Compliance with adjuvant treatment guidelines in endometrial cancer

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Compliance with adjuvant treatment guidelines in endometrial cancer: room for improvement in high risk patients

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HIGHLIGHTS

- Optimal adjuvant therapy for endometrial cancer is subject of debate.
- In low and low-intermediate risk patients compliance to guidelines was 98%.
- In high risk patients compliance to guidelines was 61%.
- Results of ongoing clinical trials in high risk patients are eagerly awaited.

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ABSTRACT

Objectives. Compliance of physicians with guidelines has emerged as an important indicator for quality of care. We evaluated compliance of physicians with adjuvant therapy guidelines for endometrial cancer patients in the Netherlands in a population-based cohort over a period of 10 years.

Methods. Data from all patients diagnosed with endometrial cancer between 2005 and 2014, without residual tumor after surgical treatment, were extracted from the Netherlands Cancer Registry (N = 14,564). FIGO stage, grade, tumor type and age were used to stratify patients into risk groups. Possible changes in compliance over time and impact of compliance on survival were assessed.

Results. Patients were stratified into low/low-intermediate (52%), high-intermediate (21%) and high (20%) risk groups. Overall compliance with adjuvant therapy guidelines was 85%. Compliance was highest in patients with low/low-intermediate risk (98%, no adjuvant therapy indicated). The lowest compliance was determined in patients with high risk (61%, external beam radiotherapy with/without chemotherapy indicated). Within this group compliance decreased from 64% in 2005–2009 to 57% in 2010–2014. In high risk patients with FIGO stage III serous disease compliance was 55% (chemotherapy with/without radiotherapy indicated) and increased from 41% in 2005–2009 to 66% in 2010–2014.

Conclusion. While compliance of physicians with adjuvant therapy guidelines is excellent in patients with low and low-intermediate risk, there is room for improvement in high risk endometrial cancer patients. Eagerly awaited results of ongoing randomized clinical trials may provide more definitive guidance regarding adjuvant therapy for high risk endometrial cancer patients.

1. Introduction

Endometrial cancer is the most common gynecologic cancer in developed countries [1,2]. Approximately 1900 women are newly diagnosed with endometrial cancer every year in the Netherlands. While most patients are diagnosed with low risk disease and have relatively

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favorable survival outcomes, there is a subgroup of patients with a higher risk of recurrence and metastasis facing unfavorable survival outcomes [3,4].

Within the Netherlands, standard primary therapy for endometrial cancer consists of hysterectomy and bilateral salpingo-oophorectomy. Generally, in patients with high risk endometrial cancer complementary lymphadenectomy or complete staging (including peritoneal sampling and omentectomy) is performed. To guide the choice of adjuvant therapy, patients are stratified into risk groups based on European Society of Medical Oncology (ESMO) clinical practice guidelines [5]. National guidelines, based on the best available evidence, recommend no adjuvant therapy in low and low-intermediate risk patients and adjuvant therapy, consisting of vaginal brachytherapy or external beam radiotherapy and/or chemotherapy, for high-intermediate and high risk patients (summarized in Table 1) [6–9]. Despite the large body of literature aimed at the evaluation of therapeutic strategies, management of high-intermediate and high risk endometrial cancer remains a controversial topic as available literature is inconsistent. The lack of unequivocal evidence has resulted in widespread variation in surgical and adjuvant management of endometrial cancer [10–12]. Variation in treatment strategies has also been demonstrated on a national level. Compliance of physicians with adjuvant therapy guidelines in early stage endometrial cancer ranged between 53% and 72% in two relatively small Dutch studies based on data from 1995 to 2008 and 1995 to 1999, respectively [13,14]. This variation in treatment may be due to the lack of high quality evidence, prompting policymakers to devise national guidelines which leave room for interpretation. Importantly, compliance with guidelines may be affected by physician factors such as judgment of benefit of therapy, as well as individual patient factors such as age, physical condition and treatment preferences [15].

