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ORIGINAL ARTICLE

Is pre-operative risk-assessment in laparoscopic treatment of presumed low-risk endometrial cancer effective?

P. A. H. H. van der Heijden · Y. P. Geels · S. H. M. van den Berg-van Erp · L. F. A. G. Massuger · M. P. M. L. Snijders

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Abstract In endometrial (pre)malignancy the pre-operative work-up is primarily based on the histopathological specimen obtained. Total laparoscopic hysterectomy with bilateral salpingo-oophorectomy (TLH + BSO) in presumed low-risk clinical stage I endometrioid endometrial carcinoma (EEC) or atypical hyperplasia (AH), is nowadays considered preferred and sufficient treatment in the Netherlands. To test the effectiveness of this pre-operative work-up, a retrospective cohort analysis was performed. Revised pre- and post-operative histopathology was compared and intra- and post-operative complications registered. In 116 consecutive patients with a pre-operative diagnosis of AH or presumed stage I, grade I or II EEC planned for TLH + BSO. In 24.1 % (28/116) revised endometrial histopathology was upgraded on the definitive hysterectomy specimen. In 3.5 % (4/116) upgrading to high-risk grade III endometrial cancer (EC) was observed. In 9.9 % (8/81) of EC cases a post-operative FIGO stage IG3, II, or III was diagnosed. The major and minor short-term complication rates of TLH + BSO were 12.1 and 7.8 %. In 13.8 % (16/116) of cases conversion to laparotomy was necessary, with a significant higher percentage of obese (68.8 %) patients in the conversion versus the successful TLH + BSO group (42 %). Clinical relevant inconsistency between pre- and post-operative histopathology or FIGO stage was observed in 9.9 % of EC cases. More extensive pre-operative risk analysis of presumed low-risk EEC may be indicated, especially for the morbid obese, harboring a substantial risk for conversion to laparotomy and complications.

Keywords Endometrial cancer · Total laparoscopic hysterectomy · Complications · Histopathology · Pre-operative · Biopsy

P. A. H. H. van der Heijden · M. P. M. L. Snijders
Department of Obstetrics and Gynaecology, Canisius-Wilhelmina Hospital, Nijmegen, The Netherlands

Y. P. Geels · L. F. A. G. Massuger
Department of Obstetrics and Gynaecology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

S. H. M. van den Berg-van Erp
Department of Pathology, Canisius-Wilhelmina Hospital, Nijmegen, The Netherlands

P. A. H. H. van der Heijden (✉)
Department of Obstetrics and Gynaecology, Maxima Medical Centre, PO Box 777, Veldhoven 5500 MB, The Netherlands
e-mail: pattyvanderheijden@gmail.com

Background

Annually, 1,900 new cases of endometrial cancer (EC) are diagnosed in the Netherlands. The incidence is increasing due to a rise in obesity and life-expectancy [1, 2]. As women with uterine cancer most often present with abnormal vaginal bleeding as an early symptom, in 75–90 % of the patients, the disease is still confined to the uterine body and classified as Fédération Internationale de Gynécologie Obstétrique (FIGO) stage I [3].

Two different risk types of EC are recognized. Type I carcinomas display well or moderately differentiated endometrioid histology and arise in relatively younger women with obesity, hyperlipidemia, and signs of hyperestrogenism. Hormonally induced atypical endometrial hyperplasia (AH) is observed as a common precursor of and already coexisting with endometrioid endometrial cancer (EEC) type I in the uterine cavity in 30–40 % of patients. Type II carcinomas include poorly differentiated endometrioid, clear cell or serous histology, and carcinosarcoma arising in an atrophic endometrial background, more often arising in non-obese, older women who demonstrate no hormonal risk factors and carry a less favorable course and prognosis [4]. According to the Dutch Guidelines, the pre-operative histopathological diagnosis is

