Risk Factors of Lymph Nodes Metastases by Endometrial Cancer: A Retrospective One-center Study

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Abstract. *Background/Aim: We aimed to identify the surgical-pathological risk factors separately for pelvic and para-aortic lymph nodes (LN) metastases in endometrial cancer (EC). Patients and Methods: The study cohort consisted of 179 patients with first diagnosis of EC, who were operated in our Institution between 2007 and 2014. Results: Pelvic and para-aortic LN dissection was performed in 115 patients (64.2%). The positive pelvic and para-aortic LN were diagnosed in 11.3% and 16.1% of cases, respectively. Patients with bad differentiated tumors (G3) showed about 5-times more risk to have affected LN. Deep infiltration of myometrium elevated the risk of pelvic LN infiltration 5 times and of para-aortic LN infiltration 14 times. G3, myometrial infiltration >50% and type II endometrial cancer correlated with a worse progression free survival (PFS) and overall survival (OS). Conclusion: Tumor grade and deep myometrial invasion were the only significant predictors of pelvic and para-aortic lymph node metastases.*

Endometrial cancer (EC) is the most common malignancy of the female reproductive tract and the fourth most common cancer overall, with approximately 300,000 new cases worldwide (1). About 88,068 new cases are registered yearly in the European Union (2). The standard surgical approach for stage I EC consists of total hysterectomy and bilateral salpingo-oophorectomy with or without lymphadenectomy, which continues to be a topic of controversy in early-stage EC.

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Several groups have identified preoperative and intraoperative risk factors for recognizing patients who may have disseminated disease in apparent early-stage EC (3-9).

EC patients in low-risk group have a substantially low (<1%) risk of lymphatic dissemination (4, 10-11). Therefore, lymphadenectomy can be omitted in this group of patients averting unnecessary morbidity and reducing costs while potentially achieving favorable oncologic outcomes (12).

Currently, there is no gold-standard for the preoperative stratification of low- and high-risk patients of lymph node metastases (13-15). Tumor grade is an important predictive factor for metastatic disease in EC (16). Unfortunately, the correlation between preoperative tumor grading based on either endometrial biopsy or uterine curettage specimen and final tumor grading after hysterectomy is not satisfactory. The discordance rate can range from 15% to 30% (17-20). Depth of myometrial invasion is too difficult to determine preoperatively; however, magnetic resonance imaging (MRI) has been shown to be the most sensitive imaging modality with promising results (21). Nevertheless, its accuracy has to be proved.

In the current study, we aimed to identify the surgical-pathological risk factors separately for pelvic and para-aortic lymph node (LN) metastases in EC patients. We assessed significant risk factors for LN metastases, as well as the prognostic impact of nodal involvement, all as exploratory analyses only due to the retrospective character of this work.

Patients and Methods

The cohort of this study consisted of all operated patients in our institution with the first diagnosis of EC between 2007 and 2014. The time periods were chosen because henceforward patients were prospectively documented in clinical tumor registries. All patients with malignant mixed Mullerian tumors (carcinosarcoma of the uterus) were excluded. All patients gave written informed consent regarding treatment and scientific data analysis. Additional ethical approval was not mandatory due to the retrospective character of the present study.

All surgeries were performed by experienced board-certified gynecologic oncologists. Patients received once-off intravenous antibiotic prophylaxis (cefuroxime 1.5gr and metronidazole 0.5gr) at induction and low-molecular-weight heparin (fraxiparin 0.3-0.4 ml/24 h) subcutaneously 12 h after the operation.

During lymphadenectomy, the iliac vessels (common, internal and external) were completely dissected and lymphatic tissue was removed in the entire obturator fossa after careful identification of the obturator nerve and lumbosacral trunk. Pelvic lymphadenectomy was extended to the crossing of ureter and common iliac artery in cranial and to the circumflex iliac vein in anterior–distal direction.

