor prognosis.[1,9] Routine lymph node sampling has not confirmed to contribute any survival benefit in randomised studies,[10,11] but is associated with increased complication rates.[11]

Preoperative endometrial biopsy by pipelle or curettage is the cornerstone in diagnostics of endometrial cancer and the first step of treatment algorithm planning for primary surgical treatment.[12] Still, final risk stratification of early stage disease has, until recently,[13] been based on assessing histologic subtype, grade and depth of myometrial infiltration in hysterectomy specimens.[9,12,14] Several retrospective studies support that status for oestrogen receptor (ER), progesterone receptor (PR) and the tumour suppressor p53 in primary tumours are independent prognostic markers.[8] This knowledge has not been systematically studied for implementation of individualised surgical therapy in endometrial cancer.[10,11] Instead, the treatment algorithm has moved towards more aggressive surgery including pelvic and para-aortic lymphadenectomy,[15,16] despite lack of established criteria and measures for reproducibility, sensitivity and negative predictive value for the procedure.[17] Systematic clinical implementation studies of biomarkers potential useful in surgically staged endometrial cancer patients have been called for.[8]

On this background, we have investigated if assessment of ER, PR and p53 in endometrial biopsies, could improve preoperative identification of patients with lymph node metastasis and poor prognosis in the prospective international multicentre trial MoMaTEC (Molecular Markers in Treatment of Endometrial Cancer).[18]

2. Materials and methods

In total, 1192 consenting endometrial carcinoma patients, have been prospectively recruited from 10 centres for collection of curettage specimens and clinical information between May 2001 through 2010 as previously reported and summarised in Fig. 1.[18] Distribution of clinicopathologic data is listed in Table 1. Histologic diagnosis from the routine pathology report and local tumour boards from each centre were utilised. Preoperative curettage histology reports, available for 1166 patients, were classified as low- versus high-risk; the latter including endometrioid grade 3, serous, clear cell, carcinosarcoma and undifferentiated subtypes. The 853 cases preoperatively classified as low-risk included 795 endometrioid grade 1 or 2 tumours and 58 hyperplasias with or without atypia or other, benign diagnoses later confirmed as endometrial carcinoma in hysterectomy specimens. Grading was performed both on the curettage and hysterectomy specimen according to World Health Organization (WHO) classification, based on

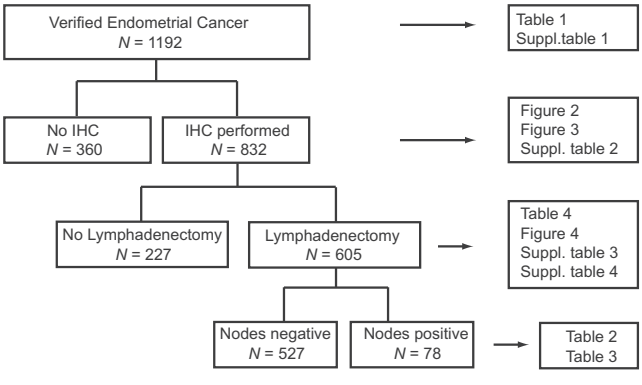

Fig. 1. Overview of patients and data available from the prospective international multicentre Molecular Markers in Treatment in Endometrial Cancer (MoMaTEC) trial with corresponding tables and figures. IHC = immunohistochemistry, N = number of cases.