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The impact on survival of two different staging strategies in apparent early stage endometrial cancer comparing sentinel lymph nodes mapping algorithm and selective lymphadenectomy: An Italian retrospective analysis of two reference centers

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HIGHLIGHTS

- Impact on survival of two nodal staging strategies in stage I endometrial cancer
- Sentinel node mapping and selective lymphadenectomy have same survival outcomes.
- Sentinel node mapping did not impaired prognosis of women with endometrial cancer.

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ABSTRACT

Objective. The role of lymphadenectomy in endometrial cancer is still uncertain. We aimed to evaluate the survival outcomes of two different strategies in apparent uterine confined disease by comparing sentinel lymph node (SLN) mapping and selective lymphadenectomy (LD).

Methods. We retrospectively reviewed women with preoperative stage I endometrial cancer underwent surgical staging with either SLN mapping, or LD in two Italian centers.

Results. Eight hundred and two women underwent surgical staging for preoperative stage I endometrial cancer were revised (145 Monza; 657 Rome). All patients underwent peritoneal washing, simple hysterectomy with bilateral salpingo-oophorectomy and nodal staging including SLN mapping, or LD. Overall 8229 lymph nodes were removed (1595 in Monza, 6634 in Rome). Pelvic lymphadenectomy was performed in 33.1% and 52.4% in Monza and Rome, respectively ($p < 0.001$). Patients with positive pelvic LN were 16.7% and 7.3%, in SLN and LD groups, respectively ($p = 0.002$). Disease-free survival (DFS) curves did not showed a statistically significant difference between centers and strategies adopted (SLN mapping, LD, SLN + LD) with a HR of 0.87 (95% CI 0.63–2.16; $p = 0.475$).

Conclusions. Survival outcomes were similar for both strategies. The SLN strategy allowed to identify a higher rate of stage IIIc1 disease even with a lower median number of lymph node removed in SLN group. Applying a SLN algorithm does not impair the prognosis of endometrial cancer patients. The clinical impact and management of low volume metastasis in high-risk patients should be further clarify.

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1. Introduction

Endometrial cancer (EC) is the most common gynecological malignancy worldwide, with an estimated 102,423 new cases in 2015 [1,2].

Despite two randomized clinical trials did not show survival benefit of systematic pelvic lymphadenectomy in early-stage EC patients, one of the main issue still debated regards the role of a comprehensive lymphadenectomy in uterine apparent confined disease [3,4].

Nevertheless, the nodal status represents one of the most important prognostic factors of those patients, allowing better planning of the adjuvant treatment.

Sentinel lymph node (SLN) biopsy is strongly emerging as the ideal compromise to evaluate the nodal involvement because not only seems to reduce the intraoperative and peri-operative morbidity of a systematic lymphadenectomy, but also it seems to improve the detection of micro-metastasis with the ultra-staging analysis [5]. By applying a well-structured SLN algorithm as proposed by Barlin et al. in 2012 [6], the false negative rate of nodal staging can be further reduced. This innovative approach was recently reinforced in a prospective study and option of SLN mapping has been recently included in the NCCN and ESGO-ESMO-ESTRO guidelines [7–9].

In this study, we retrospectively analyzed data from two Italian reference centers with a different surgical staging approach in patients with apparent confined stage EC. Our aim was to compare the SLN strategy with the selective lymphadenectomy (LD) strategy in terms of surgical and pathological outcomes, and the impact of the two approaches on survival.

2. Patients and methods

2.1. Inclusion criteria

Women with preoperative histological proven biopsy of EC apparent confined to the uterine body at pre-operative work-up, were retrospectively revised. Data were extracted from two reference Italian centers database (*San Gerardo Hospital in Monza, and Fondazione Policlinico Universitario A. Gemelli in Rome*). All enrolled women underwent a surgical intervention with staging aims including peritoneal cytological evaluation, total simple hysterectomy, bilateral salpingo-oophorectomy laparoscopically or with a traditional open approach. Lymph node staging included SLN mapping, pelvic and aortic lymphadenectomy.

