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IMPACT OF SYSTEMATIC PELVIC LYMPHADENECTOMY ON SHORT TERM POSTOPERATIVE QUALITY OF LIFE IN PATIENTS WITH EARLY STAGE ENDOMETRIAL CANCER

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ABSTRACT

Objective: to determine the potential impact of systematic lymphadenectomy vs. no lymphadenectomy on the perioperative change in QoL in patients undergoing surgical treatment for early stage endometrial cancer.

Patients and methods: Patients scheduled for surgical treatment of clinically early stage endometrial cancer at the Department of gynecological oncology at the University Clinic of Gynecology and Obstetrics in Skopje, in the period January – December 2018 were approached for participation. Eligible subjects were divided into two groups: Group 1 (no LND) consisted of 60 patients who had hysterectomy plus bilateral salpingo-oophorectomy without lymph node dissection (LND); Group 2 consisted of 24 patients who had hysterectomy plus salpingo-oophorectomy plus systematic pelvic LND. Quality of life was quantified using a standardized and validated questionnaire (FACT-G) preoperatively and 30 days after surgical treatment.

Results: The patients in the LND group exhibited statistically significantly lower postoperative scores for FACT-G (87.7 vs 75.8 for the no LND and LND groups respectively, $p=0.002$), as well as for the physical wellbeing domain (23.4 vs. 20, $p=0.004$) and emotional wellbeing domain (20.7 vs 17, $p=0.008$). Twelve patients from the group with no lymphadenectomy (20%) experienced a clinically significant decline in the postoperative QoL, compared to 12 patients (50%) in the lymphadenectomy group ($p=0.006$).

Conclusion: There was a significant decrease in the postoperative QoL 30 days after surgery in patients that undergo systematic pelvic lymphadenectomy for early stage endometrial cancer compared to patients that do not.

Key words: quality of life, endometrial cancer, lymphadenectomy

INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy in the developed world and the sixth most common malignant disorder worldwide accounting for up to 6% of all malignancies. Approximately 320000 new cases are identified each year [1]. The highest incidence rates are registered in the developed countries of North America and Europe, where endometrial cancer is the most common malignant neoplasm of the female genital tract and the fourth most common location in women after breast, lung and colorectal cancer [2]. Endometrial cancer is the second most common malignant neoplasm in women (after breast cancer) in The Republic of North Macedonia with an estimated 400 new patients diagnosed annually [1], and a corresponding age-standardized incidence rate of 24.3 per 100000 women.

Traditionally, endometrial cancers have been classified into two types, based on histopathology: type 1 are low-grade estrogen related endometroid adenocarcinomas that are usually diagnosed early and have a favorable prognosis, while type 2 endometrial cancers are high grade endometroid adenocarcinomas, papillary serous and clear cell carcinomas and carcinosarcomas [3]. The latter group of cancers are hormone independent and are associated with a more aggressive tumor behavior and poorer prognosis.

Metastatic spread, be it regional or through the vascular and/or lymphatic systems, is the most important prognostic factor that influences the overall patient survival. The most frequent location for metastatic spread of endometrial cancers are the pelvic lymph nodes. The uterus drains through three main lymphatic trunks: utero-ovarian (infundibulopelvic), parametrial and presacral trunk which drain into the external iliac, common iliac, internal iliac, presacral and para-aortic lymph node basins [4]. Although theorized and described, direct lymphatic metastasis to the para-aortic lymph nodes with negative pelvic nodes occurs rarely in endometrial cancer patients [5]. Systematic pelvic and/or para-aortic lymph node dissection (LND) has been well recognized as a cornerstone of surgical staging of endometrial cancer ever since the International Federation of Gynecology and Obstetrics (FIGO) moved from clinical to surgical staging of endometrial cancer [6]. The comprehensive FIGO surgical staging algorithm for endometrial cancer recommends a procedure that includes total hysterectomy and bilateral salpingo-oophorectomy, peritoneal washing and pelvic and/or

para-aortic lymphadenectomy. The therapeutic benefits of lymphadenectomy, however, remain controversial and a matter of scientific debate, especially in patients with early stage endometrial cancer. Patients undergoing systematic pelvic and para-aortic lymphadenectomy experience longer operative times and are exposed to greater risk of intraoperative and postoperative complications than patients treated with hysterectomy with bilateral salpingo-oophorectomy alone [7], which in turn, negatively impacts the quality of life (QoL).

OBJECTIVE

The aim of the study was to determine the potential impact of systematic lymphadenectomy vs. no lymphadenectomy on the perioperative change in QoL in patients undergoing surgical treatment for early stage endometrial cancer.

