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Original research

Management of endometrial cancer in Italy: A national survey endorsed by the Italian Society of Gynecologic Oncology

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HIGHLIGHTS

- Endometrial carcinoma is a frequent cancer, but with discrepant clinical management.
- A survey on endometrial cancer management in Italy was performed.
- This survey demonstrate a significant improvement over the last decades in Italy.
- High-risk cases only, properly selected, could be referred to reference centers.

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ABSTRACT

Introduction: Endometrial carcinoma (EC) is a frequent cancer in developed countries, but with evidence for discrepant clinical management. Under the auspices of the Italian Society of Gynecologic Oncology (SIOG), we conducted a survey among Italian centers with ≥20 surgeries for gynecological cancer per year, trying to depict a reliable picture of EC management in our country. **Methods**: The questionnaire focused on preoperative/surgical staging and adjuvant treatment. Of the 283 questionnaires delivered, 35% were sent back. **Results**: Diagnostic hysteroscopy is performed in 78% of centers. In clinical stage I, 52% adopt a laparotomic access, 15% totally laparoscopic, 9% laparoscopic/vaginal, 2% vaginal, 22% tailored approach. Elective use of laparoscopy significantly differs between institutions ($p < 0.001$): 40% (≥20 EC/yr) vs. 12% (<20). Pelvic and aortic lymphadenectomy is selectively performed by 77% and 68% of centers, respectively, depending on pre/intraoperative factors. Non-endometrioid histology, poor-grade and deep myoinvasion are indicated as the highest-risk factors. Adjuvant therapy is given to pathologically node-negative patients by 60%, and to intermediate-risk patients by 47%. Elective adjuvant treatment is still radiotherapy, but chemotherapy is adopted, mostly combined with radiation, by 40%. There is a multidisciplinary team in 64% of centers, but in 59% adjuvant treatment is to be administered outside the institution. **Conclusions**: These data demonstrate a significant improvement in the clinical care achieved over the last decades in Italy. Centralization of EC treatment would not be

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feasible neither useful. High-risk cases could be selected by an appropriate clinical screening, and these only referred to reference centers.

1. Introduction

Endometrial carcinoma (EC) is the fourth most common cancer among women in Italy, accounting for 5% of all malignant neoplasms with 8200 estimated new cases for 2013 (incidence trend 1996–2010: +0.7%). About 70% of these patients are diagnosed at an early stage, resulting in a favorable prognosis, with 5-year overall survival rate of 77% (survival trend 1990–2007: +4%) [1].

Despite being the most common gynecological cancer in developed countries, there is evidence for many differences and discrepancies in the clinical management [2].

Both the preoperative and surgical staging are still object of controversies. There is no general agreement on basic questions, such as the routine use of diagnostic hysteroscopy, and on which imaging technique should be considered as indispensable. With respect to surgery, lymph node dissection (LND) represents the main point of discussion, based on the lack of evidence of its therapeutic impact [3,4]. When and how should it be performed? Various are the algorithms (if any) adopted by different centers, including or not intraoperative frozen sections of the uterine specimen.

Also, the indications to adjuvant treatment (and which?) are not uniform and seem to be more dependent on local habits and resources rather than on data of evidence. Such a clinical scenario reflects the scientific uncertainties still present but may be also related to missing update of information [5].

Under the auspices of the Italian Society of Gynecologic Oncology (SIOG), we have conducted a survey among the Italian centers involved in the gynecologic cancer care, trying to depict a reliable picture of the EC management in our country.

2. Methods

Data were collected by means of a questionnaire concerning specific diagnostic and therapeutic options. This questionnaire was mailed to the gynecologic centers listed in the Italian National Health Service (NHS) directory. Selected were only those centers with at least 20 surgical operations for gynecological cancer, per year.

Of the 283 questionnaires delivered, 99 (35%) were filled in and sent back by the end of January 2013. Sixty-one percent and 39% were from Northern and Central-Southern Italian institutions, respectively. Most questionnaires (78%) were from General Hospitals, while the remaining 21% from Teaching Hospitals/Cancer Centers. Overall, only 42% of centers have treated more than 20 cases of EC in the last year.

