Less-favourable prognosis for low-risk endometrial cancer patients with a discordant pre-versus post-operative risk stratification

European Journal of Cancer 78 (2017) 82–90

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Less-favourable prognosis for low-risk endometrial cancer patients with a discordant pre- versus post-operative risk stratification

F.A. Eggink [a], C.H. Mom [b], K. Bouwman [a], D. Boll [c], J.H. Becker [d], C.L. Creutzberg [e], G.C. Niemeijer [f], W.J. van Driel [g], A.K. Reyners [h], A.G. van der Zee [a], G.L. Bremer [i], N.P. Ezendam [j], R.F. Kruitwagen [k,l], J.M. Pijnenborg [m], H. Hollema [n], H.W. Nijman [a,*], M.A. van der Aa [j]

[a] *University of Groningen, University Medical Center Groningen, Department of Obstetrics and Gynecology, Groningen, The Netherlands*
[b] *VU University Medical Center, Center for Gynecologic Oncology Amsterdam, Amsterdam, The Netherlands*
[c] *Catharina Hospital, Department of Obstetrics and Gynecology, Eindhoven, The Netherlands*
[d] *St. Antonius Hospital, Department of Obstetrics and Gynecology, Nieuwegein, The Netherlands*
[e] *Leiden University Medical Center, Department of Radiation Oncology, Leiden, The Netherlands*
[f] *University Medical Center Groningen, Department of UMC Staff, Groningen, The Netherlands*
[g] *Antoni van Leeuwenhoek Hospital, Center for Gynecologic Oncology Amsterdam, Amsterdam, The Netherlands*
[h] *University of Groningen, University Medical Center Groningen, Department of Medical Oncology, Groningen, The Netherlands*
[i] *Zuyderland Medical Center, Department of Obstetrics and Gynecology, Heerlen/Sittard, The Netherlands*
[j] *Netherlands Comprehensive Cancer Organization, Department of Research, Utrecht, The Netherlands*
[k] *Maastricht University Medical Center, Department of Obstetrics and Gynecology, Maastricht, The Netherlands*
[l] *GROW – School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, The Netherlands*
[m] *Radboud University Medical Center Nijmegen, Department of Obstetrics and Gynecology, Nijmegen, The Netherlands*
[n] *University of Groningen, University Medical Center Groningen, Department of Pathology, Groningen, The Netherlands*

Received 6 January 2017; received in revised form 23 February 2017; accepted 12 March 2017
Available online 14 April 2017

KEYWORDS
Endometrial cancer;
Risk stratification;

Abstract ***Background:*** Pre-operative risk stratification based on endometrial sampling determines the extent of surgery for endometrial cancer (EC). We investigated the concordance of pre- and post-operative risk stratifications and the impact of discordance on survival.

* *Corresponding author*: University Medical Center Groningen, Department of Obstetrics and Gynecology, Room Y4.218, PO 30.001, 9700 RB Groningen, The Netherlands. Fax: +31 (0)50 3611806.
E-mail address: h.w.nijman@umcg.nl (H.W. Nijman).

http://dx.doi.org/10.1016/j.ejca.2017.03.010

Histology;
Clinical decision-making;
Overall survival

Methods: Patients diagnosed with EC within the first 6 months of the years 2005–2014 were selected from the Netherlands Cancer Registry (N = 7875). Pre- and post-operative risk stratifications were determined based on grade and/or histological subtype for 3784 eligible patients.

Results: A discordant risk stratification was found in 10% of patients: 4% (N = 155) had high pre- and low post-operative risk and 6% (N = 215) had low pre- and high post-operative risk. Overall survival of patients with high pre- and low post-operative risk was less favourable compared to those with a concordant low risk (80% versus 89%, p = 0.002). This difference remained significant when correcting for age, stage, surgical staging and adjuvant therapy (hazard ratio 1.80, 95% confidence interval 1.28–2.53, p = 0.001). Survival of patients with low pre- and high post-operative risk did not differ from those with a concordant high risk (64% versus 62%, p = 0.295).

Conclusion: Patients with high pre- and low post-operative risk have a less favourable prognosis compared to patients with a concordant low risk. Pre-operative risk stratifications contain independent prognostic information and should be incorporated into clinical decision-making.

1. Introduction

Endometrial cancer (EC) is the most common gynaecologic malignancy in developed countries, affecting approximately 1 in 37 women [1]. Standard treatment for patients with low-risk EC typically consists of hysterectomy and bilateral salpingo-oophorectomy. In patients with high-risk disease, lymphadenectomy or complete surgical staging and adjuvant therapy is recommended. Adjuvant therapy usually involves vaginal brachytherapy (VBT) or external beam radiotherapy (EBRT), sometimes with chemotherapy. Factors that are used to stratify patients into risk groups are histological subtype, grade, stage and lymphovascular space invasion (LVSI) [2–7].

