EJGO European Journal of Gynaecological Oncology

The opinion of gynecologists on the management of early-stage, high-grade endometrioid endometrial cancer

Y.P. Geels[1], L.J.M. van der Putten[1], E.M. van der Steen-Banasik[2], M.P.M.L. Snijders[3], L.F.A.G. Massuger[1], J.M.A. Pijnenborg[4]

[1] Department of Obstetrics and Gynecology, Radboud university medical center, Nijmegen
[2] ARTI Institute for Radiation Oncology, Arnhem; [3] Department of Obstetrics and Gynecology, Canisius-Wilhelmina Hospital, Nijmegen
[4] Department of Obstetrics and Gynecology, TweeSteden Hospital, Tilburg (The Netherlands)

Summary

Purpose of investigation: There is no consensus on the management of Stage I endometrioid endometrial cancer (EEC) with grade 3 histology. This study evaluates the opinion of gynecologists in The Netherlands on the management of Stage I, grade 3 EEC. *Materials and Methods:* Members of the Dutch Gynecologic Oncology Working Group were requested to complete a digital questionnaire on the management of Stage I, grade 3 EEC. Actual treatment of patients with Stage I, grade 3 EEC was assessed by analysis of PALGA, the Dutch Pathology Registry. *Results:* Most gynecologists prefer routine lymphadenectomy or complete staging (62.3%), while these were actually performed in 27.3% of the cases. Gynecologic oncologists are more likely to perform a lymphadenectomy than general gynecologists. There was a wide variation of clinical practice. *Conclusion:* The results of this study underline the need for additional research into management of Stage I, grade 3 EEC as well as the need for conclusive guidelines.

Key words: Endometrioid histology; Endometrial cancer; Grade 3; Questionnaire; Lymphadenectomy; Guidelines.

Introduction

Cancer of the uterine corpus is the most common gynecologic malignancy in the Western world, with incidence and mortality rates of respectively, 1,913 and 484 in The Netherlands in 2011 [1]. Most patients present with endometrioid endometrial cancer (EEC) at an early stage, and have a favorable prognosis. Standard treatment of clinical Stage I EEC consists of hysterectomy and bilateral salpingo-oophorectomy. Based on the PORTEC trials, in The Netherlands, vaginal brachytherapy (VBT) is recommended when two out of three risk factors (age $\geq$ 60 years, myometrial invasion (MI) $\geq$ 50%, and grade 3 histology) are present, and external beam radiotherapy (EBRT) is recommended when all three are present [2-4].

The Dutch guidelines on the treatment of endometrial cancer were revised in 2010 on several aspects as shown in Table 1 [4]. Most important were recommendations to consider more extensive diagnostics in high-risk patients, a shift from pelvic and para-aortic lymphadenectomy to lymph node sampling, and the consideration of chemotherapy in high-risk patients. However, in the revised guideline, the management of patients with clinical Stage I, grade 3 EEC is still left to the clinicians' opinion.

The primary aim of this study was to analyze the opinion of gynecologists in The Netherlands on the management of clinical Stage I, grade 3 EEC and to assess differences between gynecologists with different levels of oncologic training. Furthermore, these opinions were compared to the recommendations of the revised guidelines and the actual treatment of patients with Stage I, grade 3 EEC in The Netherlands.

Materials and Methods

Gynecologic cancer care in The Netherlands is organized by regional hospitals around tertiary referral centers. Gynecologic oncologists are trained as fellows and work in referral centers. Patients with endometrial cancer can be treated by both general gynecologists and gynecologic oncologists and are referred on indication. The Dutch Gynecologic Working Group is a division of the Dutch Society of Obstetrics and Gynecology and both gynecologic oncologists and general gynecologists can become a member.

A digital questionnaire was spread among all (around 200) members of the Dutch Gynecologic Oncology Working Group. Questions are related to the following, fictive case: *a 55-year-old patient is diagnosed with poorly differentiated (grade 3), clinical Stage I, endometrioid endometrial cancer by either pipelle or dilatation and curettage. Medical history does not obstruct surgery.* Questions (shown in Table 2) ranged from the diagnostic work-up to the primary and adjuvant therapy. After every section, there was space for comments (questions 6, 16, and 19).