The questionnaire focused on three principal areas: 1) preoperative staging (evaluation of: cervical infiltration, depth of myometrial invasion, lymph node status, endometrial tumor size, dosage of serum tumor markers, revision of external pathological diagnosis); 2) surgical staging and therapy (type of hysterectomy in FIGO Stage I, histotype, tumor size and infiltration of cervical canal under consideration for surgical management, peritoneal cytology, intraoperative frozen sections, criteria for LND, surgical conduct in the presence of obvious intraperitoneal metastasis); 3) adjuvant treatment (which categories are considered at high- and intermediate-risk, any change in the risk assessment in the absence of LND, indications for adjuvant therapy in node-negative patients, adjuvant treatment in high- and intermediate-risk, presence of an intra-institutional department of pathology, radiotherapy and medical oncology, capability of performing a brachytherapy, where and by whom the choice of any adjuvant treatment is made).

3. Results

3.1. Preoperative staging

The great majority of centers believe that the evaluation of myometrial invasion (94%), cervical canal (93%), lymph node status

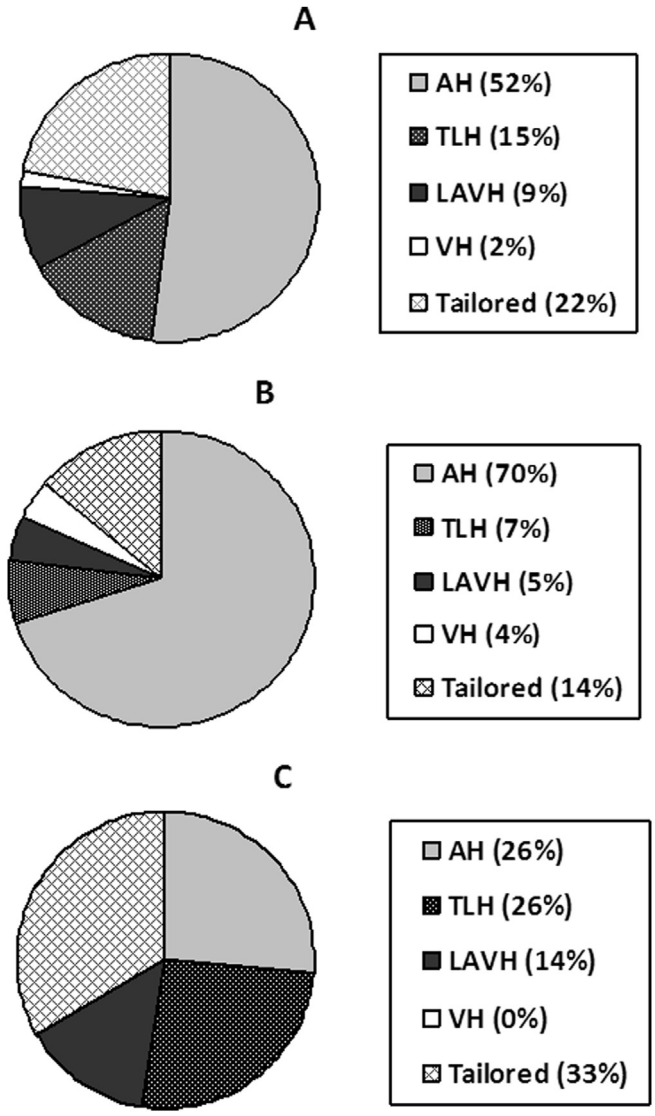

Fig. 1. Surgical staging and treatment: A) Overall; B) General Hospitals with <20 cases of cancer/year; C) Teaching Hospitals/Cancer Centers with >20 cases of cancer/year (Legend: AH, abdominal hysterectomy; TLH, total laparoscopic hysterectomy; LAVH, laparoscopy-assisted vaginal hysterectomy; VH, vaginal hysterectomy; Tailored, based on patient/disease characteristics).