To guide the choice of surgical treatment and extent of surgical staging, accurate pre-operative stratification of patients into low- and high-risk groups is essential. In case of clinical early-stage disease, pre-operative risk stratification is based on pre-operative endometrial samples, obtained by micro-curettage or curettage. The post-operative risk stratification is used to guide adjuvant therapy, and is based on the histological examination of tissue removed during surgery. Importantly, the post-operative risk stratification is currently viewed as the gold standard.

Discordance between pre- and post-operative risk stratifications may result in over- or under-treatment and may ultimately affect survival. In a high-risk EC cohort studied by Di Cello *et al.* [8], failure to recognise high-risk disease pre-operatively resulted in less-favourable survival outcomes compared to patients who were adequately stratified. On the other hand, the prospective MoMaTEC trial demonstrated that patients with discordant risk stratification had an intermediate prognosis compared to patients with concordant low- or high-risk stratifications [9]. Studies based on larger patient cohorts are needed to clarify the effect of discordant risk stratification on survival of EC patients.

We aimed to investigate the concordance of pre- and post-operative risk stratifications in a large, unselected, population-based cohort, and to evaluate whether discordant risk stratification influences prognosis.

2. Methods

2.1. Data collection

Data from all consecutive patients diagnosed with EC between 1st January and 1st July of every year within the period 2005–2014 were retrospectively retrieved from the Netherlands Cancer Registry (NCR). The NCR contains data from all patients diagnosed with cancer in the Netherlands from 1989 onwards. The data of newly diagnosed patients are entered into the NCR after automated notifications from the Dutch Pathology Network (PALGA). The PALGA database contains the pathology assessments from all national pathology departments. It was established in 1971, and plays an important role in facilitating epidemiological research in the Netherlands. Within the NCR, information on vital status is obtained by annual linkage to the Municipal Personal Records Database and was available up to 1st February 2016.

Patients who were selected from the NCR were matched with pathology assessments in the PALGA database. All pathology assessments that were available within 6 months before and 6 months after surgery were retrieved. Pathology assessments from tissue specimens taken outside of that period were considered irrelevant for this study.

2.2. Risk stratification

Pre-operative risk stratification was determined from the available pathology assessments retrieved from the PALGA database. Post-operative risk stratification was determined from the available data in the NCR, which are based on the final pathology assessments of hysterectomy specimens. Patients were considered to be at low risk if histology showed grade 1 or 2 endometrioid adenocarcinoma, grade 1 or 2 adenocarcinoma not otherwise specified (NOS) or grade 1 or 2 mucinous adenocarcinoma. Patients were considered to be at high risk if histology showed grade 3 adenocarcinoma (endometrioid, NOS, mucinous) or clear cell, serous or carcinosarcoma histology. Tumour types registered as 'other' included squamous-cell carcinomas, adenosquamous carcinomas and pseudosarcomatous carcinomas that were not further specified. As survival of this group resembled that of the endometrioid tumours, patients were considered to be at low risk when grade 1 or 2, and high risk when grade 3 (data not shown).

2.3. Outcomes

Concordance of pre- and post-operative risk stratifications and overall survival were defined as primary outcomes.

2.4. Data analysis

Differences between pre- and post-operative concordance groups were determined by chi-squared test or Fisher's exact test. In case of continuous variables, a Kruskal–Wallis followed by Mann–Whitney U test was used. Overall survival was used as a primary survival outcome measure, and estimated using Kaplan–Meier analyses. Overall survival was calculated from date of histological diagnosis to date of last follow-up or date of death. To correct for possible confounders (age, stage, surgical staging and adjuvant therapy), multivariable survival analysis was performed using Cox regression. As no information was available regarding the exact surgical procedures that were performed, surgical staging was defined as removal of at least one lymph node during surgery. Within the Cox regression analyses, no correction was applied for tumour type and grade because of co-linearity between these variables and risk stratification. Differences were considered statistically significant at $p < 0.05$. Data analysis was performed using SPSS data analysis and statistical software, version 22.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patient selection and characteristics

Data from 7875 patients diagnosed with EC between 1st January and 1st July 2005–2014 were retrieved from the NCR. In total, 4191 patients were excluded from analysis (Fig. 1). Six-hundred and twenty patients were excluded from the analysis as they did not undergo surgery, and the post-operative risk stratification could therefore not be determined. A further 1724 patients were excluded because no pathology assessment of the pre-operative