To assess actual practice of performing lymphadenectomies, the Dutch nationwide network and registry of histo- and cytopathology (PALGA) was consulted [5]. All patients diagnosed pre-operatively with grade 3 EEC between July 2009 and June 2010 were selected. In the pathology report, it was mentioned

Revised manuscript accepted for publication April 3, 2014

7847050 Canada Inc.
www.irog.net

Table 1. — *Summary of the old and the new Dutch guideline for Stage I endometrial cancer.*

	Old	New [4]
Diagnostics	History taking, examination, transvaginal ultrasound, and chest radiography. CA-125 when extra-uterine disease is suspected. No CT-scan or MRI.	History taking, examination, transvaginal ultrasound, and chest radiography. CA-125 when extra-uterine disease is suspected. CT-scan or MRI can be considered in patients with grade 3 histology.
Surgery	Hysterectomy and bilateral salpingo-oophorectomy. A lymphadenectomy might be considered in patients with grade 3 histology.	Hysterectomy and bilateral salpingo-oophorectomy. Sampling of suspicious nodes.
Adjuvant Therapy	When ≥ 2 risk factors* are present, vaginal brachytherapy is advised. If there is both grade 3 histology and MI ≥ 50%, external beam radiotherapy is advised. Chemotherapy is not advised.	When ≥ 2 risk factors* are present, vaginal brachytherapy is advised. If there is both grade 3 histology and MI ≥ 50%, external beam radiotherapy is advised. Possibly in combination with chemotherapy.

* Risk factors: age ≥ 60 years, grade 3 histology and myometrial invasion (MI) ≥ 50%.

whether lymph nodes were received postoperatively and what their origin was. Only completely documented cases were eligible for inclusion. As clinical FIGO Stage is not registered in this database, this search contained patients suspected of all stages EEC.

IBM SPSS 20 was used for statistical analysis. The difference in answers between gynecologic oncologists and general gynecologists was calculated using the Pearson's chi square, the Fisher's exact test, and bivariate regression analysis. Results were considered significant at a p value ≤ 0.05. Further analysis of the data was observational.

Results

A total of 61 out of 200 gynecologists returned the questionnaire, leading to a response rate of 30%. All answers are shown in Table 2. Half of the responders (n=31) were gynecologic oncologists. There was no consensus among responders concerning the need for abdominal CT-scan and CA-125 measurement. With respect to the primary treatment, 37.7% would omit routine lymphadenectomy (n=21), or recommend sampling of suspicious lymph nodes only (n=2). The majority of the responders, 62.3% (n=38) was in favor of more extensive surgical staging. The age of the patient did not influence the opinion on initial management for most responders. In case no lymphadenectomy was performed, 91.8% (n=56) recommended adjuvant treatment. When a lymphadenectomy was performed and nodes were proven to be negative, only 54.1% (n=33) recommended (at least) adjuvant radiotherapy.

The number of gynecologic oncologists opting to perform a systematic lymphadenectomy was significantly higher compared to general gynecologists (77.5% *vs.* 46.7%, p = 0.02), with an odds ratio of 3.9 (95% CI 1.3-11.8, p = 0.02) in univariable regression analysis. There were no other significant differences.

It was commented that an abdominal CT-scan could be helpful in diagnosing metastases (n=6) and nodal disease (n=5). Nine responders recommended abdominal CT only in case of an elevated CA-125 or in combination with CA-125 measurement. Three responders preferred MRI for assessing myometrial invasion. There were no comments concerning primary surgery. Three responders found it impossible to decide on adjuvant treatment without knowing the extent of myometrial invasion.

Seventy patients retrieved by the PALGA search were treated for grade 3 EEC between July 2009 and June 2010, and the database contained complete information on primary surgical treatment in 55 (79%). In total, 14 patients (25.5%) underwent a lymphadenectomy. Nine (16.4%) underwent a pelvic lymphadenectomy and five (9.1%) both a pelvic and para-aortal lymphadenectomy. Positive nodes were found in three of these 14 cases (23%).

Discussion

This study shows that there is no agreement in The Netherlands concerning the diagnostic work-up and primary and adjuvant treatment for patients with Stage I, grade 3 EEC, where the guideline is not strictly directive. Compared to general gynecologists, gynecologic oncologists are much more likely to perform a systematic lymphadenectomy in this group of patients.

Literature concerning the diagnostic work-up of clinical Stage I, grade 3 EEC is inconclusive and the guideline therefore states that CA-125 measurement and CT or MRI may be considered [6]. This is represented in the questionnaire, with no agreement concerning necessity of a CT-scan and CA-125 measurement.

Interestingly, the guideline recommends sampling of suspicious lymph nodes, whereas the majority of gynecologists feel that a lymphadenectomy should be performed. This was significantly more among gynecologic oncologists compared to general gynecologists, which might be explained by the fact that the former have had more surgical training and are more confident to perform a lymphadenectomy. Several large studies have presented conflicting data on the role of routine lymphadenectomy in clinical Stage I EEC [7-9]. This controversy led to the revised Dutch guideline against routine lymphadenectomy, in contrast with the American guideline, which recommends complete surgical staging when grade 3 histology is present [10].