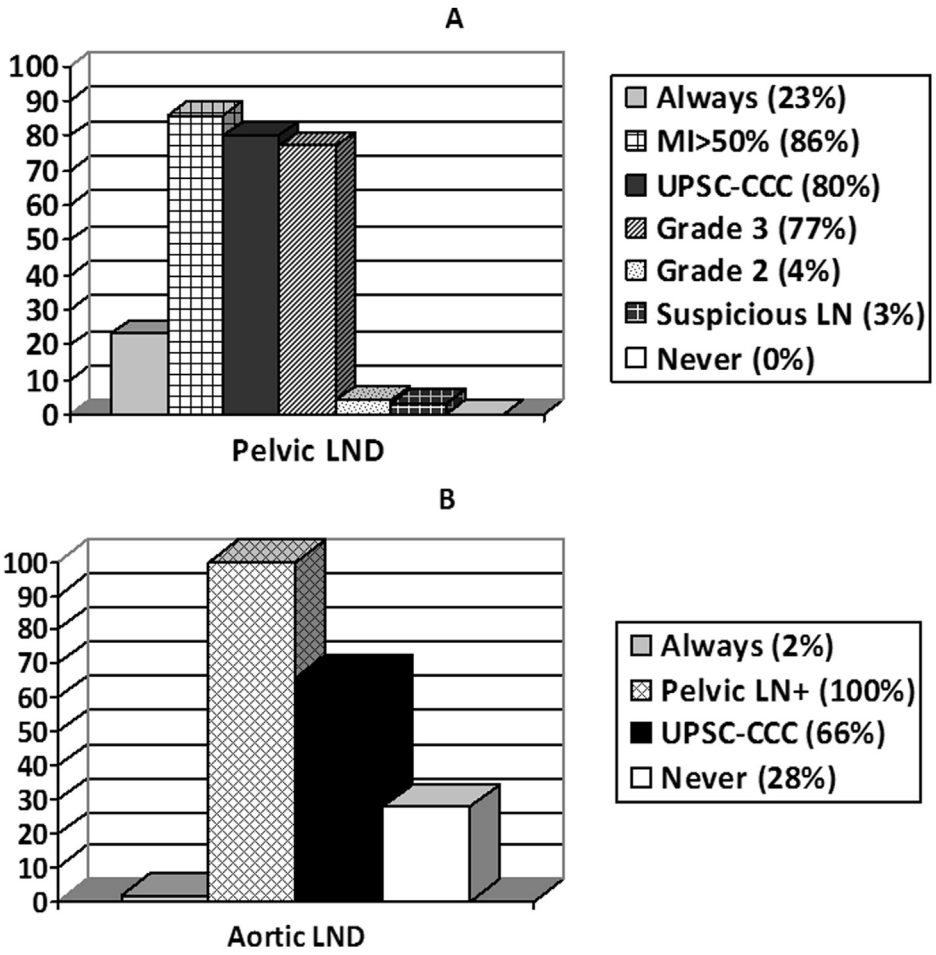

Fig. 2. Indication to LND: A) Pelvic LND; B) Aortic LND (Legend: LND, lymphadenectomy; MI, myometrial infiltration; UPSC–CCC, uterine papillary-serous/clear cell carcinoma; LN, lymph node).

(85%), and endometrial tumor size (71%) must be included into the preoperative staging. In this respect, there are no significant differences among the institution either the case-volume patterns. The diagnostic techniques routinely adopted (alone or in combination) are the following: hysteroscopy (78%), transvaginal ultrasound (TVUS) (61%), magnetic resonance imaging (MRI) (52%), computed tomography (CT) (40%).

Pre-surgical dosage of tumor serum markers is routinely performed in 78% of centers. In these centers, CA125, alone or in combination, is always included in the preoperative workup. Combined CA125 and CA19-9 dosage is performed in 52%, while 25% of centers adopt a markers panel (CA125, CA19-9, CA15-3, CEA ± AFP and TPA).

Revision of external pathological diagnosis is routinely performed in 51% of centers to verify histotype and grade in referred patients.

3.2. Surgical staging and therapy

Peritoneal cytology is routinely performed in 94% of institutions.

About the surgical treatment in clinical stage I, 52% of centers adopt a laparotomic access, 15% a totally laparoscopic, 9% a combined laparoscopic and vaginal, and 2% a vaginal access. The remaining 22% tailor the surgical approach – i.e. they modify the access – depending on the disease and patient characteristics (Fig. 1). Tailoring surgical approach and the elective use of laparoscopy significantly differ between the institution pattern: 33% vs. 14% ($p = 0.010$), and 40% vs. 12% ($p < 0.001$) for institutions treating ≥20 and <20 EC cases/year, respectively (Fig. 1). The type of hysterectomy performed in case of clinical FIGO stage I disease is extrafascial (pubovesical cervical fascia removed) in 80% of institutions, simple (intrafascial, pubovesical cervical fascia preserved) hysterectomy in 18%, type B radical (paracervix removed at the intersection of ureter with the uterine artery) hysterectomy in 1%; bilateral salpingo-oophorectomy is routinely performed.

