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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

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