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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Sentinel lymph node mapping in patients with stage I endometrial carcinoma: a focus on bilateral mapping identification by comparing radiotracer Tc99^{m} with blue dye versus indocyanine green fluorescent dye

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Abstract
Purpose The aim of this study was to compare technetium radiocolloid (Tc99^{m}) + blue dye (BD) versus Indocyanine green (ICG) fluorescent dye in terms of the overall detection rate and bilateral sentinel lymph node (SLN) mapping in patients with endometrial carcinoma.
Methods Patients from five European centers with apparently confined clinical stage I endometrial cancer were reviewed. A comparison was made between women who received SLN mapping with pelvic and/or aortic lymphadenectomy (LND), and women who underwent SLN algorithm (SA), was also performed between the two groups.
Results Three hundred and forty-two (342) women were involved (147 in the Tc99^{m} + BD group and 195 in the ICG group). The overall detection rate of SLN biopsy was 97.3% (143/147) for women in the Tc99^{m} + BD group and 96.9% (189/195) for women in the ICG group ($p = 0.547$). The bilateral mapping rate for ICG was 84.1%—significantly higher with respect to the 73.5% obtained with Tc99^{m} + BD ($p = 0.007$). No differences in overall sensitivity (OS) and overall false negative rate (FNR) were seen between LND and SA (p value = 0.311), whereas the negative predictive value (NPV) was in favor of SA group (p value = 0.030).
Conclusions In this study, fluorescent mapping using ICG resulted equivalent to the standard combined radiocolloid and BD, but real-time SLN mapping achieves a higher bilateral detection rate. The added value that this fast emerging technology promises to give certainly warrants future studies to further consolidate the advantages there are over the standard technique.

Keywords Sentinel lymph node mapping · Laparoscopic surgery · Fluorescence tracer · Endometrial cancer

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Introduction

Endometrial cancer is the most common gynecological malignancy in Europe, with an estimated 102,423 new cases in 2015 (GLOBOCAN 2012). Women with endometrial cancer display a characteristic clinical profile including estrogenic excess, high body mass index (BMI), diabetes and other components of metabolic syndrome.

For adequate surgical staging in women with early-stage EC, a hysterectomy, bilateral salpingo-oophorectomy and lymph nodes assessment must be performed, except in the cases of young women that are candidates for fertility-preserving therapy (Pronin et al. 2015). However, for women with early endometrial cancer, full lymph node dissection

remains debated, particularly after viewing the results of two randomized trials on the benefits of lymphadenectomy in this population (Panici et al. 2008; Kitchener et al. 2009).

Sentinel lymph node (SLN) mapping is increasingly more present in this debate and comes in halfway between no dissection and systematic lymphadenectomy. SLN represents the standard of care for melanoma, breast cancer and early-stage vulvar cancer, but it is increasingly more interesting in the staging of many other malignancies including gastric cancer, colorectal cancer and more recently, cervical and endometrial tumors (Takeuchi and Kitagawa 2015; Huynh and Bilchik 2015; Jewell et al. 2014).

Different techniques of injections and various tracers have been used for mapping, in order to find the most feasible and safest method of findings SLN and to have the least rate of false negative (i.e., negative SLN but with one or more positive lymph nodes in other regions): Lymphoscintigraphy with radiocolloid ($Tc99^m$) and intra-operative detection with gamma probe has been the initial standard of care. In order to increase the overall detection rate (ODR), a blue dye (BD) injection could have been added, achieving an ODR between 70 and 100%[9]. Notwithstanding, in the last few years, many institutions have introduced indocyanine green (ICG), a fluorescent dye, with near-infrared imaging for SLN mapping (How et al. 2015; Porcu et al. 2016).

ICG is a fluorescent tracer largely used in medicine, especially in ophthalmic angiography and in evaluating hepatic function, but only recently has been validated for SLN mapping. It allows for real-time intra-operative mapping with either a traditionally open and laparoscopic approach, resulting in less discomfort for patients and reduced costs to hospitals rather than using of $Tc99^m$ or robotic surgery (NCCN 2016; Sinno et al. 2014). In recently published studies, ICG alone achieves ODR and bilateral mapping comparable to the combined technique (i.e., $Tc99^m$ plus blue dye) and these results, associated with a minimally invasive laparoscopic approach, appears to be a valid tool for SLN for the future.

The primary objective of this European multicenter study is to compare the combined technique $Tc99^m$ with BD versus ICG dye in terms of the overall detection rate and bilateral mapping in patients with stage I endometrial cancer, surgically staged with either minimally invasive laparoscopic or the traditional open approach.