All patients gave their informed consent to the proposed surgery including SLN mapping and/or LD, as standard of care in both the Departments. According to the ESMO-ESGO-ESTRO classification [8] women were classified in four subgroups of risk related to final pathologic assessment:

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

2.2. Monza Centre (SLN mapping group)

The center incorporated SLN mapping in 2010 and until February 2014 the procedure was performed by using radiocolloid and blue dye or blue dye alone. Subsequently, from February 2014 ICG was included in the SLN mapping protocol as already reported [10,11].

After initial experience and completion of learning curve, routinely pelvic with or without aortic LD as standard surgical procedure was omitted. When pelvic lymphadenectomy was also performed, SLN's were sent separately for the analysis and the anatomic location of lymph nodes were defined by using the Reiffenstuhel nomenclature [12]. According to MSKCC algorithm [7], a side specific pelvic and aortic lymphadenectomy was performed in case of failed mapping in a hemipelvis. Women with histologically proven grade 2 endometrioid tumors

with myometrial invasion of >50% at preoperative imaging examination or any grade 3 endometrioid carcinoma, carcinosarcoma, serous carcinoma, or clear cell carcinoma underwent PET/CT scan. Pelvic and aortic up to renal vessels lymphadenectomy was performed for those cases which presented 18F-FDG PET/CT findings considered positive for lymph-nodal involvement [13].

2.3. Sentinel node mapping

Until February 2014 SLN mapping was performed in 2 steps. Firstly, preoperative lymphoscintigraphy was performed with 4 cervical injections (3–6–9–12 o'clock positions) of 200 to 300 μ Ci radiolabelled filtered TC99-albumin nanocolloid in 0,2 to 0,3 mL volume. The second step was performed in surgery room with the cervical injection of 2 mL of blue dye (1 mL for each side at 3 and 9 o'clock positions).

From February 2014, the fluorescence near-infrared SLN mapping using Indocyanine green (ICG) was introduced. At the surgery time, initial laparoscopic evaluation was mandatory to evaluate the feasibility of the surgical procedure.

Cervical injection of ICG was performed at the 3 and 9 o'clock positions with a total of 4–5 mL of ICG solution (ICG powder 25 mg vial was diluted in 20 mL of aqueous sterile water.)

For each side, 1 mL was injected 1 cm into the stroma and 1 mL at superficial level. In case of open approach to surgery, SLN mapping was performed by using the Storz VITOM II exoscope for fluorescence mapping [14].

2.4. Roma Centre (LD group)

In all cases, frozen section analysis of the uterus was performed. During surgical exploration, any suspicious node was removed and sent for frozen section. Pelvic lymphadenectomy was performed in presence of myometrial invasion >50%, or in undifferentiated grade of differentiation. When removed, pelvic nodes were sent to frozen section analysis; aortic lymphadenectomy was performed only in presence of positive pelvic nodes at frozen section analysis.

2.5. Nodal pathologic assessment protocols

2.5.1. Traditional pathologic evaluation

The examination of the routinely processed hematoxylin and eosin (H&E) was applied by both centers, including a half-section of the lymph node followed by paraffin embedding. The standard protocol differs between the two centers since in Rome each lymph node was sectioned by half and was examined using two sections, whereas in Monza only one section for each lymph node was performed.

2.5.2. Ultrastaging pathologic evaluation

All the nodes, on initial routine section, were examined by hematoxylin and eosin (H&E). Only the SLN without macroscopic metastasis were examined according to the pathologic ultrastaging protocol. The node was cut perpendicular to long axis and two adjacent 5 μ m sections were cut at each of 2 levels 50 μ m 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), as well as one negative control slide for a total of five slides for block. Macrometastasis contain a metastatic deposit >2 mm. Micrometastasis was defined as a metastatic deposit ranging from 0.2 mm up to 2 mm in size. Isolated tumor cells were defined as single tumor cells or a cluster of malignant epithelial cells <0.2 mm, as seen on corresponding H&E sections and not just immunohistochemical (IHC) staining.

2.5.3. Statistical analysis

Absolute and percentage frequencies were used to describe patient's population. Survival curves were built and plotted using the Kaplan-

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