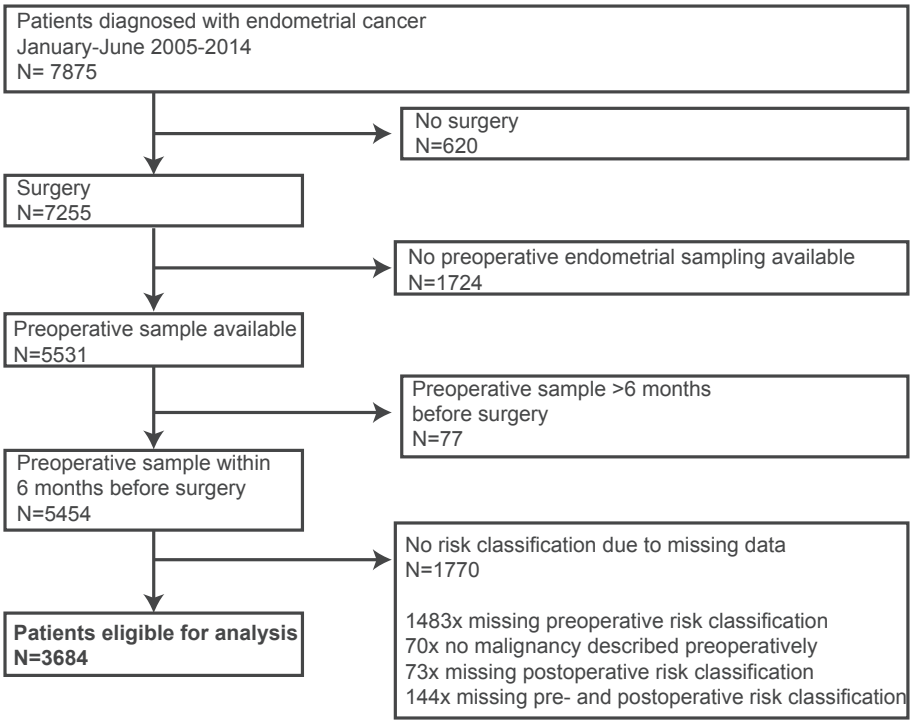

Fig. 1. Flowchart demonstrating which patients were eligible for analysis.

endometrial sample was available in the PALGA database, and 77 patients were excluded because the available pre-operative sample was obtained more than 6 months before surgery. Of the remaining 5454 patients, 1770 were excluded from the analysis because of missing data which were needed to determine risk stratification in pre- and/or post-operative samples or because the pre-operative sample was registered as non-malignant.

In total, 3684 patients were included in the present study. These patients were most frequently diagnosed as International Federation of Gynecology and Obstetrics (FIGO) stage I (80%), endometrioid type (79%) and grade 1 (41%) disease (Table 1). Most patients (83%) did not undergo surgical staging. No adjuvant therapy was administered in 61% of patients, whereas 13% received VBT, 21% received EBRT, 2% received radio-chemotherapy and 3% received chemotherapy alone.

3.2. Concordance of pre- and post-operative risk stratifications

We assessed the concordance between pre- and post-operative risk stratifications of the 3684 patients who were eligible for the analysis (Fig. 2). Concordant risk stratification was found in 3314 patients (90%). Of these concordant tumour samples, 2491 (75%) were considered to be at low risk and 823 (25%) were considered to be at high risk. In total, 370 (10%) patients were identified with discordant risk stratification. One hundred fifty-five patients (4%) were stratified as high risk pre-operatively and low risk post-operatively, and 215 patients (6%) were stratified as low risk pre-operatively and high risk post-operatively.

Table 1
Clinicopathologic characteristics of selected patients.

	N = 3684	
	N	%
Age at diagnosis (years)		
Mean (range)	67 (27–94)	
FIGO stage		
I	2949	80
II	303	8
III	313	9
IV	112	3
Unknown	7	0
Post-operative tumour type		
Endometrioid	2923	80
Serous	219	6
Clear cell	76	2
Adenocarcinoma NOS	260	7
Mucinous	16	0
Carcinosarcoma	173	5
Other	17	0
Post-operative grade		
1	1493	41
2	1154	31
3	1037	28
Surgical staging		
No	3049	83
Yes	635	17
Adjuvant therapy		
None	2263	61
VBT	474	13
EBRT	764	21
Radio + chemotherapy	62	2
Chemotherapy	120	3
Hormone therapy	1	0

EBRT, external beam radiotherapy; N, number of patients; NOS, not otherwise specified; VBT, vaginal brachytherapy; FIGO, International Federation of Gynecology and Obstetrics.

3.3. Survival of patients with discordant and concordant risk stratifications

Kaplan–Meier survival analyses were performed to evaluate whether discordant risk stratification influenced survival outcomes (Fig. 3). Median follow-up of all patients was 48 months. Patients with a low pre-operative risk stratification had favourable survival outcomes compared to patients with a high pre-operative risk stratification ($p < 0.001$, Fig. 3A). Likewise, patients with a low post-operative risk stratification had favourable survival outcomes compared to patients with a high post-operative risk stratification ($p < 0.001$, Fig. 3B).