Compliance of physicians with evidence-based guidelines has been viewed as an important indicator for quality of care [16–19]. In this study we aimed to assess compliance of physicians with national adjuvant therapy guidelines by conducting a population-based study in patients diagnosed with endometrial cancer in the Netherlands between 2005 and 2014.

2. Methods

2.1. Data collection

Data were retrieved from the Netherlands Cancer Registry (NCR), which contains clinicopathologic characteristics from all patients diagnosed with cancer from 1989 onwards in the Netherlands. Data from all consecutive patients diagnosed with endometrial cancer between January 1st, 2005 and January 1st, 2015 were requested. Patients that did not undergo surgery and those with residual tumor after surgery were excluded from analyses.

Table 1
Risk groups and corresponding adjuvant treatment guidelines in the Netherlands.

Risk group	FIGO stage	Grade	Tumor type	Age	Recommended adjuvant therapy
Low + low-intermediate	IA	1–2	Endometrioid	–	None
	IB	1–2	Endometrioid	<60	
	IA	3	Endometrioid	<60	
High-intermediate	IB	1–2	Endometrioid	≥60	Radiotherapy, VBT preferred over EBRT
	IA	3	Endometrioid	≥60	
High	IB	3	Endometrioid	–	EBRT, chemotherapy may be considered
	II–III	–	Endometrioid	–	
	I–III	–	Clearcell	–	
	I–II	–	Serous	–	
	III	–	Serous	–	Chemotherapy, radiotherapy may be considered

VBT: vaginal brachytherapy; EBRT: external beam radiotherapy.

The NCR is linked to the Municipal Personal Records Database to obtain information on vital status of patients in the registry. For our analyses the information concerning vital status was available up to February 1st, 2016. Tumor stage according to International Federation of Gynecology and Obstetrics (FIGO) 2009 criteria was determined from the pathological Tumor lymph Node Metastasis (TNM) classification, which was available in the NCR. Data with regard to adjuvant therapy were available in the NCR and categorized into the following groups: no adjuvant therapy, vaginal brachytherapy (VBT), external beam radiotherapy (EBRT), radiotherapy and chemotherapy, chemotherapy and hormonal therapy. Information concerning socioeconomic status (SES) was based on reference data from the Netherlands Institute for Social Research. Scores were derived from income, education and occupation per four-digit postal code. Patients were assigned to three SES categories: low (1st–3rd decile), intermediate (4th–7th decile) and high (8th–10th decile).

Within the Netherlands, care for patients with gynecologic cancers is divided into 8 regions which comprise at least one academic/specialized referral hospital. Region of treatment hospital was available in the NCR, to guarantee anonymity of hospital-specific-data regions were categorized 1 through 8.

2.2. Classification in risk groups and corresponding adjuvant therapy guidelines

Patients were classified into one of four risk groups according to national guidelines (Table 1). As presence of lymph vascular space invasion was not registered in the NCR, this could not be taken into account in the stratification. Because adjuvant therapy is not recommended in both low risk and low-intermediate risk patients these groups were combined. A sub-analysis was performed on high risk patients with FIGO stage III serous disease as recommended adjuvant therapy for these patients varies from that in other high risk patients. Patients with stage IV disease were analyzed separately because individualization of therapy is recommended for this group. For each risk group corresponding adjuvant therapy guidelines are depicted in Table 1.

2.3. Outcomes

Compliance of physicians with guidelines was defined as the primary outcome. Adjuvant therapy guidelines state that in high risk patients EBRT is recommended and chemotherapy may be considered, we therefore regarded EBRT with or without chemotherapy as compliant with the guideline. Adjuvant therapy guidelines are slightly different for high risk patients with FIGO stage III serous disease. For this subgroup of high risk patients adjuvant therapy guidelines recommend chemotherapy with or without radiotherapy, we therefore regarded chemotherapy with or without radiotherapy (EBRT or VBT) as compliant with the guideline.

Assessment of variation in compliance between the periods 2005–2009 and 2010–2014, between the eight oncologic regions within the Netherlands and the impact of compliance on overall survival were defined as secondary outcomes.