obtained using Pipelle or hysteroscopic biopsies to retrieve a representative endometrial specimen. The pre-operative work-up of presumed low-risk EEC includes routine blood testing and chest x-ray, without the use of extra radiological techniques like Magnetic Resonance Imaging (MRI). Thus, in presumed low-risk clinical stage I endometrial (pre)malignancy, i.e., AH or grade I or II EEC, hysterectomy with bilateral salpingo-oophorectomy (BSO) without lymphadenectomy is considered as sufficient surgical treatment (http://www.oncoline.nl/endometriumcarcinoom). Adjuvant radiotherapy, minimizing the risk of loco-regional recurrence, is tailored to post-operative histopathological and well-defined clinical risk factors, the so-called post-operative radiation therapy for endometrial carcinoma (PORTEC) criteria. [5].

Recently, a well-designed prospective randomized Dutch trial comparing total abdominal hysterectomy (TAH) with total laparoscopic hysterectomy (TLH + BSO) revealed superior results for the laparoscopically treated patients. However, as pointed out by Mourits et al., laparoscopic treatment may not be without harm to certain patient groups [6]. In high-risk type II endometrial cancer, a maximal surgical intervention is indicated including pelvic/para-aortic lymphadenectomy and/or omentectomy and/or peritoneal biopsies. This procedure leads to more complete surgical FIGO staging, indicating possible necessary adjuvant chemotherapy and/or radiotherapy. In the Netherlands, this procedure is centralized and performed by well-trained gynecologic oncologists (http://www.oncoline.nl/endometriumcarcinoom).

Thus, correct pre-operative assessment of low- versus high-risk EC including histopathological and clinical aspects appears crucial to individualize the surgical treatment. Pre-operative incorrect diagnosis of tumor histology, grade III, or advanced FIGO stage carries the risk of surgical undertreatment [7]. With respect to the preferred laparoscopic route in low-risk EEC, pre-operative risk analysis of co-morbidity resulting in a potential higher chance for complications may also be of importance.

The purpose of this retrospective analysis on a consecutive series of pre-operatively presumed low-risk AH or EEC patients planned for TLH + BSO is, first, to analyze the level of consistency between pre- and post-operative data on histopathology and presumed FIGO stage I and second, to analyze the operative results of TLH + BSO procedure in terms of short-term major and minor complications.

Methods

A retrospective analysis was conducted on all consecutive patients ($n = 116$), pre-operatively diagnosed with AH or grade I or II clinical FIGO stage I EEC, scheduled for TLH + BSO between January 2006 and November 2012 at the Canisius-Wilhelmina Hospital, Nijmegen. Patients with pre-operative high-risk EC, i.e., grade III EEC or non-endometrioid type were not included. Clinical data on age, parity, menopausal status, co-morbidity, body mass index (BMI in kilogram per cubic meter), with a BMI of >30 categorized as obese according to World Health Organization criteria, presenting symptoms at time of diagnosis and post-operative FIGO stage of disease were registered from the medical charts (http://www.who.int/gho/ncd/risk_factors/bmi_text/en/).

Pre-operative histopathological diagnosis of AH or grade I or II EEC was based on endometrial biopsy, performed with Pipelle and/or diagnostic hysteroscopy in all patients, according to the national guidelines in the diagnostic work-up of postmenopausal or irregular bleeding (http://nvog-documenten.nl/index.php?pagina=/richtlijn/pagina.php&fSelectTG_62=75&fSelectedSub=62&fSelectedParent=75).

Histopathological review

All histopathological slides of the pre- and post-operative specimens were retrieved from the archive and revised by a gynecopathologist (SvB) and an experienced Ph.D. researcher (YG), unaware of original pathology report and clinical outcome of patients. Review of pre- and post-operative specimens included systematic determination of the endometrium: benign, hyperplasia, or carcinoma, and in case of carcinoma, histological type and tumor grade. When in the initial report only "low-grade" EEC was described, grade II EEC was classified. Review of post-operative specimens included determination of the endometrium as well, and in case of malignancy: histological type, tumor grade, depth of myometrial invasion (>50 or <50 %), lympho-vascular space invasion, and cervical, tubal, or ovarian metastatic growth. In case of discrepancy between the reviewers, consensus was reached reviewing the slides together.

