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Original Paper

An Analysis of Approaches to the Treatment of Endometrial Cancer in Western Europe: a CTF Study

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The role of this research is to define the clinical-therapeutic approach to endometrial cancer currently being followed in some of the most important centres of reference for gynaecological cancer in Western Europe. Data was collected by means of a questionnaire, concerning specific diagnostic and therapeutic options, sent to 115 leading centres for gynaecological oncology in Western Europe, and 82 responses were received. The analysis of the management of this neoplasia in Western European countries shows significant differences regarding some particular clinical conditions. Only 24.4% of the interviewed centres stated that they perform lymphadenectomy routinely, whereas it is most commonly reserved for specific pathological conditions. The presence of lymph node spread is generally considered to be the most important prognostic element, and currently, radiotherapy of the pelvis appears to be the treatment of choice either as the sole postsurgical therapy (57%) or in combination with systemic treatment. An adjuvant treatment in stage I lymph node-negative patients is adopted in the large majority of the centres (70.5%) when poorly differentiated cancer (46%) and/or deep myometrial invasion (33.3%) are present. In this condition, radiotherapy appears to be the therapy of choice. Histotype and grading are generally recognised as important risk factors and result in treatment modification; the high percentage of primary surgical modifications is considerable (63.4%) in stage I grade 3 cancers that primarily require lymphadenectomy or recourse to radical hysterectomy. The results of our study indicate that there is no leading therapy in the advanced stages of endometrial cancers, but each therapeutic modality is adopted to more or less the same extent.

Key words: endometrial carcinoma, diagnosis, treatment
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INTRODUCTION

ENDOMETRIAL CARCINOMA was once considered a neoplasm with a relatively favourable prognosis because a large number of cases are clinically diagnosed at an early stage, and are therefore limited to the corpus uteri [1, 2]. In addition, the tumour has a more favourable prognosis than carcinoma of the uterine cervix [1, 3–6] and a lower incidence of lymph node metastases in the early stages compared to cervical carcinoma [2, 4]. The survival rate for some subgroups of patients (neoplasia of corpus uteri with infiltration only initially involving the myometrium, in the absence of pathological risk factors and if treated by adequate surgical therapy) is very high [2, 7].

However, wider knowledge of the natural history of endometrial carcinoma, its real potential for lymph node spread and the high level of correction of clinical stage after intensive anatomical-surgical evaluation, have produced a substantial revision of such considerations.

Beyond the various definitions of stage [8], other prognostically important pathological factors have been indicated in endometrial cancer which are of considerable importance in the planning of treatment. Among these, histotype [9, 10], histological grade [11–13], myometrial invasion [14–17], capillary-like space invasion [18–20], peritoneal cytology [21–24], and lymph node metastases [7,11,12,25] are currently considered to carry different weight in the definition of prognosis and in the planning of postsurgical treatment.

The role of specific diagnostic procedures such as hysteroscopy and lymphadenectomy, and the impact of these postoperative prognostic factors in the management of the tumour are unanimously accepted in the literature. The aim of this study was to define the clinical therapeutic approach to endometrial cancer now being followed in some of the most important centres of reference for gynaecological cancer in Western Europe.

A complete list of contributors is presented at the end of the paper.

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MATERIALS AND METHODS

Data were collected by means of a questionnaire on specific diagnostic and therapeutic options, sent to 115 leading centres for gynaecological oncology in Western Europe. There were 82 responses by the end of April 1994 from centres which treated at least 25 cases of endometrial carcinoma per year (mean 44.5; median 30.0; range 25–250). Because of the wide range of cases treated in each centre, the number of institutions with different patients loads was as follows: 25–49 patients, 59 centres; 50–74 patients, nine centres; 75–100 patients, seven centres; >100 patients, seven centres.

The questionnaire focused on the following items:

(1) *Surgical staging and therapy*
- role of cervico-hysteroscopy in presurgical staging;
- role and effort in lymphadenectomy;
- indications for enlarged hysterectomy;
- indications for vaginal hysterectomy;
- role of peritoneal cytology in surgical staging and choice of therapy.

(2) *Adjuvant treatment*
- adjuvant treatment in FIGO stage Ic;
- indications for postsurgical adjuvant treatment in pathological stage I lymph node-negative cases;
- adjuvant treatment in pT1 lymph node-positive cases;
- indications for brachytherapy of the vaginal vault in pathological stage I neoplasia.

(3) *Treatment modifications*
- management according to age and menopausal status;
- possible different management according to histotype and histological grade.

(4) *Management of advanced FIGO stages (III–IV)*

RESULTS

Role of cervico-hysteroscopy in presurgical staging

In spite of a wider use of cervico-hysteroscopy in the diagnosis of endometrial pathology, only 27/82 (32.9%) institutions use this procedure as a standard presurgical staging of endometrial pathology, while 47 (57.3%) usually omit this examination. In 8 (9.7%), it is performed in specific situations, such as suspected cervical involvement, or dependent upon accessibility to this technique.