Table 2. — *Questionnaire and responses.*

1.	What is your background?	
	Resident	-
	Gynecologist	3 (4.9%)
	Gynecologist with oncology as area of interest	27 (44.3%)
	Gynecologic oncologist	31 (50.8%)
2.	How many years are you registered?	16 (sd 8.4)
3.	What would be the primary surgical treatment?	
	TAH/VH + BSO*	21 (34.4%)
	TAH/VH + BSO + lymph node sampling	2 (3.3%)
	TAH/VH + BSO + pelvic lymphadenectomy	12 (19.7%)
	TAH/VH + BSO + pelvic and para-aortal lymphadenectomy	23 (37.7%)
	Total surgical staging	3 (4.9%)
	(**Total abdominal hysterectomy/vaginal hysterectomy with bilateral salpingo-oophorectomy*)	
4.	If the patient was 65 years old, would this change the surgical treatment?	
	No	59 (96.7%)
	Yes	2 (3.3%)
5.	If so, what would the primary treatment be?	
	TAH/VH + BSO	-
	TAH/VH + BSO + lymph node sampling	-
	TAH/VH + BSO + pelvic lymphadenectomy	2 (100%)
	TAH/VH + BSO + pelvic and para-aortal lymphadenectomy	-
	Total surgical staging	-
	Not applicable	59
7.	Would you make an abdominal CT-scan?	
	No	26 (42.6%)
	Yes	35 (57.4%)
8.	If so, would it change your policy?	
	No	12 (34.3%)
	Yes, I would only perform a lymphadenectomy if there are enlarged nodes on the CT-scan	12 (34.3%)
	Unknown	11 (31.4%)
	Not applicable	26
9.	Would you measure CA-125?	
	No	25 (41%)
	Yes	35 (57.4%)
	Unknown	1 (1.6%)
10.	If so, would it change your policy?	
	No	23 (65.7%)
	Yes, I would only perform a lymphadenectomy if the CA125 is elevated	5 (14.3%)
	Unknown	7 (20%)
	Not applicable	26
11.	If the patient was 65 years old, would this change your choice in diagnostics?	
	No	57 (93.4%)
	Yes	3 (4.9%)
	Unknown	1 (1.6%)
12.	Would you make an abdominal CT-scan?	
	No	-
	Yes	3 (100%)
	Not applicable	58
13.	If so, would it change your policy?	
	No	2 (66.7%)
	Yes, I would only perform a lymphadenectomy if there are enlarged nodes on the CT-scan	-
	Unknown	1 (33.3%)
	Not applicable	58
14.	Would you measure CA-125?	
	No	1 (33.3%)
	Yes	2 (66.7%)
	Not applicable	58
15.	If so, would it change your policy?	
	No	2 (100%)
	Yes, I would only perform a lymphadenectomy if the CA125 is elevated	-
	Not applicable	59
17.	If there was no lymphadenectomy performed, what should the adjuvant treatment be?	
	No adjuvant therapy	-
	Radiotherapy according to the PORTEC 1-2 trials, if applicable participation in the PORTEC 3 trial	56 (91.8%)
	Radiotherapy according to the PORTEC 1-2 trials and chemotherapy	2 (3.3%)
	Chemotherapy	-
	Unknown	3 (4.9%)
18.	If a lymphadenectomy was conducted, all nodes were negative and there was no sign of extra-uterine disease, what should the adjuvant treatment be?	
	No adjuvant treatment	27 (44.3%)
	Radiotherapy according to the PORTEC 1-2 trials, if applicable participation in the PORTEC 3 trial	33 (54.1%)
	Unknown	1 (1.6%)

The Dutch guideline is based, among others, on the PORTEC I and II trials concerning adjuvant therapy [2, 3]. Nevertheless, none of the responders felt that observation alone was safe enough for patients who did not undergo a lymphadenectomy, which illustrates the hesitation of gynecologists to follow the guideline by omitting a routine lymphadenectomy. A problem with the consideration of adjuvant therapy in the questionnaire (questions 17 and 18, Table 2) is the fact that the extent of myometrial invasion, required in deciding on adjuvant treatment, is not given.

When looking at the actual treatment of patients with grade 3 EEC, there was a large discrepancy between the opinion on routine lymphadenectomy and the actual amount of lymphadenectomies performed (25.5%). The total number of patients treated for grade 3 EEC as retrieved from the PALGA-registry should be considered a random sample, as it is known that not all cases are labeled systematically in this system and are therefore missed during a search. It has to be noted that the clinical stage is not recorded in the PALGA-registry.