Materials and methods

Patient population

This retrospective study included women with preoperative stage I endometrial cancer from five centers: Monza, Berne, Madrid, Varese and Verona. All patients received complete surgical staging, including simple hysterectomy, bilateral salpingo-oophorectomy and SLN biopsy with or without systematic pelvic and/or aortic lymphadenectomy. The validated SLN algorithm of the Memorial Sloan Kettering group (Barlin et al. 2012) was applied in three participant centers (Monza, Berna, Madrid) once the learning curve was completed after at least 30 cases per surgeon.

The SPIES Full HD D-Light P ICG technology (Karl Storz, GmbH &CO, Mittelstrasse, Tuttlingen, Germany) was used by all the participating centers. The VITOM II exoscope, a rigid lens telescope connected to the SPIES Full HD D-Light P ICG camera, was used for the traditional open procedures.

Informed consent was obtained from all individual participants included in the study.

Preoperative lymphoscintigraphy

Before the introduction of fluorescent tracer, SLN mapping was performed using the combined radiocolloid technique and the BD intra-operative injection. The preoperative LSG was performed the day before or the morning of the planned surgery with a cervical injection of 200–300 μCi radiolabeled filtered technetium $Tc99^m$ albumin nanocolloid.

After the dynamic acquisition, an anterior planar static image was done, and a SPECT/CT study was performed if necessary, 3 h after the radiotracer injection, with a hybrid system composed of a dual-head gamma camera with a low-dose X-ray tube installed in its gantry (Infinia Hawkeye 4,GE Medical Systems), as previously described (Buda et al. 2016a, b).

Intra-operative tracers injection

The method of cervical injection of the BD or ICG was the same in all centers.

Overall, 4 mL of BD were injected into the cervix (2 mL per injection, on each side at the 3 and 9 o'clock positions). The ICG (Indocyanine Green, PULSION Medical Systems SE, Feldkirchen, Germany) concentration used was 1.25 mg/mL. For each patient, a 25 mg vial with ICG powder was diluted in 20 cc of sterile aqueous water. Four mL of this ICG solution was injected into the cervix using the same modality as for the BD. For both tracers, the dye was injected slowly: One mL of solution was injected with penetration to a depth of one cm into the stroma, and 1 mL was injected superficially on the right and the left of the cervix after the induction of general anesthesia. In one center (Berne), patients were injected with 8 to 10 ml of ICG with the same approach.

Pathology evaluation

All women were staged after definitive histology according to the 2009 International Federation of Gynecology and Obstetrics classification. An expert gynecologic oncology pathologist, highly skilled in the analysis of SLNs, evaluated all surgical samples and SLN. All lymph nodes were handled in a standardized manner. Lymph nodes with macroscopic metastases were sectioned, and the SNs that appeared normal were cut perpendicular to the long axis. Two adjacent 5-μm sections were cut at each of 2 levels 50 μm, apart from each block in which metastatic carcinoma—detectable in a routine section stained with hematoxylin and eosin (H&E)—was not present. 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 5 slides per block was stained as well. All other non-SNs were only examined by routine H&E.

Micrometastasis (MM) was defined as a metastatic deposit within the lymph nodes ranging from 0.2 mm to no more than 2 mm in size. Isolated tumor cells (ITCs) were defined as single tumor cells or cluster of malignant epithelial cells less than 0.2 mm.

Statistics

Absolute and percentage frequencies were used to describe categorical items, while median values and ranges were assessed for continuous variables. The statistical outcome measures were reported as recently proposed in a systematic review, including the "overall outcomes" and the "algorithm-specific outcomes" (Cormier et al. 2015). Stata software 9.0 (Stata Corporation, College Station, Texas) was used for performing the statistical analysis. All calculated p values were two-sided, and p values <0.05 were considered statistically significant.