In the case of serous and clear cell histology, the laparotomic approach is believed mandatory by 61% of centers, while additional surgical procedures necessary by 94% (pelvic LND: 91%; omentectomy: 72%; appendectomy: 56%; aortic LND: 54%). In the presence of infiltration of the cervical canal the surgery conduct is a type B radical hysterectomy in 76%, and a type C radical hysterectomy in 14%, while is still an extrafascial hysterectomy in the remaining 10% of centers (none treating ≥20 cases per year). The majority (75%) of centers do not take into consideration the endometrial tumor size for the surgical management. Only 31% of centers routinely perform an intraoperative frozen section analysis on the uterine specimen (81% of Teaching Hospitals/Cancer Centers). Twenty-six percent do not consider it valid and necessary, 13% do not have such a facility, 16% consider frozen section useful only if macroscopic examination of the myometrial and cervical canal infiltration is doubtful, and 13% adopt different criteria.

When considering the retroperitoneal LND, 24% of centers are used to perform a lymph node sampling, 72% as systematic procedure (≥20 pelvic nodes; ≥10 aortic nodes), while 3% resection of

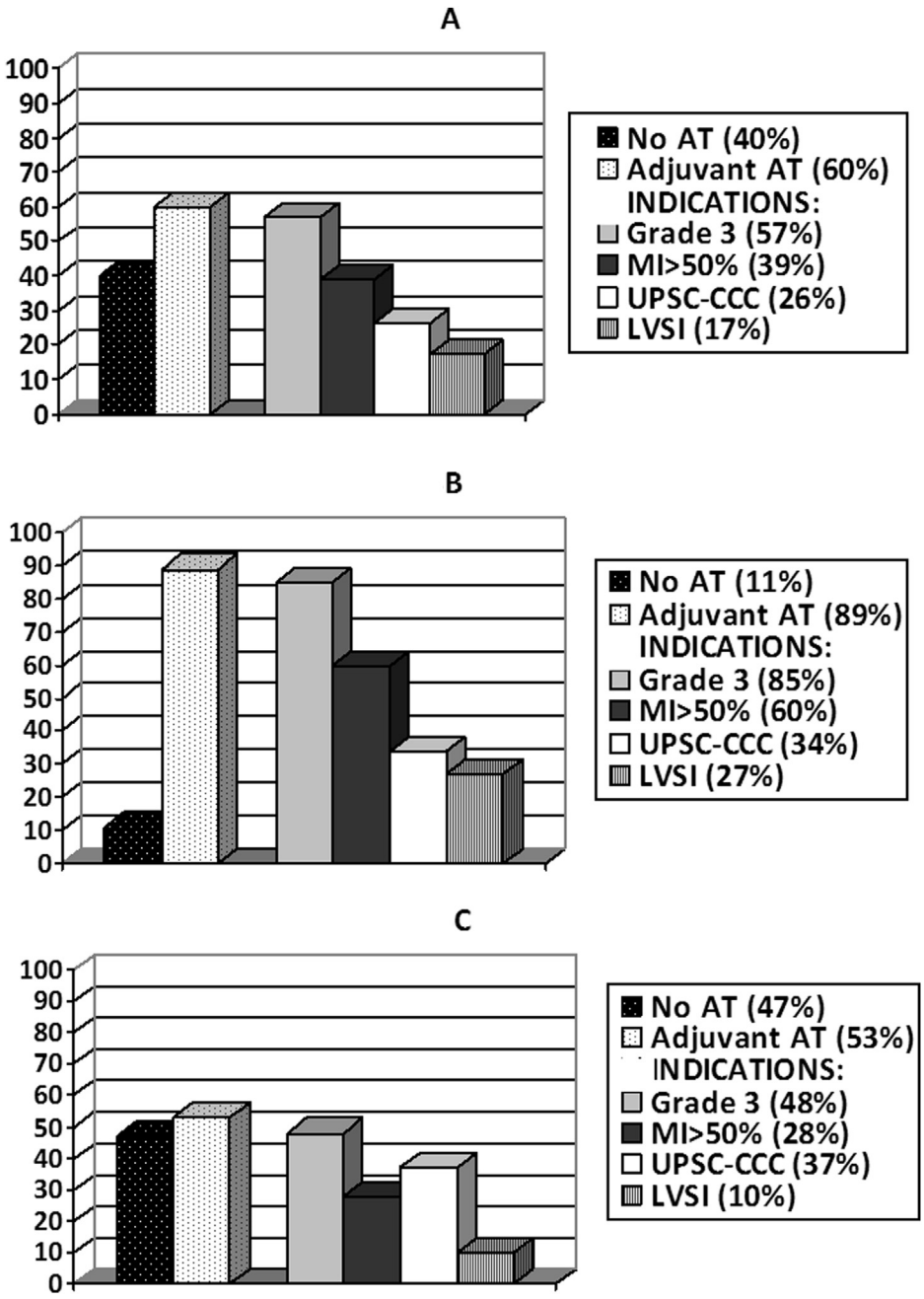

Fig. 3. Adjuvant therapy in FIGO stage I with negative lymph nodes: A) Overall; B) General Hospitals with <20 cases of cancer/year; C) Teaching Hospitals/Cancer Centers with >20 cases of cancer/year (Legend: AT, adjuvant therapy; MI, myometrial infiltration; LVSI, lymph vascular space involvement; UPSC–CCC, uterine papillary-serous/clear cell carcinoma).

suspicious nodes only. With respect to whether and when performing pelvic LND, 23% of centers perform it routinely, while the remaining do it, depending on the following factors: >50% myometrial infiltration (86%), serous or clear cell histology (80%), poorly differentiated tumors (77%), moderately differentiated tumors (4%), suspicious nodes (3%) (Fig. 2A). Aortic LND is never performed in 28% of institutions, routinely in 2%, while 68% do it, depending on the following factors: pelvic nodes suspected or positive at frozen sections (100%), serous or clear cell histology (66%) (Fig. 2B). Significant differences do not emerge in this respect through the comparison of centers by institution and case-volume patterns.

With respect to cases with intra-abdominal spread, surgery with cytoreductive intent is believed inappropriate by only 8% of centers. Ninety percent consider that the presence of obvious intraperitoneal metastasis changes the surgical behavior, by the following additional procedures: omentectomy (89%), appendectomy (57%), pelvic (53%) and aortic LND (35%).