For the para-aortic lymph node dissection, the para-colic gutter was incised along the respective lateral borders of the ascending and descending colon, opening up the entire retroperitoneal space up to the renal veins. The anterior, lateral and medial aspects of abdominal aorta and inferior vena cava were completely stripped off all lymphatic tissue. Data were transformed according to the 7th edition of TNM classification (22) and the 2009 edition of FIGO classification (23) for all patients to obtain better comparability to the current pathologic work-up.

Patients were enrolled in a follow-up program of assessments at 3-month intervals.

All statistical analyses were performed using SPSS 16.0 (Chicago, IL, USA). The risk of lymph node metastasis was analyzed with binary logistic regression analysis in univariate models; significant results were transferred to a multivariate model with backward testing. Progression-free (PFS) and overall survival (OS) were assessed with the Kaplan–Meier method, differences were calculated using the log-rank test and prognostic factors were identified using uni- and multivariate Cox regression models, also with backward testing. Comparison of two or more groups of discrete variables was performed with Fisher's exact test or the χ^2 test. All *p*-values were two-sided and $p<0.05$ was considered significant. However, because of the retrospective exploratory character of the analyses, even significant *p*-values were supposed to generate hypotheses only.

Results

We identified 179 patients who met the above-mentioned criteria. The median age at the first diagnosis of EC was 66 year (range=30-87). A large proportion (88.3%) of patients had an endometroid endometrial cancer. The other cases were distributed to 7.3% serous endometrial cancer, 3.9% clear cell endometrial cancer and 0.6% undifferentiated endometrial cancer. One fifth (20.8%) of cases had a bad differentiated endometrial cancer (G3). Tumor volume could be assessed in 163 patients (91% of our collective). More than half (63.2%) of these patients had a tumor diameter >2 cm, whereas 85.7% of G3 tumors had a tumor diameter >2 cm (odds ratio (OR)=4.4, 95% confidence interval (CI)=1.5-14, $p=0.005$).

In 80.4% of patients, the tumor was confined to the uterus (48% in stage Ia, 21.8% in stage Ib and 10.6% in stage II) in comparing with TNM classification (48.6% of patients have T1a, 24.6% T1b and 12.8% T2), which means that the lymph node dissection results in up-staging of 1 (0.6%) patient with FIGO Ia, 5 (2.8%) patients with FIGO Ib and 4 (2.2%) patients in FIGO II; respectively. The deep infiltration of myometrium (>50%) was confirmed pathologically in 48.9% of cases. Almost three quarters (73%) of G3 tumors showed >50% myometrial infiltration (OR=3.6, 95%CI=1.5-8.7, $p=0.003$). Infiltration of lymph vessels was diagnosed in 20.1% and of blood vessels in 8.7%. A high proportion (81.3%) of deep infiltrated tumors had a tumor diameter of more than 2 cm (OR=5.1, 95%CI=2.4-11.1, $p<0.001$).

Pelvic and para-aortic lymph node dissection was indicated in 115 patients (64.2%). Only 16.5% of them had positive lymph nodes (N1). The positive pelvic lymph nodes were diagnosed in 11.3% of cases (7.2% of the whole cohort) and the positive para-aortic lymph nodes were diagnosed in 16.1% (15 of 93 patients who received a para-aortic lymphadnectomy) and 8.4% of the whole cohort. Distant metastases (M1) were diagnosed in 3.4% of cases. Complete resection (R0) could be achieved in 96.4%.

Estrogen receptors could be assessed in 67 patients (37.4%) and were positive (expression >10%) in 50 patients (74.6%), whereas progesterone receptors were positive only in 57.1% of patients (expression >10%).

Assessing the conventional pathological risk factors in terms of PFS and OS, they showed statically significant worse prognosis in patients with G3 *versus* G1/2, myometrial infiltration >50% *versus* <50%, type II *versus* type I histology, absence of estrogen receptors *versus* >10% expression of estrogen receptors, absence of progesterone receptors *versus* >10% expression of progesterone receptors and positive LN metastases *versus* negative or not assessed LN (*p* for PFS and OS=0.0001 and 0.0001, 0.0001 and 0.0001, 0.002 and 0.005, 0.015 and 0.002, 0.021 and 0.01, 0.0001 and 0.0001, respectively). These results are illustrated in Figure 1.