PATIENTS AND METHODS

The study was designed as a prospective cohort study and was conducted at the Department of gynecologic oncology at the University clinic of gynecology and obstetrics, University "Ss. Cyril and Methodius", Skopje, Republic of North Macedonia. Eligible consecutive patients scheduled for surgical treatment of endometrial cancer at the Department between January and December 2018 were approached for participation in the study. Inclusion criteria were: presence of a histologically verified endometrial cancer that was presumed early stage based on preoperative evaluation. Patients that were unfit for surgical treatment were excluded from the study. Written consent for participation was obtained from all patients and the study was approved by the Ethical committee of the Medical faculty at the University "Ss. Cyril and Methodius", Skopje, Republic of North Macedonia.

Contrast CTs of the abdomen and chest were performed to exclude lymphadenopathy and/or extrauterine disease. Patients were then classified into two groups, based on the ESMO-ESGO-ESTRO recommendations for endometrial cancer treatment [8]: group 1 (no LND) were patients with low risk endometroid endometrial cancer (clinically stage I, grade 1/2, myometrial invasion <50%) and were treated with total abdominal hysterectomy with bilateral salpingo-oophorectomy without lymph node dissection; group 2 (LND) were patients with intermediate/high risk endometrial cancer (clinical stage I of endometoid cancer grade 3 and/or myometrial invasion ≥50%, patients with clinical stage II and all patients with non-endometroid

histology) which were treated with total abdominal hysterectomy with bilateral salpingo-oophorectomy and systematic pelvic lymph node dissection.

All surgeries were performed via laparotomy by five surgeons from the Department in a standardized fashion. The lymphadenectomy included dissection of the external iliac, internal iliac, obturator, presacral and common iliac nodes up to the bifurcation of the aorta in accordance with the Department's protocol. No para-aortic lymph node dissection was performed given that all patients were early stage and the risk of para-aortic involvement was low [5].

The main endpoint of the study was the postoperative change in quality of life, measured by the Functional Assessment of Cancer Therapy-General (FACT-G) score [9], version 4. The FACT-G questionnaire consists of 27 questions, grouped in four domains: physical well-being (PWB), social well-being (SWB), emotional well-being (EWB) and functional well-being (FWB). The PWB, SWB and FWB domains have 7 questions and score 0-28, while EWB has 6 questions and scores 0-24. The answers in the FACT-G questionnaire are formulated as a 5-point Likert scale (0- "not at all" to 4 - "very much"), and the values are summed up to form a total score of 0-108.

The questionnaire was translated in Macedonian and was self-administered by the patients, with a researcher available, should the patient have any questions or issues. Patients filled out the questionnaire on admission and approximately 30 days post-surgery, during the first follow-up visit at our Outpatient department.

To assess the postoperative change in the quality of life, the study used the "minimally important difference" (MID) concept [10]. The MID concept is defined as the lowest difference in the overall score or any domain sub-score that is perceived by the patient as an improvement or deterioration, consequently influencing the management of the patient [10]. The study employed a distribution-based method to calculate MID. For the purposes of this study, QoL one-month post-surgery was categorized as "deteriorated" if the postoperative FACT-G (or relevant domain) score was at least 5 points lower than the preoperative score (MID=5). The data was used to transform the raw scores into a categorical dichotomous variable indicating a decline in overall QoL (or relevant domain).

We also recorded and analyzed the following variables: body mass index (BMI), level of education (high school

or lower vs. university degree), marital status (married/living with a partner vs. divorced/widowed), place of residence (urban vs. rural), comorbidities and smoking. The following comorbidities were recorded: diabetes, history of a major thrombotic event, chronic renal failure, history of immunosuppression and chronic cardio-vascular conditions (excluding hypertension).

The data was digitized and entered into a database. The statistical analysis was carried out using the SPSS statistical software package version 23 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.). Standard descriptive statistics were done and data was displayed using frequencies, percent, mean and standard deviation (SD), where appropriate. The difference in the FACT-G score and the associated domains pre- and postoperatively were compared using the Mann Whitney's U test for independent samples. The differences in the distributions of the listed categorical variables in the two groups of patients were tested using the Chi square test and Fisher's exact test, depending on the group size. A value of $p < 0.05$ was considered statistically significant.

RESULTS

A total of 91 patients were recruited in the study. Of those, 7 patients (7.7%) were excluded from statistical analysis: 6 (6.6%) patients with incomplete questionnaires and one patient (1%) who was unavailable for evaluation one month after surgery. The remaining 84 patients (92.3%) were selected for analysis, 60 patients in group 1 (no LND) and 24 patients in group 2 (LND).