When combining pre- and post-operative risk stratifications, the post-operative results enable better stratification into good and poorer survival (Fig. 3C). Less favourable overall survival was seen in patients with a high pre- and low post-operative risk compared to patients with a concordant low risk ($p = 0.002$). No difference in survival was found between patients with a low pre- and high post-operative risk, and patients with a concordant high risk ($p = 0.295$). Five-year overall survival was 89% in patients with a concordant low risk, 80% in patients with a high pre- and low post-operative risk, 64% in patients with a low pre- and high post-operative risk and 62% in patients with a concordant high risk.

Multivariable Cox survival analysis demonstrated an independent prognostic value of risk stratification when correcting for age, FIGO stage, surgical staging (defined as removal of one lymph node during surgery) and adjuvant therapy (Table 2). Compared to patients with a concordant low risk, less-favourable survival was found in patients with a high pre- and low post-operative risk (hazard ratio [HR] 1.80, 95% confidence interval [CI] 1.28–2.52, $p = 0.001$), patients with a low pre- and high post-operative risk (HR 2.40, 95% CI 1.87–3.08, $p < 0.001$) and patients with a concordant high risk (HR 2.91, 95% CI 2.46–3.45, $p < 0.001$). Multivariable analysis in which surgical staging was defined as removal of at least 10 lymph nodes during surgery confirmed the presence of unfavourable survival in the high pre- and low post-operative risk groups compared with the concordant low-risk group (HR 1.766, 95% CI 1.256–2.481, $p < 0.001$, data not shown).

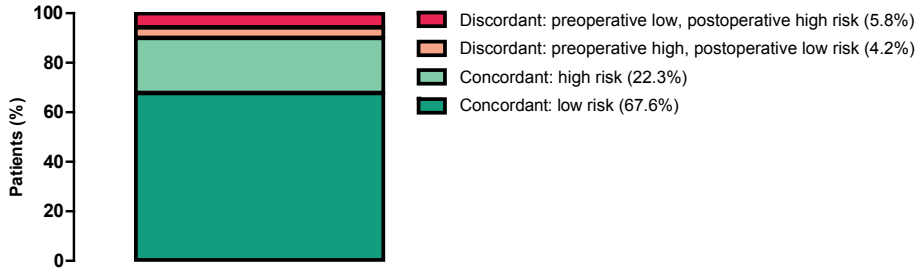

Fig. 2. Concordance of pre- and post-operative risk stratifications.

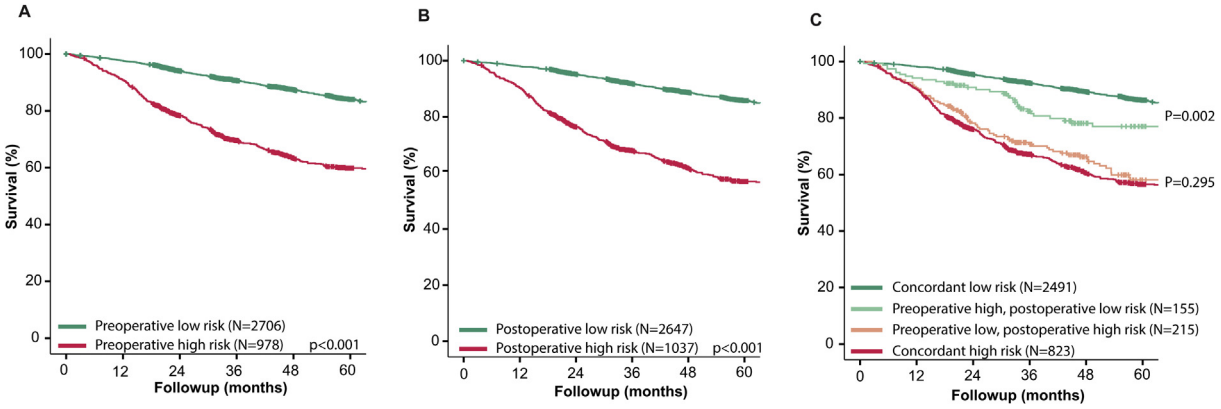

Fig. 3. Kaplan–Meier survival curves according to pre-operative risk stratification (A), post-operative risk stratification (B) and combined pre- and post-operative risk stratifications (C).

3.4. Characteristics and survival of patients with missing pre- and/or post-operative risk stratification

Unexpectedly, a large number of patients was excluded from the analysis because of missing pre- and/or post-operative risk stratifications. The prompted us to investigate the clinicopathological characteristics and survival of these patients. Compared with the 3684 patients who were included in our analyses, the 1770 patients excluded because of missing data were more frequently diagnosed with low-risk disease, and were therefore less likely to receive surgical staging and adjuvant therapy (Supplemental Table 1).

4. Discussion

To our knowledge, this is the largest population-based study focussing on concordance of pre- and post-operative risk stratifications based on the histological type and grade of EC. A 10% discordance was determined in pre- and post-operative risk stratifications of 3684 patients diagnosed with EC. Less-favourable overall survival was seen in patients with high pre- and low post-operative risk stratifications compared to those with concordant low-risk stratifications.