2.4. Statistical analyses

Compliance of physicians was assessed for all risk groups, and comparisons were made between compliance with guidelines in patients diagnosed in the periods 2005–2009 and in 2010–2014. Similarly, comparisons were made between compliance in the eight oncologic regions in the Netherlands. Differences between groups were determined by Chi^2 test or Fisher's Exact test. Overall survival was measured from date of diagnosis until date of death or last follow-up. Impact of compliance on overall survival was estimated using Kaplan Meier analyses and accompanying log-rank tests. Multivariable analyses were performed in

which survival was corrected for age, type of tumor, grade, FIGO stage and socioeconomic status based on postal code. In all statistical analyses 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 characteristics

A total of 14,564 endometrial cancer patients were eligible for analysis (Table 2). The majority of patients were diagnosed with FIGO stage I (58% stage IA and 28% stage IB) endometrioid (91%) endometrial cancer. Most patients did not receive any adjuvant therapy (64%).

A total of 7531 patients (52%) were stratified as low and low-intermediate risk, 3042 as high-intermediate risk (21%), and 2995 as high risk (20%). One hundred and forty patients (1%) were categorized as FIGO stage IV and analyzed separately, and 856 patients (6%) could not be categorized due to missing information. Risk stratification was validated by survival analysis, which confirmed the presence of three independent prognostic groups (Fig. 1).

3.2. Compliance according to risk groups (N = 13,568)

Compliance of physicians with adjuvant therapy guidelines was assessed for patients that were categorized as low and low-intermediate, high-intermediate or high risk. Overall, compliance with guidelines was 85%. Within our database, patients that were not treated according to adjuvant therapy guidelines had unfavorable overall survival outcomes compared to patients that were treated according to the guidelines. Mean overall survival was 105 months in the compliant group versus 82 months in the non-compliant group ($p < 0.001$, data not shown). This remained significant when correcting for age, type of tumor, grade, FIGO stage and socioeconomic status (adjusted HR 1.33, 95% CI 1.20–1.46, $p < 0.001$, Supplemental Table 1).

Table 2
Clinicopathologic characteristics of endometrial cancer patients eligible for analysis (N = 14,564).

	N	%
Age at diagnosis (years)		
Mean (range)	66 (25–100)	
FIGO stage		
IA	8469	58
IB	4070	28
II	1072	7
III	792	5
IV	140	1
Unknown	21	0
Tumor type		
Endometrioid	13,175	91
Clearcell	220	1
Serous	618	4
Other	551	4
Grade		
1	7088	49
2	4090	28
3	2228	15
Unknown	1158	8
Adjuvant therapy		
None	9396	64
VBT	1986	14
EBRT	2762	19
Radio- and chemotherapy	177	1
Chemotherapy	222	2
Other	21	0

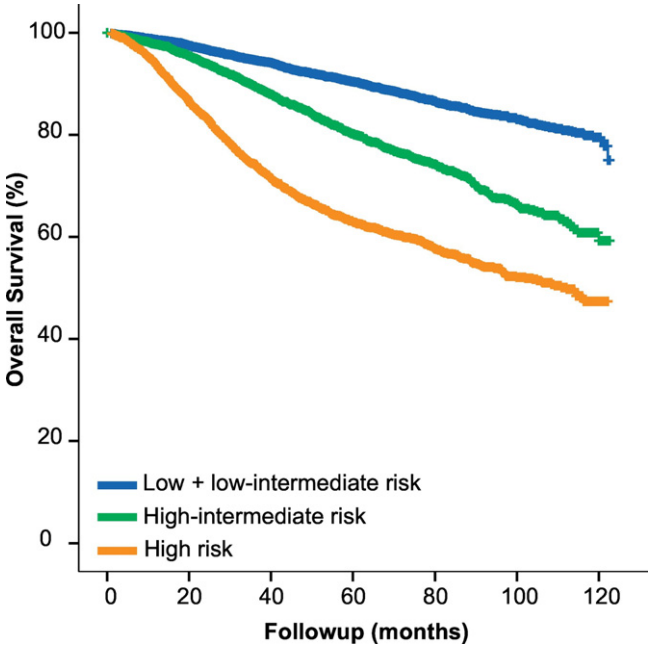

Fig. 1. Survival of patients with low + low-intermediate, high-intermediate or high risk endometrial cancer.