The demographic and clinical characteristics of the patients included in the study are summarized in Table 1. The groups were homogenous. The average age of patients in group 1 (no LND) was 60.9 ± 8 , while the average age of patients in group 2 (LND) was 62.5 ± 7.8 . The mean BMI were 33.7 ± 7.8 and 31.5 ± 6.4 for group 1 (no LND) and group 2 (LND), respectively. Most of the patients had a high school degree or lower education (95% and 79.2% for the no LND and LND groups, respectively), were married/living with a partner (80% and 95.8% for the no LND and LND groups, respectively), came from urban communities (66.7% for both groups) and were non-smokers (95% and 95.8%, respectively). Approximately half of the patients in both groups had at least one comorbidity (53.3% vs. 45.8% for the no LND and LND groups, respectively). Thirty-two patients (53.3%) from the no LND group were Stage IA, 24 (40%) were Stage IB and 4 patients (6.7%) were

upstaged to Stage II on the final pathology report. Seven (29.2%) patients from the LND group were surgical Stage IA, 5 (20.8%) were Stage IB, 8 (33.3%) were Stage II, while 4 (16.7%) patients had pelvic node involvement and were Stage IIIC1. The pathology report confirmed endometrioid histology in the vast majority of patients in the no LND group (96.7%), and only two patients (3.3%) had a revised diagnosis of mixed histology on the final pathohistology report. The following histologic types were recorded in the LND group: poorly differentiated endometrioid in 14 patients (58.3%), mixed in 4 (16.7%) and serous and clear cell carcinomas in 3 (12.5%) of the patients each. The median number of retrieved lymph nodes in the LND group was 14 with a range of 6-27.

Table 1. Summary of the relevant demographic and clinical patient characteristics

Parameter	Group 1 (no LND) n=60	Group 2 (LND) n=24
Age, mean±SD	60.9±8	62.5±7.8
BMI, mean±SD	33.7±7.8	31.5±6.4
Degree of education, n (%) High school or lower University diploma	57 (95%) 3 (5%)	19 (79.2%) 5 (20.8%)
Marital status, n (%) Married/living with a partner Divorced/widowed	48 (80%) 12 (20%)	23 (95.8%) 1 (4.2%)
Employment status, n (%) Employed/retired Unemployed	40 (66.7%) 20 (33.3%)	15 (62.5%) 9 (37.5%)
Place of residence, n (%) Urban community Rural community	40 (66.7%) 20 (33.3%)	16 (66.7%) 8 (33.3%)
Comorbidities, n (%) Absent Present	28 (46.7%) 32 (53.3%)	13 (54.2%) 11 (45.8%)
Smoking, n (%) Non-smoker Smoker	57 (95%) 3 (5%)	23 (95.8%) 1 (4.2%)
Surgical stage, n (%) IA IB II IIIC1	32 (53.3%) 24 (40%) 4 (6.7%)	7 (29.2%) 5 (20.8%) 8 (33.3%) 4 (16.7%)
Final histology, n (%) Endometrioid Mixed Serous Clear cell	58 (96.7%) 2 (3.3%)	14 (58.3%) 4 (16.7%) 3 (12.5%) 3 (12.5%)
Number of nodes, median (range)		14 (6-27)

The comparison between the preoperative and postoperative QoL in both groups is presented in table 2. No statistically significant differences were identified in the preoperative overall and domain scores (p=0.28, 0.4,

0.77, 0.41 and 0.1 for FACT-G, PWB, FWB, SWB and EWB respectively). The patients in the LND group exhibited statistically significantly lower average scores for FACT-G (87.7 vs 75.8 for the no LND and LND groups respectively, p=0.002), as well as for the physical wellbeing domain (23.4 vs. 20, p=0.004) and emotional wellbeing domain (20.7 vs 17, p=0.008). The differences for the scores on the functional wellbeing and social wellbeing scales were not statistically significant (p=0.09 and 0.07, respectively).

Table 2. Comparison of pre- and postoperative FACT-G and domain scores*

	Group 1 (no LND) (mean ±SD)	Group 2 (LND) (mean. ±SD)	p†
Preoperative			
FACT-G	87.8±14.3	82.3±20.7	0.28
PWB	23.5±4.4	22.2±5.7	0.4
FWB	20.9±4.6	20.2±5.5	0.77
SWB	22.8±3.8	21.5±5.1	0.41
EWB	20.5±3.2	18.5±5.8	0.1
Postoperative			
FACT-G	87.7±17.3	75.8±22.6	0.002
PWB	23.4±5.1	20±6.1	0.004
FWB	20.8±5.4	18.4±6	0.09
SWB	22.8±4.7	20.3±6.1	0.07
EWB	20.7±4.9	17 ±6.6	0.008

*LND - systematic lymph node dissection; PWB-physical wellbeing; FWB-functional wellbeing; SWB-social wellbeing; EWB-emotional wellbeing. †Mann Whitney U test

The clinical significance of the difference in postoperative QoL was evaluated using the MID concept. Twelve patients from the group with no lymphadenectomy (20%) experienced a clinically significant decline in the postoperative QoL, compared to 12 patients (50%) in the lymphadenectomy group and the difference was statistically significant (p=0.006, Table 3).