In previous studies, the concordance of pre- and post-operative risk stratification rates ranged from 58% to 84%; therefore, the 90% concordance demonstrated within this study is relatively high [8–11]. Werner *et al.* [9] demonstrated an 84% concordance between the pre- and post-operative risk stratifications. In their study, based on the prospectively collected data of 1288 patients, 30% of patients were post-operatively stratified as having high-risk disease. This is in line with our data, in which 28% of patients were post-operatively stratified as having high-risk disease. Interestingly, Werner *et al.* reported that within the group of patients with a discordant risk stratification, 73% were upgraded from low risk to high risk after assessment of the post-operative sample, whereas within the present study, this group comprised only 58% of the patients with discordant risk stratification (6% of the total study population).

As the pre-operative risk stratification is used to guide the extent of surgical treatment, incorrect risk stratification may lead to under- or over-treatment and may therefore influence survival outcomes. The consequence of not recognising high-risk disease pre-operatively is subject of debate. One study, based on 109 patients, demonstrated that failure to identify high-risk EC patients in the pre-operative setting seemed to result in unfavourable survival outcomes due to sub-optimal surgical staging [8]. Conversely, another study, based on 1374 patients, concluded that failure to recognise high-risk disease pre-operatively was associated with a 17% increase in disease-specific survival, a finding which may suggest the presence of tumour

Table 2
Univariable and multivariable Cox regression analysis for overall survival.

	Univariable analyses			Multivariable analyses		
	HR	95% CI	p-value	HR	95% CI	p-value
Age	1.066	1.059–1.074	<0.001	1.061	1.054–1.069	<0.001
Risk classification						
Concordant low	ref	ref	ref	ref	ref	ref
High pre-operative, low post-operative	1.686	1.202–2.364	0.002	1.797	1.278–2.527	0.001
Low pre-operative, high post-operative	3.324	2.618–4.219	<0.001	2.397	1.869–3.074	<0.001
Concordant high	3.742	3.233–4.331	<0.001	2.913	2.459–3.452	<0.001
Post-operative tumour type						
Endometrioid	ref	ref	ref			
Serous	3.783	3.066–4.668	<0.001			
Clear cell	2.595	1.796–3.750	<0.001			
Adenocarcinoma NOS	1.156	0.895–1.494	0.267			
Mucinous	0.305	0.043–2.166	0.235			
Carcinosarcoma	4.598	3.702–5.710	<0.001			
Other	1.651	0.738–3.691	0.222			
Post-operative grade						
1	ref	ref	ref			
2	1.578	1.297–1.919	<0.001			
3	4.416	3.713–5.254	<0.001			
FIGO stage						
I	ref	ref	ref	ref	ref	ref
II	2.209	1.792–2.723	<0.001	1.978	1.582–2.474	<0.001
III	4.577	3.838–5.460	<0.001	4.268	3.469–5.250	<0.001
IV	8.146	6.383–10.396	<0.001	5.121	3.907–6.711	<0.001
Surgical staging						
No	ref	ref	ref	ref	ref	ref
Yes	1.461	1.241–1.721	<0.001	0.653	0.541–0.789	<0.001
Adjuvant therapy						
None	ref	ref	ref	ref	ref	ref
VBT	1.059	0.831–1.349	0.645	0.863	0.676–1.102	0.238
EBRT	1.830	1.567–2.137	<0.001	0.841	0.706–1.001	0.051
Radio + chemotherapy	2.054	1.296–3.254	0.002	0.825	0.509–1.337	0.435
Chemotherapy	5.852	4.538–7.546	<0.001	1.371	1.016–1.850	0.039
Hormone therapy	0.001	0.000–0.000	0.919	0.000	0.000–0.000	0.923

EBRT, external beam radiotherapy; HR, hazard ratio; CI, confidence interval; N, number of patients; NOS, not otherwise specified; VBT, vaginal brachytherapy; FIGO, International Federation of Gynecology and Obstetrics.
Note: 'ref' means the reference category. This is sometimes also noted as 'reference' or '1.00'.

heterogeneity [9]. Our analyses, based on a much larger cohort, failed to show any change in survival in high-risk EC patients with discordant pre-operative risk stratification. If our multivariable analysis is re-run without correcting for adjuvant therapy, no difference in survival is demonstrated in our cohort. The lack of survival impact of adjuvant therapy in this multivariable model confirms the lack of survival benefit attained by administration of adjuvant therapy in high-risk EC patients, as shown in various landmark studies regarding this topic [7,12,13]. The overlapping survival outcomes of patients with low pre- and high post-operative risk and patients with concordant high risk within our study may be the result of two factors with opposing survival impact: improved survival outcomes because of the presence of tumour heterogeneity (as previously proposed by Werner *et al.* [9]), and reduced survival outcomes because of surgical under-treatment of patients with low pre- and high post-operative risk (as previously proposed by Di Cello *et al.* [8]). Indeed, within the present retrospective study, patients with low pre- and high post-operative risk were often not surgically staged (Table 3), and surgical staging was associated with favourable survival outcomes in multivariable analysis (HR 0.653, 95% CI 0.541–0.789, $p < 0.001$, Table 2). Prospective trials are warranted to elucidate the potential therapeutic effect of surgical staging in high-risk EC.