Compliance was 98% in the low and low-intermediate group, 78% in the high-intermediate and 61% in the high risk group ($p < 0.001$, Fig. 2A). There were no differences in compliance between the periods 2005–2009 (85%) and 2010–2014 (85%, $p = 0.847$, Fig. 2B). Compliance with guidelines varied from 80 to 90% in the eight oncologic regions ($p < 0.001$, Supplemental Fig. 1).

3.3. Compliance in high risk patients (N = 2995)

The compliance with the guidelines of only 61% in high risk patients prompted us to conduct a sub-analysis on this group. Of the 2995 high risk patients within our database 55% received EBRT, 11% received brachytherapy, 5% received radio- and chemotherapy, 4% received chemotherapy alone and 25% did not receive any adjuvant therapy (Supplemental Fig. 2). Unfavorable survival was demonstrated in patients that were not treated according to adjuvant therapy guidelines compared to those that were treated according to the guidelines. Mean overall survival was 86 months in the compliant group versus 76 months in the non-compliant group ($p < 0.001$, data not shown). This remained significant when correcting for age, type of tumor, grade, FIGO stage and socioeconomic status (adjusted HR 1.28, 95% CI 1.12–1.46, $p < 0.001$, data not shown).

Compliance with guidelines for high risk patients decreased from 64% in 2005–2009 to 57% in 2010–2014 ($p < 0.001$, Fig. 3A). A decrease was seen in the administration of EBRT (from 61% to 49%), while an increase in administration of VBT (from 7% to 14%) and combined radio- and chemotherapy (from 3% to 7%, data not shown) was observed. Compliance with guidelines in this group of patients showed large variation between the eight oncologic regions, ranging from 48 to 73% ($p < 0.001$, Fig. 3B).

3.4. Compliance in high risk patients with FIGO stage III serous disease (N = 124)

Another sub-analysis was conducted for high risk patients with FIGO stage III serous disease, as the adjuvant therapy guidelines for this group are different from other high risk patients. An evaluation of the administered adjuvant therapy revealed that 36% received chemotherapy, and 19% received radio- and chemotherapy, both of which are in compliance

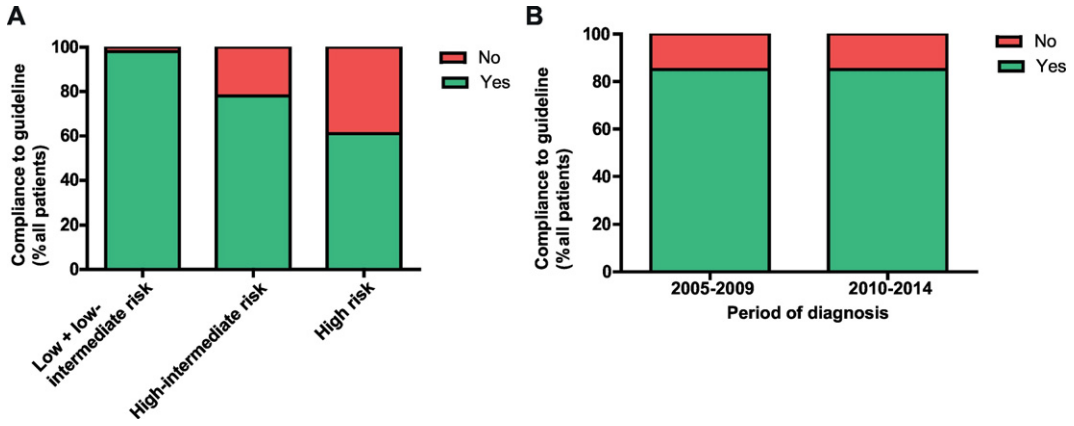

Fig. 2. Compliance with adjuvant therapy guidelines in low, low-intermediate, high-intermediate and high risk endometrial cancer patients (N = 13,568). A) Percentage of patients treated according to adjuvant therapy guidelines per risk group ($p < 0.001$). B) Percentage of patients treated according to adjuvant therapy guidelines per period of diagnosis ($p = 0.847$).