3.3. Adjuvant treatment

The prerequisite was to establish which category of patients, based on final pathology report, is to be considered at enough risk of recurrence to justify an adjuvant treatment. First of all, the "special" histology is considered a high-risk factor, regardless of stage, by over 80% of centers (84% and 82% for serous and clear cell histotype, respectively) (100% of Teaching Hospital/Cancer Centers

and Hospitals with ≥20 cases per year). As expected, almost all centers (96%), consider FIGO stage III and IV (intra-abdominal), completely cytoreduced, at high-risk. The invasion of cervical stroma *per se* (FIGO stage II) is considered a high-risk parameter by 71% of centers, and adjuvant brachytherapy is judged adequate by all of them. Looking at the disease confined to the uterine corpus, the association of poor differentiation (G3) and deep myometrial invasion (>50%) is indicated as the highest risk subgroup for the endometrioid histotype by the majority of centers (82%). Interestingly, G3 alone is considered a high-risk factor by only 37% in the presence of <50% myometrial invasion, as well as >50% myometrial invasion in well or moderately-well differentiated tumors is shown as a high-risk marker by 34% of centers. The intermediate-risk is often identified by the association of a moderate differentiation (G2) and >25% myometrial invasion (IB-G2: 53%; IA-G2: 49%), but also by G3 in the presence of <25% (33%) and 25–50% myometrial invasion (44%).

Not performing a (at least pelvic) LND and the evidence of lymph vascular space invasion (LVSI) affects the risk grouping in 51% and 52% of centers, respectively. Adjuvant therapy, however, is given by 60% of centers even in the case of negative lymph nodes after a systematic pelvic LND in pathologically FIGO stage I disease. In particular, among these centers, adjuvant therapy is considered indicated in the presence of: G3 (57%), >50% myometrial infiltration (39%), "special" histotype (26%), LVSI (17%) (Fig. 3).

Forty-seven percent of centers also include the intermediate-risk in the group for which adjuvant treatment is indicated. The proportions significantly differ between General Hospitals with <20 cases of cancer/year (82%), and Teaching Hospitals/Cancer Centers with >20 cases of cancer/year (16%) (Fig. 4). The first-choice adjuvant treatment in high-risk patients is external radiation therapy (with or without brachytherapy) in 45% of centers. Chemotherapy is included, mostly combined with radiation, by 40% of centers (Table 1). Adjuvant options in the intermediate-risk patients are listed in Table 2 (Table 2).