The effects of pre-operatively not recognising low-risk disease are less controversial. Both the study by Werner *et al.* and our study clearly demonstrate less favourable survival outcomes for patients with low-risk EC that were pre-operatively stratified as high risk compared to patients with a concordant low risk [9]. These data suggest the presence of tumour heterogeneity and/or mixed morphologic characteristics, which has previously been demonstrated in 5% or more of endometrial tumours [14,15]. The presence of minor serous or clear cell components (threshold of 5%) has been shown to adversely affect survival outcomes. Therefore, the presence of tumours with a mixed histology may provide a plausible explanation for the less-favourable survival of patients with high pre- and low post-operative risk

Table 3
Characteristics of patients in the four pre- and post-operative combined risk groups.

	Low–Low		High–Low		Low–High		High–High	
	N = 2491		N = 155		N = 215		N = 823	
	N	%	N	%	N	%	N	%
Age at diagnosis (years)								
Mean (range)	66 (27–93)		67 (43–89)		68 (30–93)		69 (42–94)	
FIGO stage								
I	2183	88	125	80	131	61	510	62
II	171	7	15	10	29	13	88	11
III	105	4	12	8	42	20	154	19
IV	27	1	3	2	13	6	69	8
Unknown	5	0	0	0	0	0	2	0
Post-operative tumour type								
Endometrioid	2307	93	135	87	150	70	331	40
Serous	0	0	0	0	26	12	193	24
Clear cell	0	0	0	0	6	3	70	9
Adenocarcinoma NOS	167	7	18	12	13	6	62	7
Mucinous	13	0	2	1	1	0	0	0
Carcinosarcoma	0	0	0	0	17	8	156	19
Other	4	0	0	0	2	1	11	1
Post-operative grade								
1	1447	58	46	30	0	0	0	0
2	1044	42	109	70	0	0	0	0
3	0	0	0	0	215	100	823	100
Surgical staging								
No	2338	94	114	74	163	76	434	53
Yes	153	6	41	26	52	24	389	47
Adjuvant therapy								
None	1806	73	101	65	73	34	283	35
VBT	313	13	21	14	30	14	110	13
EBRT	350	14	33	21	86	40	295	36
Radio + chemotherapy	12	0	0	0	8	4	42	5
Chemotherapy	10	0	0	0	18	8	92	11
Hormone therapy	0	0	0	0	0	0	1	0

EBRT, external beam radiotherapy; N, Number of patients; NOS, not otherwise specified; VBT, vaginal brachytherapy; FIGO, International Federation of Gynecology and Obstetrics.

stratifications within the present study [16]. In line with this, our data suggest that patients with a high pre- and low post-operative risk classification may require additional therapy to ensure local control of disease, as has been demonstrated in patients with high-intermediate and high-risk disease [7,17]. Collectively, our data suggest that the pre-operative risk stratification comprises independent prognostic information which should be integrated into clinical decision-making.

A strategy to further improve the pre-operative risk classification, and potentially overcome the problems associated with endometrial sampling of heterogenic/mixed tumours, may be to incorporate molecular alterations into clinical decision-making, as recently reviewed by Bendifallah *et al.* [18]. This strategy is already in use for breast cancer and ovarian cancer [19,20]. Indeed, molecular alterations in pre-operative endometrial samples have been shown to predict the alterations in post-operative samples with a concordance of 88% for immunohistochemical and 99% for DNA techniques [21]. In the specific case of EC, four molecular subtypes have been identified by the Cancer Genome Atlas Network: *POLE*-ultramutated, microsatellite unstable-hypermutated, p53-mutant and those with no specific molecular profile [22]. Clinically applicable molecular classification strategies using formalin-fixed paraffin-embedded specimens have been devised by groups in Canada and the Netherlands [23,24]. The Canadian group has previously demonstrated a concordance of 89% between classification of pre- and post-operative samples using the Proactive Molecular Risk classification tool for Endometrial cancers (ProMisE), which is in agreement with the 90% concordance seen within the present study [25]. Furthermore, a recent publication of the Canadian group demonstrated improved stratification of patients according to clinical outcomes by the ProMisE compared with traditional stratification by clinicopathologic factors [26]. Moreover, the Dutch group evaluated a strategy in which molecular alterations were combined with established clinicopathologic factors (LVSI, L1CAM expression and CTNNB1 mutation), which resulted in an improved post-operative risk assessment compared with pathology assessment, centralised pathology review or molecular classification alone [27].