Surgery

The TLH + BSO surgical procedure consisted of laparoscopic hysterectomy with bilateral salpingo-oophorectomy without pelvic and/or para-aortic lymphadenectomy as described by Mourits et al. [6] All data on operative time, estimated blood loss (milliliter), conversion to laparotomy and intra- and post-operative complications were retrieved from the Dutch standardized operation and complication registration documents used (http://www.nvog.nl/vakinformatie/Pati%C3%ABntveiligheid/Complicatieregistratie/Complicatieregistratie+en+bespreking.aspx).

Statistical analysis

Comparisons were made between reviewed pre-operative and post-operative histopathological results. Patient characteristics for the successful laparoscopic group were compared with the patient characteristics of the group who underwent conversion to laparotomy using Pearson's chi-Square (χ^2) test and Fisher's exact test. Occurrence of major and minor complications was compared for the laparoscopic and the conversion group using Fisher's exact test. All statistical analyses were performed using SPSS 19. The P values presented are two-sided and $P<0.05$ was considered statistically significant.

Ethical approval board

All patient characteristics remained unidentifiable receiving the standard treatment according to the Dutch Guidelines (http://www.oncoline.nl/endometriumcarcinoom), (http://nvog-documenten.nl/index.php?pagina=/richtlijn/pagina.php&fSelectTG_62=75&fSelectedSub=62&fSelectedParent=75). Therefore, approval from the Ethical Approval Board was not necessary.

Findings

Patient characteristics

Patient characteristics are shown in Table 1. Age ranged from 41 to 89 years (median, 62 years). In 53/116 (45.7 %) patients, a BMI of more than 30 was noted.

Histopathology

Table 2 summarizes the differences between the original histopathology and revised histopathology for both pre- and post-operative specimens. Post-operatively, in total, 83 patients were diagnosed with a malignancy, including two patients diagnosed with ovarian malignancy: one with extra/ovarian serous carcinoma showing normal endometrium with serous tumor cells coexisting inside the uterus, and one with an adult granulosa cell tumor of the ovary showing normal endometrium without AH. Of the 81 patients with EC, 79 patients after review were diagnosed with EEC, 1 with grade III mixed clear cell/endometrioid carcinoma, and 1 with grade III mixed serous/endometrioid carcinoma. Twenty-six patients were diagnosed with AH and seven revealed no malignancy nor AH in the hysterectomy specimen.

Post-operative diagnosis was upgraded from AH to EEC and from grades I or II to III in 28/116 (24.1 %) patients. In 4/116 (3.5 %) patients, there was an upgrading to grade III, with 1 patient being upgraded because of mixed clear cell and 1 patient because of mixed serous histology.

Table 1 Patient characteristics in 116 consecutive patients planned for TLH + BSO

	$N=116$
Age (years)	
Mean (SD)	61.8 (8.5)
Parity	
Nulliparous (%)	10 (8.6)
Multiparous (%)	106 (91.4)
Median	2
Range	0–6
Missing data	1
Menopausal status	
Premenopausal (%)	8 (6.9)
Climacteric (%)	4 (3.5)
Postmenopausal (%)	105 (90.5)
Co-morbidity factors	
Obesity (BMI>30) (%)	53 (45.7)
BMI mean (SD)	30.0 (6.35)
Diabetes (%)	18 (15.5)
Previous abdominal surgery (%)	37 (31.9)

SD standard deviation, *BMI* body mass index

In case of EEC, deep myometrial invasion (extending to outer half of the myometrium, i.e. >50 %) was observed post-operatively in 26/81 (32.1 %) of the patients. In 76/81 (93.8 %) patients, FIGO stage I was diagnosed (54 FIGO stage IA and 22 FIGO stage IB); in 5/81 patients (6.2 %) FIGO stage II or III and in two patients, an ovarian malignancy was diagnosed. All patients were adjuvantly treated according to the PORTEC criteria, i.e., when two of three risk factors were present, patients underwent post-operative radiotherapy [5, 8].