Another issue concerns the decision making process. A pathology service/department is available in the same institution in 83% of centers, and a dedicated pathologist (exclusively assigned to gynecologic oncology) in only 18%. Is each case discussed within a team, or any therapeutic decision is taken by a single specialist? There is a multidisciplinary team in 64% of centers, and in most (84%) of the reference centers. This team is composed by a gynecologist, a medical oncologist, and a radiation oncologist in 55% of cases; by a gynecologist and a medical oncologist in 26%, by a gynecologist and a radiation oncologist in 14%, and by a medical oncologist and a radiation oncologist in 5%. In the absence of a team, the single specialist in charge of therapeutic decisions is the medical oncologist (52%), the gynecologist (45%), and the radiation oncologist (3%). A medical oncology department is present in 89% of centers, while a radiotherapy department is available in the same institution in only 42% of centers, with brachytherapy facilities in about two-third of cases (67%). These data justify the need for performing adjuvant treatment outside the institution in the majority of centers (59%).

4. Discussion

As expected, many controversial aspects of EC management have emerged from the present survey. EC is the most frequent gynecological malignancy, and is treated in reference centers as well as in general hospitals. This is why the authors, endorsed by the Italian Society of Gynecologic Oncology (SIOG), decided to send the questionnaire not only to leading institutions or to the Society members but also to low case-volume centers. Overall, less than half (42%) of responders have treated more than 20 EC cases in the last year, and this likely reflects the actual disease management in our country, as well as the geographical distribution of centers (61% Northern, and 39% Central-Southern Italy). The 35% compliance (of the 283 questionnaires sent, 99 were filled in and sent back) can be

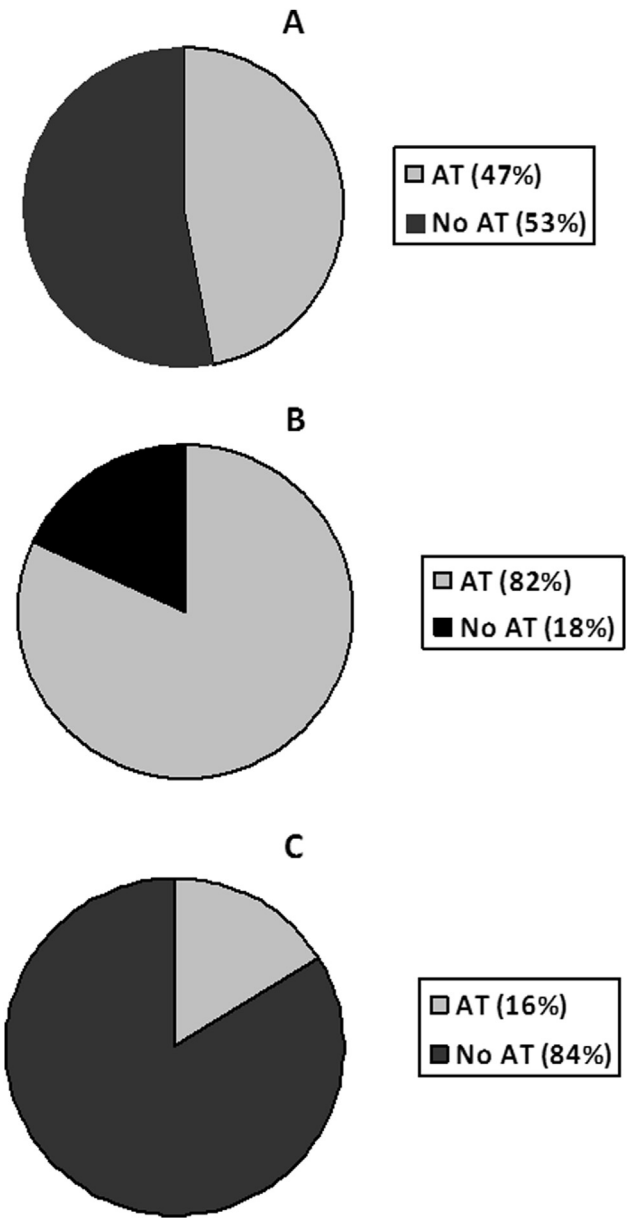

Fig. 4. Adjuvant therapy in intermediate-risk: A) Overall; B) General Hospitals with <20 cases of cancer/year; C) Teaching Hospitals/Cancer Centers with >20 cases of cancer/year (Legend: AT, adjuvant therapy).

Table 1
First-choice adjuvant treatment in the high-risk group of patients.