The major strength of this study is that it compared gynecologists' opinions, the guideline, and actual treatment. Results demonstrated that variation is low among the points of consensus, and variation was large among the points of doubt in the management of Stage I, grade 3 EEC. Moreover, it showed that while gynecologists tend to follow the guidelines on routine lymphadenectomy, it is not the optimal treatment in their opinion. Many studies have looked at either endometrioid endometrial cancer with good prognosis or non-endometrioid endometrial cancer with poor prognosis, leading to comprehensive guidelines. For Stage I, grade 3 EEC, however, the guidelines remain inconclusive. In a time of centralization and standardization of care, the finding that gynecologists tend to comply with the guidelines will hopefully lead to more research into Stage I, grade 3 EEC and subsequently to comprehensive guidelines.

It is known from literature that the response rates of questionnaires among physicians, and especially gynecologists, is very poor, even when an incentive is used [11]. The major limitation of this study was the low response rate. However, while the authors did not have the funding to provide an incentive, their response rate is comparable to that of a questionnaire with an incentive. Another weakness of this study may be the fact that the myometrial invasion was not given in the case description, as pointed out by several responders. Despite these points, the authors feel that the current data support the sense of urgency to find consensus on the management of Stage I, grade 3 EEC.

Conclusion

In conclusion, the current study illustrates that gynecologists in The Netherlands adhere well to the guidelines concerning the management of clinical Stage I, grade 3 EEC. However, with respect to the lymphadenectomy there is a discrepancy between: 1) the opinion and the guideline, 2) the opinion of gynecologic oncologists and general gynecologists, and 3) the opinion and the actual performed lymphadenectomy in grade 3 EEC. Moreover, there is little agreement on decisions left to the discretion of the gynecologist. Although the actual treatment is in line with the guideline, these data show the need for agreement on the management of patients with clinical Stage I grade 3 EEC.

References

[1] "Dutch Cancer Figures" [Netherlands Cancer Registry Web site]. Available at: www.cijfersoverkanker.nl. Accessed January 2013.
[2] Nout R.A., Smit V.T., Putter H., Jurgenliemk-Schulz I.M., Jobsen J.J., Lutgens L.C., *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.
[3] Creutzberg C.L., van Putten W.L., Koper P.C., Lybeert M.L., Jobsen J.J., Warlam-Rodenhuis C.C., *et al.*: "Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma". *Lancet*, 2000, *355*. 1404.
[4] "Endometrial Cancer" [Oncoline cancer clinical practice guidelines Web site]. October 24, 2011. Available at: www.oncoline.nl/endometriumcarcinoom. Accessed January 2013.
[5] Casparie M., Tiebosch A.T., Burger G., Blauwgeers H., van de Pol A., van Krieken J.H., *et al.*: "Pathology databanking and biobanking in The Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive". *Cell. Oncol.*, 2007, *29*. 19.
[6] Amant F., Mirza M.R., Creutzberg C.L.: "Cancer of the corpus uteri". *Int. J. Gynaecol. Obstet.*, 2012, *119*, S110.
[7] Benedetti Panici P., Basile S., Maneschi F., Alberto Lissoni A., Signorelli M., Scambia G., *et al.*: "Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial". *J. Natl. Cancer Inst.*, 2008, *100*. 1707.
[8] Kitchener H., Swart A.M., Qian Q., Amos C., Parmar M.K.: "Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study". *Lancet*, 2009, *373*. 125.
[9] Bendifallah S., Koskas M., Ballester M., Genin A.S., Darai E., Rouzier R.: "The survival impact of systematic lymphadenectomy in endometrial cancer with the use of propensity score matching analysis". *Am. J. Obstet. Gynecol.*, 2012, *206*. 500 e1.
[10] "Uterine neoplasms" [National Comprehensive Cancer Network (NCCN) Web site]. February 21, 2013. Available at: www.nccn.org. Accessed February 2013.
[11] Delnevo C.D., Abatemarco D.J., Steinberg M.B.: "Physician response rates to a mail survey by specialty and timing of incentive". *Am. J. Prev. Med.*, 2004, *26*. 234.

Address reprint requests to:
L.J.M. VAN DER PUTTEN, M.D.
Radboud university medical center
791 Department of Obstetrics and Gynaecology
P.O. Box 9101, 6500HB,
Nijmegen, (The Netherlands)
e-mail: Louis.vanderputten@radboudumc.nl