Role and effort in lymphadenectomy

Only 20/82 centres (24.4%) declared they performed lymphadenectomy routinely, whereas in 5 (6.1%) centres it is not a standard surgical procedure. In 57/82 institutions (69.5%), lymphadenectomy is performed for selective clinico-surgical conditions: FIGO stage greater than Ib (27.2%), G3 histological grade (25.0%), deep myometrial invasion (20.6%), enlarged nodes (5.4%), histotype (2.2%) and S-phase (1.1%). Old age in 13% of cases and obesity in 5.4% of cases are considered contraindications. Only one centre (1.2%) declared it adopted the laparoscopic removal of suspicious lymph nodes.

Indications for enlarged hysterectomy

Enlarged hysterectomy (Piver II–III) is routinely performed in five of 81 institutions (6.2%), but never used in nine (11.1%). In the majority of cases (67/81: 82.7%), radical surgery is adopted for specific conditions, including FIGO stage over Ist (73.1%), younger age (10.2%), poorly differentiated tumour (3.8%) and other factors (12.9%) (one centre did not answer this question).

Regarding the elective surgical management in stage II cancer, radical hysterectomy (Piver II–III) is the management of choice for the vast majority of centres (62/78: 79.5%), while only 16/78 (20.5%) adopt simple hysterectomy (Piver I).

Indications for vaginal hysterectomy

Considering the vaginal approach in surgical management, 31/82 centres (37.8%) consider it to be totally inadvisable, while 51 (62.2%) suggest that it may be required for specific clinical conditions, such as obesity (31.3%), old age (22.4%), prolapse (16.4%), poor performance status (14.9%), stage I in the elderly (8.9%) or anesthesiological risk (6.0%).

Peritoneal cytology

Peritoneal cytology is routinely performed in 66/79 (83.5%) institutions, but for 20/79 (25.3%) centres it has no value at all, either in prognosis or in treament planning, for 31/79 (39.2%) centres it only has prognostic value, and for 28/79 (35.4%) it provides an indication for postsurgical treatment (three centres did not respond). The type of adjuvant treatment used by these 28 centres is predominantly radiotherapy (46.4%) or chemotherapy (25%).

Adjuvant treatment in FIGO stage Ic

The majority of western oncological centres (70/79: 88.6%) consider postsurgical adjuvant treatment in the presence of deep myometrial invasion to be necessary (no answer from three centres). This treatment is predominantly based on radiotherapy of the pelvis alone (63.3%) or associated with systemic treatment (20.3%). Systemic treatment is rarely adopted (Figure 1). Seven centres were involved in randomised clinical trials on this problem and in particular, in two cases the randomisation is radiotherapy versus observation and in five centres (Italian Study Group) radiotherapy versus chemotherapy.

Postsurgical adjuvant treatment in pathological stage I lymph node-negative cases

This question was answered by 78/82 centres and 23/78 (29.5%) of the institutions declare that there is no indication for postsurgical adjuvant treatment in this condition, while 55/78 (70.5%) recognise particular indications (Table 1) including poorly differentiated tumours (G3) (46.0%), deep myometrial invasion (33.3%), and participation in clinical trials on this problem (6.3%).

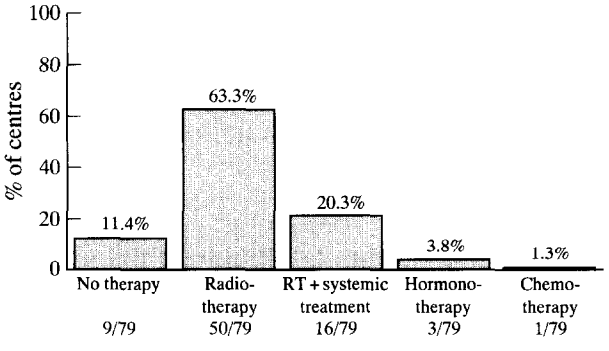

Figure 1. Suggested postsurgical treatment in FIGO (1988) stage Ic endometrial cancer. No response: three centres.

Table 1. Indications for postsurgical adjuvant treatment in stage I lymph node-negative endometrial cancers

Indications (n = 63)	n	(%)
Histological grade G3	29	(46.0)
Deep myometrial invasion (Ic)	21	(33.3)
Clinical trial	4	(6.3)
Peritoneal cytology positivity	3	(4.8)
Vascular space invasion	3	(4.8)
S-phase	2	(3.2)
Inadequate surgery	1	(1.6)
Total indications	63	

Fifty-five of 78 (70.5%) centres in Western Europe: postsurgical adjuvant treatment is indicated (see table). Twenty-three of 78 (29.5%) centres: not indicated. Four of 82 centres: no answer.