Adjuvant treatment	*n*	%
External radiotherapy ± brachytherapy	44	45
External radiotherapy ± brachytherapy + sequential chemotherapy	22	23
Concurrent chemo-radiation ± brachytherapy	15	15
Chemotherapy	2	2
Brachytherapy	0	0
Hormone therapy	0	0
Multiple options	14	15
Missing	*2*	*2*
Total	**99**	**100**

Table 2
First-choice adjuvant treatment in the intermediate-risk group of patients.

Adjuvant treatment	*n*	%
External radiotherapy ± brachytherapy	20	20
External radiotherapy ± brachytherapy + sequential chemotherapy	1	1
Concurrent chemo-radiation ± brachytherapy	1	1
Chemotherapy	1	1
Brachytherapy	2	2
Hormone therapy	0	0
As in high-risk	14	14
No therapy	52	53
Missing	*8*	*8*
Total	**99**	**100**

considered suboptimal, and a limit of the study. Such a rate, however, seems to be in the range of similar surveys reported in the literature. Higher rates are generally observed when a questionnaire is selectively sent to leading centers, members of a Society, etc (our questionnaire was sent to all hospital with at least 20 surgical operations for gynecological cancer, per year).

The great majority (78%) of centers adopt hysteroscopy as a diagnostic tool and part of the preoperative staging. This is in contrast with the 6.2% reported about ten years ago in a similar survey by leading centers of gynecological oncology in North America [6], and reflects the different attitude with respect to hysteroscopy between US and Europe. A European survey, performed about fifteen years ago on leading centers, showed, in fact, a routine pre-surgical use of hysteroscopy in 32.9% of institutions [7]. Actually, hysteroscopy is usually included in international guidelines as the final step in the diagnostic pathway, but differences still remain [8–10]. Our data suggest that, at least in Italy, its use in endometrial pathology is currently widespread. Abdomen–pelvis MRI or CT are not routinely included in the staging workup, but performed, however, in about 50% of cases, with or without a previous TVUS, with or without suspected cervical involvement and/or extra-uterine spread. This seems to be unnecessary in many cases [9], and it is likely to be relevant to a potential cost–benefit analysis [11].

During the last decade, the surgical approach to EC has changed with an increasing proportion of cases undergoing a laparoscopic intervention [12,13]. Overall, 24% of centers declare to routinely perform a laparoscopic (total or vaginally assisted) surgery, and a further 22% to tailor the surgical approach depending on the patient and disease characteristics. In fact, the laparoscopic option (as well as the indication to tailor the choice) is significantly more adopted in the high case-volume centers (40% and 33%, respectively) compared to those with low case-volume (12% and 14%, respectively) ($p < 0.001$ and $p = 0.010$). This does not mean that laparoscopic/robotic surgery has become the first choice option in EC. It is considered, however, in almost half of the cases, at least in leading centers. In the case of serous papillary and clear cell tumors, a laparotomic approach is believed mandatory by 61% of centers, and the surgical staging is performed in accordance with the rules defined for ovarian cancer by 94% [14,15]. Also, regardless of histotype, in the presence of intra-abdominal spread, surgery with cytoreductive intent is believed appropriate by 92% of centers. Both these findings are representative of an adequate practice pattern [8–10].

With respect to the type of hysterectomy, it is clear that, in clinical FIGO stage I disease, there is no room anymore for a type B–C radical hysterectomy (optioned by only one center), in accordance with national and international recommendations [8–10]. On the other hand, 10% low case-volume centers believe that an extrafascial hysterectomy is to be performed in the presence of clinical infiltration of the cervical canal. It is still surprising, however, that 20.5% and 9.9%, respectively of leading European and North American institutions had reported the same procedure as the elective intervention in FIGO stage II disease [6,7].

One of the major issues in EC therapy is the value of LND. Regardless of the ambiguous international guidelines [8–10], it is to be underlined that the majority of centers (72%) consider LND, when performed, as a systematic procedure (≥20 pelvic nodes; ≥10 aortic nodes). Pelvic and aortic LND, however, is routinely performed in 23% and 2% of institutions, respectively. Thus, the majority of centers perform it only in selective clinical–surgical conditions. This fact underlines that an algorithm based on preoperative but especially intraoperative findings is followed in most centers. This is in contrast with the unavailability or non adoption of intraoperative frozen section analysis on the uterine specimen in 70% of institutions (but in less than 20% of Teaching Hospitals/Cancer Centers). In spite of the data recently generated [3,4], the proportion of centers performing LND has not changed dramatically over the last decades, at least looking at the Western Europe. In 1995, pelvic LND was routinely performed in 24.4% of European leading centers [7]. It is of interest to mention that a recent survey conducted by the North-Eastern German Society of Gynecological Oncology (NOGGO) in selected centers of 24 countries, showed a different attitude with respect to routine LND among diverse geographical macroareas: US–UK 35%, Asia 73%, Southern Europe 28%, Central Europe 56% [16].