Table 3. Comparison of patients with clinically significant decline in postoperative QoL*

Postoperative QoL	Group 1 (no LND) n (%)	Group 2 (LND) n (%)	p†
FACT- Unchanged	G 48 (80%)	12 (50%)	0.006
F A C T - G Diminished	G 12 (20%)	12 (50%)	

*LND-systematic lymph node dissection; QoL-quality of life. †Chi square test

DISCUSSION

Nodal assessment in patients with newly diagnosed endometrial carcinoma is an important aspect of the initial management of these patients. This prospective study evaluated the impact of lymphadenectomy on the early postoperative QoL in patients with clinically early stage endometrial cancer. The average FACT-G scores one-month post-surgery were significantly lower in patients undergoing lymphadenectomy compared to patients that underwent hysterectomy with bilateral lymphadenectomy alone. Additionally, 50% of the patients in the lymphadenectomy group experienced a clinically significant decrease in quality of life, physical and emotional wellbeing, compared to 20% in the no lymphadenectomy group.

Published data on the impact of systematic lymph node dissection on the QoL is scarce. A population-based retrospective study in the Netherlands evaluated the health-related QoL in patients with FIGO Stage I/II endometrial cancer receiving lymphadenectomy, external beam radiotherapy (EBRT) or both [11]. Lymphedema, gastrointestinal tract symptoms, diarrhea, back and pelvic pain, and muscular joint pain were the most commonly reported symptoms. The lymphadenectomy cohort had higher lymphedema scores (7%) and the cohort who received radiotherapy had higher bowel symptom scores (15%). The group that received lymphadenectomy and radiotherapy had the highest symptom scores (21%). The authors showed that, despite different symptom patterns, in patients who had pelvic lymphadenectomy (e.g. lymphedema), radiotherapy (e.g. diarrhea) or both, no clinical differences in overall QoL were observed compared with women not receiving adjuvant therapy, lymphadenectomy or both. Angioli et al [12] compared patients undergoing lymphadenectomy for endometrial cancer vs. patients who received hysterectomy with bilateral salpingo-oophorectomy alone. In their series of 95 patients, only lymphedema interfered with patients' QoL, while other associated morbidities from the surgery did not impact QoL and global health status was not statistically significantly different between the groups. Both studies were retrospective by design and evaluated long term impact of lymphadenectomy on QoL at least 12 months after surgery when other factors such as adjuvant therapy might influence the results.

In a recent study of QoL in endometrial cancer patients [13], authors found that the global health scores were lower and pain scores were higher in women who received

EBRT. Given that no patients in that series underwent pelvic lymph node dissection, the authors used SEER data for lymph node metastases to identify patients that could safely forego EBRT and found that EBRT could be avoided in 39.5% of their patients with no difference in survival, noting that that increase in lymphedema is a tradeoff to avoid symptoms from EBRT, accepting that a small percentage of patients will have worse symptoms owing to a combination of treatments. The authors concluded that performing lymphadenectomy to triage patients for adjuvant treatment can improve (QoL) and lower health provider costs with no difference in survival. In our series, adjuvant EBRT was avoided in 29.2% of the node-negative patients with high-risk endometrial cancer.

Systematic lymphadenectomy in patients with endometrial cancer increases the operative times and are the risk of intraoperative and postoperative complications compared to hysterectomy and bilateral salpingo-oophorectomy alone [14, 15]. Indeed, the extent of the surgical procedure and the associated increase in perioperative morbidity could explain the decline in the short term postoperative QoL and physical wellbeing. Aljabri et al [16] studied a cohort of 76 patients undergoing major aortic surgery and detected a significant decrease in the physical well-being 5 weeks post-surgery. The extent of surgical resection was found to negatively influence the short term postoperative physical wellbeing in patients surgically treated for gastric and colorectal cancer [17,18], and similar data was published in a longitudinal study of a series of patients with hepatic resections [19]. The statistically significant postoperative deterioration of the physical QoL after extensive surgical procedures could be due to the acute systemic inflammatory response after major surgery, including "sickness behavior" [20] and the unattainability of complete postoperative rehabilitation in certain cases [21].