Inevitably, the retrospective design of the present study has some limitations. First of all, this study is

based on the data from the NCR and the PALGA database. We thus depend heavily on the quality and availability of data within these two registries. Because of the absence of information on recurrences, no progression-free survival or disease-free survival analyses could be performed. Secondly, the retrospective nature of the present study, in combination with the anonymous nature of the data available in the NCR and PALGA database, impeded the recovery of missing data. As myometrial invasion and lymph vascular invasion were not reliably available pre-operatively, we did not include these factors into the risk stratification. Furthermore, the presence of missing data unfortunately led to the exclusion of a large number of patients from our analyses. Finally, as the NCR does not register the presence of comorbidities, it was not possible to correct for this possible confounder in the multivariable analysis. As an estimation for cause-specific survival, a relative survival analysis was performed according to the Ederer II method (data not shown). This analysis did not show any differences between 5-year relative survival outcomes and 5-year overall survival outcomes of the four risk groups. The possibility that comorbidities confounded our results is thus deemed unlikely.

In conclusion, within this population-based analysis, a 90% concordance was demonstrated between pre- and post-operative risk stratifications. Less-favourable survival was demonstrated in patients with a pre-operative high and post-operative clinicopathologic low risk compared to patients with concordant low risk. Our data underline the independent prognostic information provided by the pre-operative sample, which should be incorporated into clinical decision-making.

Funding

This work was supported by the Dutch Cancer Society grant RUG 2014-7117 to HWN. The funders had no role in collection and analysis of the data, interpretation of the results or writing of the manuscript. The views and opinions expressed in the manuscript are those of the authors and do not necessarily reflect those of the Dutch Cancer Society.

Conflict of interest statement

None declared.

Acknowledgements

The authors thank the Netherlands Cancer Registry and the Dutch Pathology Network for providing the data used in this manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2017.03.010.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5–29. http://dx.doi.org/10.3322/caac.21254.
[2] Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. Cancer 1987;60:2035–41.
[3] Lee K-B, Ki K-D, Lee J-M, Lee J-K, Kim JW, Cho C-H, et al. The risk of lymph node metastasis based on myometrial invasion and tumor grade in endometrioid uterine cancers: a multicenter, retrospective Korean study. Ann Surg Oncol 2009;16:2882–7. http://dx.doi.org/10.1245/s10434-009-0535-0.
[4] Convery PA, Cantrell LA, Di Santo N, Broadwater G, Modesitt SC, Secord AA, et al. Retrospective review of an intraoperative algorithm to predict lymph node metastasis in low-grade endometrial adenocarcinoma. Gynecol Oncol 2011;123:65–70. http://dx.doi.org/10.1016/j.ygyno.2011.06.025.
[5] Milam MR, Tao X, Coleman RL, Harrell R, Bassett R, Dos Reis R, et al. Neoadjuvant chemotherapy is associated with prolonged primary treatment intervals in patients with advanced epithelial ovarian cancer. Int J Gynecol Cancer 2011;21:66–71. http://dx.doi.org/10.1097/IGC.0b013e3182013e2f.
[6] Koskas M, Bassot K, Graesslin O, Aristizabal P, Barranger E, Clavel-Chapelon F, et al. Impact of lymphovascular space invasion on a nomogram for predicting lymph node metastasis in endometrial cancer. Gynecol Oncol 2013;129:292–7. http://dx.doi.org/10.1016/j.ygyno.2013.02.027.
[7] Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Wárlám-Rodenhuis CC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. Lancet 2000;355:1404–11. http://dx.doi.org/10.1016/S0140-6736(00)02139-5.
[8] Di Cello A, Rania E, Zuccalà V, Venturella R, Mocciaro R, Zullo F, et al. Failure to recognize preoperatively high-risk endometrial carcinoma is associated with a poor outcome. Eur J Obstet Gynecol Reprod Biol 2015;194:153–60. http://dx.doi.org/10.1016/j.ejogrb.2015.09.004.
[9] Werner HMJ, Trovik J, Marcickiewicz J, Tingulstad S, Staff AC, Engh ME, et al. A discordant histological risk classification in preoperative and operative biopsy in endometrial cancer is reflected in metastatic risk and prognosis. Eur J Cancer 2013;49:625–32. http://dx.doi.org/10.1016/j.ejca.2012.09.006.
[10] Nofech-Mozes S, Ismiil N, Dubé V, Saad RS, Ghorab Z, Grin A, et al. Interobserver agreement for endometrial cancer characteristics evaluated on biopsy material. Obstet Gynecol Int 2012;2012:1–6. http://dx.doi.org/10.1155/2012/414086.
[11] Helpman L, Kupets R, Covens A, Saad RS, Khalifa MA, Ismiil N, et al. Assessment of endometrial sampling as a predictor of final surgical pathology in endometrial cancer. Br J Cancer 2014;110:609–15. http://dx.doi.org/10.1038/bjc.2013.766.
[12] Blake P, Swart A, Orton J, Kitchener H. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis. Lancet 2009;373:137–46. http://dx.doi.org/10.1016/S0140-6736(08)61767-5.
[13] Kong A, Johnson N, Kitchener HC, Lawrie TA. Adjuvant radiotherapy for stage I endometrial cancer: an updated Cochrane systematic review and meta-analysis. J Natl Cancer Inst 2012;104:1625–34. http://dx.doi.org/10.1093/jnci/djs374.
[14] Williams KE, Waters ED, Woolas RP, Hammond IG, McCartney AJ. Mixed serous-endometrioid carcinoma of the

