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The impact of the type of nodal assessment on prognosis in patients with high-intermediate and high-risk ESMO/ESGO/ESTRO group endometrial cancer. A multicenter Italian study

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ABSTRACT

Objectives: The majority of endometrial cancers (EC) are discovered while the disease is confined to the uterine body. The presence of lymph nodes metastases impairs the prognosis. In this study, we evaluated the possible impact on survival of sentinel lymph node (SLN) mapping algorithm and selective lymphadenectomy (LD) in early stage EC, according to the ESMO-ESGO-ESTRO risk subgroup classification.
Methods: We retrospectively analyzed the database from two collaborative institutions including women with high-intermediate (HI) and high-risk (HR) ESMO/ESGO/ESTRO groups that underwent surgical staging with either SLN mapping, or selective LD.
Results: Two-hundred and sixty-six women were overall identified, 121 in HI and 145 in HR group, respectively. LD was performed in 139 patients (52.5%), whereas SLN mapping algorithm in 61 patients (23%). Sixty-six patients in Rome center were not staged (24.8%). Aortic dissection was performed in 29 women (10.9%). The 3-year comparison did not show a significant difference between strategy adopted for nodal staging (SLN mapping, LD, and SLN + LD) on both disease-free survival [HR: 0.82; 95% CI 0.53 −1.28; p = 0.390], and overall survival [HR: 0.78; 95% CI 0.47−1.31; p = 0.355].
Conclusions: In this study focused on women in the HI and HR groups we did not find difference in the 3-years DFS and OS when comparing the SLN strategy with selective lymphadenectomy, or the SLN algorithm. The SLN strategy did not seem to not compromise the prognosis of high risk patients.

Introduction

The knowledge of regional lymph node status provides important prognostic information in women with early stage endometrial cancer (EC) and, more importantly, can limit the necessity of adjuvant therapies in patients with negative lymph nodes [1,2]. Systematic lymphadenectomy did not show to have significant improvements in survival or reduced disease relapse in women with apparent early stage disease [3,4]. Notwithstanding, the definition of low or high risk is usually performed postoperatively, based on a risk stratification system including the most important pathological prognostic features. In view of the evidence of the PORTEC-1 and GOG99 studies [5,6], which highlighted the inadequate prognosis of women with LVSI and grade 3 disease in an intermediate group of risk, the ESMO/ESGO/ESTRO guidelines recently added the high-intermediate group to the new risk classification regarding recommendations for adjuvant therapy [7].

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Sentinel lymph node (SLN) mapping is emerging as an accurate procedure to evaluate the nodal status of women with apparent confined endometrial cancer. This approach seems to be just as effective as lymphadenectomy in the detection of metastasis and will probably become the standard in early stage disease [8].

In addition, in recent large retrospective series comparing the survival impact of SLN vs lymphadenectomy, survival differences between the two groups [9] were not observed.

The aim of our study was to analyze the impact of the type of nodal assessment on recurrence and overall survival related to the ESMO/ESGO/ESTRO high-intermediate and high-risk groups.

Materials and methods

The Institutional Review Board approval for this collaborative analysis was obtained from both participating institutions and all patients signed an informed consent document regarding the proposed surgical approaches: laparoscopic or traditional open surgery.

Data was extracted from the database of two Italian centers (*San Gerardo Hospital in Monza, and Fondazione Policlinico Universitario A. Gemelli in Rome*). The nodal staging included SLN mapping, and/or pelvic and aortic lymphadenectomy (LD).

Women were classified in four subgroups of risk based on the final pathologic results, accordingly to the ESMO-ESGO-ESTRO classification [7].

1 *low risk:* G1-G2, stage IA endometrioid EC, with negative lymphovascular space invasion;
2 *intermediate risk:* G1-G2, stage IB endometrioid EC, with *negative* lymphovascular space *invasion*;
3 *high-intermediate risk:* endometrioid stage IA G3, regardless of LV status, or endometrioid G1-G2 with unequivocally LVSI positive regardless of myometrial invasion;
4 *high-risk:* stage IB, G3 endometrioid, regardless of LV status, stage II, III, stage II–III endometrioid with no residual disease, or type 2 EC.