Clinical relevant inconsistencies

Table 3 shows the patient data on clinical relevant post-operative upgrading and/or upstaging occurring in 8/81 (9.9 %) of patients with malignant histopathology (4 because of post-operative upgrading to grade III; 5 because of upstaging to > stage I).

Conversion to laparotomy

In total, 100/116 patients (86.2 %) underwent a successful TLH + BSO, in 16/116 patients (13.8 %) intra-operative conversion to laparotomy was necessary. The reasons not to proceed with laparoscopic surgery mentioned in the operation report were too many adhesions in five patients, too large size of the uterus in three patients to remove the uterus vaginally,

Table 2 Pre-operative versus reviewed post-operative endometrial histopathology and FIGO staging

Histology and grade (%)	Pre-operative $N=116$	Revision	Post-operative	Revision $N=116$
Atrophy/dp	0	2	6	3 (2.6)
Hyperplasia	0	0	5	4 (3.5)
AH	45 (38.8)	36	24	26 (22.4)
EEC G1	41 (35.4)	51	48	55 (47.4)
G2	30 (25.7)	27	28	22 (19.0)
G3	0	0	1	2 (1.7)
Clear cell G3	0	0	1	1 (0.9)
Mixed G3	0	0	1	1 (0.9)
*	0	0	1	1 (0.9)
#	0	0	1	1 (0.9)
Myometrial invasion if endometrial carcinoma present				$N=81$
No invasion				19 (23.5)
<½				36 (44.4)
>½				26 (32.1)
FIGO stage after revision of endometrial hysterectomy specimens				$N=81$
IA				**54**
G1				43
G2				9
G3				2
IB				**22**
G1				15
G2				6
G3				1
II				**2**
G1				2
III				**3**
A G1				1
A G2				1
C2G3				1

Dp disordered proliferative, # adult granulosa cell tumor of the ovary, * extra ovarian serous carcinoma

technical in two patients (i.e., strategically in 10/16 patients) besides intra-operative bleeding in three patients, bladder lesion in one patient and anesthesiological problems in two patients (i.e., intra-operative complications in 6/16 patients).

Complications

Fourteen major complications were observed in nine patients (Table 4). The major and minor short-term complication rates of TLH + BSO were 12.1 and 7.8 %, respectively. Nine major complications occurred in five patients who underwent a successful TLH + BSO procedure versus five major complications in four patients who underwent conversion to laparotomy (25 % of 16 patients, $P=0.022$). The minor complication rate was 50 % in the conversion group, versus 6.0 % in the TLH + BSO group ($P=0.001$). Comparison of co-morbidity factors between the TLH + BSO group and the conversion group reveals a significantly higher percentage (68.8 %) of obese patients compared to the group in whom the TLH + BSO was successful (42.0 %, $P=0.049$).

Conclusions

In this retrospective cohort analysis on daily practice in pre- versus post-operative histopathology and FIGO stage in 116 presumed low-risk endometrial (pre)malignancy-patients planned for TLH + BSO, diagnosis was either changed from AH to EEC, or from EEC grade I or II upgraded to grade III or non-endometrioid histology in 24 % of cases. This figure is somewhat higher than 15–20 % upgrading reported by Daniel et al., however, they only analyzed pre-operative grade I EEC patients [9]. In 32 % of the 81 patients with EC in the current study, deep myometrial invasion (>50 %) was observed. This percentage is also somewhat higher compared to 25 % described by Ben-Shachar et al., but in their study, again, only patients with EEC grade I were included [10]. Of course, grade and absolute depth of myometrial invasion are closely interrelated as described recently by our group [11] Advanced FIGO stage was found in 6.2 % of patients, which is lower than the 10.5 % described by Ben-Shachar et al., however, in our patient cohort information, lymph node status is absent ruling out occult stage III disease.