Tumor volume of more than 2 cm was a significant risk factor regarding only PFS ($p=0.017$) but not OS ($p=0.075$).

Patients with bad differentiated tumors (G3) showed about 5 times more risk to have affected pelvic lymph nodes (OR=5.8, 95%CI=1.5-23.2, $p=0.006$) and affected para-aortic lymph nodes (OR=5.8, 95%CI=1.6-22.6, $p=0.005$).

With deep infiltration of myometrium (>50%), the risk of pelvic lymph node infiltration was elevated 5 times (OR=5.4, 95%CI=1-37.1, $p=0.005$) and that of para-aortic lymph node infiltration 14 times (OR=14.4, 95%CI=1.8-311.4, $p=0.005$).

The risk of lymph node metastases in pelvic and para-aortic region increased 3 times in non-endometroid comparing the endometroid EC; however, this result was statistically not significant.

The tumor size of more than 2 cm also increased the risk of affected pelvic and para-aortic lymph nodes for more than 6 times. However, this result was not statistically significant.

A summary of estimated risk of positive pelvic and para-aortic lymph nodes in endometrial cancer cases regarding the surgical-pathologic criteria is given in Table I.

Table I. *Estimated risk of positive pelvic and para-aortic lymph nodes in endometrial cancer cases regarding the surgical-pathological criteria.*

Risk factor		G3	Myometrium infiltration>50%	Non-endometroid	T >2cm
Pelvic LN metastases	OR	5.818	5.392	3.333	6.6
	Sensitivity	61.5%	84.6%	30.8%	92.3%
	Specificity	78.4%	49.5%	88.2%	35.5%
	Positive predictive value	26.7%	17.7%	25.0%	16.7%
	Negative predictive value	94.1%	96.2%	90.9%	97.1%
	p-Value	0.006	0.005	N.S	N.S
Para-aortic LN metastases	OR	5.8	14.368	3.4	6.851
	Sensitivity	66.7%	93.3%	33.3%	93.3%
	Specificity	74.4%	50.6%	87.2%	32.9%
	Positive predictive value	33.3%	26.9%	33.3%	23.0%
	Negative predictive value	92.1%	97.5%	87.2%	95.8%
	p-Value	0.005	0.005	N.S.	N.S.

LN, Lymph node; OR, odds ratio; N.S, not significant.

Discussion

Lymph node metastases represent the most important prognostic factor in early stage endometrial cancers (24-25). The 5-year progression-free survival was 90% in a 1991 analysis of the Gynecologic Oncology Group (GOG)-33 database in unselected early-stage endometrial cancer patients without any lymph node metastases, dropped to 75% in patients with pelvic and to 38% in patients with para-aortic lymph node metastases, respectively (26).

Our current results suggest 11.3% and 16.1% prevalence of the pelvic and para-aortic lymph node metastases by EC, respectively. Akbayir *et al*. reported 10.1% incidence rate of pelvic lymph node involvement in patients with all stages of EC cancer (9). A similar result was demonstrated by Chi *et al*. (9%) as well (27).