The analysis was limited to women in **the** high-intermediate and high-risk groups.

SLN mapping group (Monza Centre)

SLN mapping was introduced in 2010. The routine pelvic surgical procedure, with or without aortic LD, was abandoned as a standard once the learning curve was completed. A side specific pelvic procedure, with or without aortic lymphadenectomy up to the renal vessels was performed in the case of failed mapping in a hemi-pelvis, as proposed by Barlin et al. [10].

In the presence of preoperative high-risk features (grade 2 endometrioid tumors with myometrial invasion $\geq$ 50% at preoperative imaging examination, or any grade 3 endometrioid carcinoma, carcinosarcoma, serous carcinoma, clear cell carcinoma) women underwent a preoperative PET/CT scan. A full pelvic and aortic lymphadenectomy up to the renal vessels was performed in those cases with 18F-FDG PET/CT uptakes, indicative of suspicious lymph-nodal involvement. These patients were not suitable for SLN biopsy.

Sentinel node mapping protocols

From October 2010 up to February 2014, SLN detection included a two-step procedure, as already published [11].

Starting from February 2014, SLN mapping with Indocyanine green (ICG) was introduced. Four to five mL of ICG solution (ICG final concentration of 1.25 mg/mL) were injected at the 3 and 9 o'clock positions (1 mL was injected deeply into the stroma and 1 mL superficially). A complete HD system was used for the real-time intraoperative SLN fluorescent detection (*Karl Storz Endoscopy, Mittelstrasse, Tuttlingen, Germany*; *PinPoint Endoscopic Fluorescence Imaging System, NOVADAQ, Mississauga, ON, Canada*) [11].

LD group (Rome Centre)

A frozen section analysis on all hysterectomy specimens was performed in all cases. A bilateral pelvic LD was performed in the presence of myometrial invasion >50%, or in case of G3 disease. Any enlarged and suspicious nodes were removed and sent for frozen section evaluation, together with the pelvic nodes, and aortic LD up to the renal vessels was performed in presence of positivity, or based on pathologic risk factors of the uterine specimen.

In both groups, the side specific pelvic lymphadenectomy included the removal of the external iliac, internal iliac, obturator, internal and common iliac nodes. The aortic LD was left to the discretion of the attending surgeon, based on each institution's internal guidelines.

Nodal pathologic assessment protocols

Traditional pathologic evaluation

The routinely processed hematoxylin and eosin (H&E) including a half-section of the lymph node followed by paraffin embedding, was applied by both Centers. As already stated, the standard protocol differed between the two centers since in Rome, each lymph node was sectioned in half and the two sections were examined, while in Monza only one section was performed [12].

Ultrastaging pathologic evaluation

A trained gynecologic pathologist processed all the SLN's. The initial routine section of all the SLN's included hematoxylin and eosin (H&E) analysis. Only the SLN's without macroscopic involvement were examined using the pathologic ultrastaging protocol. The node was cut perpendicular to the long axis and two adjacent 5 μm sections were cut at each of 2 levels, 50 μm apart. At each level, one slide was stained with H&E and the other with immunohistochemistry using the AE1/AE3 anticytokeratin antibody (DAKO Company, Glostrup, Denmark). One negative control slide for a total of five slides per block was retained. Macrometastasis was considered a metastatic deposit greater than 2 mm. Micrometastasis was defined as a metastatic deposit ranging from 0.2 mm to no more than 2 mm in size. Isolated tumor cells were defined as single tumor cells or a cluster of malignant epithelial cells less than 0.2 mm, as seen on corresponding H&E sections and not just by immunohistochemical (IHC) staining.

Statistical analysis

Absolute and percentage frequencies were used to describe the patient population. Survival curves were built and plotted using the Kaplan–Meier method in which Disease-Free Survival (DFS) was defined as the time from surgery to the earliest recurrence of relapse or death. Fisher's exact test and the sum rank test were used to analyze the differences between groups of patients. A univariate and multiple factor logistic regression model was used to estimate the odds ratios and the p-values for association between outcomes (death and relapse) and tumor or patient parameters. Stata software 9.0 (Stata Corporation, College Station, Texas, USA) was used for the statistical analysis and a p-value < 0.05 was deemed as statistical significance.

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