Results

Between 2010 and 2016, a total of 342 women were included: one hundred and forty-seven in the $Tc99^m$ + BD group and 195 in the ICG group. Patients and tumor characteristics are listed in Table 1. Median ages, BMI, grade of differentiation and number of SLN removed per patient were well balanced between the groups. In the $Tc99^m$ + BD group, 36% of patients had lymphovascular space invasion (LVSI) compared with 17% in the ICG cohort ($p < 0.0001$). Endometrioid histology was statistically more present in the ICG group (84.6%; $p = 0.007$). The median number of SLN was 3 (range 0–9) in $Tc99^m$ group and 3 (range 0–18) in ICG group. The overall detection rate of the SLN mapping was 97.3 and 96.9% in $Tc99^m$ and ICG, respectively ($p = 0.547$). A statistically significant difference was recorded for the bilateral detection rate in favor of ICG group (73.5 vs 84.1%; $p = 0.007$). Figure 1 shows the differences of SLN mapping between the groups. Minimally invasive laparoscopic surgery was performed in 86.4 and 95.4% of $Tc99^m$ and ICG, respectively ($p = 0.003$). In two cases, conversion to standard open surgery occurred: In one case conversion was required because the presence of large uterine fibroids; in the second case, in the presence of wide adhesion syndrome a bowel lesion occurred that could not resolved by laparoscopy. The anatomical distribution of the SLN was similar in both groups, and the vast majority of mapped nodes were located in the external iliac area

Table 1 Characteristics of 342 patients

	TC^{99} + blue ($N = 147$)	ICG ($N = 195$)	p value
Age (years)			
Median (range)	66 (39–87)	65 (29–89)	0.072[a]
BMI (kg/m^2)			
Median (range)	27.5 (17–50)	28.1 (15–56)	0.244[a]
Stage (final pathology)			
N.A.	–	2 (1%)	0.032[b]
EIN	–	6 (3.1%)	
IA	80 (54.4%)	123 (63.1%)	
IB	29 (19.7%)	27 (13.9%)	
II	8 (5.4%)	10 (5.1%)	
IIIA	1 (0.7%)	5 (2.6%)	
IIIB	1 (0.7%)	1 (0.5%)	
IIIC1	20 (13.6%)	11 (5.6%)	
IIIC2	5 (3.4%)	8 (4.1%)	
IV	3 (2%)	2 (1%)	
Histology (final pathology)			
EIN	0 (0%)	6 (3.1%)	0.010[b]
Endometrioid	116 (78.9%)	165 (84.6%)	
Other	31 (21.1%)	24 (12.3%)	
Grade			
G1	56 (38.1%)	68 (35.2%)	0.191[b]
G2	47 (32%)	70 (35.7%)	
G3	23 (15.6%)	49 (25%)	
NA	21 (14.3%)	8 (4.1%)	
LVSI			
Yes	53 (36.1%)	34 (17,4%)	<0.0001[b]
No	94 (63.9%)	149 (76.5%)	
N.A.	–	12 (6.1%)	

BMI body mass index, *EIN* endometrial intraepithelial neoplasia, *TC^{99}* Technetium 99 radiocolloid, *ICG* indocyanine green, *NA* not available, *LVSI* lymphovascular space invasion

[a] Rank sum test

[b] Fisher's exact test

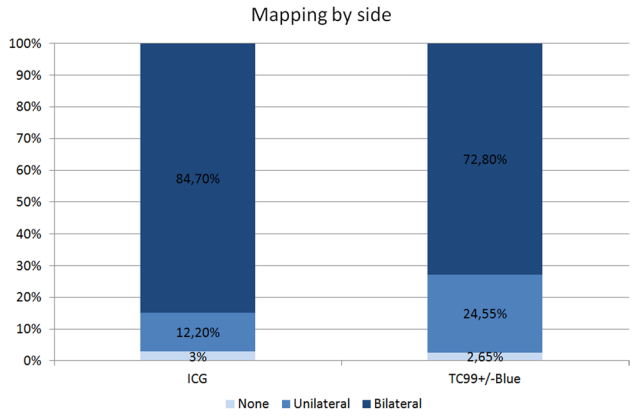

Fig. 1 SLN mapping by group

and the obturator fossa. On final pathology, 320 women (92%) were node negative. Overall, 22 patients presented nodal involvement (8%). Metastases were discovered in 12/147 women (8.1%) in the $Tc99^{m}$ + BD group and in 10/195 women (5.1%) of the ICG group ($p = 0.181$). Among 993 SLNs removed, 71 lymph nodes presented metastasis (7.1%). Low volume metastases were identified in 20/38 of the SLN in the $Tc99^{m}$ + BD group (16 MM and 4 ITC) and in 9 SLN in the ICG group (8 MM and 1 ITC). Patients with MM or ITC only in the lymph nodes were 18/43 (41.8%), including 13/25 in the $Tc99^{m}$ + BD group and 5/18 in the ICG group. Surgical characteristics are displayed in Table 2. The overall sensitivity (OS) and overall false negative rate (FNR) were not statistically significant between patients underwent SLN mapping with lymphadenectomy and patients who received SLN mapping algorithm (p value = 0.311). The negative predictive value (NPV) was in favor of the SLN algorithm group (p value = 0.030). Table 3 resumes the latest analysis as recently proposed (Cormier et al. 2015).