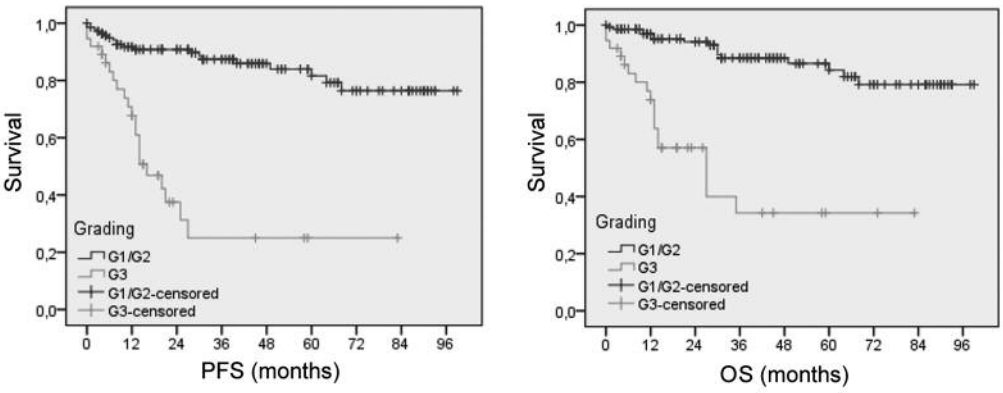
After excluding the low-risk early-stage EC, a new published study from our institution concluded that 21.1% of patients had positive LN metastases: 18% showed positive pelvic LN and 14.8% positive para-aortic LN; while 3.1% showed isolated para-aortic LN metastases. The overall frequency of paraaortal lymph node dissemination has been estimated in other studies to be up to 17 % (26, 28, 29).

In the GOG-33 study, the probability of finding metastatic disease was strongly correlated with final tumor grade. The risk of nodal spread in clinical stage I with grade 1 disease was 3% for pelvic and 2% for para-aortic nodes, while the risk of nodal spread for grade 3 disease in the same stage was 18% for pelvic and 11% for para-aortic nodes (28). Our findings supported these results and demonstrated that grade 3 increased the risk for pelvic and para-aortic lymph node metastases about 6 times (sensitivity was 61.5% and 66.7%, respectively, for pelvic and para-aortic lymph node metastases). A higher tumor grade was also associated with a greater chance of pelvic lymphatic dissemination in a study of Zhang *et al*. (30) (G1, 2.2%; G2, 5.0%; G3, 12.7%) but the sensitivity of grade for predicting pelvic node metastasis in this study was as low as 41.7%, which is comparable to the study by Zuurendonk *et al*. (31) (45%) and suggested that grade 3 could no longer be an independent risk factor for LN metastases. Furthermore, Geisler *et al*. (32) concluded, after studying 349 patients with endometrioid adenocarcinoma of the endometrium who underwent a complete pelvic and para-aortic lymphadenectomy, that positive lymph nodes (including isolated para-aortic lymph nodes) are common in all grades.

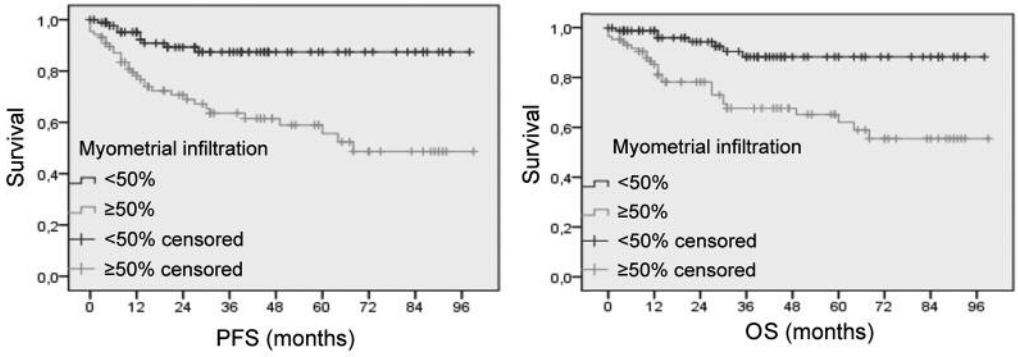
We found, in our current study, that the deep myometrial invasion was the most important risk factor of para-aortic lymph node metastases (OR=14.37, sensitivity=93.3%) and one of the independent risk factors for pelvic lymph node involvement (OR=5.39, sensitivity=84.6%). This result supports the findings of Zhang *et al*. (30), Creasman *et al*. (28) and Chi *et al*. (27) regarding the risk of pelvic lymph node metastases. Zuurendonk *et al*. reported that the depth of myometrial invasion had low sensitivity (55%) in the prediction of pelvic node involvement and, therefore, it could not be a good predictor of pelvic LN metastases. Akbayir *et al*. (9) reached the same conclusion after performing a multivariate analysis claiming that the endocervical glandular, which is not compatible with the new FIGO staging system 2009 (23), and stromal involvement, as well as lymphovascular space invasion (LVSI), could be better predictors.