In the present study, post-operative upgrading and/or upstaging was clinically relevant in 9.9 % of EC patients (three patients because of upgrading to grade III or non-endometrioid histology, five patients because of FIGO > stage I, one patient because of both). These patients were surgically undertreated according to the Dutch guidelines (http://www.oncoline.nl/endometriumcarcinoom). Although surgical re-staging including pelvic and para-aortic lymphadenectomy is proposed to these patients, patients and clinicians may be reluctant with repeated abdominal surgery because of an increased risk of complications. Instead, these high-risk patients are most often treated with adjuvant radio- and/or chemotherapy. However, doing so ignorant of pelvic and/or para-aortic lymph node status, adjuvant therapy may in turn be over-treatment, leading to potential unnecessary morbidity. In this respect, a more thorough pre-operative analysis of "clinical behavior markers" may be applied, indicating aggressive tumor biology more exact than histopathology and grade alone. Differences in carcinogenic pathways between the two EC types are already apparent. Type I carcinomas are characterized by diploid tumors, expression of estrogen and progesterone receptors, *PTEN* alterations, microsatellite instability and mutations of *KRas* and *CTNNB1*. Type II carcinomas on the contrary, are often aneuploid, and show over expression of

Table 3 Clinical relevant inconsistencies between pre-operative and reviewed post-operative

Histopathology and FIGO staging in 8 patients				
Patients	Pre-operative	Post-operative	Myometrial invasion (%)	FIGO stage
1	EEC G2	EEC G3	<50	IA G3
2	EEC G1	Mixed G3	<50	IA G3
3	EEC G2	EEC G3	>50	IB G3
4	AH	EEC G1	>50	II G1
5	EEC G1	EEC G1	<50	II G1
6	EEC G2	EEC G1	>50	IIIA G1
7	EEC G2	EEC G2	>50	IIIA G2
8	EEC G2	CC G3	>50	IIIC2 G3

p53 and Her2/neu [12–15]. Analysis of aforementioned markers on the pre-operative specimen may lead to more individualized and effective surgical treatment planning for the low- versus high-risk patients. Furthermore, standard pre-operative MRI and/or intra-operative frozen section assessment of myometrial invasion may be useful in assessment of correct FIGO stage. However, as the accuracy of pre-operative MRI assessment may be only 70.7 % [16] and as already 90. 1 % of AH and EEC patients in this series was already pre-operatively correct classified as low-risk, standard use of pre-operative radiological imaging techniques may not be cost-effective. On the other hand, as was recently recognized by two large randomized studies comparing surgery for early endometrial cancer with or without lymphadenectomy, there appears no benefit for standard pelvic and/or para-aortic lymphadenectomy in this presumed low-risk patient category [17, 18].

In 116 TLH + BSO procedures, the major complication (12.1 %) and conversion (13.8 %) rates were comparable to the figures of 14.6 and 10.8 % in the prospective study of

Table 4 Number and types of short-term complications and co-morbidity factors in 116 patients with completed TLH + BSO or conversion to laparotomy