The therapeutic role of lymphadenectomy remains a matter of scientific debate. A large retrospective analysis of the US National Cancer Institute's Surveillance, Epidemiology, and End Results program (SEER) databases [22] included 39396 patients treated for endometrial cancer from 1988 to 2001. The authors compared the therapeutic outcomes of 12333 patients undergoing systematic lymph node dissection vs 27063 patients that had no lymph node dissection and found that the extent of lymph node resection was associated with improved survival among women with intermediate- or high-risk endometrial cancer.

Two randomized control trials [14, 15] have disputed the impact of lymphadenectomy on the survival of patients with endometrial cancer. Between both studies, a total of 1922 patients were randomized to systematic lymph node dissection vs no lymph node dissection in addition to standard hysterectomy with bilateral salpingo-oophorectomy to evaluate the possible survival benefit of lymphadenectomy. The cumulative results of these studies reported that lymphadenectomy did not improve disease-free survival (pooled HR, 1.23; 95% CI 0.96–1.58) and overall survival (pooled HR, 1.07; 95% CI, 0.81–1.43). The results of the of these studies have been widely disputed due to methodological inconsistencies, mainly the large proportion of low-risk cases and lack of clear protocols for adjuvant therapy especially in patients with nodal disease.

Lymph node assessment remains crucial for proper staging and adjuvant therapy tailoring in patients with endometrial cancer. Completely foregoing lymph node dissection would lead to improper staging and under- or over-treatment, with adjuvant therapy decisions based on patient and uterine features alone. For example, adjuvant chemotherapy has been shown to provide a significant improvement in overall survival in patients with extrauterine disease, including nodal involvement [8]. Sentinel lymph node (SLN) mapping has emerged as a viable, less-invasive alternative to comprehensive LND since its introduction in endometrial cancer in 1996 [23]. Two studies have demonstrated non-inferiority of sentinel lymph node mapping over systematic lymphadenectomy in endometrial cancer. The FIRES trial [24] was conducted on 385 patients with clinical stage I endometrial cancer. Patients underwent sentinel lymph node biopsy followed by a comprehensive LND and the authors demonstrated that the sentinel lymph node biopsy failed to identify lymph node involvement in 3% of node-positive patients yielding a false negative predictive value of 0.4% across all patients. The trial of Soliman et al. [25] recruited 123 patients with high-risk endometrial cancer and had a false negative predictive value of 1.4% across all patients. A recent study, focusing on the QoL aspect of sentinel lymph node mapping [26] concluded that the benefit of SLN mapping over comprehensive LND lies in the reduction of lymphatic morbidity and subsequent improvement in QoL.

This study is limited by the relatively small sample size, therefore all observed differences between the groups of patients with deteriorated and identical/improved

postoperative QoL, should be interpreted with caution. The systematic lymphadenectomy group included only patients with presumed early stage disease with no evidence of nodal involvement on preoperative imaging to limit the confounding effect of the extensive surgical resection and/or para-aortic lymph node dissection that would be required in the treatment patients with extrauterine disease and/or bulky nodal disease. The MID concept in the study was used to identify only the subset of patients with deteriorated postoperative QoL, based on the valid evidence that QoL is diminished 30 days after surgery.

CONCLUSION

The evaluation of quality of life provides additional information from the patients' perspective related to the disease burden and treatment effectiveness. QoL is a multi-dimensional dynamic concept reflecting the patient's subjective perception of the influence of the disease and the associated treatment. The concept incorporates changes in physical, social, emotional and functional wellbeing that can present at any time beginning at moment the patient is diagnosed, during the treatment and long after the patient has finished the treatment.

Our study identified a clinically significant decrease in the postoperative QoL 30 days after surgery in patients that undergo systematic pelvic lymphadenectomy for early stage endometrial cancer compared to patients that do not. Systematic lymph node dissection is, certainly, not devoid of adverse effects. Although there might not be a discernable therapeutic benefit from LND, it remains the cornerstone of proper surgical staging, facilitating the tailoring of postoperative adjuvant treatment.

Women undergoing surgery for endometrial cancer should be counseled about the potential benefits of surgical staging including LND, which can influence their postoperative treatment in a significant manner, as well as the possible negative impact of the treatment on the short-term QoL. Sentinel lymph node mapping might be a viable alternative for these patients as it is associated with a better QoL and reduced perioperative morbidity, compared to comprehensive LND, without impeding the reliability of the staging procedure. QoL data may, in some cases, facilitate expectation management and coping strategies an enable endometrial cancer to patients to make better-informed decisions about the treatment about their treatment.

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