In this study, we did not find any significant association between pelvic and para-aortic LN metastases and the tumor diameter when 2 cm is determined as a cut-off value. Tumor volume of more than 2 cm was a significant risk factor regarding only PFS but not OS. This is consistent with the findings of Akbayir *et al*. (9) and Geisler *et al*. (32).

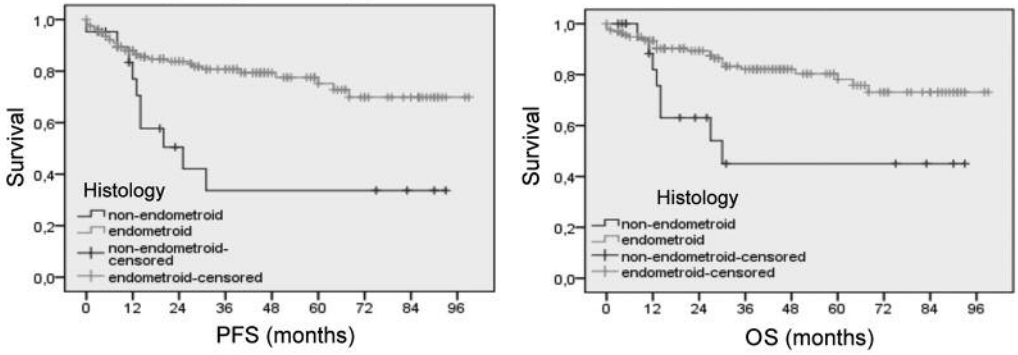
A. Grading: G3 *vs.* G1/2



B. Myometrial infiltration: >50% *vs.* <50%



C. Histology: Type I *vs.* Type II



D. Estrogen receptors: >10% *vs.* ≤10%

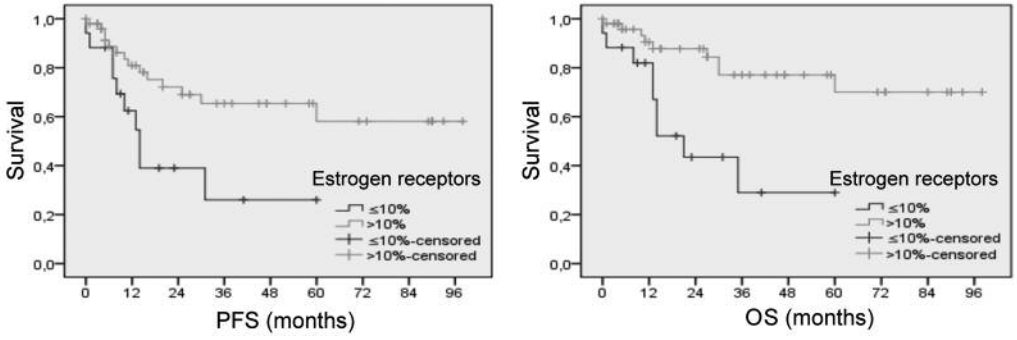


Figure 1. *Continued*

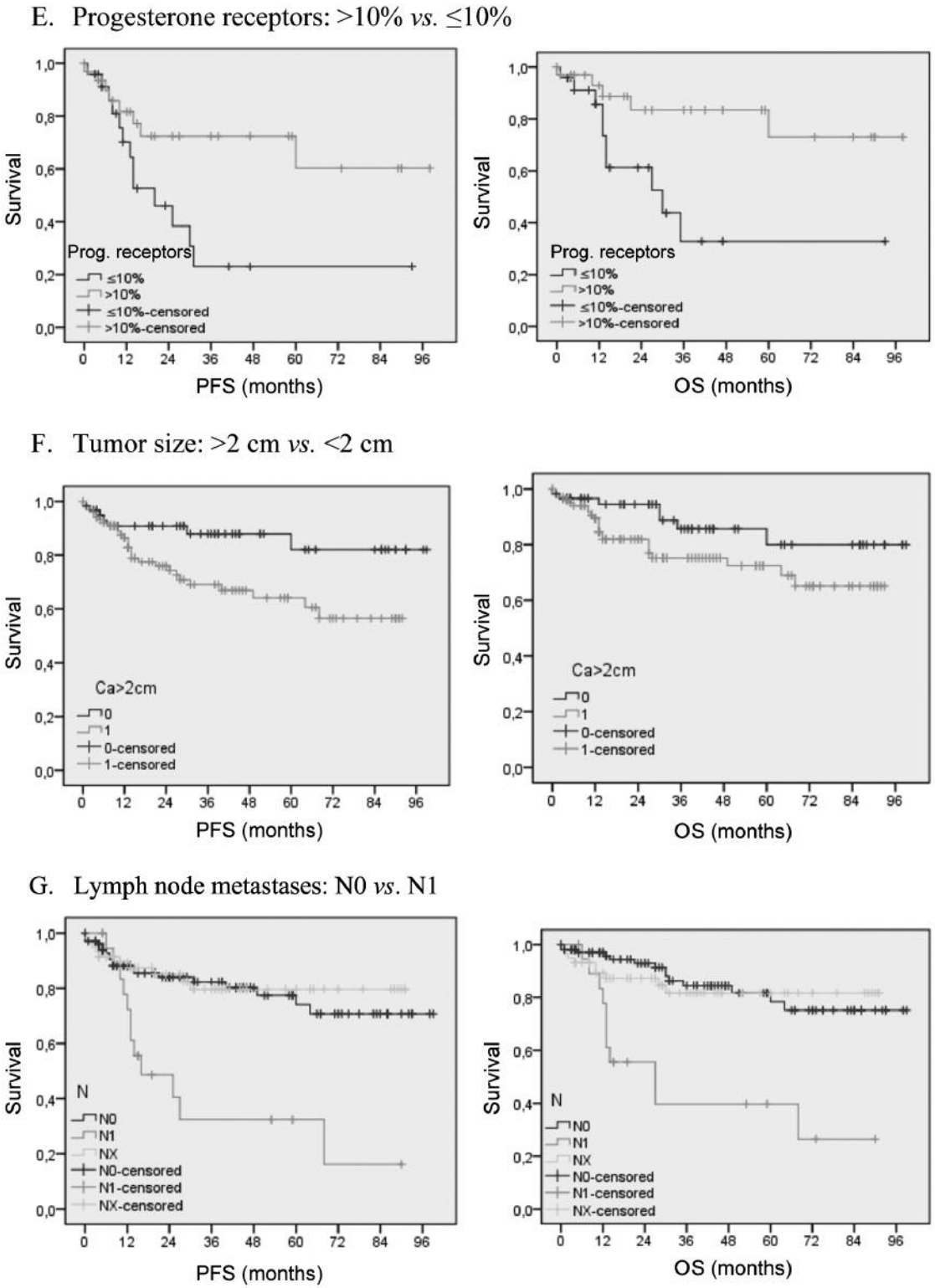


Figure 1. *Assessing the conventional pathological risk factors in terms of progression-free (PFS) and overall survival (OS). A: Grading: G3 vs. G1/2; B: Myometrial infiltration: >50% vs. <50; C: Histology: Type I vs. Type II; D: Estrogen receptors: >10% vs. ≤10%; E: Progesterone receptors: >10% vs. ≤10%; F: Tumor size: >2 cm vs. <2 cm; G: Lymph node metastases: N0 vs. N1.*

Conclusion

In conclusion, we showed that tumor grade and deep myometrial invasion were the only significant predictors of pelvic and para-aortic lymph node metastases. G3, myometrial infiltration >50% and type II endometrial cancer correlate with a worse PFS and OS. Tumor size >2 cm correlates only with worse PFS but not with a worse OS.

Conflicts of Interest

There exists no financial or personal conflict of interest by any of the authors to declare.

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