Table 2. Brachytherapy on the vaginal vault in pathological stage I endometrial cancer

Indications* (n = 67)	n	(%)
Grade 3	29	(43.3)
Stage Ic	22	(32.8)
Inadequate surgery	4	(5.9)
Lymph node-positive	3	(4.5)
Clinical trials	2	(2.9)
Other	7	(10.4)
Total indications	67	

Never adopted in 20/78 centres (25.6%). Systematically adopted in 10/78 centres (12.8%). Adopted only if dictated by particular indications*: 48/78 centres (61.5%). No response: four centres.

Adjuvant treatment in pT1 lymph nodes-positive cases

All centres in Western Europe perform postsurgical adjuvant treatment in pT1 lymph node-positive cases (no response from three centres). Radiotherapy is the treatment of choice, either alone (57.0%) or in combination with systemic treatments (38.0%), while systemic treatment alone is seldom used (Figure 2).

Indications for brachytherapy of the vaginal vault in pathological stage I neoplasia

Brachytherapy is routinely used in 10 (12.8%) centres, while 20 (25.6%) institutions never perform this therapeutic approach. In 48 institutions (61.5%), the predominant indications for brachytherapy were dictated by poorly differentiated tumours (43.3%), deep myometrial invasion (32.8%) and inadequate surgery (5.9%) (Table 2) (no response from four centres).

Management according to age and menopausal status

Sixty-eight of 81 (83.9%) centres (one centre did not answer this question) declared that their management did not differ according to menopausal status, and 13/81 (16.0%) declared that they may discuss ovarian preservation with premenopausal patients with well differentiated cancer. Alternatively, only 9/81 centres (11.1%) adopted the standard protocol for patients over 75 years of age. In this subgroup of older patients, 72/81 centres (88.9%) adopted a different treatment, and the deviation from standard management involved: type of surgery in 41/72 (56.9%), choice of postsurgical therapy in 32/72 (44.4%), and greater recourse to primary radiotherapy in 13/72 (18%). In particular, modification of therapy in patients over 75 years involved omission of lymphadenectomy and less recourse to radical hysterectomy.

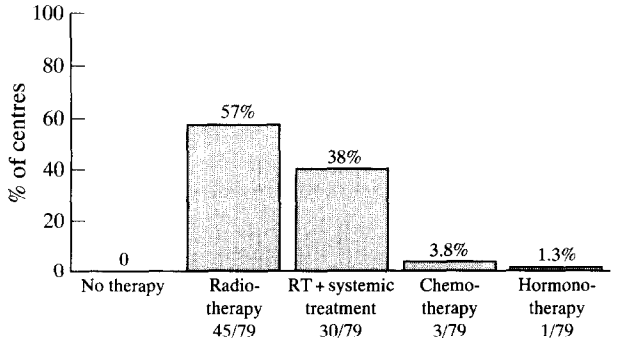

Figure 2. Suggested postsurgical adjuvant treatment in pathological stage 1 lymph node-positive endometrial cancers (79 centres in Western Europe).

Histotype and grading

Histotype is considered an important risk factor in modifying the management of the neoplasia in 60 (75.9%) of the institutions (no response from three centres). Among the various histotypes, serous papillary (43.7%), clear cells (32.8%) and adenosquamous cancer (15.6%) are those most frequently reported as indicative in modifying the treatment. It is widely held that histological grade must be taken into account in the planning of treatment (68/77 centres: 88.3%), in the choice of both primary surgery and postsurgical adjuvant treatment (five centres did not respond). In particular, the suggested treatment programmes in stage I grade 3 cancer involve surgery alone in 63.4% of centres and recourse to postsurgical radiotherapy in 23.2% of centres (Table 3).

Management of advanced stages (FIGO III–IV)

A wide variety of treatment regimens is used for advanced stages of endometrial cancers; among these, a multimodal approach is adopted in 62/78 (79.5%) institutions, while radiotherapy alone is performed in six of 78 (7.7%) and elective primary surgery in 10/78 (12.8%) centres (four centres did not respond). Analysis of the combined treatment shows that surgery is performed in 40.3% centres, radiotherapy in 64.5%, chemotherapy in 59.7% and hormonotherapy in 45.2% of centres (Table 4).

DISCUSSION

Even though there is general agreement on the usefulness of surgical staging and primary surgery in endometrial cancer,

Table 3. Suggested treatment programmes in stage I grade 3 endometrial cancer

	n	(%)
Surgery alone	52/82	(63.4)
Adjuvant radiotherapy	19/82	(23.2)
Presurgical therapy	3/82	(3.6)
Systemic treatment	3.82	(3.6)

Five centres did not answer.