with the guidelines. Furthermore, 27% received EBRT, 1% received brachytherapy and 17% did not receive any adjuvant therapy (Supplemental Fig. 3). Patients treated according to adjuvant therapy guidelines had favorable survival outcomes compared to those that were not treated according to guidelines. Mean overall survival was 57 months in the compliant group versus 39 months in the non-compliant group ($p = 0.017$, data not shown). This difference disappeared when correcting for age and socioeconomic status (adjusted HR 1.49, 95% CI 0.90–2.45, $p = 0.119$, data not shown).

Compliance with the guidelines improved from 41% in 2005–2009 to 66% in 2010–2014 for patients with high risk FIGO stage III serous disease ($p = 0.007$, Fig. 4A). Between the eight oncologic regions compliance with guidelines ranged from 21 to 100% ($p = 0.014$, Fig. 4B).

3.5. Analysis of adjuvant treatment in patients with FIGO stage IV disease (N = 140)

National guidelines recommend individualization of adjuvant treatment in patients with FIGO stage IV disease. Within the study period, the most frequently administered adjuvant treatment for patients with FIGO stage IV disease was chemotherapy (43%, Supplemental Fig. 4). Thirty percent of patients did not receive any adjuvant therapy. When comparing the periods 2005–2009 and 2010–2014, the administration of chemotherapy increased from 30% to 49%, and the administration of EBRT decreased from 34% to 9%, respectively (data not shown). The administration of chemotherapy for patients with FIGO stage IV disease varied between 20% and 69% across the eight oncologic regions in the Netherlands ($p = 0.537$, statistical significance not reached due to small numbers, data not shown).

4. Discussion

Within the current study, compliance of physicians with national adjuvant therapy guidelines was assessed in 13,568 endometrial cancer patients between 2005 and 2014. Compliance was highest in low and low-intermediate risk patients (98%), and lowest in high risk patients (61%). Within the high risk patients a decrease in compliance with guidelines was demonstrated between the periods 2005–2009 and 2010–2014. Low, but increasing, compliance with guidelines was determined in a sub-analysis of high risk patients with FIGO stage III serous disease. Large variations were seen in clinical practice for high risk patients between the eight oncologic regions in the Netherlands.

Within the study period almost all patients with low and low-intermediate risk were treated according to the national guidelines. The specific guideline for low and low-intermediate risk groups is based on a strong body of evidence from the 'Post-Operative Radiation Therapy in Endometrial Cancer' (PORTEC) 1 and 2 studies and (pooled) trial results from the 'A Study in the Treatment of Endometrial Cancer' (ASTEC) and 'A Phase III Randomized Trial Comparing TAH BSO versus TAH BSO Plus Adjuvant Pelvic Irradiation in Intermediate Risk, Carcinoma of the Endometrium' (EN.5) trials [7,8,20–23]. These studies demonstrated that postoperative radiotherapy reduces locoregional recurrence in early stage endometrial cancer, but does not improve overall survival. In patients with low and low-intermediate risk (loco-regional recurrence risk of <5%) postoperative radiotherapy is not indicated. The excellent compliance with guidelines for low and low-intermediate risk patients may largely be attributable to the availability of high quality evidence supporting this guideline.