Table 2 SLN mapping and lymph node pathological characteristics according to the tracer used (N = 342)

	TC^{99} + blue ($N = 147$)	ICG ($N = 195$)	p value
Type of surgery			
S-LPS	127 (86.4%)	186 (95.4%)	0.003[b]
Open surgery	20 (13.6%)	9 (4.6%)[c]	
SLN per patients			
Median (range)	3 (0–9)	3 (0–18)	0.592[a]
Overall Detection rate (ODR)			
No mapping	4 (2.7%)	6 (3.1%)	0.547[b]
At least one side mapping	143 (97.3%)	189 (96.9%)	
Mapping by side			
Unilateral	35 (23.8%)	25 (12.8%)	0.007[b]
Bilateral	108 (73.5%)	164 (84.1 %)	
Pts with positive LN			
N (%)	12 (8.2%)	10 (5.1%)	0.181[b]
Pts with positive SLN			
N (%)	25 (17.5%)	18 (9.5%)	0.025[b]
Positive SLN			
N (%)	38/400 (9.5%)	33/593 (5.6%)	0.013[b]
Type of metastasis			
N (%)			0.105[b]
Macrometastasis	18/38 (47.4%)	24/33 (72.7%)	
Micrometastasis	16/38 (42.1%)	8/33 (24.2%)	
ITC	4/38 (10.5%)	1/33 (3.1%)	

Pts patients, *S-LPS* standard laparoscopy, *TC^{99}* Technetium 99 radiocolloid, *ICG* indocyanine green, *LN* lymph nodes, *SLN* sentinel lymph node, *ITC* isolated tumor cell

[a] Rank sum test

[b] Fisher's exact test

[c] Two cases with conversion to open surgery due to intra-operative complications

Discussion

In this large European multicenter retrospective study, we compared the historical standard technique for SLN mapping including radiocolloid and blue dye, with the fluorescent mapping using ICG during a laparoscopic approach of apparent early-stage endometrial cancer.

The need to perform routine pelvic and/or aortic lymphadenectomy in apparently confined early-stage endometrial cancer represents a controversial and debated issue, since two randomized studies did not demonstrate a significant benefit for survival in the lymphadenectomy arm in patients with early endometrial cancer (Panici et al. 2008; Kitchener et al. 2009). Since there is limited evidence of preoperative tools to predict the subgroup of patients at risk of nodal involvement, the application of a well-defined surgical algorithm is essential for the management of endometrial cancer patients. According to the "Mayo Clinic criteria" (AlHilli and Mariani 2014), approximately 27% of women can avoid a full lymphadenectomy because of the low risk of nodal metastasis. However, the Mayo Criteria is not easily reproducible with the same sensibility from other pathologic institutions (Kumar et al. 2014). In this scenario, sentinel node mapping has emerged worldwide as a promising strategy for the surgical staging of endometrial cancer patients. Moreover, SLN technique has been integrated into the NCCN (National Comprehensive Cancer Network) guidelines for endometrial cancer recently updated (NCCN 2016). Moreover, the ESMO Consensus Conference on

Table 3 Overall and algorithm-specific outcomes of the study (as proposed by Cormier et al. 2015)

	TC^{99m} + ICG LND ($N = 142$)
Overall sensitivity	30/34 (88.2%)
Overall NPV	108/112 (96.4%)
Overall FNR	4/34 (11.7%)
	TC^{99m} + ICG Algorithm ($N = 167$)
Algorithm sensitivity	11/11 (100%)
Algorithm NPV	156/156 (100%)
Algorithm FNR	0/11 (0%)

Note Thirty-eight patients with no mapping or unilateral mapping were excluded from the analysis as proposed by Cormier[12] because did not underwent systematic LND, or the algorithm due to clinical co-morbidity or intra-operative issues

LND Lymphadenectomy, *TC^{99m}* Technetium 99 radiocolloid, *ICG* Indocyanine green, *NPV* Negative predictive value, *FNR* False negative rate

endometrial cancer (Colombo et al. 2016) has recognized SLN mapping as a feasible experimental procedure that allows increased detection of low volume metastasis (micrometastasis and ITC). A recent large retrospective cohort of 1135 patients with low-risk endometrial carcinoma compared the surgical staging approach of the Mayo Clinic including full lymphadenectomy versus sentinel node algorithm of the Memorial Sloan Kettering (Zahl Eriksson et al. 2016). The SLN algorithm yielded a higher detection rate of stage IIIC1, and the SLN algorithm even results in removal of fewer total lymph nodes as compared to lymphadenectomy. The detection rate of stage IIIC2 disease was the same for both the algorithms. The authors conclude that in this low-risk population (endometrioid tumor with less than 50% myometrial invasion), the SLN algorithm does not appear to compromise the oncological outcome, a short-term three-year follow-up. The long-term result of the SENTI-ENDO study (Derai et al. 2015) confirmed the same survival results as the short term and demonstrated no significant difference in terms of recurrence rate and progression-free survival between SLN group and lymphadenectomy group.