Table 4. Combined treatment in advanced (FIGO stage III–IV) endometrial cancer (62/78 centres in Western Europe: 79.5%)

Combined treatment	*n*	(%)
With surgery	25/62	(40.3)
With radiotherapy	40/62	(64.5)
With chemotherapy	37/62	(59.7)
With hormonotherapy	28/62	(45.2)
Not specified	11/62	(17.7)

analysis of the management of this neoplasia in Western European countries shows significant differences regarding some particular clinical conditions.

In spite of the wide diffusion of cervico-hysteroscopy in outpatient detection of endometrial pathology, this procedure is part of standard diagnostics in less than half the centres in Western Europe. One of the major problems in endometrial cancer treatment involves the role of lymphadenectomy. Only 24.4% of the centres that responded stated that they perform lymphadenectomy routinely, whereas it is most commonly reserved for specific pathological conditions, such as grade, histotype, myometrial invasion evaluated by preoperative magnetic resonance or intra-operative gross evaluation of the myometrium. The presence of lymph node invasion is generally considered the most important prognostic element which heavily influences postsurgical decision-making. In fact, there is general agreement in the adoption of an adjuvant treatment in such a condition. At present, radiotherapy on the pelvis appears the treatment of choice, either as the sole postsurgical therapy (57.0%) or in combination with systemic treatment. The use of systemic treatment alone is quite limited and predominantly based on chemotherapy (3.8%), while hormonotherapy has almost been abandoned (1.3%).

An adjuvant treatment in pT1 lymph node-negative patients is adopted in the large majority of the centres (70.5%) when poorly differentiated cancer and/or deep myometrial invasion are present. In this condition, radiotherapy appears to be the therapy of choice either alone (63.3%) or in combination with systemic treatment (20.3%). Particularly for stage Ic, systemic treatment is seldom used. Hormonotherapy is adopted in 3.8% of the centres, even though long-term analysis of a randomised study failed to detect any benefit from medroxyprogesterone acetate as adjuvant treatment in such a condition [26].

Histotype and grading are generally recognised as important risk factors and result in treatment modification. The high percentage of primary surgical modifications is considerable (63.4%) in stage I grade 3 cancers that primarily require lymphadenectomy or recourse to radical hysterectomy. This approach may be questionable, such as the choice of presurgical therapy in 3.6% of the centres. In fact, it should be noted that in the evaluation of histological grade, there is a higher frequency of error if the tissue is obtained by uterine curettage compared to analysis of the uterus *in toto*, which progressively increases with the progress of dedifferentiation [2, 13, 27].

It is notable that approximately one third of the centres (37.8%) consider vaginal hysterectomy to be inappropriate. Obviously, vaginal hysterectomy does not allow lymph node exploration, lymph node sampling or intensive surgical pathological abdominal staging. Nevertheless, it may be a non-elective procedure in cases of obesity, old age and high anesthesiological risk. However, these conditions reflect the same cases in which routine lymphadenectomy is not performed, even through the laparotomic approach.

The treatment of advanced endometrial cancers (FIGO stages III–IV) is individualised in many centres and, consequently, it is difficult to identify specific, common guidelines for these cases. It may be emphasised, however, that for 12.8% of the centres, elective primary surgery is the first step, followed by further integrated treatments planned on the basis of surgical pathological staging, while radiotherapy alone has a limited role, being practised in only 7.7% of the centres. Sixty-two centres stated that they adopt a multimodal combined treatment in which surgery (albeit not primary) is used in 40.3%, radiotherapy in 64.5%, chemotherapy in 59.7% and hormonotherapy in 45.2% of cases. These results indicate that there is no leading therapy in the advanced stages of endometrial cancers, but each therapeutic modality is adopted to more or less the same extent.

Conflicting data emerge on the usage of peritoneal cytology. While it is routinely performed in 83.5% of the institutions, in a quarter of these cases, it is not considered to be of any value either for prognosis or for treatment planning. This reflects the controversial role of peritoneal cytology as an independent prognostic factor [11, 21–28]. Consequently, in 39.2% of the centres, treatment decisions should not be based on these findings alone, but only if backed by other poor prognostic factors correctly evaluated after surgical pathological staging.

In conclusion, the need for a large scale multicentre clinical trial covering these controversial aspects appears evident: systemic lymphadenectomy versus lymph node sampling; adjuvant treatment versus observation in FIGO stage Ic (in fact seven of the responding 82 centres are involved in randomised multicentre clinical trial on this problem); radiotherapy versus chemotherapy in stage I lymph node-positive cases; treatment versus no treatment in positive peritoneal cytology; combined therapy including surgery versus combined therapy without surgery in advanced stages.

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