As far as the adjuvant treatment is concerned, the major issue is represented by the group of patients with the disease confined to the uterine corpus [5]. As expected, there is no general agreement not only on which patients are to be considered at enough risk of recurrence to justify an adjuvant therapy, but also on which therapy is to be given and whether a lymph node negative status following LND can spare further treatment in patients with high-risk tumors. In fact, these controversies do reflect the uncertainties in the clinical management felt in the health community worldwide. If combined poor grade of differentiation and deep myometrial invasion is indicated as the highest risk subgroup for the endometrioid histology by very most centers, only about one third of them consider one of these a high-risk factor *per se* in the absence of the other. In particular, deep myometrial infiltration seems to be considered a high-risk factor *per se* in a lesser extent, compared to that reported by similar surveys in the past years (83–89%) [6,7], and our data confirm the decreasing trend reported in a more recent survey [17]. International recommendations usually consider deep myometrial infiltration as an indication to adjuvant therapy regardless of the presence of any additional prognosticator. Different options including observation are, however, allowed even within the same guideline [9]. About half of centers include the intermediate-risk in the group for which adjuvant treatment is to be administered, although this is true only in 16% of Teaching Hospitals/Cancer Centers compared with 82% of General Hospitals with low case-volume. Furthermore, the borders between high- and intermediate-risk areas are definitely still unclear.

Sixty percent of centers give patients adjuvant therapy even in the case of negative lymph nodes after a pelvic LND in pathological FIGO stage I with additional high-risk factors. This rate is not very different from 70 to 77% observed in the previous surveys [6,7]. It is evident that such a clinical question is still to be answered. Two international trials, one evaluating the need for adjuvant therapy in node-negative patients (NCT01244789), the other (upcoming, Gynecologic Cancer Intergroup) addressing the role of LND as part of the decisional tree, are expected to clarify this issue in the next years.

The first-choice adjuvant treatment in high-risk patients is still external radiation (with or without brachytherapy) in 45% of centers. Chemotherapy, as sequential or concurrent, is added by a

further 38%, while given alone by only 2%. As expected, there is evidence for an increased use of additional chemotherapy compared with the previous surveys (4–20%). The recent survey by NOGGO confirms such a trend with a 40% chemo-radiation in Southern Europe [16].

From the present survey, emerges that there is a multidisciplinary team in 64% of centers, and in most reference centers. These data demonstrate a significant improvement in the clinical care achieved over the last decades in our country. Nevertheless, if a medical oncology department is present in the same institution in almost 90% of cases, a radiotherapy department/service is available only in about 40% (including brachytherapy in less than 30%). These data justify the need for performing adjuvant treatment outside the institution in about 60% of centers, often in the absence of an effective local-regional oncological network. Overall, the EC patient management and, particularly, the decision making process at specific clinical knots, can be critical, especially in non-reference hospitals. This is due to controversial scientific issues still to be solved, and to the lack of facilities and specific knowledge in the peripheral, low case-volume centers. EC is, however, a relatively frequent disease, and centralization of treatment would not be feasible neither useful, surgical treatment of low-risk EC being feasible in non-specialized centers. High-risk cases (non endometrioid, poorly differentiated, extrauterine spread) could be selected if the clinical screening was appropriate, and these only referred to experienced centers. Standardization of the clinical workup and referral of selected cases to a network of centers (still to be identified) represent our next task.

Ethical approval

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Author contribution

Stefano Greggi (SIOG Executive Board): study concept, study design, quality control, data interpretation, manuscript editing.

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Cono Scaffa (SIOG Member): data collection National Cancer Institute of Naples, literature search, data and statistical analysis, manuscript drafting.

Paolo Scollo (SIOG President): data collection Hospital Cannizzaro of Catania, manuscript review.

Conflict of interest statement

All authors declare no financial support or relationships that may pose conflict of interest.

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