Our study confirms the findings of other investigators that explored the feasibility of ICG in endometrial cancer. We did not find differences in terms of overall detection rate, however, that of the injection of a fluorescent dye in the cervix was significantly superior to the standard combined technique in terms of bilateral mapping ($p = 0.002$). Furthermore, no significant differences between the participant centers were found in terms of detection rate and bilateral mapping. As recently proposed by Cormier (Cormier et al. 2015), we also reported the overall and the specific-algorithm outcomes of our study (Table 3). The overall sensitivity (OS) and overall false negative rate (FNR) were not statistically significant between patients underwent SLN mapping plus lymphadenectomy and patients who received SLN mapping algorithm (p value $= 0.311$). However, the negative predictive value (NPV) was in favor of the SLN algorithm group (p value $= 0.030$). A recent meta-analysis compared the combination of blue dye and technetium with ICG in uterine malignancies. No differences in terms of overall detection rate and false negative rate between the groups were recorded. Even if not statistically significant, ICG recorded a better bilateral detection rate (Ruscito et al. 2016).

Despite the sample size represents the strength of our study, we are aware of it limitations. The retrospective nature of this multicenter analysis does not allow to draw definitive conclusion regarding the best tracer to use for SLN mapping, even if fluorescence real-time mapping with ICG seems to added a higher rate of bilateral mapping when compared to radiocolloid and blue dye. Moreover, we cannot establish the additional value of SLN mapping and it impacts on adjuvant treatment and survival of the identification of low volume metastasis, since we had only 8% of patients with positive node. Notwithstanding, 18/43 women with positive lymph nodes in this cohort had only MM or ITC in the SLN's.

Although the best technique and the ideal dye for SLN mapping are not completely defined in endometrial cancer, and fluorescent mapping using ICG requires the acquisition of a dedicated equipment (Handgraaf et al. 2014) for both traditional and robotic approaches, the near-infrared real-time technology can be supported by many objective reasons: (1) In obese endometrial cancer patients, it seems to be superior to colorimetric dye; (2) ICG has a good toxicity profile and it is easy to use in both cervical and hysteroscopic injection; (3) the use of a fluorescent tracer does not require the injection of radiocolloid in the Nuclear Medicine Department with the SPECT/CT acquisition before surgery to locate SLN's; (4) women avoid the discomfort that results from the preoperative injection of radiocolloid and seem to improve the quality of life perceived by the patients (Buda et al. 2016a, b); and (5) the use of ICG seems to be useful during the surgical procedure after SN mapping, allowing the surgeon to complete the procedure without staining the operative field as occasionally occurred with blue dye, particularly in very obese patients. There are still several unresolved issues and points of discussion regarding the staging of endometrial cancer, including the identification of the best tracer to use for SLN mapping. Some answers will likely emerge from the results of an ongoing prospective multicenter trial being carried out by Rossi et al. on the use of ICG during robotic surgery in case of early-stage endometrial cancer and cervical cancer.

Conclusions

Our results support the use of ICG for real-time SLN mapping during traditional laparoscopic approach in women with an apparent clinical stage I uterine-confined disease. ICG resulted equivalent to the combined radiocolloid and blue dye, but achieves a higher bilateral detection rate. Thus, by applying a well-defined algorithm as already established by the MSKCC group (Barlin et al. 2012), this procedure can further reduce the overall number of complete lymphadenectomies, thus impacting the QoL and long-term morbidity of patients without impairing the oncological outcomes (Buda et al. 2016a, b). The added value implicated by this emerging technology certainly warrants future studies to establish ulterior advantages which could: facilitate surgical operations, reduce postoperative morbidity, guide the choice of adjuvant treatments related to low volume metastasis discovered by ultrastaging and the favorably impact the survival of patients with endometrial cancer (clinical trial.gov identifier: NCT01673022).

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Compliance with ethical standards

Conflict of interest We declare that we have no conflict of interest.

Ethical approval For this type of study, formal consent is not required.

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