uterus: pathologic and cytopathologic analysis of a high-risk endometrial carcinoma. Int J Gynecol Cancer 1994;4:7–18.
[15] Carcangiu ML, Chambers JT. Uterine papillary serous carcinoma: a study on 108 cases with emphasis on the prognostic significance of associated endometrioid carcinoma, absence of invasion, and concomitant ovarian carcinoma. Gynecol Oncol 1992;47:298–305.
[16] Quddus MR, Sung CJ, Zhang C, Lawrence WD. Minor serous and clear cell components adversely affect prognosis in "mixed-type" endometrial carcinomas: a clinicopathologic study of 36 stage-I cases. Reprod Sci 2010;17:673–8. http://dx.doi.org/10.1177/1933719110368433.
[17] Nout RA, Smit VTHBM, Putter H, Jürgenliemk-Schulz IM, Jobsen JJ, Lutgens LCHW, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. Lancet 2010;375:816–23. http://dx.doi.org/10.1016/S0140-6736(09)62163-2.
[18] Bendifallah S, Darai E, Ballester M. Predictive modeling: a new paradigm for managing endometrial cancer. Ann Surg Oncol 2016;23:975–88. http://dx.doi.org/10.1245/s10434-015-4924-2.
[19] Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature 2012;490:61–70. http://dx.doi.org/10.1038/nature11412.
[20] Yang D, Khan S, Sun Y, Hess K, Shmulevich I, Sood AK, et al. Association of BRCA1 and BRCA2 mutations with survival, chemotherapy sensitivity, and gene mutator phenotype in patients with ovarian cancer. JAMA 2011;306:1557–65. http://dx.doi.org/10.1001/jama.2011.1456.
[21] Stelloo E, Nout RA, Naves LCLM, Ter Haar NT, Creutzberg CL, Smit VTHBM, et al. High concordance of molecular tumor alterations between pre-operative curettage and hysterectomy specimens in patients with endometrial carcinoma. Gynecol Oncol 2014;133:197–204. http://dx.doi.org/10.1016/j.ygyno.2014.02.012.
[22] Cancer Genome Atlas Research Network, Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, Shen H, et al. Integrated genomic characterization of endometrial carcinoma. Nature 2013;497:67–73. http://dx.doi.org/10.1038/nature12113.
[23] Talhouk a, McConechy MK, Leung S, Li-Chang HH, Kwon JS, Melnyk N, et al. A clinically applicable molecular-based classification for endometrial cancers. Br J Cancer 2015;113:299–310. http://dx.doi.org/10.1038/bjc.2015.190.
[24] Stelloo E, Bosse T, Nout RA, MacKay HJ, Church DN, Nijman HW, et al. Refining prognosis and identifying targetable pathways for high-risk endometrial cancer; a TransPORTEC initiative. Mod Pathol 2015;28:836–44. http://dx.doi.org/10.1038/modpathol.2015.43.
[25] Talhouk A, Hoang LN, McConechy MK, Nakonechny Q, Leo J, Cheng A, et al. Molecular classification of endometrial carcinoma on diagnostic specimens is highly concordant with final hysterectomy: earlier prognostic information to guide treatment. Gynecol Oncol 2016;143:46–53. http://dx.doi.org/10.1016/j.ygyno.2016.07.090.
[26] Talhouk A, McConechy MK, Leung S, Yang W, Lum A, Senz J, et al. Confirmation of ProMisE: a simple, genomics-based clinical classifier for endometrial cancer. Cancer 2017:1–12. http://dx.doi.org/10.1002/cncr.30496.
[27] Stelloo E, Nout RA, Osse EM, Ju rgenliemk-Schulz IJ, Jobsen JJ, Lutgens LC, et al. Improved risk assessment by integrating molecular and clinicopathological factors in early-stage endometrial cancer - combined analysis of PORTEC cohorts. Clin Cancer Res 2016:1–10. http://dx.doi.org/10.1158/1078-0432.CCR-15-2878.