	Overall $n=116$	TLH $n=100$	Conversion $n=16$	P value
Co-morbidity factors (%)				
Obese (BMI>30)	53	42 (42.0)	11 (68.8)	0.049
Hypertension	55	45 (45.0)	10 (62.5)	0.207
Diabetes	18	13 (13.0)	5 (31.3)	0.058
Previous abdominal surgery	37	31 (31.0)	6 (37.5)	0.586
Perioperative complication rates (%)				
Patients with major complications	9 (7.8)	5 (5.0)	4 (25.0)	0.022
Type of major complications	14	9	5	
Bowel injury	1 (0.9)	1 (1.0)	0	
Bladder injury	2 (1.7)	1 (1.0)	1 (6.3)	
Infection	3 (2.6)	2 (2.0)	1 (6.3)	
Ileus	2 (1.7)	1 (1.0)	1 (6.3)	
Hemorrhage*	3 (2.6)	1 (1.0)	2 (12.5)	
Hematoma*	3 (2.6)	3 (3.0)	0	
Patients with minor complications (%)				
Type of minor complications	14 (12.1)	6 (6.0)	8 (50.0)	0.001
Urinary tract infection, fever <38	3 (2.6)	1 (1.0)	2 (12.5)	
Urinary retention needing catheter	1 (0.9)	1 (1.0)	0 (0)	
Fever <38	2 (1.7)	0 (0)	2 (12.5)	
Hemorrhage/hematoma without transfusion	7 (6.0)	4 (4.0)	3 (18.8)	
Wound dehiscence without intervention	1 (0.9)	0 (0)	1 (6.3)	

BMI body mass index

*requiring intervention

Mourits et al. [6]. In several prospective controlled studies, it has been shown that TLH is an effective, minimally invasive, safe alternative to total abdominal hysterectomy [19, 20]. Most studies show reduced incidence of treatment-related morbidity, a shorter hospital stay, less blood loss, less pain, and quicker resumption of daily activities with the laparoscopic approach compared to laparotomy. However, most studies are based on healthier populations, bearing benign uterine problems. In contrast, Mourits et al. showed no evidence of a lower major complication rate for TLH + BSO over total abdominal hysterectomy by laparotomy in endometrial (pre)malignancy. In addition, no differences in the quality of life were reported. However, they also did observe a benefit for TLH in the treatment-related outcomes (i.e., less blood loss, shorter operating times, shorter hospital stay) [6].

In our analysis, patients who underwent a conversion to laparotomy showed a significantly higher percentage of major as well as minor complications, post aut propter the conversion. Also, patients with a BM of >30 showed a significantly higher risk for conversion to laparotomy. In recent literature, it is often mentioned that patients with a high BMI and older patients benefit most from TLH [19, 20]. However, the current opinion about TLH for endometrial cancer might be based on overoptimistic reports due to a paucity of randomized trials. In this respect, it is interesting that de Bijen et al. recently reported the opposite, indicating that TLH is not cost-effective in patients with a BMI over 35, based on major complication-free rates as a primary measure of effect. In their opinion, TLH should not be recommended in patients with a BMI of >35 due to a high conversion rate and unfavorable cost effectiveness [21]. Potentially, reference to centers of excellence in operating the morbid obese may be of help. As endometrial cancer incidence is rising in overweight and elderly patients bearing significant co-morbidity, being able to select patients pre-operatively at substantial risks on conversion and complications would help a great deal, counseling the individual patient on risks and benefits of TLH versus TAH.

Although all histopathological specimens were reviewed, this analysis has some limitations; first being retrospective. Second, we did not compare the pre- versus post-operative differences regarding histopathology, FIGO stage, and complication rates in patients treated primarily by laparotomy. Thus, there could be a bias of patient selection on choosing the approach of surgery. However, in this consecutive series, a substantial number of obese patients (45.7 %) and patients with previous abdominal surgery (31.9 %) were included, undergoing a laparoscopic procedure.

In conclusion, 9.9 % of patients with presumed low-risk EEC or AH treated with TLH + BSO were post-operatively diagnosed with high-risk endometrial cancer and thus surgically undertreated. Furthermore, conversion from TLH + BSO to laparotomy (13.8 %) was accompanied by a significantly increased risk of major and minor complications. The chance of conversion appeared significantly higher in obese patients. Centralization of surgery for the morbid obese patients might lead to reduction of these complication rates. Furthermore, a more thorough pre-operative work-up of presumed low-risk EEC is considered by including biomarkers of high-risk tumor behavior and MRI-imaging giving more insight into myometrial invasion and FIGO stage.

Conflict of Interest None of the authors had conflicting interests in this study.

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