Compared to patients with low or low-intermediate risk, a lower compliance of physicians with guidelines was observed in patients with high-intermediate and high risk endometrial cancer. The

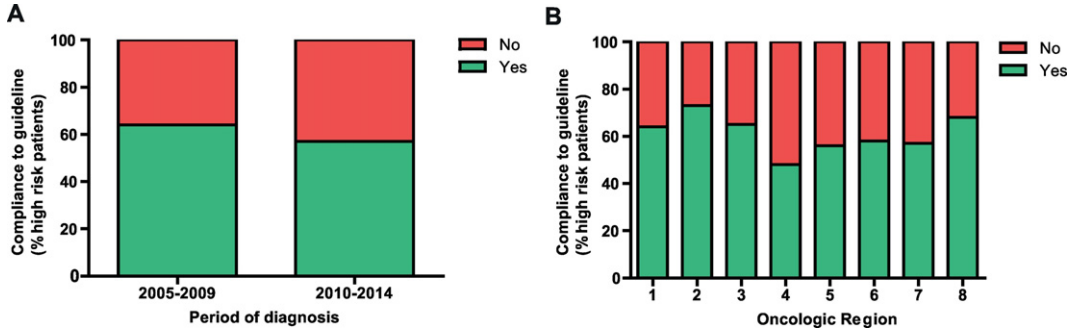

Fig. 3. Compliance with adjuvant therapy guidelines in high risk endometrial cancer patients (N = 2995). A) Percentage of patients treated according to adjuvant therapy guidelines per period of diagnosis ($p < 0.001$). B) Percentage of patients treated according to adjuvant therapy guidelines per oncologic region ($p < 0.001$). The number of high risk endometrial cancer patients was 435 in region 1, 218 in region 2, 539 in region 3, 353 in region 4, 282 in region 5, 653 in region 6, 250 in region 7 and 263 in region 8.

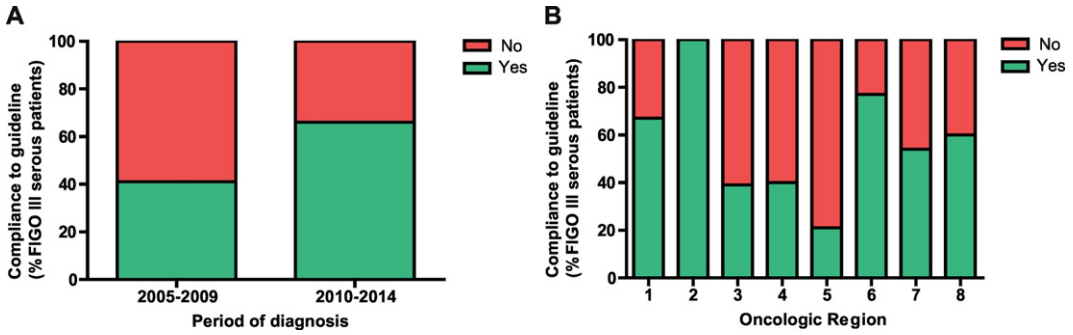

Fig. 4. Compliance with adjuvant therapy guidelines in high risk FIGO stage III serous endometrial cancer patients (N = 124). A) Percentage of patients treated according to adjuvant therapy guidelines per period of diagnosis (p = 0.007). B) Percentage of patients treated according to adjuvant therapy guidelines per oncologic region (p = 0.014). The number of high risk FIGO stage III serous endometrial cancer patients was 21 in region 1, 2 in region 2, 23 in region 3, 10 in region 4, 14 in region 5, 26 in region 6, 13 in region 7 and 15 in region 8.

indication for adjuvant radiotherapy in high-intermediate and high risk endometrial cancer is largely based on results from the PORTEC-1 and 2 studies [7,20,22,23]. Importantly, no difference in overall or disease free survival was demonstrated in these studies. The lack of survival benefit from adjuvant radiotherapy (EBRT and VBT) compared to observation was also confirmed by in other studies such as the ASTEC study and a Cochrane review [8,9]. Considering the lack of survival benefit of adjuvant radiotherapy and the risk of potential toxicity [20,23,24], it is possible that some high-intermediate and high-risk patients may have been deemed unfit or unwilling to undergo radiotherapy. In this regard, comorbidities and patient preferences may have affected compliance with guidelines in high-intermediate and high-risk patients, but this could not be assessed as this information was not available in the NCR.

Within the study period a strong increase in administration of chemotherapy for high risk patients, and specifically for patients with FIGO stage III serous disease, was demonstrated. An increase in administration of chemotherapy was also described in an evaluation of clinical practice regarding adjuvant therapy for endometrial cancer in Germany between 2009 and 2013 [25]. This change in clinical practice may be attributed to studies suggesting a beneficial role for chemotherapy in high risk patients [26–28]. The eagerly awaited results from the PORTEC 3 and Gynecologic Oncology Group (GOG) 0258 may provide more definitive direction regarding chemotherapy as therapeutic modality in the management of high risk endometrial cancer patients.

Although an increase in use of adjuvant chemotherapy in FIGO stage III serous disease was seen, its value in this specific group of patients is subject of debate. Available literature is inconsistent and of low quality as it is based on retrospective analyses or unplanned subgroup analyses from randomized controlled trial data. For example, a comprehensive review by the Society of Gynecologic Oncology concluded that platinum/taxane chemotherapy should be considered in the treatment of early- and advanced stage serous endometrial cancer [29]. In contrast, an analysis of patients participating in GOG chemotherapy trials demonstrated that response to chemotherapy was not associated with histology [30]. Furthermore, an unplanned data-driven subgroup analysis on results from the NSGO/EORTC study did not demonstrate any survival benefit from radiotherapy in combination with chemotherapy compared to radiotherapy alone in patients with serous and clear cell tumors (overall survival was 77% and 78%, respectively) [27]. It is likely that low compliance with guidelines in adjuvant treatment of patients with high risk FIGO stage III serous endometrial cancer is attributable to the lack of unequivocal evidence on this topic. Importantly, the relatively small number of patients with high risk FIGO stage III serous endometrial cancer within our cohort may have influenced the clinical variation between the 8 oncologic regions.

In an effort to decrease differences in clinical management of endometrial cancer worldwide, an ESMO-ESGO-ESTRO consensus conference was held in 2014 [31]. At this conference a multidisciplinary panel comprising 40 experts in the management of endometrial cancer developed evidence-based guidelines on selected clinically relevant topics. The effect of these new evidence-based guidelines on discrepancies in management of endometrial cancer around the globe, and on compliance of physicians with guidelines within the Netherlands, remains to be elucidated.

While our database comprises a large population-based sample of patients, the retrospective design of this study has some limitations. First of all, no information was available concerning the presence of lymph vascular space invasion. This prognostic factor could therefore not be incorporated into the risk stratification. Secondly, the NCR does not register presence of comorbidity. As such, comparison of survival in patients treated according to guidelines and patients treated otherwise could not be corrected for the presence of comorbidity. To address this in part, we corrected for socioeconomic status which is known to be associated with comorbidity [32]. Furthermore, progression free survival could not be assessed due to the absence of information on recurrences. Finally, it was impossible to evaluate whether noncompliance was attributable to patient factors (such as refusal of therapy or frailty) or to clinician factors (such as negative judgment of benefit of therapy) as information regarding reasons for noncompliance were lacking. Prospective registration of reasons for noncompliance with adjuvant therapy guidelines in endometrial cancer is warranted to gain insight in reasons for noncompliance, especially considering current emphasis on shared decision-making.

In conclusion, we assessed compliance of physicians with national adjuvant therapy guidelines in 13,568 endometrial cancer patients between 2005 and 2014. While compliance with guidelines was excellent in low and low-intermediate risk patients, there is room for improvement in high risk endometrial cancer patients. Though recent efforts aimed at reducing the lack of international consensus regarding clinical management of endometrial cancer may have provided some guidance, large clinical studies are warranted to resolve the remaining controversies. In line with this, results of ongoing randomized clinical trials are eagerly awaited.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygyno.2017.05.025.

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Disclosure statement

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